Title
Studies toward the Cyathane and Cyanthiwigin Diterpenes

Author
Miller, Laura Carolyn

Publication Date
2010

Peer reviewed|Thesis/dissertation

Studies toward the Cyathane and Cyanthiwigin Diterpenes

by

Laura Carolyn Miller

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair
Professor Matthew B. Francis
Professor Mary C. Wildermuth

Spring 2010

Abstract

Studies toward the Cyathane and Cyanthiwigin Diterpenes

by

Laura Carolyn Miller

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor Richmond Sarpong, Chair

The cyathanes and cyanthiwigins are a large family of natural products isolated from terrestrial and marine sources. The compounds share a [5-6-7] fused-ring structure, with two all-carbon quaternary centers at the ring junctions and a *trans*-B-C ring fusion. There is a variety of oxygenation and unsaturation patterns about the tricyclic skeleton, leading to a wide range of biological activity for the natural products, including antibiotic, anti-inflammatory, anticancer and neurotrophic indications. The exciting biological activity and unique structure of the cyathane diterpenoids has inspired much synthetic interest following the isolation of these natural products.

Rather than targeting a single cyathane diterpenoid, we planned to develop a general strategy to provide access to many of the natural products. We divided the cyathane family of natural products into two main categories, the cyanthiwigins and other cyathane diterpenes, on the basis of the *syn*- or *anti*-relationship of the angular methyl groups at the ring fusion positions. From a common dienol precursor derived from the Hajos-Parrish ketone, we successfully forged the cores of the cyanthiwigin and cyathane natural products through a divinylcyclopropane Cope rearrangement. We were also able to install the second all-carbon quaternary center through an atom-transfer method.

In a second-generation approach, we streamlined the strategy using a rhodium-mediated cyclopropanation of a central diene precursor to perform a cyclopropanation/Cope rearrangement cascade to form the tricyclic core of the cyanthiwigin and cyathane natural products. Using the Rh_2[DOSP]$_4$ catalysts, we were able to effect a resolution of the racemic diene, furnishing two enantioenriched diastereomeric tricycles that are applicable to the total syntheses of cyanthiwigin G and cyathin A_3.

Finally, we developed a strategy for the stereoselective installation of the second all-carbon quaternary center in the [*3,3*] sigmatropic rearrangement. This approach involves application of the cyclopropanation/Cope rearrangement cascade to a diene with the second methyl group in place prior to cyclopropanation, or incorporation of the requisite cyclopropyl

derivative through a Suzuki coupling. Either method should provide a powerful strategy to stereoselectively install the second all-carbon quaternary center of the cyathane and cyanthiwigin natural products.

Table of Contents

Chapter 3: Second Generation Rhodium-Carbenoid Approach to the Tricyclic Core

Chapter 4: Studies Toward the Installation of the Second All-Carbon Quaternary Center

Acknowledgements

I would like to thank my research advisor Richmond Sarpong for his overall enthusiasm and infectious passion for organic chemistry. I will also be forever grateful to him for placing me in 844 Latimer where I not only had a great view, but wonderful labmates, overall creating a great work environment. Eric Simmons, Cameron Smith, Alison Hardin, and more recently, Jessica Kisunzu and Gary Gallego, have all contributed to creating a fun and entertaining atmosphere. In that regard, I would especially like to thank Eric Simmons and Alison Hardin for always being willing sounding-boards for ideas and great resources for chemistry in general. I am appreciative of the Sarpong Group at large. Thank you all for making the group a place from which I am proud to come. Also, thanks to Scott West, Alison Hardin, Jess Wood, Jesse Cortez and Steve Heller for proofing my thesis.

Over the years I have had the privilege to work with many people. Thanks to Maina Ndungu for laying the groundwork for the cyathane project by developing the initial route to the tricyclic core. I am also grateful to the Davies group, and specifically Yajing Lian, for their collaborative efforts on the cyclopropanation/Cope rearrangement chemistry and their generous donation of $Rh_2[DOSP]_4$ and $Rh_2[PTAD]_4$ catalysts. I also had the honor to work with two excellent undergraduates, Katrina Uychaco and Brian Ikkanda, whom I would like to thank for their enthusiasm and hard work.

To Scott West, I cannot imagine surviving graduate school without you. Hopefully Strada's business will not be horribly impacted by our absence.

I am also grateful to the Berkeley Chemistry Department in general. I would like to thank all of the research groups for chemicals, equipment and helpful discussions. In particular I would like to thank the Toste group for use of their chiral HPLC, as well as the Ellman group for use of their chiral HPLC, polarimeter and cold room. Also, thanks to Rudi Nunlist and Chris Canlas for their help in the NMR facility, and a big thank you to Lynn Keithlin for always being a great resource on the 4^{th} floor.

For funding the cyathane project, I am grateful to the American Cancer Society and the NIH. I would also like to thank Eli Lilly for a graduate fellowship and Eli Lilly along with the Women Chemists' Committee for a travel grant that allowed me to present at the 238^{th} National ACS Conference. Finally, thanks to Bristol-Myers Squibb for their donation of 2-methyl-1,3-cyclopentanedione.

Above all, I would like to thank my friends and family for their unending support. I would not have gotten here without you.

Chapter 1
Cyathane and Cyanthiwigin Natural Products

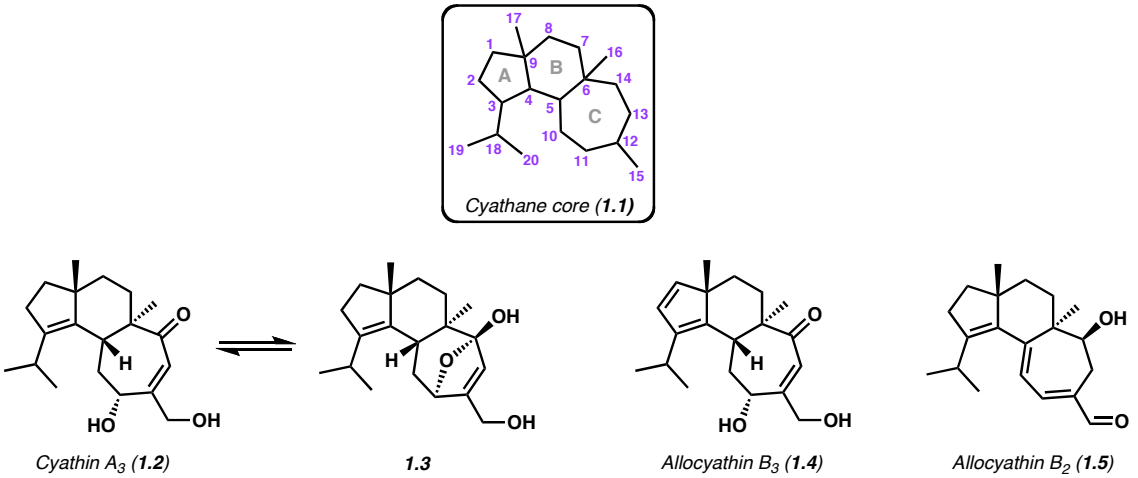
1.1. Introduction

Since the first isolation of natural products with the cyathane skeleton in the 1970s, these compounds have garnered much attention, both due to their biological activity and unique [5-6-7] tricyclic core. The number of isolated natural products in this family continues to grow, with the current tally around one hundred members. The varied biological activity and numerous structural permutations among the cyathane diterpenes have also inspired over 20 synthetic approaches to this class of compounds.

1.2. Isolation, Structure and Biological Activity

Spurred by the antibiotic activity of metabolites produced by the bird's nest fungus *Cyathus helenae,* Ayer and coworkers isolated the first natural products in the cyathin family from the cultured fungus in the 1970s.[1,2] The initial report determined the structures of cyathin A_3 (**1.2**, Fig. 1.2.1) and allocyathin B_3 (**1.4**).[2] The cyathins have a [5-6-7] fused tricyclic core (**1.1**), numbered as shown in Fig. 1.2.1. Assignment of these natural products was complicated by the presence of a mixture hydroxyketone **1.2** and hemiketal **1.3**, which are in equilibrium. This equilibration is common with cyathanes sharing this motif.

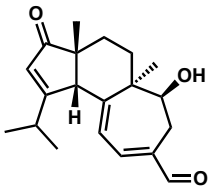
Figure 1.2.1. Examples of cyathin natural products.



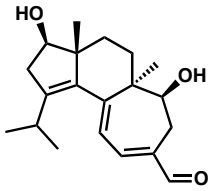
Notable general features present in cyathane natural products include two angular methyl groups at the ring junctions (C9 and C6) and a *trans*-B-C ring fusion. Various levels of oxygenation and unsaturation about the tricyclic core are found in the cyathane congeners and have proven to be challenging to install synthetically (see Chapter 1.4). In the years following the first isolation of the cyathane diterpenes, a variety of other cyathins were isolated, including allocyathin B_2 (**1.5**), from *C. helenae* and other terrestrial fungal sources.[3-8] These compounds exhibit antibiotic activity toward both gram-positive and gram-negative bacteria.[1,8]

Recently, the glaucopines[9,10] (e.g., **1.6**, Fig. 1.2.2) and related cyrneines[11,12] (e.g., **1.7**) have been isolated from the mushrooms *Sarcodon glaucopus* and *Sarcodon cyrneus*. These natural products have been shown to have both anti-inflammatory properties[9] and to promote neurite outgrowth with similar activity as nerve growth factor (NGF).[11,12] Neurotrophic compounds have the potential to treat neurodegenerative disorders such as Parkinson's and Alzheimer's.

Figure 1.2.2. Selected glaucopine and cyrneine natural products.



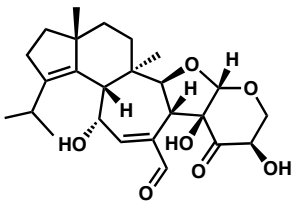
*Glaucopine C (**1.6**)*



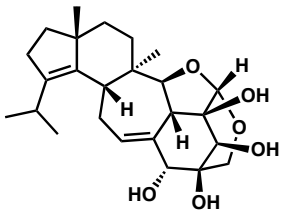
*Cyrneine A (**1.7**)*

Shortly after the isolation of the cyathins, a series of closely-related glycosylated cyathane diterpenes were isolated. The striatals[13-15] (e.g., **1.8**, Fig. 1.2.3) were isolated from several *Cyathus* fungi and possess antibiotic, antifungal[15,16] and leishmanicidal[17] activity. The erinacines[18-26] (e.g., **1.9**) are metabolites produced by *Hericium* species. In addition to being kappa opioid receptor agonists,[27] the erinacines have garnered much attention due to their ability to induce NGF production.[15,20]

Figure 1.2.3. Examples of striatal and erinacine compounds.



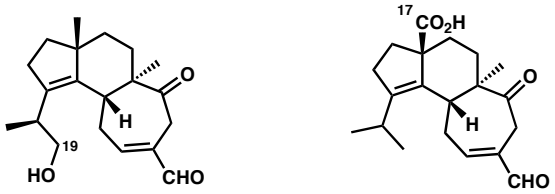
*Striatal C (**1.8**)*



*Erinacine E (**1.9**)*

Another subset of the cyathanes, the sarcodonins[28-32] (e.g., **1.10**, Fig. 1.2.4) and scabronines[33-36] (e.g., **1.11**), were both isolated from *Sarcodon scabrosus*. Compared to the cyathins, these natural products have a more highly oxygenated structure. The sarcodonins possess a hydroxyl group at C19, whereas the C17 methyl group in the scarbronines has been oxidized to a carboxylic acid. The sarcodonins exhibit antibiotic,[31] anti-inflammatory[29,30] and anti-proliferative activity.[37] Similar to the erinacines, the scabronines promote NGF synthesis.[34,36,38]

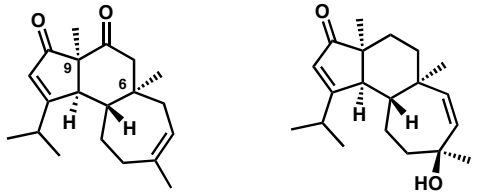
Figure 1.2.4. Selected sarcodonin and scabronine natural products.



*Sarcodonin G (**1.10**)* *Scabronine G (**1.11**)*

In 1992, Kashman and coworkers isolated cyanthiwigins A-D (e.g., **1.12**, Fig. 1.2.5) from the marine sponge *Epipolasis reiswigi*.[39] Additional cyanthiwigins (e.g., **1.13**) were later found in *Myrmekioderma styx*.[40,41] Similar to the cyathins, cyanthiwigins possess angular methyl groups at C6 and C9, however, in the cyanthiwigins, the methyl groups are in a *syn*-relationship rather than the *anti*-relationship found in the other cyathane diterpenes. The cyanthiwigins display a range of biological activity, from anti-HIV and anti-TB activity to cytotoxic effects on primary tumor lines.[41] Cyanthiwigin B also acts as a synergistic antibiotic, presumably by blocking efflux pumps, allowing an antibiotic to remain in the microbe and kill it more effectively.[42]

Figure 1.2.5. Examples of cyanthiwigin diterpenoids.

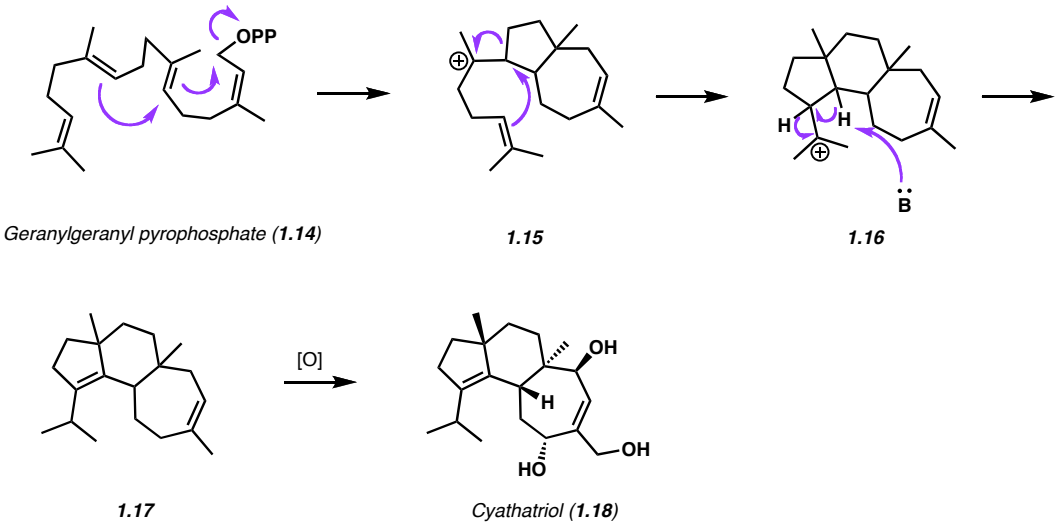


*Cyanthiwigin B (**1.12**)* *Cyanthiwigin U (**1.13**)*

1.3. Biosynthesis

To determine the biosynthetic pathway that leads to the cyathanes, Ayer and coworkers conducted feeding studies on the production of cyathatriol (**1.18**, Scheme 1.3.1) by *Cyathus earlei*.[43] The C_{20} framework suggested that the cyathanes were diterpenes constructed via the isoprenoid pathway. The C_{20} precursor to diterpene natural products, geranylgeranyl pyrophosphate (**1.14**), is constructed from units of acetyl CoA and acetoacetyl CoA. Ayer fed the fungus sodium acetate labeled with ^{13}C at the C1 position, and analyzed the enriched cyathatriol that was produced. On the basis of these studies, Ayer and coworkers proposed a cationic cyclization of geranylgeranyl pyrophosphate (**1.14**) to form bicycle **1.15**. A Wagner-Meerwein migration expands the B-ring, and subsequent cyclization forms the A-ring of the tricycle (**1.16**). The tertiary carbocation is quenched via a 1,2-hydride shift and deprotonation to form the cyathane skeleton (**1.17**). A series of oxidations furnishes cyathatriol (**1.18**).

Scheme 1.3.1. Cyathatriol biosynthesis.

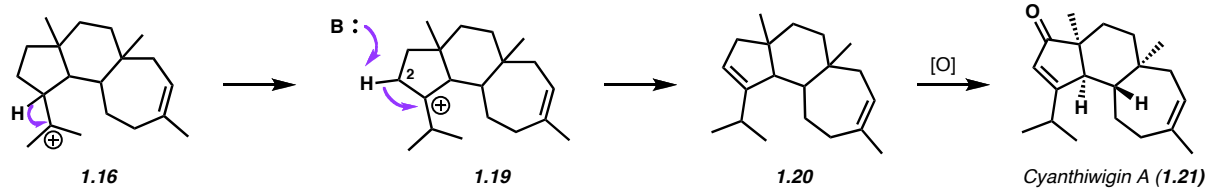


*Geranylgeranyl pyrophosphate (**1.14**)* *1.15* *1.16*

1.17 *Cyathatriol (**1.18**)*

No biosynthetic studies have been pursued on the cyanthiwigin natural products, primarily due to technical difficulties associated with culturing marine organisms in such studies. First, the organism must be successfully grown in a controlled environment over extended periods due to the slow growth rates of the species. An additional issue is the possible presence of symbiotic microorganisms, which may be the ultimate source of the natural products under study. On the basis of the Ayer study,[43] Kashman and Rudi have proposed a related biogenesis for the cyanthiwigin diterpenoids (Scheme 1.3.2).[44] Tricycle **1.16** undergoes a 1,2-hyride shift to form tertiary carbocation **1.19**. In the cyanthiwigins, deprotonation is proposed to occur at C2 to quench the positive charge and form **1.20**, which is elaborated to the natural products by a series of oxidations.

Scheme 1.3.2. Cyanthiwigin biogenesis.



1.16 *1.19* *1.20* *Cyanthiwigin A (**1.21**)*

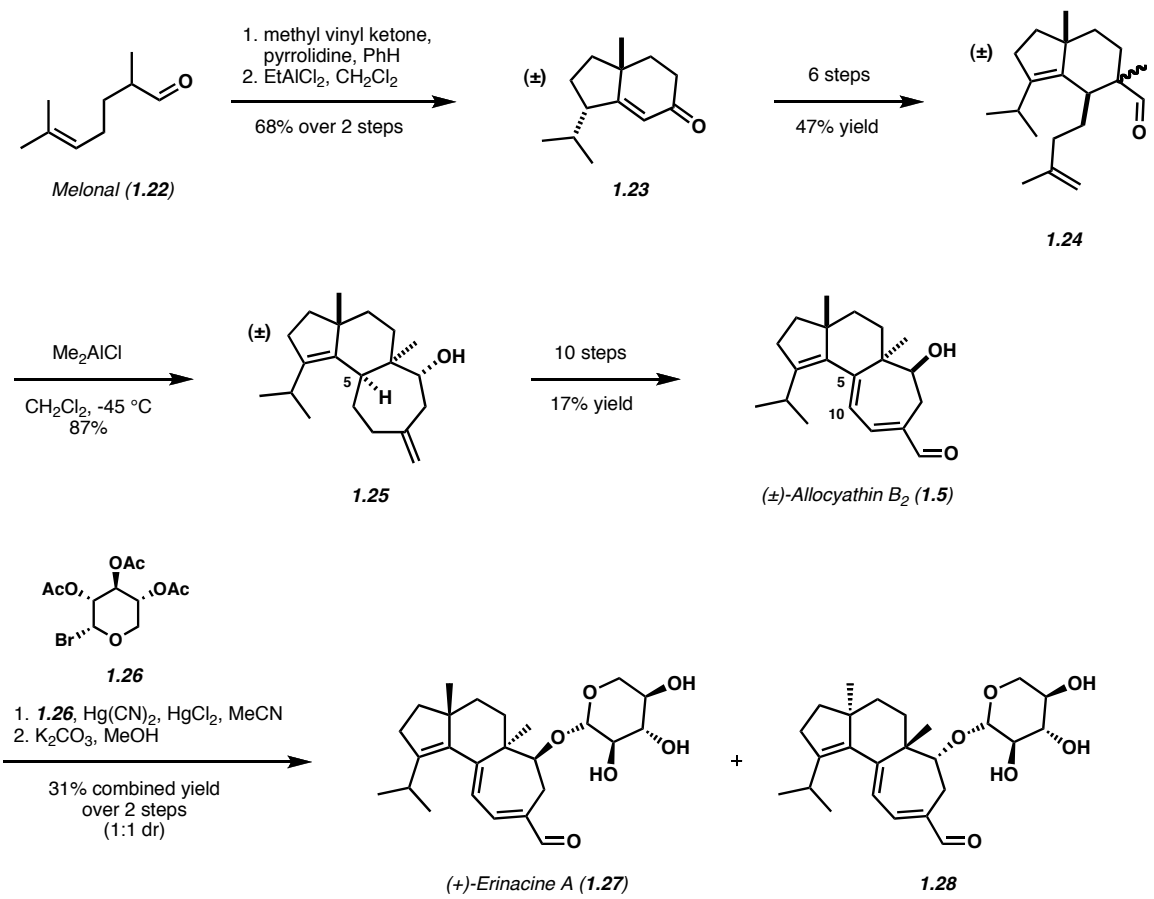
1.4. Previous Synthetic Approaches

The unique core of the cyathane family of natural products has intrigued synthetic organic chemists since their isolation. Synthetic efforts in this area have led to the publication of a variety of synthetic approaches to the cyathane core,[45-57] as well as fourteen total syntheses to date. The strategies toward the cores have recently been covered,[58,59] and the total syntheses will be discussed below.

1.4.1. Allocyathin B_2

Allocyathin B_2 (**1.5**), which lacks a *trans*-B-C ring fusion by virtue of unsaturation between C5-C10, has been a popular target due to its simplified structure. It was the first cyathin to succumb to total synthesis, along with erinacine A (the allocyathin B_2-xyloside) in work by Snider and coworkers.[60,61] In their approach, they used their previously reported methodology,[62] involving a Lewis acid-mediated addition of alkenes to enones, to quickly access bicycle **1.23** starting from melonal (**1.22**, Scheme 1.4.1). The bicycle was carried forward in 10 steps to aldehyde **1.24**. Next, the key intramolecular carbonyl ene reaction was catalyzed by dimethylaluminum chloride to form the seven-membered ring. Unfortunately, the B-C ring fusion was *cis* instead of the required *trans*-configuration found in the cyathane diterpenoids. However, they were able to target allocyathin B_2, which ablates the C5 stereocenter. From tricycle **1.25**, the synthesis of (±)-allocyathin B_2 was achieved in 10 steps. Overall, the first total synthesis of (±)-allocyathin B_2 was accomplished in 19 steps from melonal (**1.22**) in a 4.4% overall yield. Erinacine A (**1.27**), the xyloside of allocyathin B_2, was then prepared through glycosylation and deprotection.

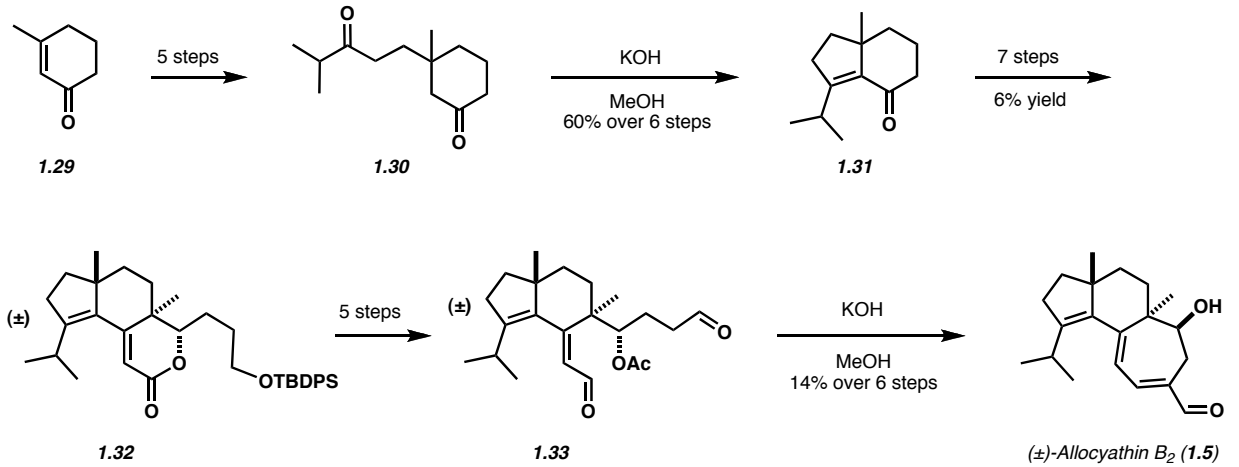
Scheme 1.4.1. Snider's approach to (±)-allocyathin B_2 and (+)-erinacine A.[60,61]



An aldol strategy was used by Tori and coworkers in 1998 to achieve the total synthesis of (±)-allocyathin B_2 (Scheme 1.4.2).[63] 3-Methylcyclohexenone (**1.29**) was advanced five steps

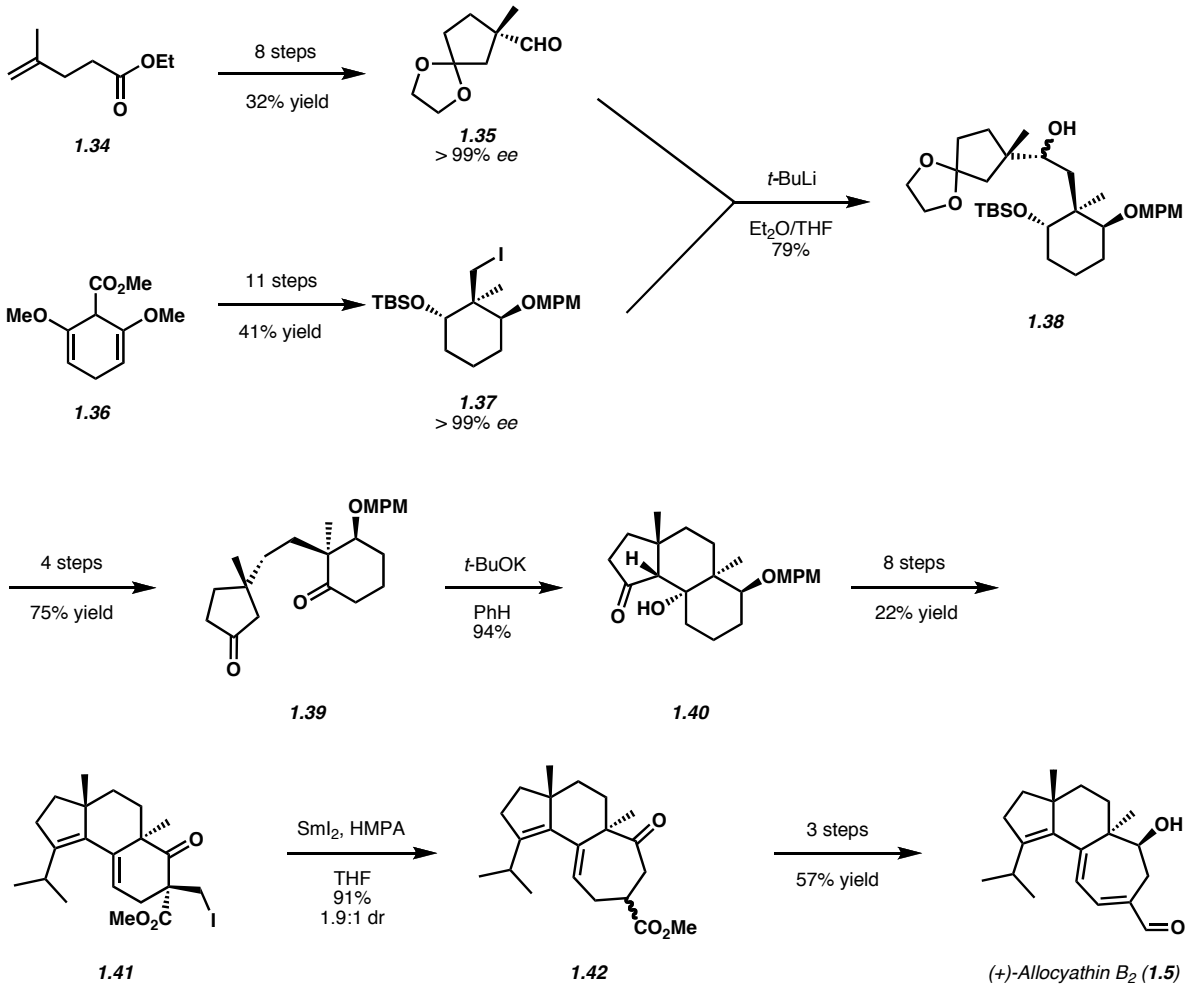
to diketone **1.30**, which undergoes the first aldol condensation in the sequence to achieve bicycle **1.31**. Further manipulations furnished tricycle **1.32**, which was carried forward to bis-aldehyde **1.33**. Aldol condensation closed the seven-membered ring, and afforded (±)-allocyathin B_2 in 19 steps and 0.5% overall yield.

Scheme 1.4.2. Tori's synthesis of (±)-allocyathin B_2.[63]



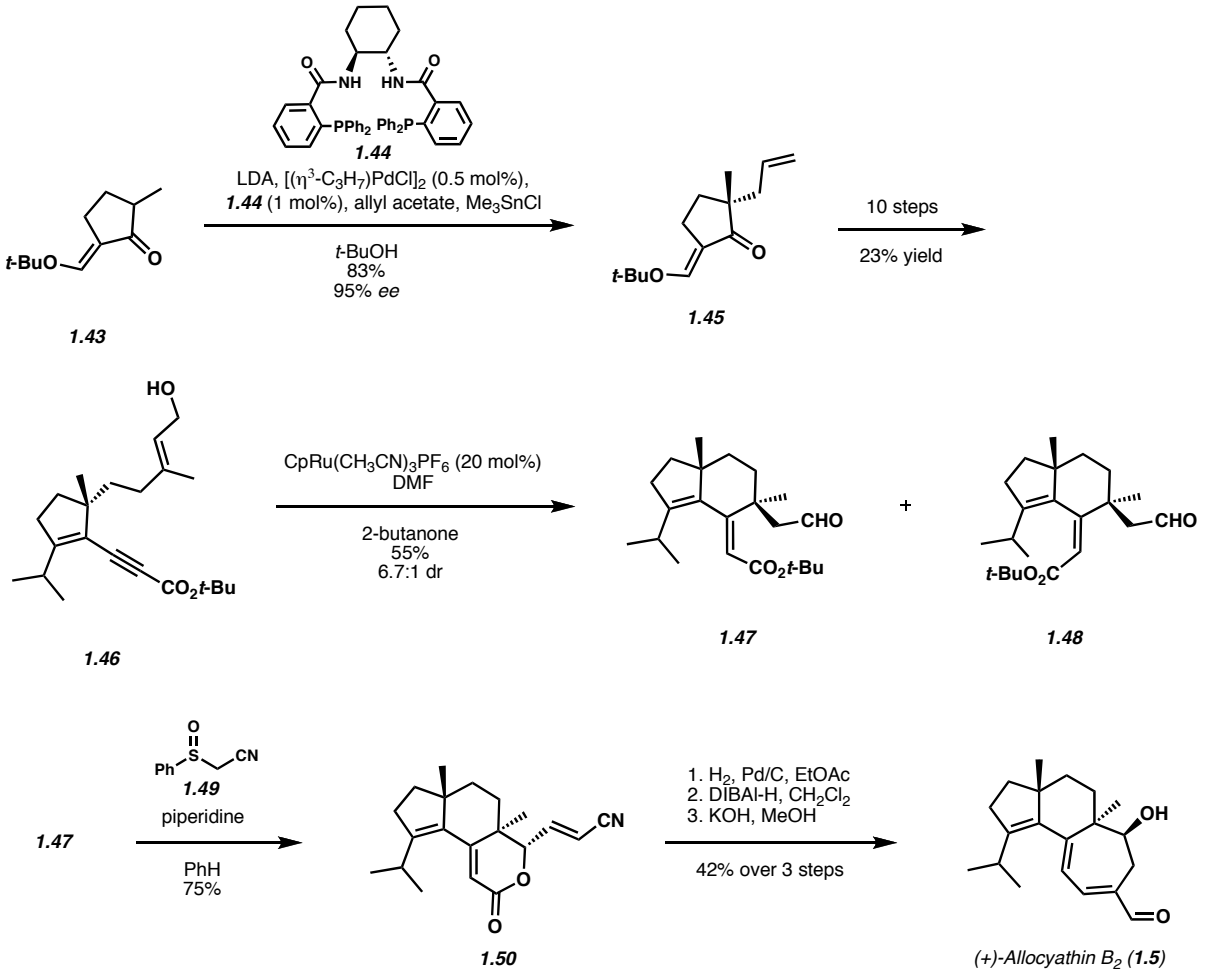
Nakada and coworkers' route to (+)-allocyathin B_2 was the first enantioselective synthesis of a cyathane natural product (Scheme 1.4.3).[64] Fragment coupling of aldehyde **1.35**[65] and iodide **1.37**[66] yielded alcohol **1.38**. The compound was elaborated in four steps to dione **1.39**, and subsequent aldol addition formed the B-ring (**1.40**). Tricycle **1.40** was further elaborated to iodide **1.41**, which underwent a samarium(II)-mediated ring expansion to form the seven-membered ring (**1.42**). The [5-6-7] tricycle (**1.42**) was advanced to the natural product, achieving an enantioselective synthesis in 29 steps with an overall yield of 3% from **1.36**.

Scheme 1.4.3. Nakada's route to (+)-allocyathin B_2.[64]



Trost and coworkers published a concise enantioselective approach to (+)-allocyathin B_2 in 2005 (Scheme 1.4.4).[67,68] Enone **1.43** was accessed from 2-methylcyclopentanone,[69] and then utilized in a palladium-catalyzed asymmetric allylic alkylation, to provide allyl ketone **1.45** in 95% *ee*. Ten additional steps were needed to form ester **1.46**, which underwent a ruthenium-catalyzed cycloisomerization to yield bicycles **1.47** and **1.48** (6.7 : 1 dr). Desired bicycle **1.47** was transformed via a hydroxylative Knoevenagel to tricycle **1.50**. The seven-membered ring was formed in the last step through an aldol condensation. The route furnished (+)-allocyathin B_2 in 17 steps from 2-methylcyclopentanone with an overall yield of 2.3%.

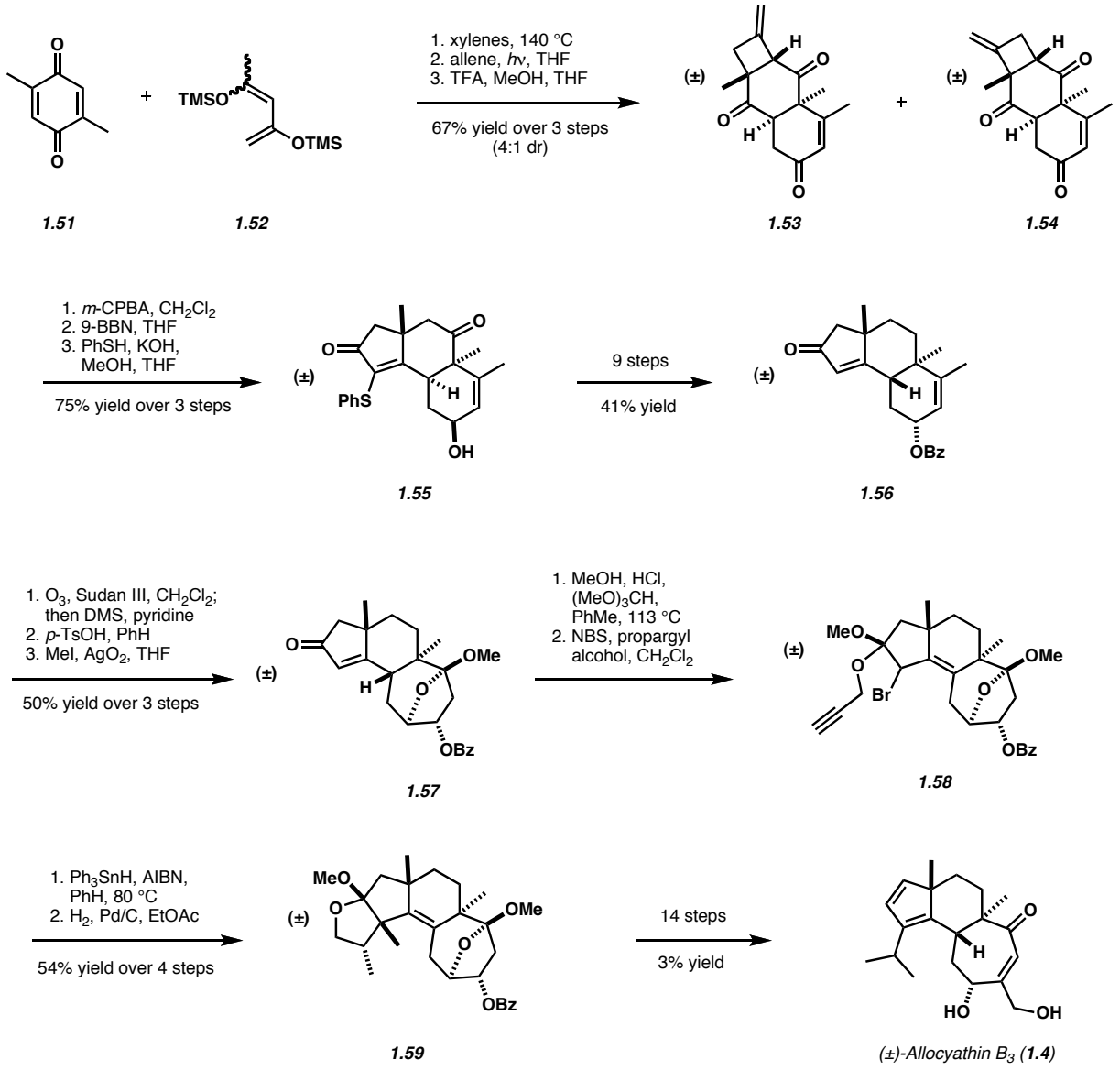
Scheme 1.4.4. Synthesis of (+)-allocyathin B_2 by Trost.[67,68]



1.4.2. Allocyathin B_3

In 2000, Ward and coworkers reported the first synthesis of (±)-allocyathin B_3 (**1.4**, Scheme 1.4.5).[70] Tricycles **1.53** and **1.54** were assembled via the Diels-Alder cycloadditon of *p*-benzoquinone **1.51** with diene **1.52**, followed by a [2+2] cycloaddition with allene and subsequent treatment with acid. The mixture of products (**1.53** and **1.54**) was carried forward by epoxidation and 1,2 reduction of the enone in the C-ring. The epoxide was opened by phenylthiolate addition, leading to the fragmentation of the cyclobutane ring, and subsequent formation of the five-membered A-ring to provide **1.55**.[45] Functional group manipulation furnished tricycle **1.56**, and subsequent ozonolysis in the presence of Sudan III cleaved the C-ring. The resulting keto-aldehyde underwent an aldol addition followed by transacylation and alkylation to furnish cyathin core **1.57**.[53] To install the isopropyl group at C3, propargyl ether **1.58** was prepared as a single diastereomer, and C-C bond formation was achieved by a radical cyclization, furnishing tetracycle **1.59** after reduction of the exocyclic double bond. (±)-Allocyathin B_3 was achieved after fourteen additional transformations, yielding the natural product in 36 steps and a 0.2% overall yield.

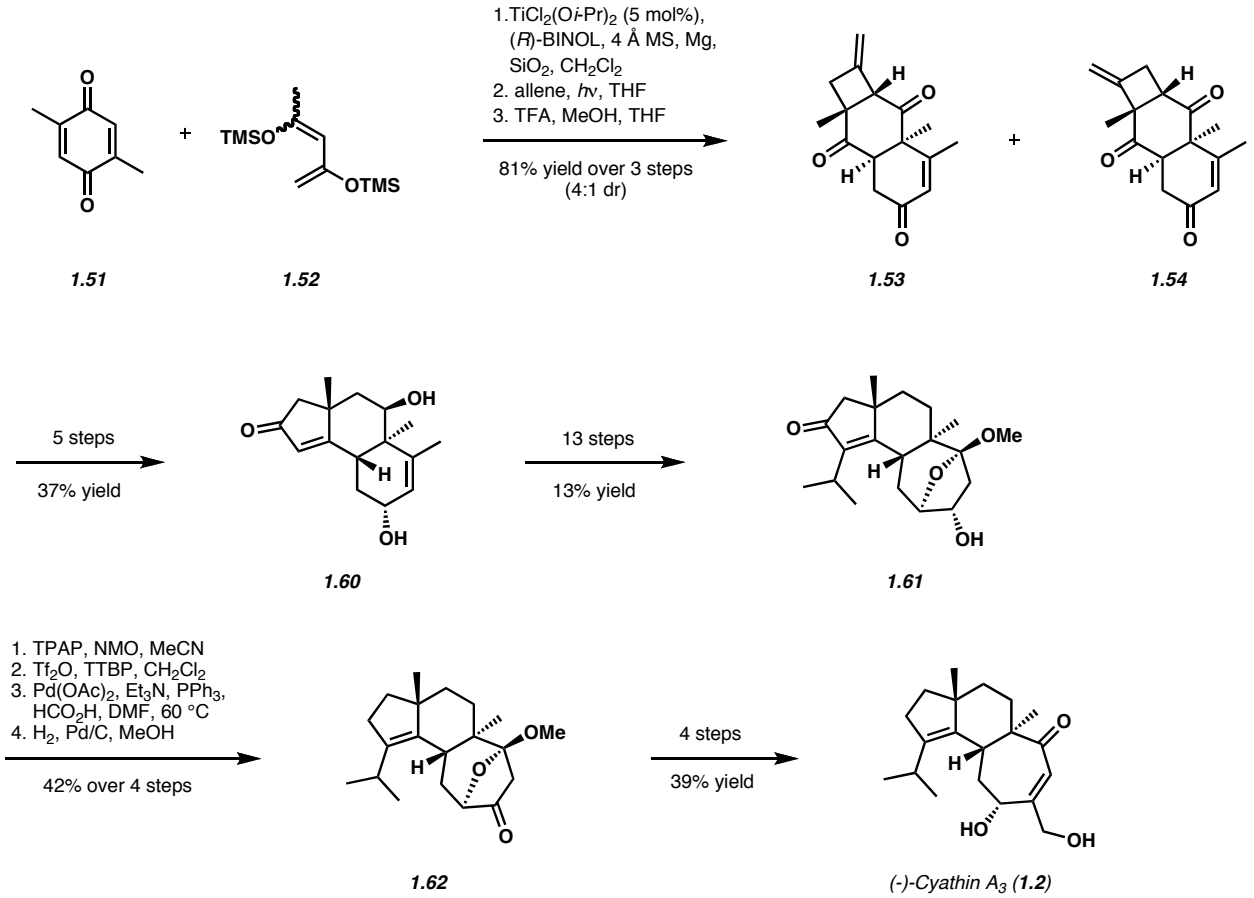
Scheme 1.4.5. Synthesis of (±)-allocyathin B_3 by Ward.[70]



1.4.3. Cyathin A_3

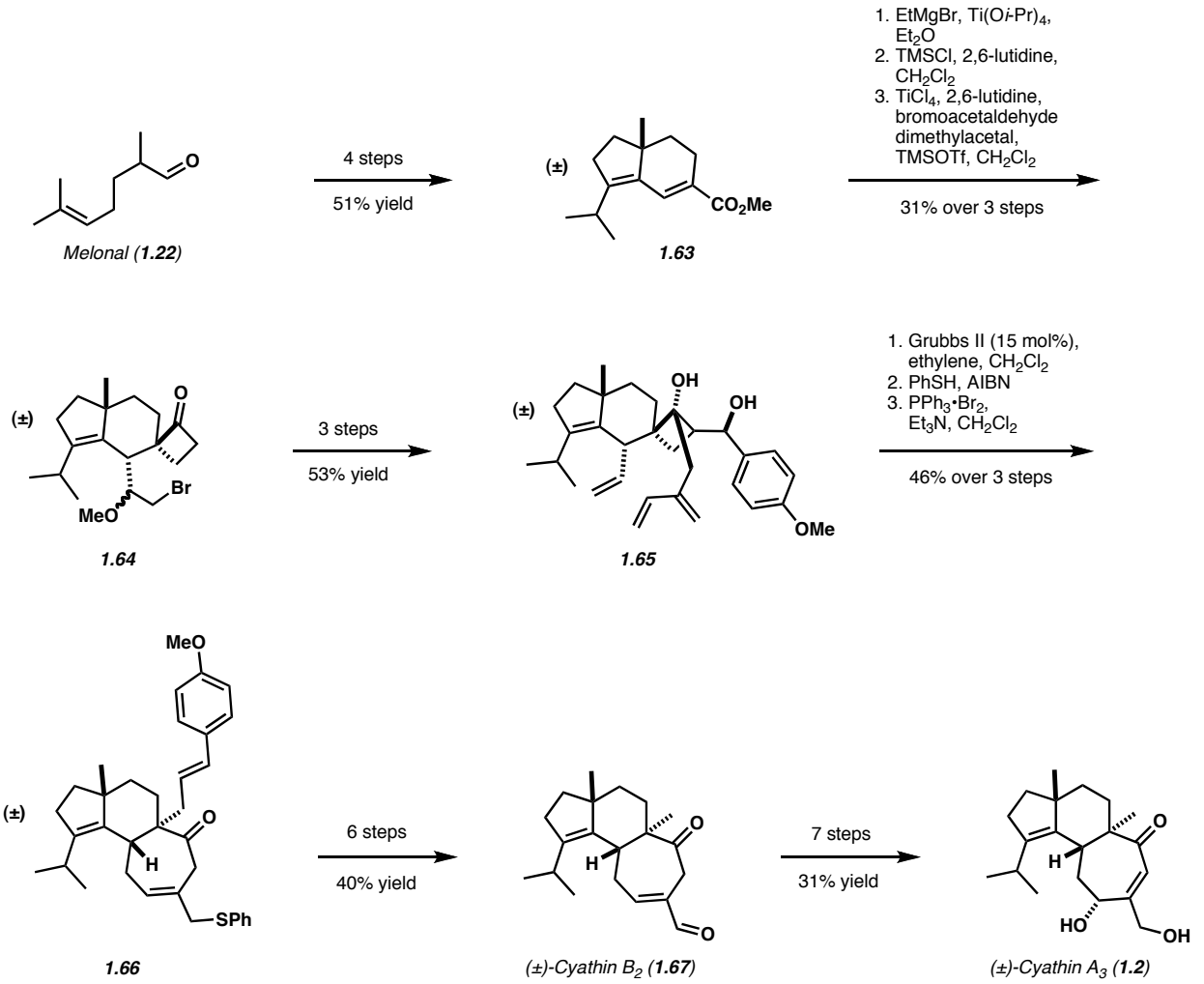
In a second-generation approach, Ward and coworkers targeted (-)-cyathin A_3 (**1.2**) in 2007 (Scheme 1.4.6).[71] They were able to render the [4+2] cycloaddition asymmetric by utilizing Mikami's catalyst[72] in the presence of magnesium and silica. The synthesis of key tricycle **1.60** was also streamlined, shortening the sequence by three steps. Tricycle **1.60** was advanced in 13 steps to **1.61**. Ward and coworkers oxidized the hydroxyl group on the C-ring of **1.61** and selectively formed the dienol triflate in the A-ring. Deoxygenation and reduction of the disubstituted double bond yielded tricycle **1.62**. Only four steps remained to carry tricycle **1.62** forward to the target (-)-cyathin A_3, achieving its synthesis in 29 steps and 0.64% overall yield.

Scheme 1.4.6. (-)-Cyathin A_3 using Ward's second-generation approach.[71]



A second approach to (±)-cyathin A_3 was published by the Cha group, along with the first total synthesis of (±)-cyathin B_2 (**1.67**, Scheme 1.4.7).[73] Starting from intermediate **1.63** utilized in the Snider synthesis,[74] a Kulinkovich cyclopropanation, followed by a ring expansion formed spirocycle **1.64**. Further manipulations yielded polyene **1.65**, which was poised for ring-closing metathesis. Grubbs' second-generation catalyst in the presence of ethylene closed the seven-membered ring. Phenylthiol addition was followed by a Grob fragmentation to open the four-membered ring to yield tricycle **1.66**. The cyathane core was carried forward to (±)-cyathin B_2 in six steps, and (±)-cyathin A_3 was accessed in an additional seven steps. Overall, (±)-cyathin B_2 was achieved in 2% yield over 19 steps, and (±)-cyathin A_3 was accomplished in 0.5% yield over 26 steps.

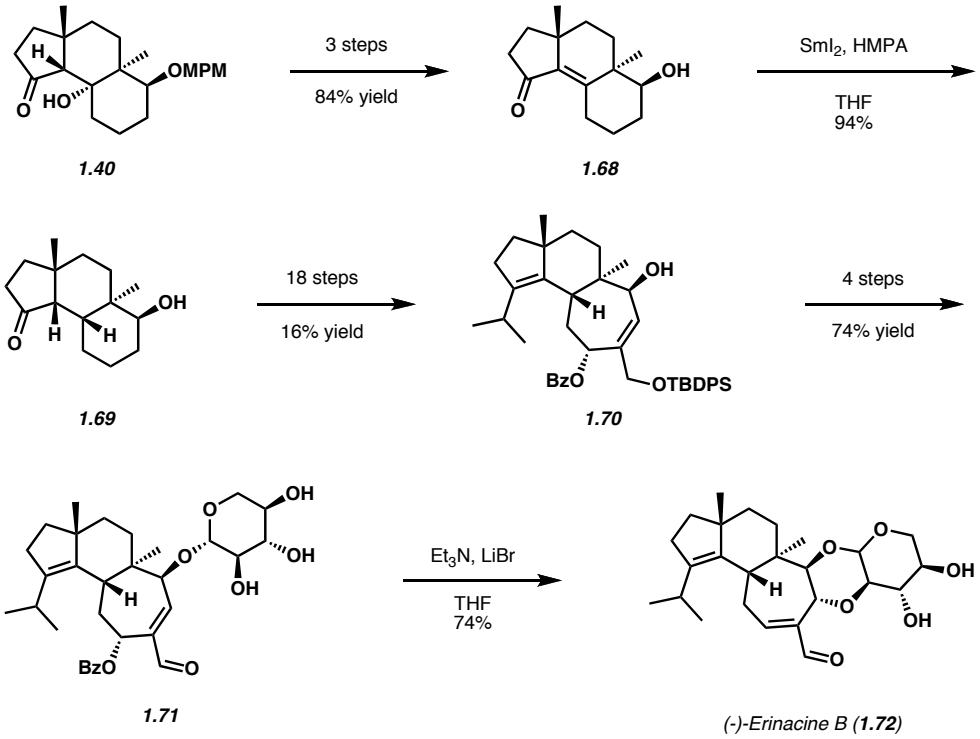
Scheme 1.4.7. Cha's total syntheses of (±)-cyathin A_3 and (±)-cyathin B_2.[73]



1.4.4. Erinacine B

In 2007 Nakada and coworkers applied their previous synthetic strategy for (+)-allocyathin B_2 (Scheme 1.4.3) to the total synthesis of (-)-erinacine B (**1.72**, Scheme 1.4.8).[75,76] Starting from tricycle **1.40**, which was utilized in their allocyathin B_2 synthesis, they prepared enone **1.68**. The B-C *trans* ring fusion was formed via reduction of enone **1.68** with samarium diiodide to provide hydroxyketone **1.69**. Analogous chemistry from their approach to (+)-allocyathin B_2 was applied to build tricycle **1.70**, from which glycosylation and functional group manipulation furnished glycosylated tricycle **1.71**. The final cascade to the natural product was performed using triethylamine and lithium bromide, affording (-)-erinacine B in 48 steps and a 1.5% overall yield.

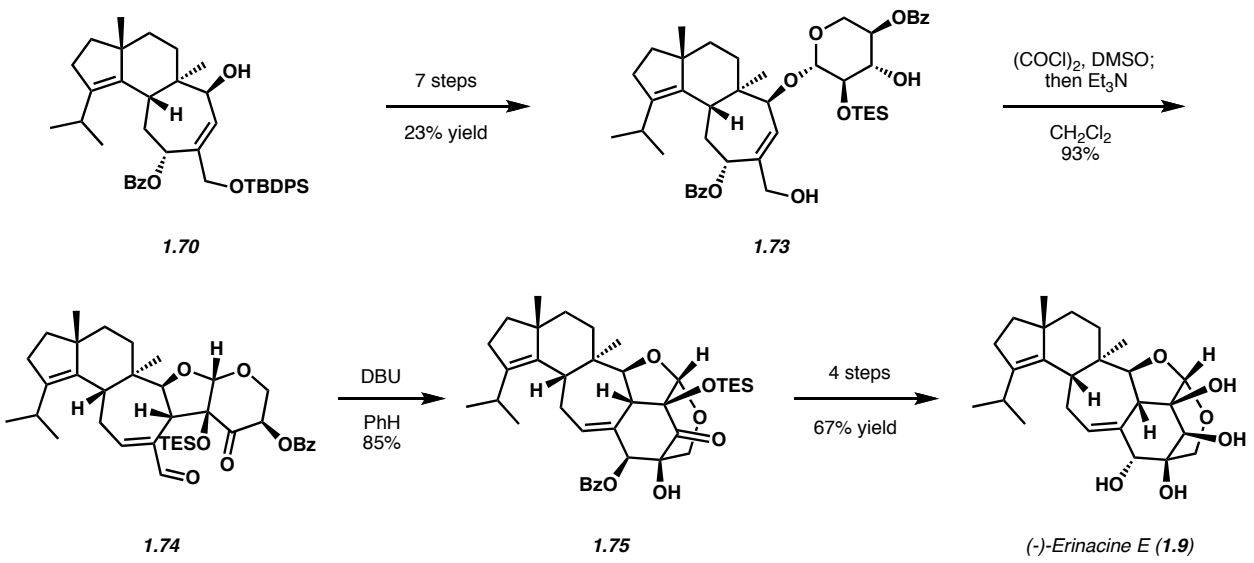
Scheme 1.4.8. Total synthesis of (-)-erinacine B by Nakada.[75]



1.4.5. Erinacine E

Additionally, Nakada and coworkers completed the total synthesis of (-)-erinacine E (**1.9**),[76] one of the most complex cyathane natural products known (Scheme 1.4.9). From tricycle **1.70**, they accessed glycosylated tricycle **1.73** in seven steps. Oxidation of the hydroxyl groups of **1.73** was followed by cyclization in situ to afford pentacycle **1.74**. Treatment with DBU closed the final ring via an aldol reaction, with subsequent transfer of the benzoyl group to furnish **1.75**. Caged intermediate **1.75** was advanced to (-)-erinacine E in a four step sequence. Nakada's strategy led to the synthesis of the natural product in 52 steps with an overall yield of 0.4%.

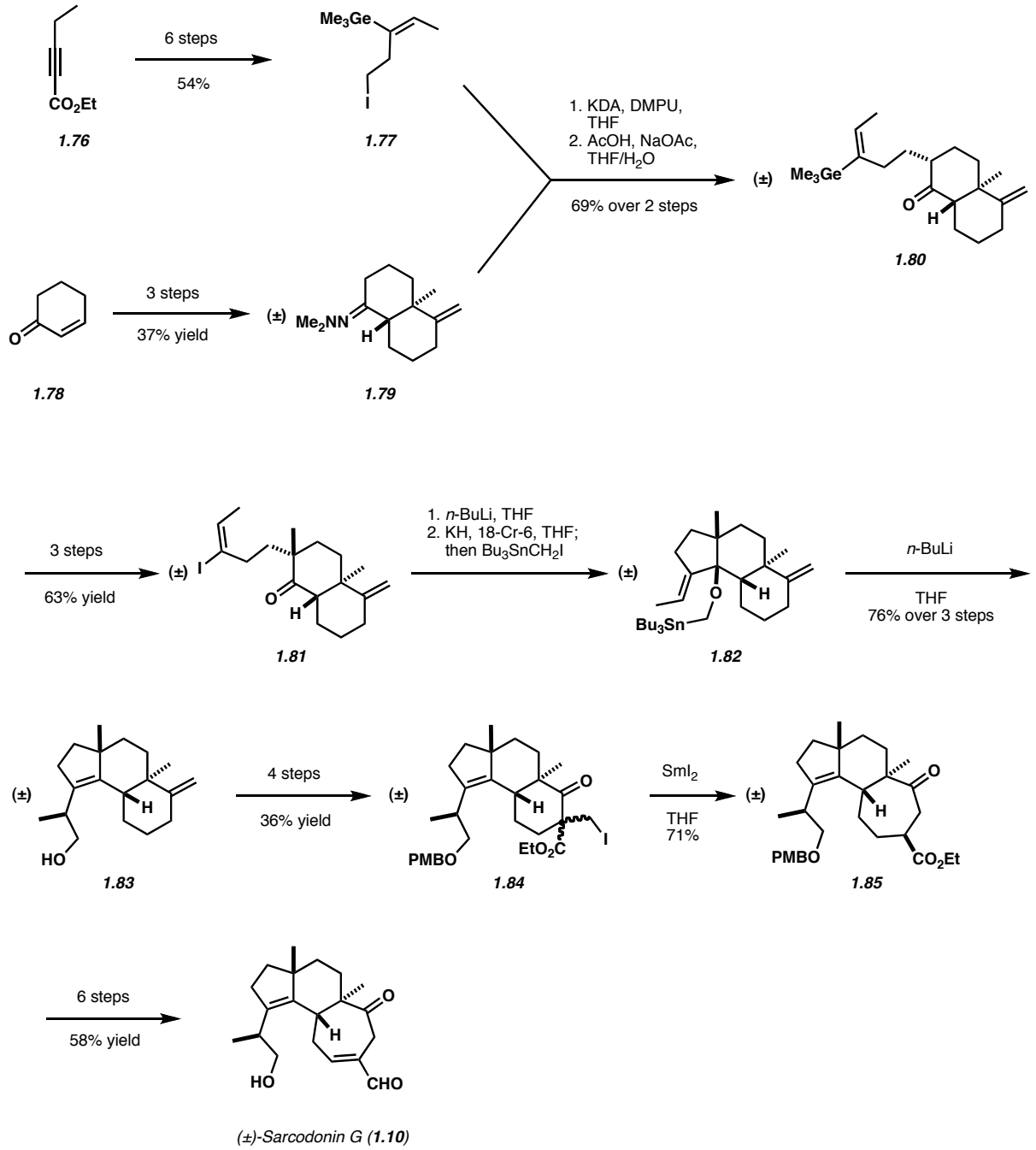
Scheme 1.4.9. Extension of Nakada's approach to (-)-erinacine E.[76]



1.4.6. Sarcodonin G

The total synthesis of (±)-sarcodonin G (**1.10**) in 2000 by Piers and coworkers was the first total synthesis of a cyathane diterpenoid possessing a *trans*-B-C ring fusion (Scheme 1.4.10).[77] In the synthetic sequence, ethyl pent-2-ynoate (**1.76**) was elaborated to alkyl iodide **1.77**, while bicyclic fragment **1.79** was derived from cyclohexenone (**1.78**).[78] Treatment of bicycle **1.79** with potassium diisopropylamide-lithium *tert*-butoxide (KDA)[79] followed by **1.77** coupled the fragments to afford ketone **1.80** after subsequent hydrolysis. Germane **1.80** was converted to vinyl iodide **1.81** over 3 steps. The A-ring was formed through lithium-halogen exchange and subsequent nucleophilic attack onto the ketone group to afford **1.82** after alkylation. Stannane **1.82** was converted to alcohol **1.83** via a Still-Mitra [2,3]-sigmatropic rearrangement[80] and advanced to iodide **1.84**. A samarium(II)-mediated ring expansion of iodide **1.84** formed the seven-membered ring, and tricycle **1.85** was converted to the natural product in an additional six steps. Piers and coworkers achieved the synthesis of (±)-sarcodonin G over 25 steps and a 2.6% overall yield.

Scheme 1.4.10. Total synthesis of (±)-sarcodonin G by Piers.[77]

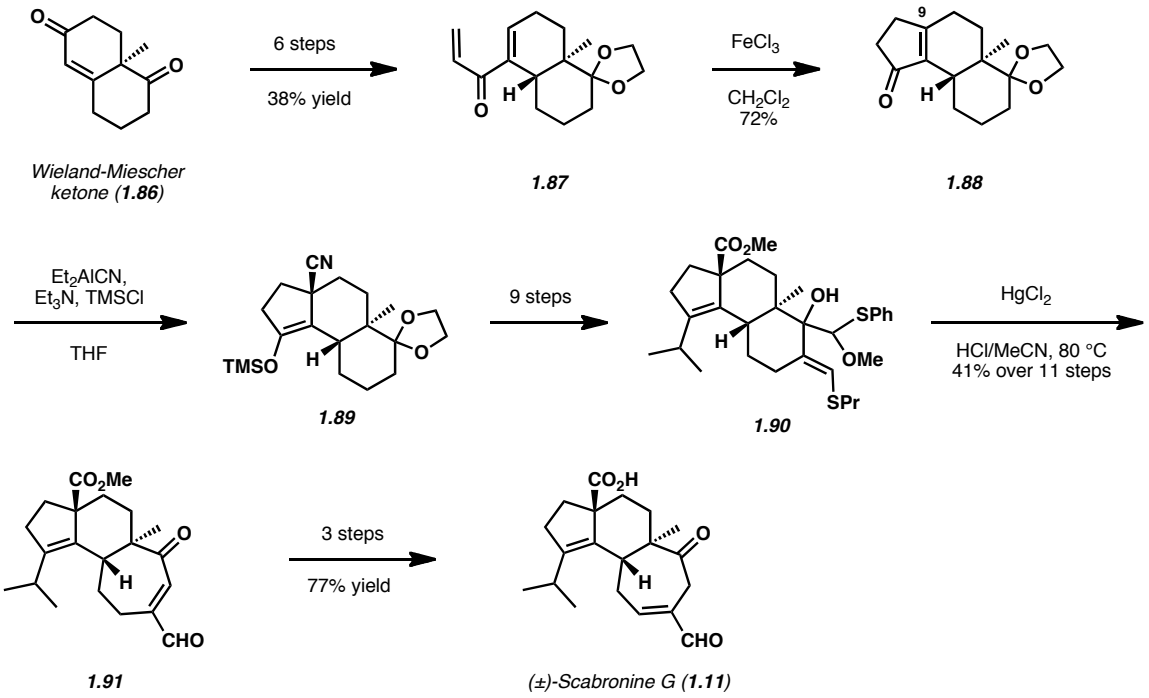


1.4.7. Scabronine G

In 2005, Danishefsky and coworkers reported an efficient route to (-)-scabronine G (**1.11**, Scheme 1.4.11).[81] Starting from the Wieland-Miescher ketone (**1.86**), they constructed dienone **1.87** in 6 steps. An $FeCl_3$-catalyzed Nazarov cyclization closed the A-ring to furnish **1.88**. The substituent at C9 was installed using Nagata's reagent to provide **1.89**. A ring expansion of advanced tricycle **1.90** furnished the seven-membered ring. Enone **1.91** was then carried forward

to (-)-scabronine G in three additional steps, providing the natural product in a total of 21 steps with an impressive 9% overall yield.

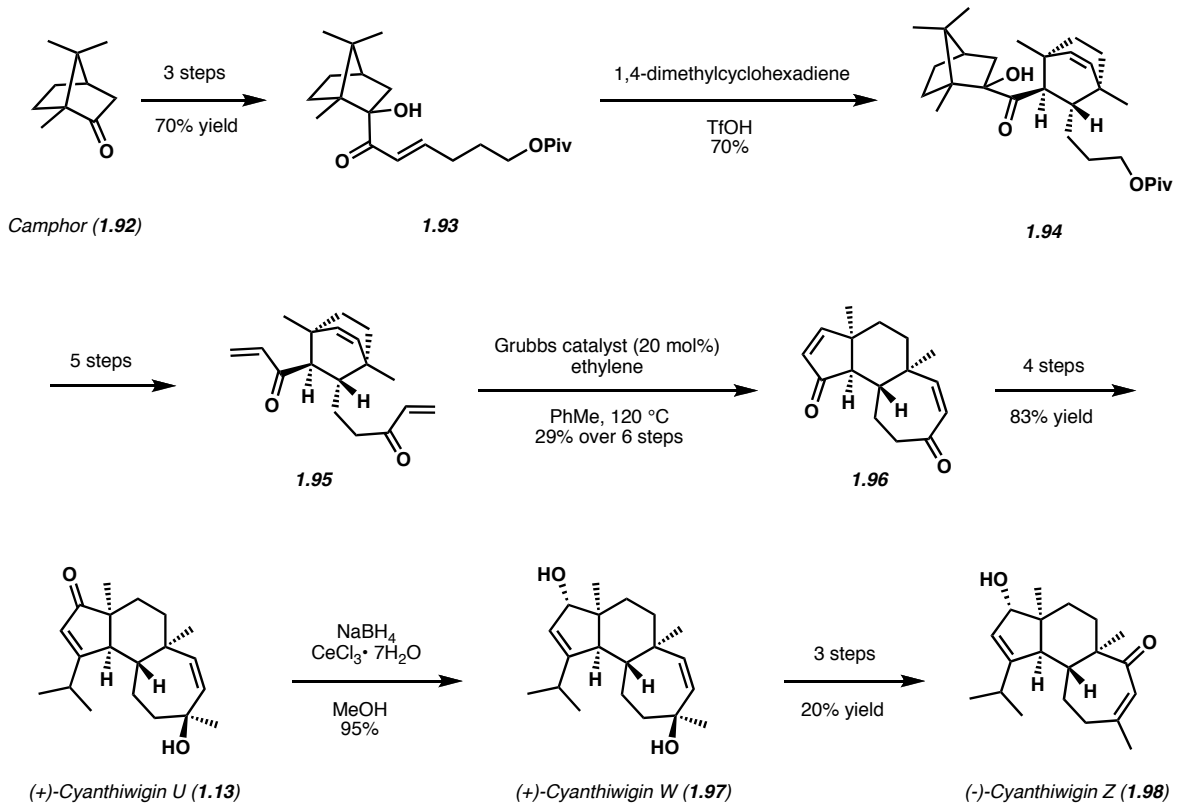
Scheme 1.4.11. (-)-Scabronine G by Danishefsky and coworkers.[81]



1.4.8. Cyanthiwigin U

The first cyanthwigin succumbed to total synthesis in 2005 with Phillips' elegant route to (+)-cyanthiwigin U (**1.13**, Scheme 1.4.12).[82] In this synthesis, camphor (**1.92**) was derivatized in three steps to form hydroxyenone **1.93**. A Diels-Alder cycloaddition with 1,4-dimethylcyclohexadiene furnished [2.2.2] bicycle **1.94**, which was brought forward to dienone **1.95** in five steps. A two-directional ring-opening/ring-closing metathesis formed [5-6-7] fused tricycle **1.96**, which was elaborated to (+)-cyanthiwigin U (**1.13**) in four steps. Luche reduction afforded (+)-cyanthiwigin W (**1.97**) and, in an additional three steps, (+)-cyanthwigin W could be converted to (-)-cyanthiwigin Z (**1.98**).[83] Overall, (+)-cyanthiwigin U was accessed in 14 steps in a remarkable 12% overall yield, (+)-cyanthiwigin W was synthesized in 15 steps in an 11% overall yield, and (-)-cyanthiwigin Z was made in 18 steps and a 2% overall yield.

Scheme 1.4.12. The Phillips approach to (+)-cyanthiwigin U, (+)-cyanthiwigin W and (-)-cyanthiwigin Z.[82,83]

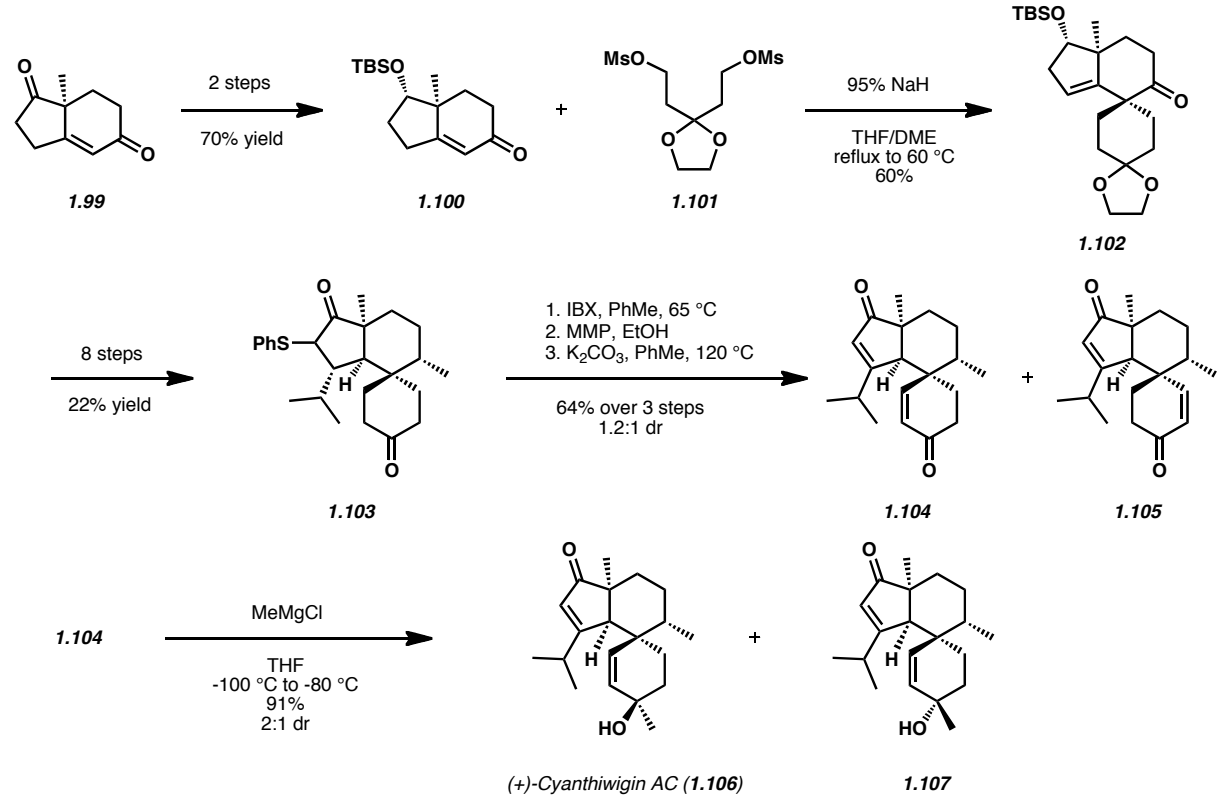


*Camphor (**1.92**)* ***1.93*** ***1.94*** ***1.95*** ***1.96*** *(+)-Cyanthiwigin U (**1.13**)* *(+)-Cyanthiwigin W (**1.97**)* *(-)-Cyanthiwigin Z (**1.98**)*

1.4.9. Cyanthiwigin AC

In 2006, Reddy and coworkers reported the total synthesis of (+)-cyanthiwigin AC (**1.106**, Scheme 1.4.13), a rearranged cyathane diterpenoid containing a [6-6] spirocycle.[84] Using reduced and silyl-protected Hajos-Parrish ketone derivative **1.100**, they created the thermodynamic enolate and alkylated twice with mesylate **1.101** to form spirocycle **1.102**. Functional group manipulation furnished dione **1.103**. Treatment of **1.103** with IBX, followed by magnesium monoperoxyphthalate (MMP) and potassium bicarbonate led to a 1.2:1 dr of dienones **1.104** and **1.105**. Desired dienone **1.104** was treated with methyl Grignard to form (+)-cyanthiwigin AC (**1.106**) and epimer **1.107**. In 15 steps, Reddy and coworkers reached (+)-cyanthiwigin AC in a 2% overall yield.

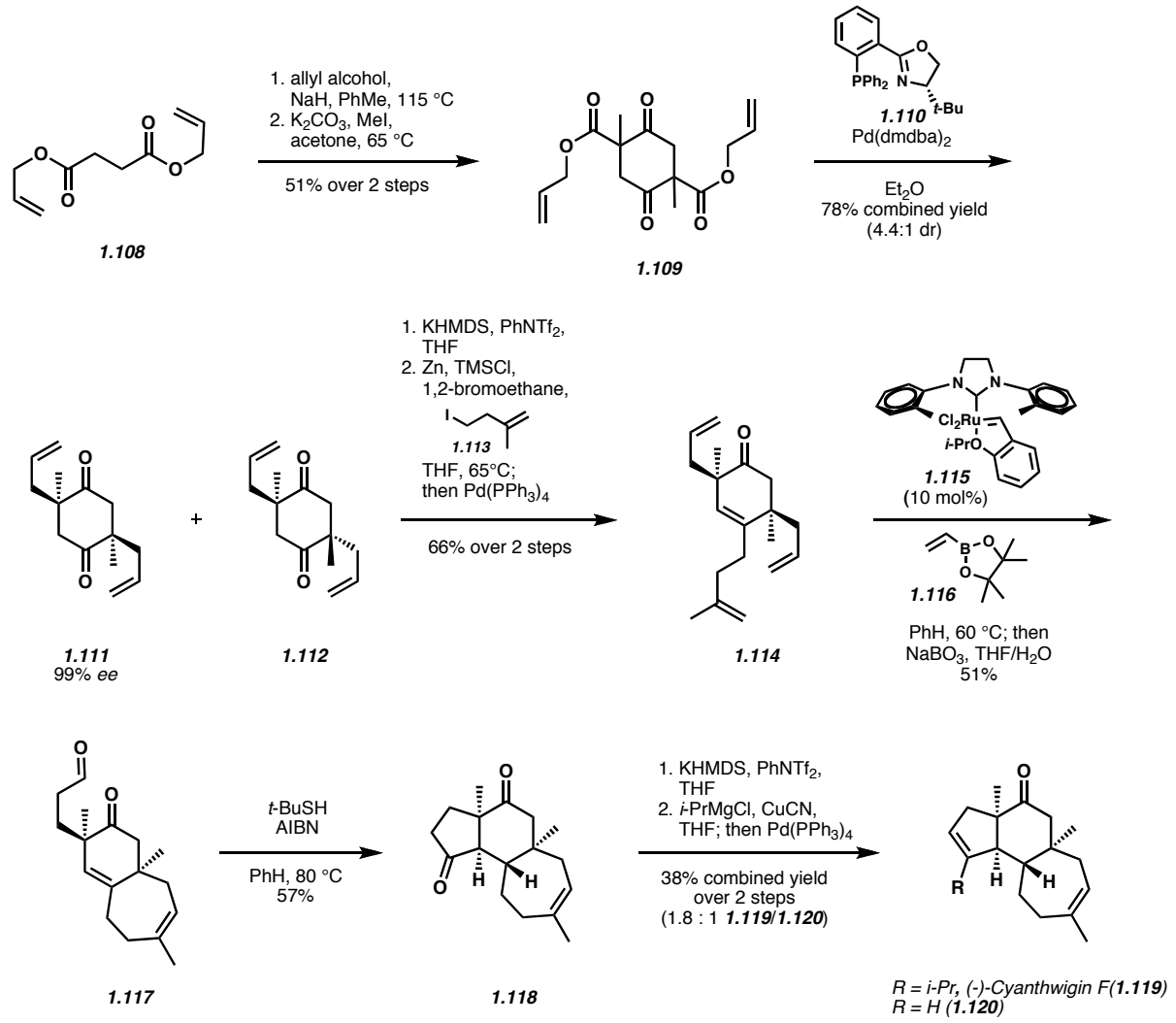
Scheme 1.4.13. Synthesis of (+)-cyanthwigin AC by Reddy.[84]



1.4.9. Cyanthiwigin F

Stoltz and Enquist reported a concise total synthesis of (-)-cyanthiwigin F (**1.119**) in 2008 (Scheme 1.4.14).[85] The synthesis began with formation of the B-ring via a tandem Claisen condensation and Dieckman cyclization of diallyl succinate (**1.108**). Both all-carbon quaternary centers were enantioselectively installed in a palladium-mediated allylation reaction to form dione **1.111**. Monotriflation of dione **1.111** was followed by cross-coupling with iodide **1.113** to furnish ketone **1.114**. The seven-membered ring was formed in a ring-closing metathesis reaction from ketone **1.114**, which in the same pot achieved a cross-metathesis with vinyl boronate **1.116** to form keto-aldehyde **1.117**, after oxidation of the boronate. The A-ring was installed through a radical cyclization, and tricycle **1.118** could be advanced to the natural product in an additional two steps. Overall, Stoltz achieved the most rapid synthesis of a cyathane diterpenoid to date, synthesizing (-)-cyanthiwigin F in nine steps and a 2% overall yield.

Scheme 1.4.14. Stoltz approach to (-)-cyanthiwigin F.[85]



1.5. Conclusion

The cyathane diterpenoids have drawn much attention from the synthetic community due to their unique structure and wide range of biological activity. A multitude of innovative approaches have been utilized to access this family of natural products. However, most strategies can only be applied to a few members of the cyathane diterpenoids, or are too long to be convenient for biological structure-activity studies.

1.6. References and Notes

(1) Allbutt, A. D.; Ayer, W. A.; Brodie, H. J.; Johri, B. N.; Taube, H. *Can. J. Microbiol.* **1971**, *17*, 1401.

(2) Ayer, W. A.; Taube, H. *Tetrahedron Lett.* **1972**, *19*, 1917.

(3) Ayer, W. A.; Browne, L. M.; Mercer, J. R.; Taylor, D. R.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 717.

(4) Ayer, W. A.; Lee, S. P. *Can. J. Chem.* **1979**, *57*, 3332.
(5) Ayer, W. A.; Nakashima, T. T.; Ward, D. E. *Can. J. Chem.* **1978**, *56*, 2197.
(6) Ayer, W. A.; Taube, H. *Can. J. Chem.* **1973**, *51*, 3842.
(7) Ayer, W. A.; Yoshida, T.; Vanschie, D. M. J. *Can. J. Chem.* **1978**, *56*, 2113.
(8) Shiono, Y.; Hiramatsu, F.; Murayama, T.; Koseki, T.; Funakoshi, T. *Chem. Biodivers.* **2008**, *5*, 1811.
(9) Curini, M.; Maltese, F.; Marcotullio, M. C.; Menghini, L.; Pagiotti, R.; Rosati, O.; Altinier, G.; Tubaro, A. *Planta Med.* **2005**, *71*, 194.
(10) Marcotullio, M. C.; Pagiotti, R.; Campagna, V.; Maltese, F.; Fardella, G.; Altinier, G.; Tubaro, A. *Nat. Prod. Res.* **2006**, *20*, 917.
(11) Marcotullio, M. C.; Pagiott, R.; Maltese, F.; Obara, Y.; Hoshino, T.; Nakahata, N.; Curini, M. *Planta Med.* **2006**, *72*, 819.
(12) Marcotullio, M. C.; Pagiotti, R.; Maltese, F.; Mwankie, G.; Hoshino, T.; Obara, Y.; Nakahata, N. *Bioorg. Med. Chem.* **2007**, *15*, 2878.
(13) Hecht, H. J.; Hofle, G.; Steglich, W.; Anke, T.; Oberwinkler, F. *J. Chem. Soc., Chem. Commun.* **1978**, 665.
(14) Steglich, W. *Pure Appl. Chem.* **1981**, *53*, 1233.
(15) Anke, T.; Rabe, U.; Schu, P.; Eizenhofer, T.; Schrage, M.; Steglich, W. *Z. Naturforsch. C* **2002**, *57*, 263.
(16) Anke, T.; Oberwinkler, F.; Steglich, W.; Hofle, G. *J. Antibiot.* **1977**, *30*, 221.
(17) Inchausti, A.; Yaluff, G.; de Arias, A. R.; Torres, S.; Ferreira, M. E.; Nakayama, H.; Schinini, A.; Lorenzen, K.; Anke, T.; Fournet, A. *Phytother. Res.* **1997**, *11*, 193.
(18) Kawagishi, H.; Masui, A.; Tokuyama, S.; Nakamura, T. *Tetrahedron* **2006**, *62*, 8463.
(19) Kawagishi, H.; Shimada, A.; Hosokawa, S.; Mori, H.; Sakamoto, H.; Ishiguro, Y.; Sakemi, S.; Bordner, J.; Kojima, N.; Furukawa, S. *Tetrahedron Lett.* **1996**, *37*, 7399.
(20) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569.
(21) Kawagishi, H.; Simada, A.; Shizuki, K.; Mori, H.; Okamoto, K.; Sakamoto, H.; Furukawa, S. *Heterocycl. Commun.* **1996**, *2*, 51.
(22) Kenmoku, H.; Sassa, T.; Kato, N. *Tetrahedron Lett.* **2000**, *41*, 4389.
(23) Kenmoku, H.; Shimai, T.; Toyomasu, T.; Kato, N.; Sassa, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 571.
(24) Kenmoku, H.; Tanaka, K.; Okada, K.; Kato, N.; Sassa, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1786.
(25) Lee, E. W.; Shizuki, K.; Hosokawa, S.; Suzuki, M.; Suganuma, H.; Inakuma, T.; Li, J. X.; Ohnishi-Kameyama, M.; Nagata, T.; Furukawa, S.; Kawagishi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2402.
(26) Ma, B. J.; Zhou, Y.; Li, L. Z.; Li, H. M.; Gao, Z. M.; Ruan, Y. *Z. Naturforsch. B* **2008**, *63*, 1241.
(27) Saito, T.; Aoki, F.; Hirai, H.; Inagaki, T.; Matsunaga, Y.; Sakakibara, T.; Sakemi, S.; Suzuki, Y.; Watanabe, S.; Suga, O.; Sujaku, T.; Smogowicz, A. A.; Truesdell, S. J.; Wong, J. W.; Nagahisa, A.; Kojima, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 983.
(28) Ma, B. J.; Liu, J. K. *J. Basic Microbiol.* **2005**, *45*, 328.
(29) Hirota, M.; Morimura, K.; Shibata, H. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 179.
(30) Kamo, T.; Imura, Y.; Hagio, T.; Makabe, H.; Shibata, H.; Hirota, M. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1362.

(31) Shibata, H.; Irie, A.; Morita, Y. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2450.
(32) Shibata, H.; Tokunaga, T.; Karasawa, D.; Hirota, A.; Nakayama, M.; Nozaki, H.; Tada, T. *Agr. Biol. Chem.* **1989**, *53*, 3373.
(33) Ma, B. J.; Zhu, H. J.; Liu, J. K. *Helv. Chim. Acta* **2004**, *87*, 2877.
(34) Kita, T.; Takaya, Y.; Oshima, Y.; Ohta, T.; Aizawa, K.; Hirano, T.; Inakuma, T. *Tetrahedron* **1998**, *54*, 11877.
(35) Ma, B. J.; Ruan, Y. *J. Antibiot.* **2008**, *61*, 86.
(36) Ohta, T.; Kita, T.; Kobayashi, N.; Obara, Y.; Nakahata, N.; Ohizumi, Y.; Takaya, Y.; Oshima, Y. *Tetrahedron Lett.* **1998**, *39*, 6229.
(37) Dong, M.; Chen, S. P.; Kita, K.; Ichimura, Y.; Guo, W. Z.; Lu, S.; Sugaya, S.; Hiwasa, T.; Takiguchi, M.; Mori, N.; Kashima, A.; Morimura, K.; Hirota, M.; Suzuki, N. *Int. J. Oncol.* **2009**, *34*, 201.
(38) Obara, Y.; Nakahata, N.; Kita, T.; Takaya, Y.; Kobayashi, H.; Hosoi, S.; Kiuchi, F.; Ohta, T.; Oshima, Y.; Ohizumi, Y. *Eur. J. Pharmacol.* **1999**, *370*, 79.
(39) Green, D.; Goldberg, I.; Stein, Z.; Ilan, M.; Kashman, Y. *Nat. Prod. Lett.* **1992**, *1*, 193.
(40) Peng, J. N.; Avery, M. A.; Hamann, M. T. *Org. Lett.* **2003**, *5*, 4575.
(41) Peng, J. N.; Walsh, K.; Weedman, V.; Bergthold, J. D.; Lynch, J.; Lieu, K. L.; Braude, I. A.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2002**, *58*, 7809.
(42) Peng, J.; Kasanah, N.; Stanley, C. E.; Chadwick, J.; Fronczek, F. R.; Hamann, M. T. *J. Nat. Prod.* **2006**, *69*, 727.
(43) Ayer, W. A.; Lee, S. P.; Nakashima, T. T. *Can. J. Chem.* **1979**, *57*, 3338.
(44) Kashman, Y.; Rudi, A. *Phytochem. Rev.* **2004**, *3*, 309.
(45) Ayer, W. A.; Ward, D. E.; Browne, L. M.; Delbaere, L. T. J.; Hoyano, Y. *Can. J. Chem.* **1981**, *59*, 2665.
(46) Dahnke, K. R.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 885.
(47) Drege, E.; Morgant, G.; Desmaele, D. *Tetrahedron Lett.* **2005**, *46*, 7263.
(48) Drege, E.; Tominiaux, C.; Morgant, G.; Desmaele, D. *Eur. J. Org. Chem.* **2006**, 4825.
(49) Magnus, P.; Shen, L. *Tetrahedron* **1999**, *55*, 3553.
(50) Miller, L. C.; Ndungu, J. M.; Sarpong, R. *Angew. Chem. Int. Ed.* **2009**, *48*, 2398.
(51) Takeda, K.; Nakane, D.; Takeda, M. *Org. Lett.* **2000**, *2*, 1903.
(52) Thominiaux, C.; Chiaroni, A.; Desmaele, D. *Tetrahedron Lett.* **2002**, *43*, 4107.
(53) Ward, D. E. *Can. J. Chem.* **1987**, *65*, 2380.
(54) Watanabe, H.; Nakada, M. *Tetrahedron Lett.* **2008**, *49*, 1518.
(55) Wender, P. A.; Bi, F. C.; Brodney, M. A.; Gosselin, F. *Org. Lett.* **2001**, *3*, 2105.
(56) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535.
(57) Nakashima, K.; Fujisaki, N.; Inoue, K.; Minami, A.; Nagaya, C.; Sono, M.; Tori, M. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955.
(58) Enquist, J. A.; Stoltz, B. M. *Nat. Prod. Rep.* **2009**, *26*, 661.
(59) Wright, D. L.; Whitehead, C. R. *Org. Prep. Proced. Int.* **2000**, *32*, 307.
(60) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.
(61) Snider, B. B.; Vo, N. H.; O'Neil, S. V. *J. Org. Chem.* **1998**, *63*, 4732.
(62) Snider, B. B.; Rodini, D. J.; Vanstraten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.
(63) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306.
(64) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897.

(65) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860.
(66) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239.
(67) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 10259.
(68) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 2844.
(69) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480.
(70) Ward, D. E.; Gai, Y. Z.; Qiao, Q. *Org. Lett.* **2000**, *2*, 2125.
(71) Ward, D. E.; Shen, J. H. *Org. Lett.* **2007**, *9*, 2843.
(72) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.
(73) Kim, K.; Cha, J. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5334.
(74) Snider, B. B.; Vo, N. H.; Oneil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.
(75) Watanabe, H.; Takano, M.; Umino, A.; Ito, T.; Ishikawa, H.; Nakada, M. *Org. Lett.* **2007**, *9*, 359.
(76) Watanabe, H.; Nakada, M. *J. Am. Chem. Soc.* **2008**, *130*, 1150.
(77) Piers, E.; Gilbert, M.; Cook, K. L. *Org. Lett.* **2000**, *2*, 1407.
(78) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 280.
(79) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794.
(80) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.
(81) Waters, S. P.; Tian, Y.; Li, Y. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514.
(82) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334.
(83) Pfeiffer, M. W. B.; Phillips, A. J. *Tetrahedron Lett.* **2008**, *49*, 6860.
(84) Reddy, T. J.; Bordeau, G.; Trimble, L. *Org. Lett.* **2006**, *8*, 5585.
(85) Enquist, J. A.; Stoltz, B. M. *Nature* **2008**, *453*, 1228.

Chapter 2
Preliminary Studies on the Tricyclic Core

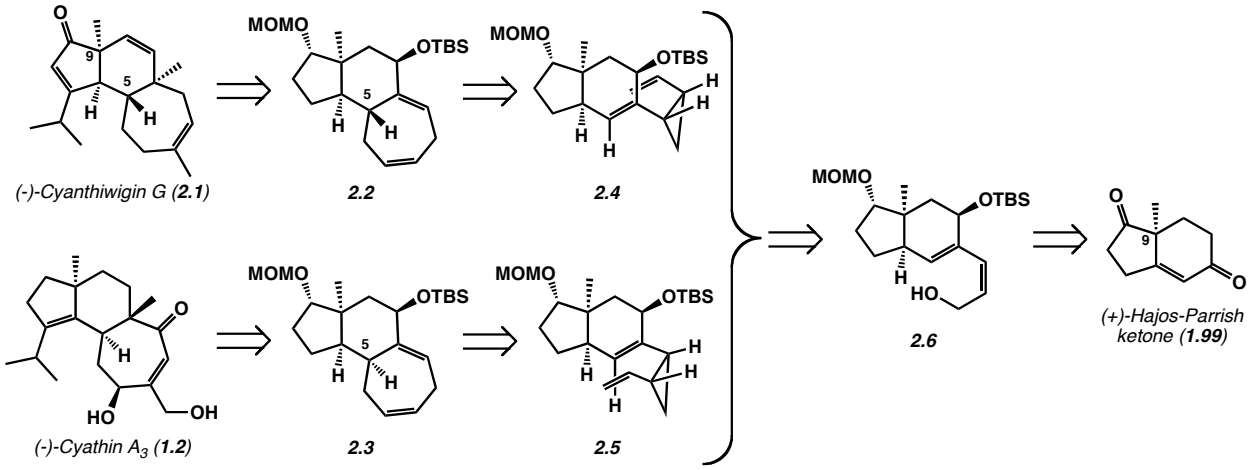
2.1. Introduction

In addition to the biological potential of the cyathane and cyanthiwigin family of natural products (see Chapter 1.2), we were drawn to these compounds because of their unique structure. The synthesis of the [5-6-7] fused-ring system that comprises the backbone of the natural products poses a synthetic challenge. Other notable challenges include the stereoselective installation of two all-carbon quaternary centers at ring fusion positions and the incorporation of the appropriate oxygenation and unsaturation pattern for the targeted cyathane or cyanthiwigin. The combination of these features, which would likely lead to new synthetic developments, made the cyathanes and cyanthiwigins attractive targets for total synthesis.

2.2. Retrosynthetic Analysis

Although numerous efforts have focused on the synthesis of specific cyanthiwigin and cyathane natural products (see Chapter 1.4), we were interested in developing a general route that would provide access to many of these bioactive diterpenoids. A divergent strategy would also afford opportunities for further derivatization of the tricyclic core in order to perform structure-activity relationship studies that would lead to a deeper understanding of the biological activity of this family of natural products. We envisioned the cyanthiwigins, exemplified by cyanthiwigin G (**2.1**, Scheme 2.2.1), and the cyathanes, for example cyathin A_3 (**1.2**), arising from simplified tricycles **2.2** and **2.3**, respectively, which are epimeric at C5. Cycloheptadienes **2.2** and **2.3** could be formed by a Cope rearrangement of the corresponding divinylcyclopropane intermediate (**2.4** and **2.5**). The divinylcyclopropanes **2.4** and **2.5** could be brought back to a

Scheme 2.2.1. Divergent retrosynthesis of representative cyanthiwigin and cyathane natural products.

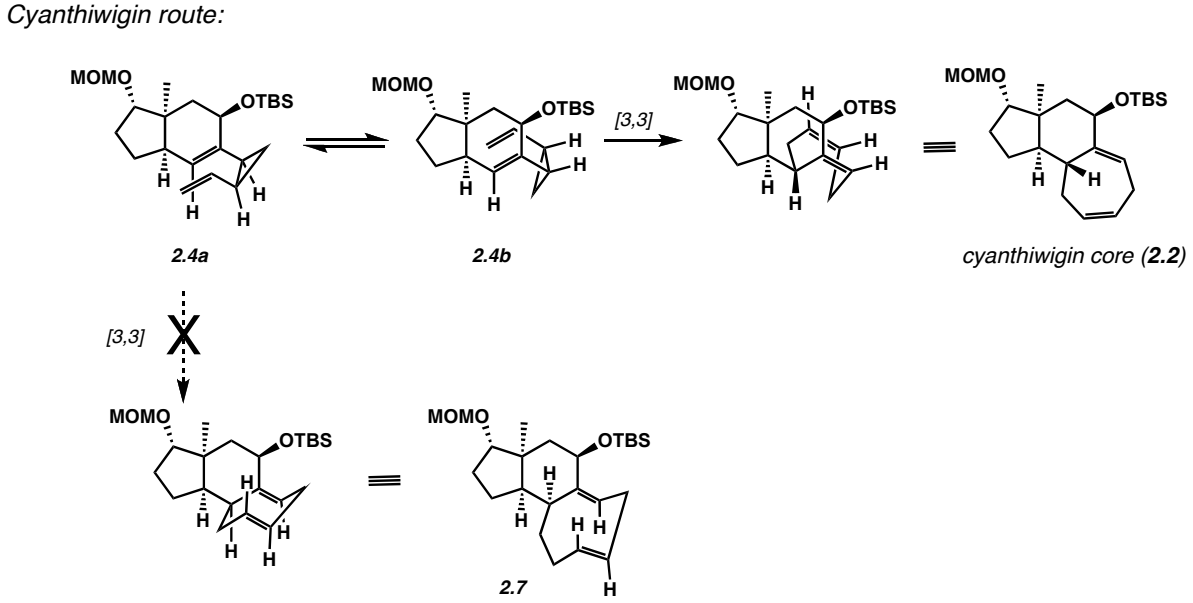


single dienol precursor **2.6**, which could ultimately be derived from the Hajos-Parrish ketone (**1.99**).[1] The Hajos-Parrish ketone is a useful starting point for the synthesis because the all-carbon quaternary center at C9 is established from the onset. Additionally, the A-B bicycle can

be synthesized in enantioenriched form, facilitating the asymmetric syntheses of the cyanthiwigin and cyathane natural products.

The key strategic element of our divergent strategy is the stereospecific [*3*,*3*] sigmatropic rearrangement of divinylcyclopropanes **2.4** and **2.5**. A single diastereomer of the divinylcyclopropane will lead to a single diastereomer of the tricycle (e.g., **2.4** to **2.2**).[2] As conveyed in Scheme 2.2.2 for the cyanthiwigin pathway, only one conformation of the divinylcyclopropane (e.g., **2.4b**) leads to the formation of *cis* double bonds in the seven-membered ring to form **2.2**. The alternative conformer, **2.4a**, would lead to extremely strained cycloheptadiene **2.7** with *trans* double bonds in a relatively small ring. The second pathway is therefore unfavorable, and only tricycle **2.2** should be formed from precursor **2.4**. A similar analysis predicts that cyathane divinylcyclopropane **2.5** should provide cycloheptadiene **2.3**. The cyclopropanation step serves as the point of divergence for the synthesis, where the diastereoselectivity of the cyclopropanation determines the tricycle formed. If excellent facial selectivity could be achieved in the cyclopropanation, then a single tricycle (i.e., the cyanthiwigin or cyathane core) would be obtained. A diastereoselective cyclopropanation would allow one to selectively target the cyanthwigins or cyathanes by funneling material exclusively through the desired pathway (e.g., **2.6** to **2.2**).

Scheme 2.2.2. Stereospecificity of the divinylcyclopropane rearrangement.

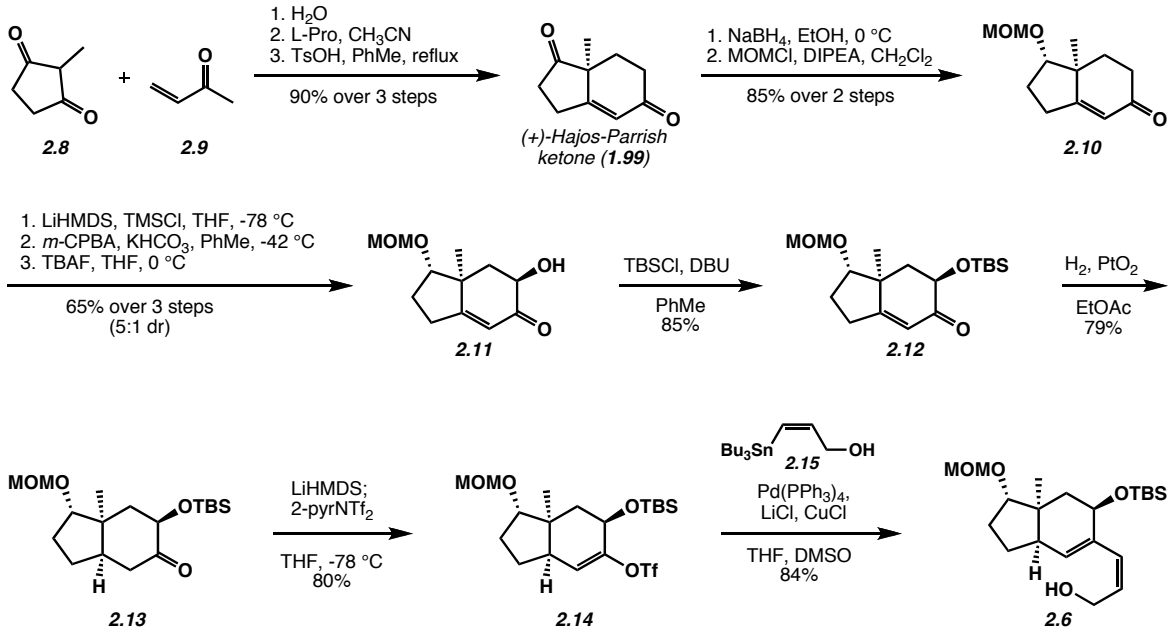


2.3. Construction of the Tricycle

The forward synthesis commenced with a Robinson annulation to form the (+)-Hajos-Parrish ketone (**1.99**, Scheme 2.3.1), using L-proline to induce asymmetry in the aldol addition step.[1] Following the precedent of Deslongchamps,[3] the ketone was selectively reduced, and the resultant hydroxyl was protected to provide methoxymethyl ether **2.10**. We initially explored the protection of the ketone as the ketal, formed from ethylene glycol in the presence of *p*-toluenesulfonic acid to form the 1,3-dioxolane. However, the ketal proved to be labile under

reaction conditions at various stages in the synthesis (i.e., in the enol triflate formation, Stille coupling, and cyclopropanation steps, *vide infra*). Due to these difficulties, we switched to the methoxymethyl ether, which proved to be much more robust throughout the synthesis.

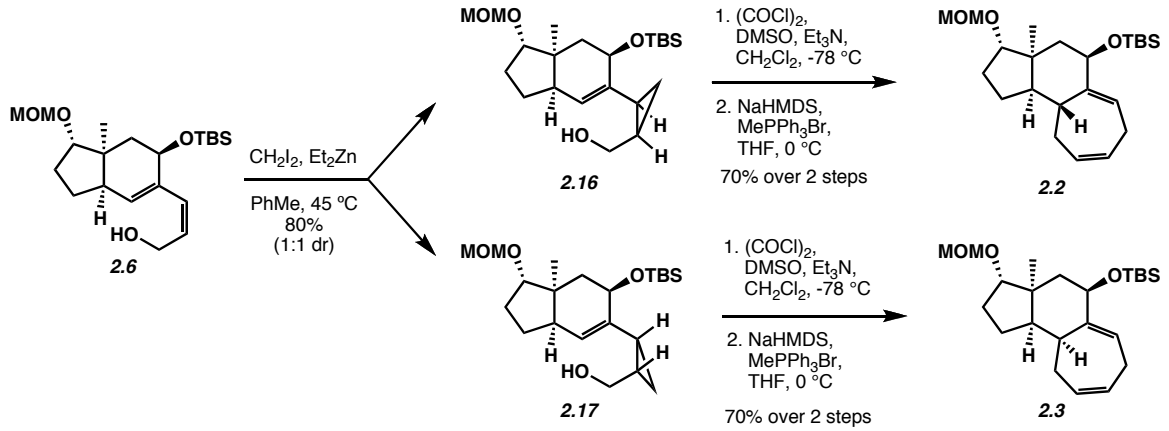
Scheme 2.3.1. Synthesis of the dienol **2.6**.



Oxygenation was installed alpha to the enone via a Rubottom sequence[4] to provide hydroxy enone **2.11** in a 5:1 dr. The hydroxyl group was then protected as the *t*-butyldimethylsilyl ether (**2.12**). Standard silyl protection conditions with imidazole caused significant epimerization of the α-hydroxy enone. After screening conditions, we found that the use of *t*-butyldimethylsilyl chloride with DBU in toluene was effective in forming the silyl ether, while avoiding epimerization. Reduction of enone **2.12** with Adams' catalyst was followed by enol triflate formation using lithium hexamethyldisilazide and trapping with Comins' reagent[5] to afford **2.14**. Stannane **2.15** was prepared according to the procedure of Corey[6,7] and coupled to enol triflate **2.14**. A Stille reaction[8] was first attempted, but only produced low yields of the desired dienol (**2.6**). The Corey-modified Stille reaction[9] was more effective to furnish cross-coupled product **2.6** in 84% yield.

Before investigating a reagent-controlled diastereoselective cyclopropanation to direct the material exclusively toward either the cyanthiwigin or cyathane pathway, we first investigated the sequence with a standard Simmons-Smith reaction[10] to verify that our planned route to the cycloheptadienes was viable. Cyclopropanation of dienol **2.6** using the standard conditions yielded a 1:1 diastereomeric ratio of products (Scheme 2.3.2). Cyclopropanols **2.16** and **2.17** were separated by flash chromatography, and advanced to the respective tricycle (**2.2** or **2.3**) separately. The primary hydroxyl group of **2.16** and **2.17** was oxidized to an aldehyde using Swern conditions. A Wittig olefination furnished the divinylcyclopropane, which cyclized under the reaction conditions to form the tricycle (**2.2** or **2.3**), validating our strategy to the [5-6-7] fused ring system.

Scheme 2.3.2. Construction of each cycloheptadiene (**2.2** and **2.3**) from dienol **2.6**.

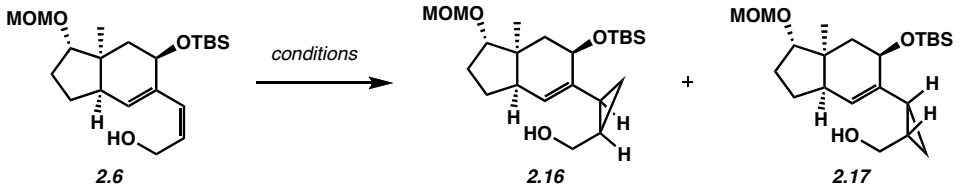


2.4. Asymmetric Cyclopropanation Studies

Concurrent with our work to elaborate tricycles **2.2** and **2.3** to the cyathane and cyanthiwigin natural products (Chapter 2.5, *vide infra*), we explored a variety of asymmetric cyclopropanation conditions to provide diastereocontrol in the cyclopropanation step. The facial selectivity of the cyclopropanation reaction determines whether the cyathane or cyanthiwigin tricycle will be constructed through the Cope rearrangement. Excellent selectivity would allow us to maximize efficiency and funnel 100% of our material through a single pathway (e.g., **2.6** to **2.2**), rather than obtaining a maximum 50% yield of the desired cyclopropanol using the standard Simmons-Smith cyclopropanation.

Our initial conditions of diethyl zinc and diiodomethane in toluene at 45 °C resulted in a 1:1.1 ratio of **2.16** to **2.17** (entry 1, Table 2.4.1). As expected, decreasing the temperature to 0 °C led to an increased formation of the cyathane diastereomer (**2.17**, entry 2). Due to steric interactions with the silyl ether, approach from the α-face is preferred. Employing a chiral bis-sulfonamide catalyst strategy developed by Kobayashi[11] and further examined by Denmark,[12] we observed variable results indicating no enhanced selectivity over the initial control studies (entries 3 and 4 vs. entries 1 and 2). We then turned to the more commonly used stoichiometric dioxaborolane ligands of Charette.[13] Treatment with the (*R*,*R*) dioxaborolane (**2.20**) led to the formation of cyathane cyclopropanol **2.17** as the sole product (entry 5). Unfortunately, the antipode (**2.21**) showed little diastereoselectivity (entry 6). It appears that there is a mismatch between dienol **2.6** and the (*S*,*S*) dioxaborolane (**2.21**), while dienol **2.6** and the (*R*,*R*) dioxaborolane (**2.20**) are a matched pair. We believe that the mismatch scenario arises from steric interactions with the silyl ether on the B-ring blocking cyclopropanation from the β-face. Cyclopropanation utilizing dioxaborolanes would allow us to funnel all of our material toward the cyathane natural products, but we would not have the flexibility to target the cyanthiwigins without losing half of our material at the cyclopropanation step. Redesign of our synthetic strategy was thus necessary to develop a general strategy to access both groups of natural products.

Table 2.4.1. Asymmetric cyclopropanation conditions.

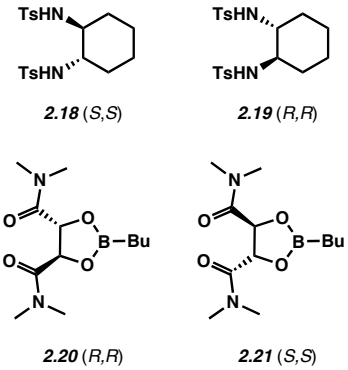


2.6 *2.16* *2.17*

Entry	Conditions	Additive	Ratio[a] *2.16:2.17*
1	CH_2I_2, Et_2Zn,[b] PhMe, 45 °C	--	1 : 1.1
2	CH_2I_2, Et_2Zn,[b] I_2, CH_2Cl_2, 0 °C to rt	--	1 : 2.1
3	CH_2I_2, Et_2Zn,[b] I_2, CH_2Cl_2, 0 °C to rt	***2.18***[c] (*S,S*)	1 : 2.4[d]
4	CH_2I_2, Et_2Zn,[b] I_2, CH_2Cl_2, 0 °C to rt	***2.19***[c] (*R,R*)	1 : 1[d]
5	CH_2I_2, Et_2Zn,[e] DME, CH_2Cl_2, 0 °C to rt	***2.20***[e] (*R,R*)	1 : > 20
6	CH_2I_2, Et_2Zn,[e] DME, CH_2Cl_2, 0 °C to rt	***2.21***[e] (*S,S*)	1 : 2.2

[a] Determined by ^{1}H NMR; [b] 1.0 M in PhMe; [c] 0.1 equiv; [d] Variable; [e] Neat; [f] 1.1 equiv.

Additives:

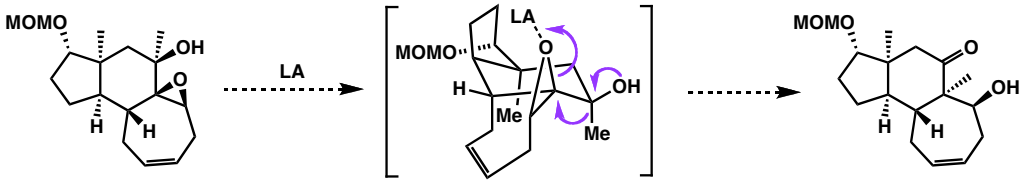


2.18 (*S,S*) ***2.19*** (*R,R*) ***2.20*** (*R,R*) ***2.21*** (*S,S*)

2.5. Attempts to Install the Second All-Carbon Quaternary Center

With the [5-6-7] fused tricycle in hand, the next key challenge was the diastereoselective installation of the second all-carbon quaternary center at the [6-7] ring fusion. The construction of all-carbon quaternary centers is a historic and ongoing obstacle in organic synthesis.[14] In our system, one route to the all-carbon quaternary center could be achieved via a semi-pinacol rearrangement of the appropriately elaborated substrate (e.g., cyanthiwigin tricycle **2.22**, Scheme 2.5.1). Upon treatment with a Lewis acid like boron trifluoride ethyl etherate (BF_3•OEt_2), the epoxide should be activated, facilitating a 1,2-methyl shift and concomitant epoxide opening to arrive at β-hydroxy ketone **2.24**. A similar strategy should also be applicable to the cyathane system.

Scheme 2.5.1. Semi-pinacol rearrangement strategy.



2.22 *2.23* *2.24*

Cleavage of the sterically-hindered silyl ether of **2.2** was required in the first step of the semi-pinacol substrate synthesis. The use of 4 Å molecular sieves accelerated the reaction, furnishing allylic alcohol **2.25** (Scheme 2.5.2). The revealed hydroxyl group directed the vanadyl acetylacetonate-mediated expoxidation. *m*-CPBA was also effective in the diastereoselective

epoxidation of allylic alcohol **2.25**, which proceeded with similar diastereoselectivity. The ketal-protected analog of the cyathane tricycle (**2.28**) was analyzed by X-ray crystallography, which confirmed the relative stereochemistry of the tricycle (Fig. 2.5.1).

Scheme 2.5.2. Construction of the semi-pinacol substrate.

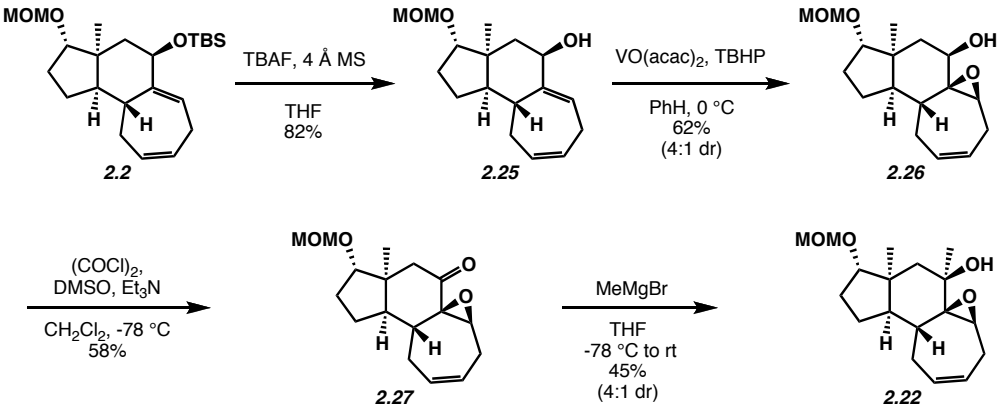
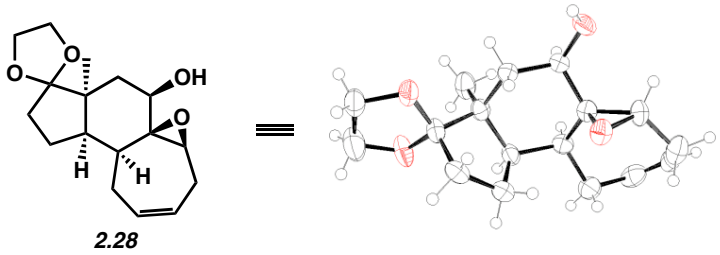


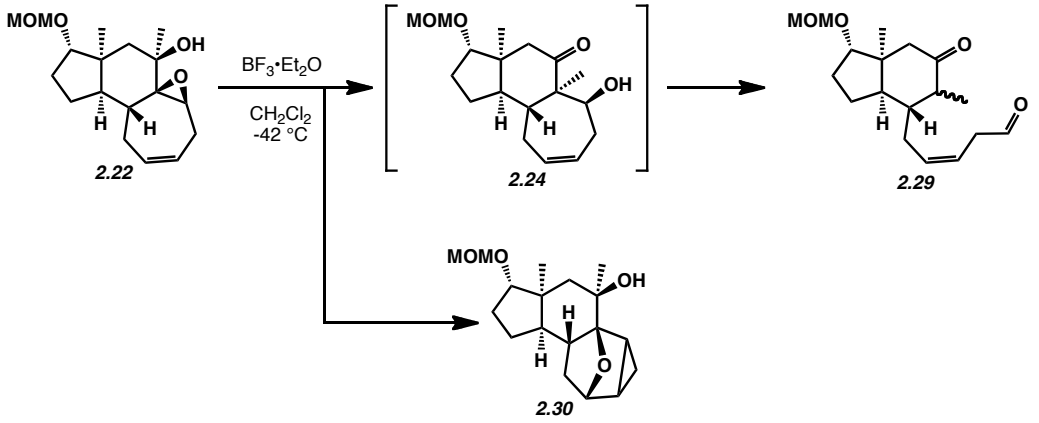
Figure 2.5.1. X-ray crystal structure of cyathane ketal **2.28**.



Ketone **2.27** was formed via a Swern oxidation of **2.26**. Grignard reagent attack proceeded from the convex face of the tricycle to yield target methyl substrate **2.22** in a 4:1 dr. Although groups with a higher migratory aptitude could also be utilized, we first investigated a methyl group as it would directly provide tricycle **2.24** upon successful rearrangement.

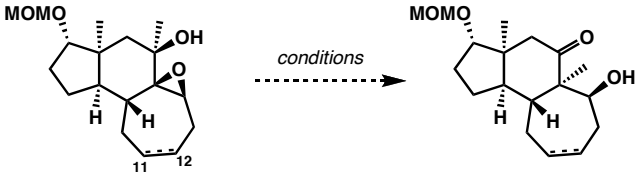
In the event, treatment of epoxide **2.22** with BF_3•OEt_2 appeared to promote the semi-pinacol rearrangement, but the rearrangement was quickly followed by a retro-aldol reaction, destroying the all-carbon quaternary center through the rupture of the seven-membered ring (**2.29**, Scheme 2.5.3). In addition to the retro-aldol product, the Lewis acid also promoted cycloisomerization to form tetrahydrofuran- and cyclopropane-containing compound **2.30**. Formation of undesired product **2.30** could be obviated by using a starting material lacking unsaturation in the seven-membered ring. This material could be obtained by hydrogenation of tricycle **2.22**.

Scheme 2.5.3. Boron trifluoride ethyl etherate-mediated reaction pathways.



Attempts to trap the semi-pinacol product using trimethylsilyl chloride or acetyl chloride, before the retro-aldol could proceed, were futile. However, we reasoned that a less active Lewis acid might promote the semi-pinacol rearrangement, without also promoting the retro-aldol. We examined a variety of conditions, a selection of which are shown in Table 2.5.1, and were in no case able to detect more than a trace of the desired product. Using BF_3•OEt_2 with the reduced tricycle (entry 1), led predominantly to the retro-aldol product. Scandium and ytterbium triflate (entries 2 and 3) were the most promising Lewis acids, but only yielded trace product. Other Lewis acids such as gallium triflate, titanium tetrachloride and tin tetrachloride (entries 4-6), led to decomposition or a complex mixture of products. Brønsted acidic conditions (*p*-toluenesulfonic acid, entry 7) also promoted formation of a complex mixture. Silyl triflates led to decomposition (entry 8) or to a complex mixture when employed with Hünig's base (entry 9). Combining the most promising Lewis acid, scandium triflate, with acetyl chloride and *N,N*-4-dimethylaminopyridine (DMAP), in an attempt to acylate the sensitive β-hydroxyl group in situ did not improve the yield beyond trace amounts of product (entry 10). These results led us to pursue an alternative approach.

Table 2.5.1. Semi-pinacol rearrangement attempts.



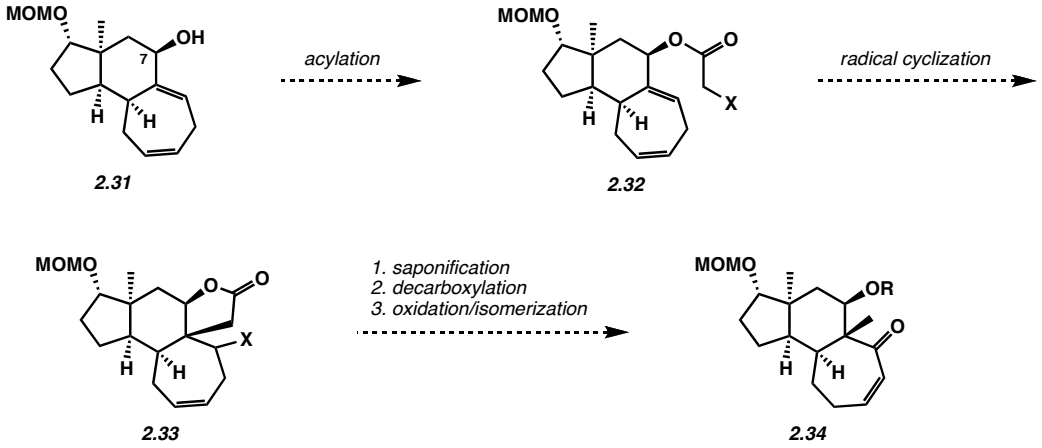
2.22 *2.24*

Entry	Conditions	Result
1	$BF_3 \cdot Et_2O$	retro-aldol[a]
2	$Yb(OTf)_3$	trace product[b]
3	$Sc(OTf)_3$	trace product[b]
4	$Ga(OTf)_3$	complex mixture[b]
5	$TiCl_4$	decomposition[b]
6	$SnCl_4$	decomposition[b]
7	*p*-TsOH	complex mixture[b]
8	TBSOTf	decomposition[b]
9	TMSOTf, DIPEA	complex mixture[b]
10	AcCl, $Sc(OTf)_3$, DMAP	trace product[b]

[a] Saturated compound; for $\Delta^{11,12}$ results, see Scheme 2.5.3; [b] $\Delta^{11,12}$.

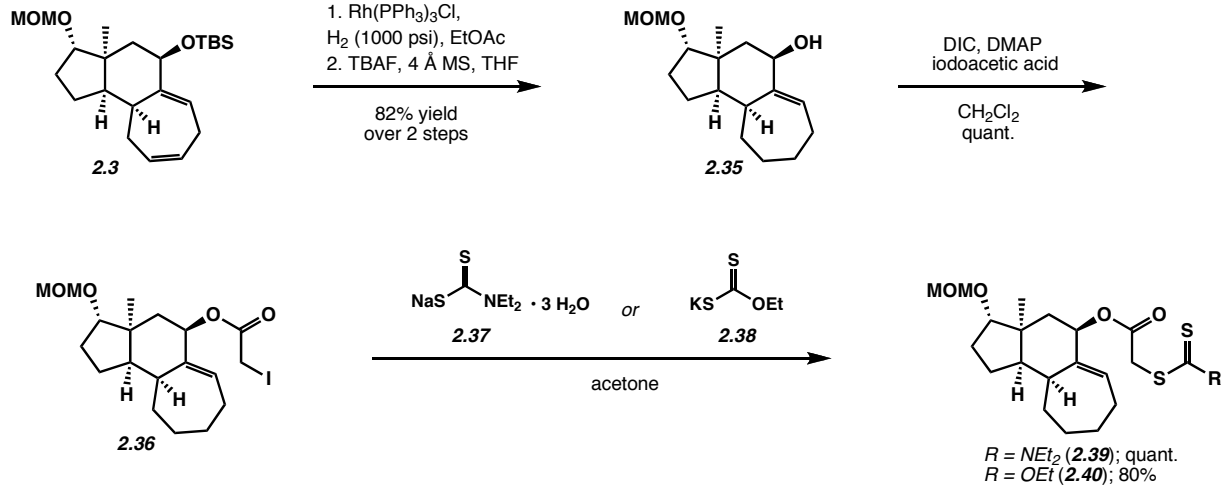
We next pursued a radical approach to install the second all-carbon quaternary center. As Stork and others have demonstrated, atom transfer reactions can be a powerful strategy to install all-carbon quaternary centers.[15] The general strategy was to acylate allylic alcohol **2.31** to form an ester with an X group alpha to the carbonyl (**2.32**, Scheme 2.5.4). After radical inititiation, the C-X bond is homolytically cleaved to provide a carbon radical which adds across the double bond to form a γ-lactone. Recombination with an X radical terminates the sequence, resulting in the overall addition of C-X across the alkene to furnish lactone **2.33**. Saponification and decarboxylation should convert the lactone to the desired methyl group. The X group should be amenable to conversion to a ketone, resulting in enone **2.34** after isomerization of the double bond into conjugation with the carbonyl. To enable access to the cyanthiwigins, a Mitsunobu reaction to invert the C7 hydroxyl group would be necessary. Inversion of the stereocenter on the B-ring sets up the atom-transfer from the desired face to install the methyl group on the α-face of the compound.

Scheme 2.5.4. Atom-transfer approach to set the all-carbon quaternary center.



We first focused on the cyathane tricycle to investigate this strategy. After the complications observed with the skipped diene in the semi-pinacol studies (see Scheme 2.5.3), we decided to reduce the disubstituted double bond from the onset (see **2.3** to **2.35**, Scheme 2.5.5), with the intention of attempting to carry through the cycloheptadiene once the downstream chemistry was established. Selective hydrogenation of cycloheptadiene **2.3** was achieved using Wilkinson's catalyst in ethyl acetate at 1000 psi of hydrogen. This step initially returned variable yields. We traced the problem back to the Swern oxidation of cyclopropanol **2.17 (**Scheme 2.3.2), where trace amounts of the methylthiomethyl ether had formed. Purification of the aldehyde, which had previously been used crude, via flash chromatography resolved the issues of catalyst poisoning. The silyl ether was then cleaved with tetrabutylammonium fluoride in the presence of 4 Å molecular sieves to furnish **2.35**. Coupling the allylic alcohol **2.35** to iodoacetic acid proceeded smoothly using diisopropylcarbodiimide and DMAP to furnish iodoester **2.36**. Although the iodoester[16] itself should be capable of atom-transfer

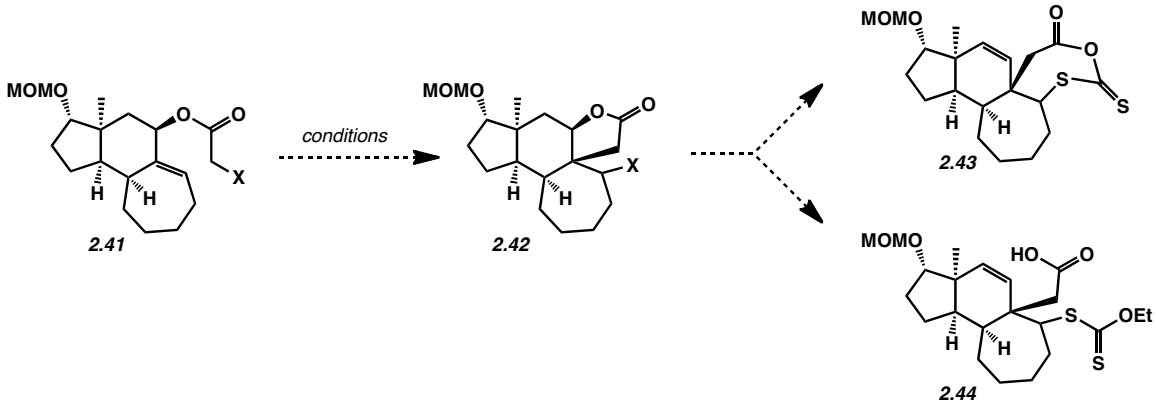
Scheme 2.5.5. Formation of atom-transfer substrates **2.36**, **2.39** and **2.40**.



chemistry, we also synthesized a dithiocarbamate[17] (**2.39**) and a dithiocarbonate[18] (**2.40**) from initial α-iodo compound **2.36** to test under the radical conditions. The advantage of using a dithiocarbamate or dithiocarbonate in group transfer chemistry is that radicals generated from these species are known to have a long effective lifetime, making addition across the alkene more facile.[18]

We screened a variety of methods for initiation of the atom-transfer reactions (Table 2.5.2). First, with iodo-substrate **2.36** we attempted to initiate the radical reaction by thermal decomposition of dilauroyl peroxide (DLP), however no reaction was observed, and starting material was recovered (entry 1). Photo-initiating bis(tributyltin) led to a complex mixture of products (entry 2). Thermal decomposition of DLP in the presence of dithiocarbamate **2.39** led to the formation of mixed thioanhydride **2.43** (entry 3). We rationalized this product as arising from elimination of the ester to introduce unsaturation in the B-ring. The carboxylate then attacked the thiocarbamate, displacing diethylamine. Tetracycle **2.43** would be appropriate for the synthesis of cyanthiwigin G (**2.1**, Scheme 2.2.1), however the mass recovery of this step was below 50%, limiting the utility of the transformation. Treatment of the dithiocarbamate (**2.39**) with a halogen lamp yielded des-thiocarbamate starting material (**2.41**, X=H; entry 4). Although the thermal decomposition of DLP was successful for the dithiocarbamate, it was ineffective for dithiocarbonate **2.40**, leading to recovery of starting material (entry 5). Photoinitiation of dithiocarbonate **2.40** yielded carboxylic acid **2.44** (entry 6), presumably through a similar elimination to open up the lactone as in the case of the dithiocarbamate. The carboxylic acid

Table 2.5.2. Atom-transfer reactions.



Entry	X	Conditions	Result (% yield)
1	I (***2.36***)	DLP,[a] PhH, 90 °C	no reaction
2	I (***2.36***)	$(Bu_3Sn)_2$, PhH, *hν*[b]	complex mixture
3	$SC(S)NEt_2$ (***2.39***)	DLP,[a] PhH, 90 °C	product ***2.43*** (39%)
4	$SC(S)NEt_2$ (***2.39***)	PhMe, *hν*[c]	product ***2.41*** (X = H)
5	SC(O)OEt (***2.40***)	DLP,[a] PhH, 90 °C	no reaction
6	SC(O)OEt (***2.40***)	PhMe, *hν*[c]	product ***2.44*** (64%)

[a] Dilauroyl peroxide; [b] 500 W mercury lamp; [c] 600 W halogen lamp at 70% capacity.

product (**2.44**) was obtained in a synthetically useful 68% yield, however, with long reaction times of over 20 h. While this approach still has promise, the tricyclic product (**2.43** or **2.44**) requires extensive functional group manipulation in order to reach the target natural products. In search of a more efficient route, we sought an alternative our approach to the cyanthiwigin and cyathane diterpenes.

2.6. Conclusion

Starting with (+)-Hajos-Parish ketone (**1.99**), we were able to construct a common dienol substrate (**2.6**) en route to the tricyclic cores of the cyanthiwigin and cyathane diterpenoids. Using a divinylcyclopropane rearrangement, we successfully forged the [5-6-7] fused core of both the cyathane and cyanthiwigin natural products. The facial selectivity of the cyclopropanation determined the diastereomer of the tricycle (**2.2** or **2.3**) formed in a divergent step. A diastereoselective cyclopropanation would allow one to target solely the cyathanes or the cyanthiwigins. While good selectivity for the cyathane cyclopropanol (**2.17**) was obtained with the (*R*,*R*) dioxaborolane (**2.20**), neither chiral bis-sulfonamide catalysts nor stoichiometric dioxaborolane additives could bias the cyclopropanation toward the formation of the cyanthiwigin cyclopropanol (**2.16**). A remaining challenge was the installation of the second all-carbon quaternary center at the B-C ring fusion. Semi-pinacol strategies were thwarted by the instability of the desired product due to a facile retro-aldol reaction. Atom-transfer reactions involving dithiocarbamate or dithiocarbonate moieties were able to form the challenging all-carbon quaternary center, but the tricycles obtained required an arduous endgame strategy to reach a cyathane or cyanthiwigin natural product.

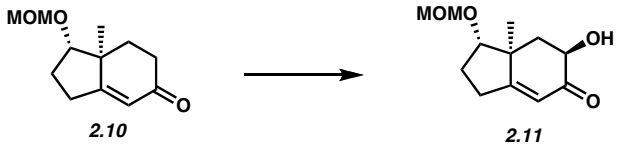
2.7. Experimental Contributions

Dr. J. Maina Ndungu developed the chemistry to the tricycles (**2.2** and **2.3**; Chapter 2.3) and obtained the crystal structure of **2.28** (Fig. 2.5.1). Laura C. Miller performed the rest of the work detailed in the chapter.

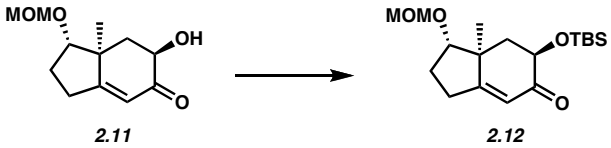
2.8. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Dichloromethane (DCM), toluene (PhMe) and triethylamine (Et_3N) were distilled over calcium hydride. Pentane was dried over 4 Å MS, and sparged with nitrogen. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500 and AV-500 MHz spectrometers with ^{13}C operating frequencies of 100, 125 and 125 MHz, respectively. Chemical

shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), m (multiplet). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley.

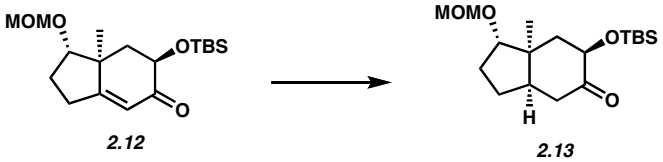


α-Hydroxy Enone (2.11): To a solution of hexamethyldisilazane (HMDS) (1.20 mL, 4.76 mmol) in THF (24 mL) at -78 °C was added *n*-BuLi (2.38 mL, 2.5 M in hexanes, 5.95 mmol) dropwise. After 5 min at -78 °C, the cold bath was removed and the mixture was allowed to return to room temperature over 20 min. The reaction mixture was subsequently cooled back to -78 °C, and a solution of **2.10**[3] (1.02 g, 4.77 mmol) in 20 mL THF was added dropwise. The resulting orange solution was stirred at -78 °C for 2 h. TMSCl (0.960 mL, 7.61 mmol) was then added dropwise, and the pale yellow solution was stirred at -78 °C for an additional 0.5 h, and then allowed to warm to room temperature over 0.5 h. The mixture was quenched with saturated aq. $NaHCO_3$ (10 mL). The aqueous layer was quickly extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a dark yellow oil. The crude product was dissolved in DCM (35 mL) and the reaction mixture was cooled to -42 °C. $KHCO_3$ (2.38 g, 23.8 mmol) and *m*-CPBA (≥77%, 1.23 g, 7.13 mmol) were added to the reaction mixture and it was stirred at -42 °C for 2 h and then allowed to warm to room temperature. H_2O (30 mL) was added, and the resulting mixture was extracted with EtOAc (3 x 45 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude pale yellow solid was dissolved in THF (40 mL) and the mixture was cooled to 0 °C. TBAF (4.75 mL, 1.0 M in THF, 4.76 mmol) was added. After 15 min, the cold bath was removed, and following 15 min of stirring at room temperature, the reaction mixture was quenched with saturated aq. NH_4Cl (30 mL). After extraction with EtOAc (3 x 45 mL), the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated to give an orange oil. Flash chromatography (1:1 hexanes/EtOAc) gave **2.11** (0.67 g) as a light yellow oil in 62% yield (5:1 dr). $\mathbf{R_f}$ 0.20 (3:2 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8, 1H), 4.35 (dd, *J* = 13.2, 5.5 Hz, 1H), 3.73 (dd, *J* = 13.2, 5.5 Hz, 1H), 3.37 (s, 3H), 2.76 (dd, *J* = 19.6, 12.1 Hz, 1H), 2.53 (dd, *J* = 12.3, 5.5 Hz, 1H), 2.48-1.85 (m, 4H), 1.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.4, 175.9, 120.4, 95.9, 84.8, 69.0, 55.4, 46.3, 43.2, 26.9, 26.4, 16.5; **IR** (film) ν_{max} 3435, 2941, 1676, 1111, 1044 cm^{-1}; **HRMS** (EI+) calcd for $[C_{12}H_{18}O_4]^+$: *m/z* 226.1205, found 226.1206.



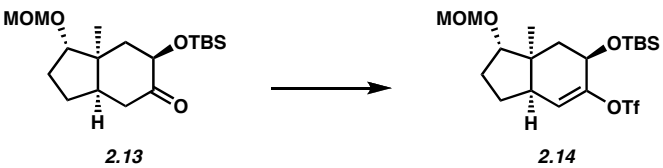
2.11 *2.12*

α-Siloxy Enone (2.12): Compound **2.11** (2.05 g, 9.06 mmol) was dissolved in PhMe (40 mL) at room temperature. TBSCl (1.66 g, 11.0 mmol) and DBU (1.62 mL, 10.9 mmol) were added sequentially. After stirring overnight (12 h), water (40 mL) was added, and the aqueous layer was separated and extracted with EtOAc (3 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (4:1 hexanes/EtOAc) to give 2.27 g of **2.12** as a clear oil in 79% yield. $\mathbf{R_f}$ 0.59 (3:2 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7, 1H), 4.36 (dd, *J* = 13.0, 5.3 Hz, 1H), 3.68 (dd, *J* = 10.0, 7.8 Hz, 1H), 3.34 (s, 3H), 2.70 (dd, *J* = 19.4, 12.0 Hz, 1H), 2.43-2.28 (m, 2H), 2.20-2.12 (m, 1H), 1.93-1.77 (m, 2H), 1.22 (s, 3H), 0.92 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.9, 172.2, 122.1, 96.1, 85.2, 70.7, 55.4, 46.4, 44.9, 27.0, 26.8, 26.4, 18.6, 16.7, -4.4, -5.4; **IR** (film) ν_{max} 2930, 1688, 1254, 1111, 1045, 1028 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{18}H_{32}O_4Si]^+$ $(M+Li)^+$: *m/z* 347.2230, found 347.2229.



2.12 *2.13*

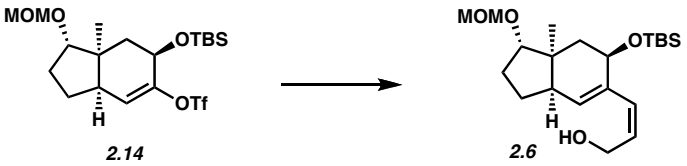
Ketone (2.13): Compound **2.12** (1.90 g, 5.58 mmol) and PtO_2 (38.2 mg, 0.167 mmol) were combined in 46 mL EtOAc. The flask was evacuated and backfilled with hydrogen (3x) and stirred under an atmosphere of hydrogen for 2.5 h. The solution was filtered through Celite and concentrated. The crude product was purified by flash chromatography (gradient of 9:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to give 1.74 g of **2.13** as a clear oil in a 91% yield. $\mathbf{R_f}$ 0.28 (9:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.65 (d, *J* = 6.7 Hz, 1H), 4.55 (d, *J* = 6.7, 1H), 4.34 (dd, *J* = 12.0, 6.4 Hz, 1H), 3.66 (d, *J* = 4.5 Hz, 1H), 3.36 (s, 3H), 2.50 (dd, *J* = 14.4, 5.9 Hz, 1H), 2.34-2.31 (m, 2H), 2.14-1.99 (m, 2H), 1.91-1.85 (m, 1H), 1.81-1.77 (m, 1H), 1.71-1.57 (m, 2H), 1.31 (s, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.4, 95.2, 84.7, 73.5, 55.5, 45.9, 44.8, 43.1, 40.0, 29.0, 27.9, 25.8, 19.3, 18.6, -4.6, -5.4; **IR** (film) ν_{max} 1730, 1253, 1119, 1048, 1035 cm^{-1}; **HRMS** (FAB+) calcd for $[C_{18}H_{35}O_4Si]^+(M+H)^+$: *m/z* 343.2305, found 343.2308.



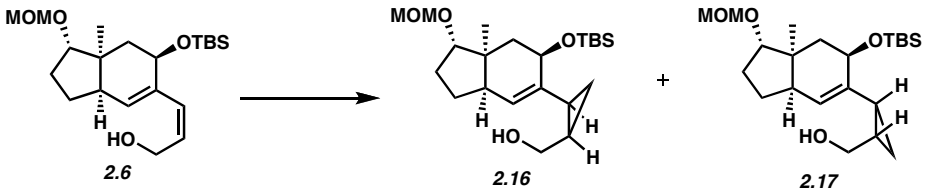
2.13 *2.14*

Enol Triflate (2.14): HMDS (1.15 mL, 5.51 mmol) was dissolved in THF (48 mL) and cooled to -78 °C. *n*-BuLi (2.30 mL, 2.5 M in hexanes, 5.69 mmol) was added dropwise. The cold bath was removed after 5 min, and the mixture was allowed to return to room temperature over 20 min.

The reaction mixture was then cooled to -78 °C and **2.13** (1.50 g, 4.38 mmol) in THF (2 mL) was added dropwise. The reaction was maintained at -78 °C for 1.5 h, after which 2-pyrNTf$_2$[5] (1.72 g, 4.80 mmol) in THF (2 mL) was added. After an additional 30 min at -78 °C, the cold bath was removed, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched by the addition of saturated aq. NH_4Cl (20 mL). The solution was separated and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a golden orange oil. Flash chromatography (gradient of 20:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) gave **2.14** (1.71 g, 82% yield) as a clear oil. $\mathbf{R_f}$ 0.35 (9:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.78 (d, *J* = 5.0 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 6.7, 1H), 4.43 (dd, *J* = 7.3, 6.3 Hz, 1H), 3.83-3.77 (m, 1H), 3.36 (s, 3H), 2.41 (dd, *J* = 12.8, 7.7 Hz, 1H), 2.18-2.08 (m, 2H), 1.80-1.66 (m, 3H), 1.57-1.47 (m, 2H), 1.07 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.2, 122.7, 95.8, 84.2, 65.7, 60.4, 55.5, 44.5, 43.7, 41.2, 30.3, 28.6, 25.8, 25.7, 19.9, 18.1, -4.1, -4.5; **IR** (film) ν_{max} 1679, 1422, 1245, 1105, 1042 cm^{-1}; **HRMS** (FAB+) calcd for $[C_{19}H_{34}F_3O_6SSi]^+$ $(M+H)^+$: *m/z* 475.1797, found 475.1790.



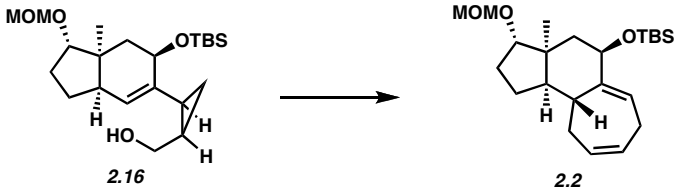
Dienol (2.6): Anhydrous LiCl (0.514 g, 12.1 mmol) was added to a Schlenk flask, which was heated to 120 °C under vacuum for 18 h. After cooling to rt and backfilling with N_2, $Pd(PPh_3)_4$ (0.240 g, 0.211 mmol) and CuCl (0.520 g, 10.5 mmol) were added. The Schlenk flask was evacuated and backfilled with N_2 (4x). A solution of **2.14** (0.944 g, 1.99 mmol) and **2.15**[6,7] (1.18 g, 3.16 mmol) in DMSO (17 mL) was added to the Schlenk flask, and then the mixture was sparged with N_2 for 15 min. The dark red-brown solution was stirred at room temperature for 17 h, before it was diluted with Et_2O (20 mL) and washed with a 5:1 brine/5% NH_4OH solution (20 mL). The aqueous layer was extracted with Et_2O (40 mL), and the combined organic layers were washed sequentially with H_2O (2 x 20 mL) and brine (2 x 20 mL). After drying over Na_2SO_4 and concentrating, the crude product was purified by flash chromatography (gradient of 9:1 hexanes/EtOAc to 2:3 hexanes/EtOAc) to afford **2.6** (0.63 g) as a clear oil in an 84% yield. $\mathbf{R_f}$ 0.22 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.11 (d, *J* = 11.5 Hz, 1H), 5.76-5.66 (m, 1H), 5.45 (d, *J* = 2.8 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.41-4.15 (m, 3H), 3.70 (s, 1H), 3.36 (s, 3H), 2.25 (s, 1H), 2.16-2.00 (m, 2H), 1.82-1.22 (m, 4H), 1.04 (s, 3H), 0.88 (s, 9H), 0.073-0.066 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.1, 131.0, 130.9, 130.2, 95.6, 85.8, 67.9, 59.6, 55.3, 44.4, 41.1, 30.4, 29.6, 25.9, 20.2, 18.2, 13.6, -4.2, -4.7; **IR** (film) ν_{max} 3385, 1631, 1253, 1081, 1042 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{21}H_{38}O_4Si]^+$ $(M+Li)^+$: *m/z* 389.2699, found 389.2701.



Cyclopropanol (2.16 and **2.17):** Diethyl zinc (6.20 mL, 1.1 M in PhMe, 6.82 mmol) was added to a solution of **2.6** (0.650 g, 1.70 mmol) in PhMe (10 mL), and the mixture was heated to 45 °C. Using a syringe pump, a solution of diiodomethane (0.410 mL, 5.10 mmol) in PhMe (1.5 mL) was added over 4 h. The mixture was stirred for a further 30 min at 45 °C and then allowed to cool to room temperature. To the solution was added saturated aq. $NaHCO_3$ (10 mL) and the mixture was filtered through Celite, extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated. The crude product was then purified by flash chromatography (gradient of 10:1 hexanes/EtOAc to 6:1 hexanes/EtOAc) to give **2.16** and **2.17** as clear oils in an 80% combined yield (0.539 g, 1:1 dr).

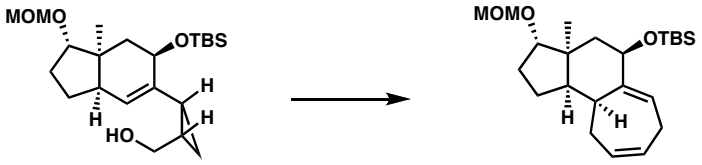
2.16: $\mathbf{R_f}$ 0.15 (4:1 hexanes/EtOAc); $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ 5.40 (d, *J* = 4.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.59 (d, *J* = 6.7, 1H), 4.23-4.15 (m, 1H), 3.66 (dd, *J* = 5.3, 3.8 Hz, 1H), 3.48 (dd, *J* = 11.1, 7.7 Hz, 1H), 3.40 (dd, *J* = 11.1, 7.3 Hz, 1H), 3.36 (s, 3H), 2.19-1.98 (m, 3H), 1.94 (dd, *J* = 15.3, 7.8 Hz, 1H), 1.69-1.63 (m, 1H), 1.59 (dd, *J* = 12.6, 5.7 Hz, 1H), 1.49-1.38 (m, 2H), 1.29-1.17 (m, 1H), 0.96 (s, 3H), 0.91 (s, 9H), 0.83-0.76 (m, 1H), 0.56 (dd, *J* = 11.3, 5.2 Hz, 1H), 0.12 (s, 3H), 0.10 (s, 3H); $^{\mathbf{13}}$**C NMR** (125 MHz, $CDCl_3$) δ 135.4, 127.2, 95.5, 85.9, 68.9, 62.4, 55.3, 44.5, 44.3, 41.4, 30.6, 29.6, 25.9, 19.9, 19.8, 18.5, 18.1, 6.4, -4.2, -4.7; **IR** (film) ν_{max} 3428, 1251, 1078, 1039 cm^{-1}; **HRMS** (EI+) calcd for $[C_{22}H_{40}O_4Si]^+$: *m/z* 396.2696, found 396.2689.

2.17: $\mathbf{R_f}$ 0.27 (4:1 hexanes/EtOAc); $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ 5.38 (d, *J* = 4.7 Hz, 1H), 4.66 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7, 1H), 4.46-4.40 (m, 1H), 3.81-3.73 (m, 2H), 3.64-3.59 (m, 1H), 3.36 (s, 3H), 2.95 (t, *J* = 9.9 Hz, 1H), 2.25-2.19 (m, 1H), 2.12-2.00 (m, 2H), 1.72-1.59 (m, 2H), 1.46-1.25 (m, 3H), 1.07 (s, 3H), 0.94 (s, 9H), 0.70-0.66 (m, 1H), 0.49 (dd, *J* = 11.1, 5.5 Hz, 1H), 0.18 (s, 3H), 0.15 (s, 3H); $^{\mathbf{13}}$**C NMR** (125 MHz, $CDCl_3$) δ 133.9, 127.7, 95.5, 86.1, 70.2, 61.2, 55.4, 44.8, 44.2, 41.7, 30.5, 30.4, 25.9, 20.7, 19.9, 18.7, 18.2, 4.6, -4.5; **IR** (film) ν_{max} 3453, 1255, 1098, 1045 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{22}H_{20}O_4Si]^+$ $(M+Li)^+$: *m/z* 403.2856, found 403.2860.

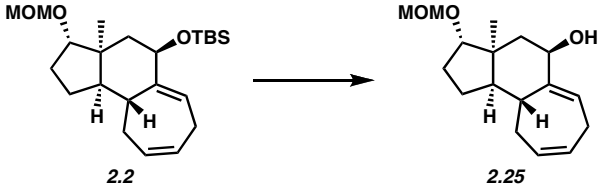


Tricycle (2.2): Oxalyl chloride (0.630 mL, 7.11 mmol) was dissolved in DCM (34 mL) and the mixture was cooled to -78 °C. DMSO (1.01 mL, 14.2 mmol) was slowly added. The mixture was stirred for 30 min before adding **2.16** (1.41 g, 3.56 mmol) dissolved in DCM (10 mL). The mixture was stirred for another 30 min at -78 °C, and Et_3N (4.00 mL, 28.7 mmol) was added. The cold bath was removed, the mixture was stirred for an additional 30 min, and then poured

onto H_2O (30 mL). The aqueous layer was separated and extracted with DCM (3 x 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude aldehyde as a yellow oil. In another flask, methyltriphenylphosphonium bromide (1.91 g, 5.33 mmol) was dissolved in THF (34 mL) and cooled to 0 °C. To the suspension was added NaHMDS (4.84 mL, 1.0 M in THF, 4.84 mmol), and the reaction mixture was stirred at 0 °C for 40 min. A solution of the crude aldehyde in THF (10 mL) was added, and the opaque orange mixture was stirred at 0 °C for 1 h, and then allowed to warm to room temperature overnight (12 h). The reaction was quenched with saturated aq. NH_4Cl (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography (gradient of 9:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to give **2.2** (1.22 g, 87% yield over 2 steps) as a clear oil. $\mathbf{R_f}$ 0.76 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.85-5.75 (m, 1H), 5.73-5.68 (m, 1H), 5.62-5.57 (m, 1H), 4.67 (d, *J* = 6.4 Hz, 1H), 4.65 (d, *J* = 6.4 Hz, 1H), 4.20 (t, *J* = 8.1 Hz, 1H), 4.15 (t, *J* = 5.2 Hz, 1H), 3.35 (s, 3H), 2.94 (d, *J* = 18.7 Hz, 1H), 2.61 (td, *J* = 18.6, 6.9 Hz, 1H), 2.44-2.36 (m, 2H), 2.18-2.10 (m, 1H), 2.08-1.89 (m, 2H), 1.83 (dd, *J* = 13.8, 6.1 Hz, 1H), 1.61-1.39 (m, 4H), 0.90 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 145.4, 130.7, 129.6, 120.6, 96.6, 84.8, 74.4, 55.2, 48.7, 43.3, 42.7, 37.6, 29.6, 28.3, 26.6, 25.9, 25.3, 23.3, 18.2, -4.6, -4.8; **IR** (film) ν_{max} 1253, 1112, 1046 cm^{-1}; **HRMS** (FAB+) calcd for $[C_{23}H_{39}O_3Si]^+$ $(M-H)^+$: *m/z* 391.2668, found 391.2670.

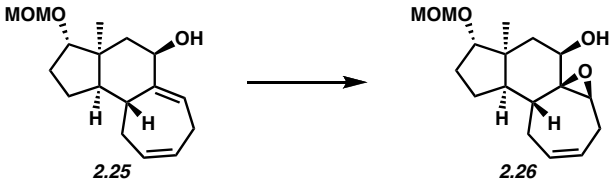


Tricycle (2.3): The reaction was run in an identical manner as that to form **2.2**, and yielded **2.3** as a clear oil in an 87% yield over 2 steps. $\mathbf{R_f}$ 0.69 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.02-5.92 (m, 1H), 5.90-5.86 (m, 1H), 5.85-5.80 (m, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 4.00 (d, *J* = 9.5 Hz, 1H), 3.54 (d, *J* = 5.6 Hz, 1H), 3.36 (s, 3H), 2.95 (d, *J* = 15.9 Hz, 1H), 2.60-2.51 (m, 1H), 2.50-2.42 (m, 1H), 2.31 (d, *J* = 10.0 Hz, 1H), 2.14-2.09 (m, 1H), 2.07-1.97 (m, 1H), 1.89-1.80 (m, 1H), 1.79-1.56 (m, 3H), 1.42 (dd, *J* = 12.3, 4.4 Hz, 1H), 1.16-1.1 (m, 4H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.2, 133.1, 129.7, 118.7, 95.1, 85.9, 70.6, 55.4, 49.9, 46.1, 43.0, 36.2, 30.5, 28.7, 25.9, 24.9, 24.7, 19.3, 18.5, -4.9, -5.0; **IR** (film) ν_{max} 1255, 1099, 1045 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{23}H_{40}O_3Si]^+$ $(M+Li)^+$: *m/z* 399.2907, found 399.2907.

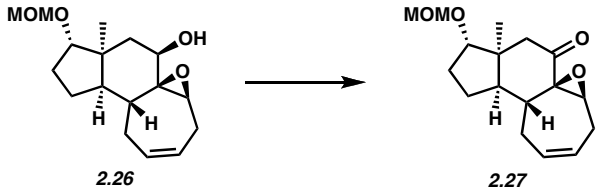


Alcohol (2.25): TBAF (1.70 mL, 1 M in THF 1.7 mmol) was added to a solution of tricycle **2.2** (0.55 g, 1.4 mmol) in THF (11 mL) with crushed 4 Å molecular sieves (1.98 g). After 19 h, the reaction was quenched with saturated aq. NH_4Cl (10 mL). The layers were separated after the solution was filtered through Celite. The aqueous layer was extracted with EtOAc (3 x 20 mL).

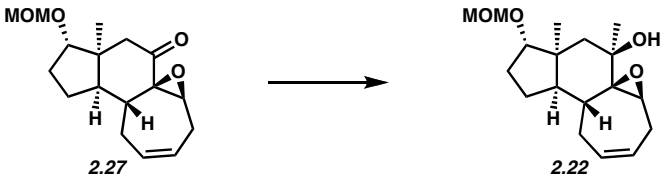
The combined organic layer was dried over Na_2SO_4 and concentrated. Flash chromatography (2:1 hexanes/EtOAc) furnished alcohol **2.25** in 82 % yield as a clear oil (0.32 g). $\mathbf{R_f}$ 0.15 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.91- 5.85 (m, 1H), 5.77 (t, *J* = 8.2 Hz, 1H), 5.72 (t, *J* = 5.9 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.17 (t, *J* = 6.1 Hz, 1H), 4.09-4.04 (m, 1H), 3.36 (s, 3H), 2.92-2.84 (m, 1H), 2.75-2.67 (m, 1H), 2.48-2.40 (m, 1H), 2.35-2.30 (m, 1H), 2.22-2.15 (m, 1H), 2.02-1.91 (m, 2H), 1.76-1.66 (m, 2H), 1.63-1.47 (m, 2H), 1.40-1.32 (m, 1H), 0.89 (s, 3H); **IR** (film) ν_{max} 3425, 3026, 1148, 1126, 1041 cm^{-1}.



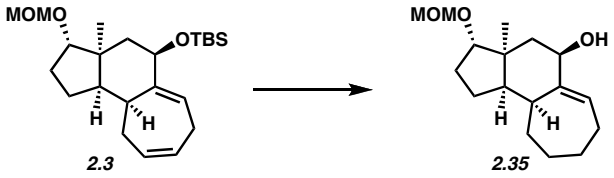
Epoxide (2.26): TBHP (0.32 mL, 5.0 M in decane, 1.6 mmol) was added at 0 °C to a solution of alcohol **2.25** (0.32 g, 1.2 mmol) and $VO(acac)_4$ (23 mg, 0.088 mmol) in a solution of benzene (11.4 mL) in a foil-covered flask. After stirring at 0 °C for 1 h, the reaction mixture was quenched with saturated aq. Na_2SO_3 solution (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The organic fraction was dried over Na_2SO_4 and concentrated. The crude product was purified via flash chromatography to give 0.21 g of epoxide **2.26** as a clear oil in a 4:1 dr (62% yield). $\mathbf{R_f}$ 0.42 (3:2 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.56-5.50 (m, 1H), 5.49-5.43 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.18-4.08 (m, 1H), 3.64-3.60 (m, 1H), 3.43 (t, *J* = 6.7 Hz, 1H), 3.37 (s, 3H), 2.65-2.53 (m, 2H), 2.48-2.40 (m, 2H), 2.23-2.13 (m 1H), 2.13-2.03 (m, 1H), 2.00-1.90 (m, 1H), 1.89-1.81 (m, 2H), 1.67-1.55 (m, 2H), 1.34 (t, *J* = 12.3 Hz, 1H), 1.21 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 130.5, 122.7, 95.2, 87.7, 62.7, 62.3, 56.2, 55.5, 47.1, 45.8, 39.5, 38.9, 34.4, 29.3, 28.7, 28.0, 21.6; **IR** (film) ν_{max} 3451, 3013, 1147, 1096, 1078, 1049, 1073 cm^{-1}.



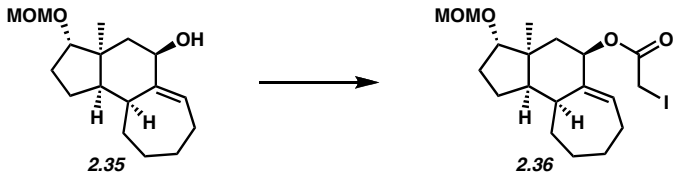
Ketone (2.27): A solution of $(COCl)_2$ (0.060 mL, 0.68 mmol) in 3.7 mL CH_2Cl_2 was cooled to -78 °C. DMSO (0.11 mL, 1.4 mmol) was added, and the reaction was stirred for 30 min at -78 °C. Alcohol **2.26** (0.10 g, 0.34 mmol) was added in 0.5 mL CH_2Cl_2. After 30 min at the same temperature, Et_3N (0.38 mL, 2.7 mmol) was added and the reaction mixture was then stirred at room temperature for 30 min. The reaction mixture was poured onto water (4 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL). The organic layer was dried over $MgSO_4$ and concentrated. After column chromatography (gradient of 4:1 hexanes/EtOAc to 3:2 hexanes/EtOAc), ketone **2.27** was isolated as a clear oil that crystallized upon standing (58 mg, 58% yield). $\mathbf{R_f}$ 0.5 (3:2 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.55-5.48 (m, 1H), 5.47-5.39 (m, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.60 (d, *J* = 6.7 Hz, 1H), 3.64 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.36 (s, 3H), 3.28 (t, *J* = 4.1 Hz, 1H), 2.86-2.76 (m, 1H), 2.75-2.68 (m, 1H), 2.68-2.62 (m, 1H), 2.55-2.49 (m, 1H), 2.48-2.39 (m, 2H), 2.28-2.15 (m, 1H), 2.11-1.95 (m, 3H), 1.69-1.58 (m, 1H), 1.42-1.30 (m, 1H), 1.03 (s, 3H).



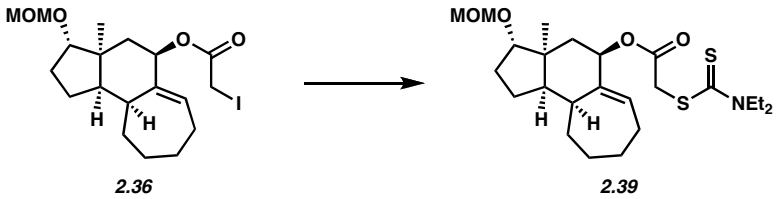
Tertiary Alcohol (2.22): To a solution of ketone **2.27** (63 mg, 0.22 mmol) in THF (2.2 mL) at -78 °C was added MeMgBr (0.080 mL, 3.0 M in Et_2O, 0.24 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h, then was allowed to return to room temperature. After 12 h, the reaction was quenched with saturated aq. NH_4Cl (2 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The organic portion was dried over $MgSO_4$ and concentrated. Flash chromatography (gradient of 4:1 hexanes/EtOAc to 2:1 hexanes/EtOAc) provided pure tertiary alcohol **2.22** as a pale yellow oil (30 mg, 45% yield, 4:1 dr). $\mathbf{R_f}$ 0.44 (3:2 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.49-5.36 (m, 2H), 4.68-4.66 (m, 1H), 4.60 (d, *J* = 6.7 Hz, 1H), 3.66 (t, *J* = 6.4 Hz, 1H), 3.54 (t, *J* = 4.1 Hz, 1H), 3.37 (s, 3H), 2.82-2.74 (m, 1H), 2.69-2.61 (m, 1H), 2.35-2.30 (m, 2H), 2.08-2.01 (m, 1H), 2.01-1.86 (m, 2H), 1.81-1.75 (m, 1H), 1.67-1.54 (m, 2H), 1.42-1.32 (m, 2H), 1.24 (s, 3H), 1.17 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 127.3, 124.8, 95.7, 86.3, 72.4, 67.7, 57.8, 55.3, 47.4, 46.8, 43.3, 40.8, 29.2, 29.2, 28.6, 27.3, 26.2, 24.0; **IR** (film) ν_{max} 3458, 1450, 1148, 1110, 1040, 916 cm^{-1}.



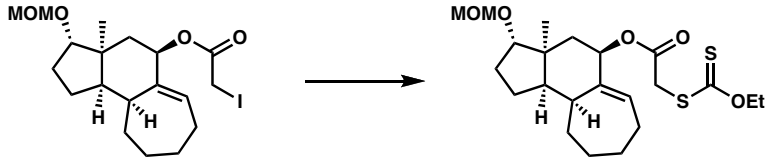
Allylic Alcohol (2.35): A solution of cycloheptadiene **2.3** (0.20 g, 0.51 mmol) and $Rh(PPh_3)_3Cl$ (25 mg, 0.027 mmol) in EtOAc (6.5 mL) was subjected to 1000 psi H_2 for 24 h. The reaction mixture was filtered through Celite and concentrated. The crude material was taken up in 5 mL THF. TBAF (0.66 mL, 1M in THF, 0.66 mmol) and crushed 4 Å molecular sieves (0.68 g) were added, and the reaction mixture was stirred for 15 h at room temperature. Saturated aq. NH_4Cl solution (5 mL) was added, and the layers were separated after filtration through Celite. The aqueous layer was extracted with EtOAc (3 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified through column chromatography to yield 0.11 g allylic alcohol **2.35** as a clear oil in 82% yield over two steps. $\mathbf{R_f}$ 0.12 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.83-5.77 (m, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 4.15-4.07 (m, 1H), 3.56 (d, *J* = 5.5 Hz, 1H), 3.36 (s, 3H), 2.49- 2.38 (m, 1H), 2.38-2.31 (m, 1H), 2.08-1.91 (m, 2H), 1.91- 1.43 (m, 11H), 1.18 (s, 3H), 1.07-1.00 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.6, 119.1, 95.1, 85.8, 70.2, 55.4, 49.9, 46.4, 43.6, 43.2, 28.7, 28.0, 26.3, 24.1, 24.0, 22.6, 19.7; **IR** (film) ν_{max} 3391, 1178, 1148, 1097, 1041 cm^{-1}.



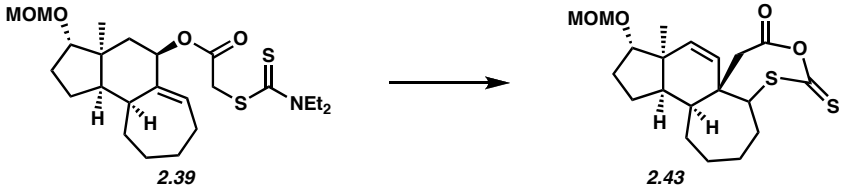
Iodoacetate (2.36): To a solution of allylic alcohol **2.35** (21 mg, 0.075 mmol) in 1 mL CH_2Cl_2 was added iodoacetic acid (18 mg, 0.099 mmol), DIC (0.020 mL, 0.13 mmol) and DMAP (1.0 mg, 8.2 x 10^{-3} mmol). The reaction flask was covered in foil and the mixture was stirred over 17 h. The reaction mixture was poured onto water (1 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layer was washed with saturated aq. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. Flash chromatography (gradient of 9:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) furnished pure iodoacetate **2.36** as a clear oil in quantitative yield (34 mg). $\mathbf{R_f}$ 0.41 (4:1 hexanes/EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 5.0 Hz, 1H), 5.29-5.23 (m, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.54 (d, *J* = 6.8 Hz, 1H), 3.79-3.65 (m, 2H), 3.57 (d, *J* = 5.5 Hz, 1H), 3.35 (s, 3H), 2.40 (s, 2H), 2.08-1.99 (m, 1H), 1.99-1.45 (m, 13H), 1.22-1.19 (s, 3H); ^{13}**C NMR** (150 MHz, C_6D_6) δ 167.7, 138.2, 121.2, 95.6, 86.0, 74.0, 55.5, 50.5, 46.8, 44.1, 39.8, 29.2, 28.9, 26.9, 25.1, 24.8, 24.8, 23.5, 20.0; **IR** (film) ν_{max}1731, 1267, 1148, 1095, 1041, 666 cm^{-1}.



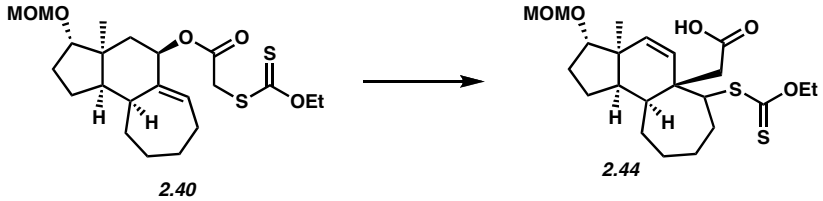
Dithiocarbamate (2.39): Sodium diethyldithiocarbamate trihydrate (38 mg, 0.17 mmol) was added to a solution of iodoacetate **2.36** (59 mg, 0.13 mmol) in 3 mL acetone. The reaction flask was covered in foil and the reaction mixture was stirred for 11 h at room temperature. A 10:1 solution of water/saturated aq. $NaHCO_3$ (2 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 4 mL). The combined organic layers were washed sequentially with water (4 mL) and brine (4 mL), then dried over Na_2SO_4 and concentrated to furnish dithiocarbamate **2.39** as pale yellow oil (62 mg, quant.). $\mathbf{R_f}$ 0.16 (4:1 hexanes/EtOAc); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 5.76 (d, *J* = 4.5 Hz, 1H), 5.33-5.26 (m, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 4.21 (s, 2H), 4.07- 3.98 (m, 4H), 3.78 (q, *J* = 7.1 Hz, 2H), 3.56 (d, *J* = 5.3 Hz, 1H), 3.35 (s, 3H), 2.44-2.35 (m, 2H), 2.08-1.98 (m, 1H), 1.98-1.52 (m, 9H), 1.52 - 1.44 (m, 2H), 1.36-1.24 (m, 6H), 1.19 (s, 3H); **IR** (film) ν_{max} 1738, 1647, 1270, 1207, 1147, 1098, 1042 cm^{-1}.



Dithiocarbonate (2.40): The reaction was run in an identical manner as that to form dithiocarbamate **2.39**, using potassium ethyl xanthogenate rather than sodium diethyldithiocarbamate trihydrate. The reaction provided dithiocarbonate **2.40** as a clear oil in an 80% yield. $\mathbf{R_f}$ 0.31 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.68 (dd, *J* = 8.9, 4.4 Hz, 1H), 5.33- 5.26 (m, 1H), 4.68-4.60 (m, 3H), 4.54 (d, *J* = 6.8 Hz, 1H), 3.95 (s, 2H), 3.56 (d, *J* = 5.4 Hz, 1H), 3.34 (s, 3H), 2.44-2.36 (m, 2H), 2.08-1.97 (m, 1H), 1.97-1.44 (m, 13H), 1.42 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 3H).

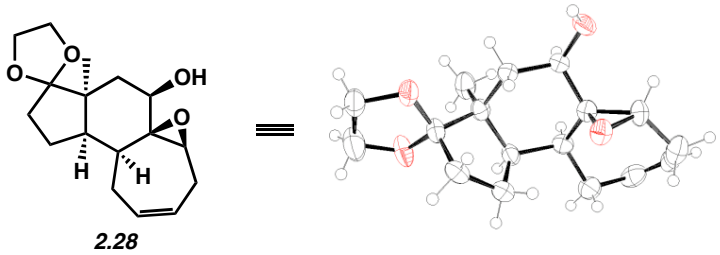


Mixed Anhydride (2.43): A solution of dithiocarbamate **2.39** (52 mg, 0.11 mmol) in 2.5 mL PhH was sparged with nitrogen for 15 min. The reaction mixture was heated to reflux, and dilauroyl peroxide was added in batches (8 x 4.0 mg, 0.011 mmol) every 2-8 h until the starting material was consumed. The reaction mixture was concentrated and purified by flash chromatography (gradient of 9:1 hexanes/EtOAc to 4:1 hexanes/EtOAc) to furnish mixed anhydride **2.43** as a yellow oil (17.1 mg, 39% yield, 2:1 dr). $\mathbf{R_f}$ 0.67 (4:1 hexanes/EtOAc); **^{1}H** (500 MHz, $CDCl_3$) δ 5.88 (d, *J* = 9.7 Hz, 1H), 5.70 (s, 1H), 5.09 (d, *J* = 9.6 Hz, 1H), 4.74-4.57 (m, 3H), 4.05 (t, *J* = 6.7 Hz, 1H), 3.71 (d, *J* = 4.5 Hz, 1H), 3.40- 3.37 (s, 3H), 2.49 (s, 1H), 2.33-2.25 (m, 3H), 2.20-1.57 (m, 10H), 1.11 (s, 3H).



Carboxylic Acid (2.44): A solution of dithiocarbonate **2.40** (11 mg, 0.024 mmol) in 1.5 mL PhMe was sparged with nitrogen for 15 min. The reaction vial was sealed and exposed to a 600 W halogen lamp at 70% capacity for 20 h. After concentration, the crude mixture was purified by column chromatography (gradient of 30:1 hexanes/EtOAc to 9:1 hexanes/EtOAc) to afford 6.8 mg of carboxylic acid **2.44** (64% yield, 3:1 dr). $\mathbf{R_f}$ 0.56 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.88 (d, *J* = 9.7 Hz, 1H), 5.70 (s, 1H), 5.09 (d, *J* = 9.4 Hz, 1H), 4.74- 4.56 (m, 4H), 3.70 (d, *J* = 4.5 Hz, 1H), 3.38 (s, 3H), 2.54-2.48 (m, 1H), 2.35-2.24 (m, 2H), 2.20- 2.07 (m, 1H), 2.03-1.92 (m, 2H), 1.90-1.55 (m, 10H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.11 (s, 3H).

X-Ray Structure of 2.28:



2.28

X-Ray Experimental Details: A fragment of a colorless blocklike crystal of $C_{17}H_{24}O_4$ having approximate dimensions of 0.17 x 0.23 x 0.30 mm was mounted on a Kapton loop using Paratone N hydrocarbon oil. All measurements were made on a Bruker APEX CCD area detector with graphite monochromated Mo-Ka radiation. Data were integrated by the program SAINT to a maximum 2θ value of 46.5°. The data were corrected for Lorentz and polarization effects. Data were analyzed for agreement and possible absorption using XPREP. An empirical absorption correction based on comparison of redundant and equivalent reflections was applied using SADABS. Structure solution by direct methods and refinement were performed using the teXsan software package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included, but not refined. The goodness of fit parameter is rather large with a value of 2.09. It is not clear why the estimated errors of the data are systematically low, but that is the root cause. There are no apparent anomalies in the data set, and the structure is a good one.

X-Ray Data:

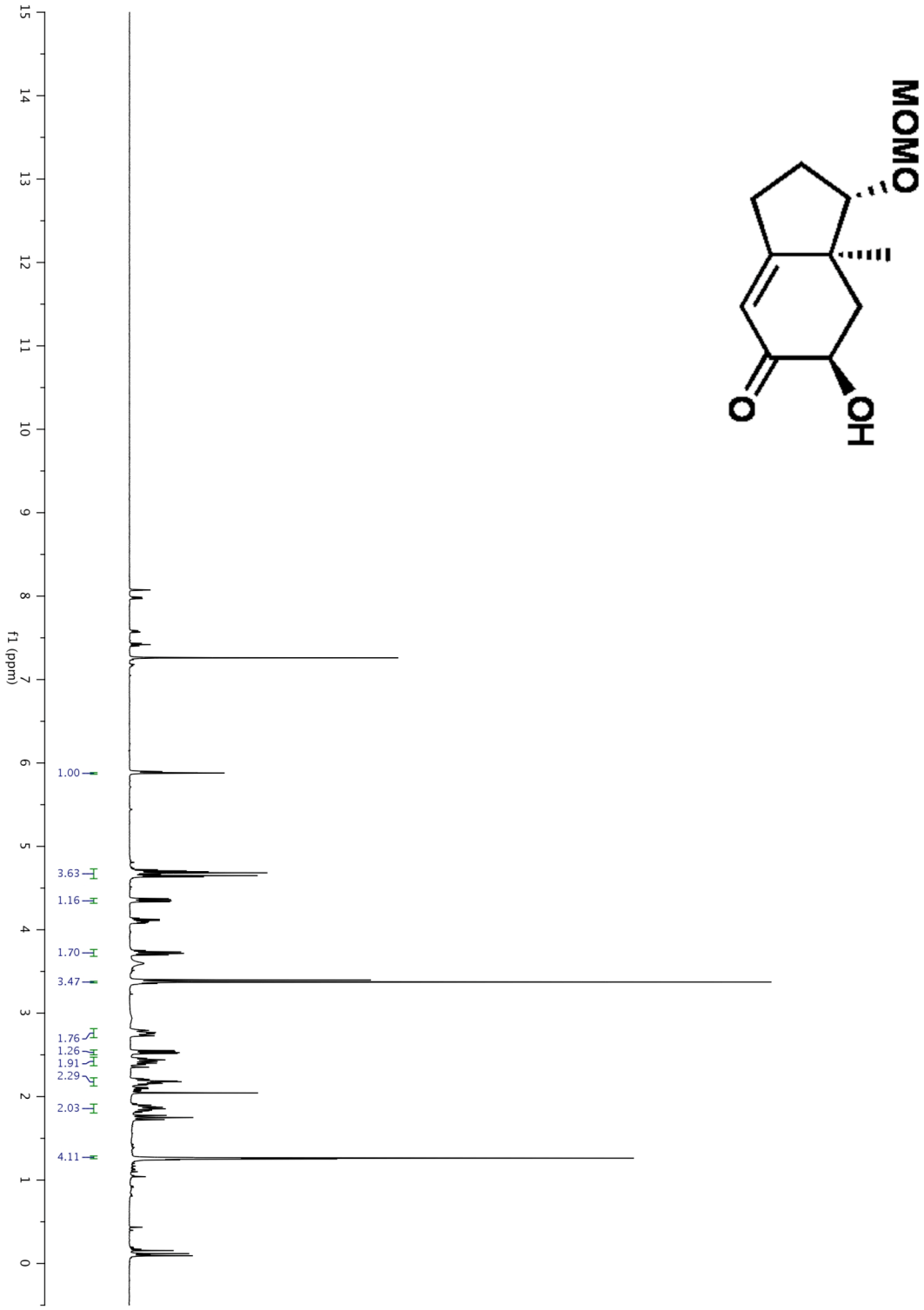
Empirical Formula	$C_{17}H_{24}O_4$
Formula Weight	292.37
T (K)	177.2
Crystal System	monoclinic
Space Group	$P2_1/n$ (#14)
a (Å)	12.681(1)
b (Å)	9.4209(9)
c (Å)	12.769(9)
β (deg)	102.961(1)
V (Å^3)	1486.6(2)
Z	4
ρ_{calcd} (g/cm^3)	1.306
μ(MoKα) (cm^{-1})	0.92
F (000)	632.00
reflctns collected	6396
ind reflctns (R_{int})	2379 (0.029)
T_{min}/T_{max}	0.83
R, R_w, R_{all}	0.042, 0.060, 0.064
GOF	2.09
max shift/error	0.00

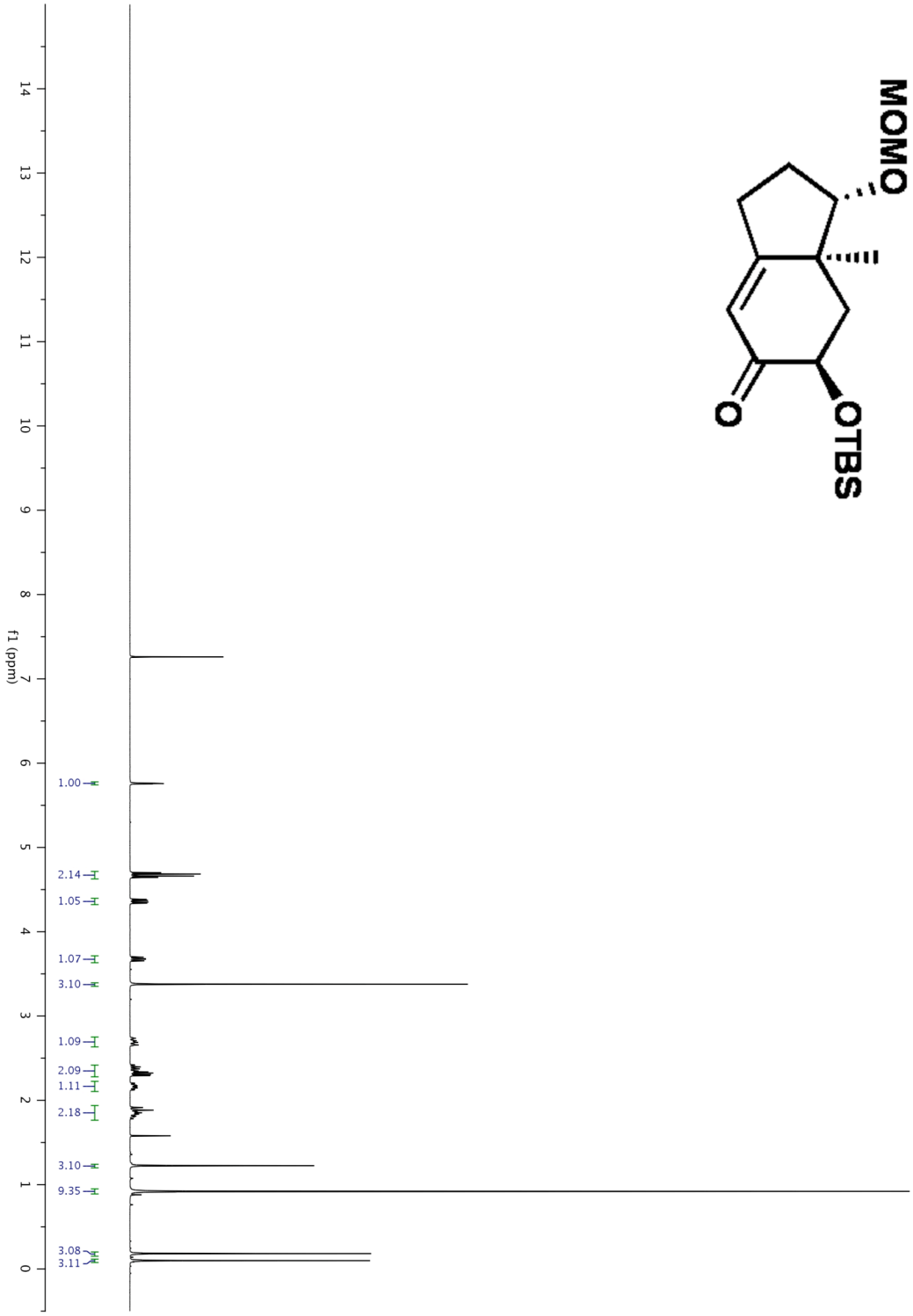
CCDC 719055 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

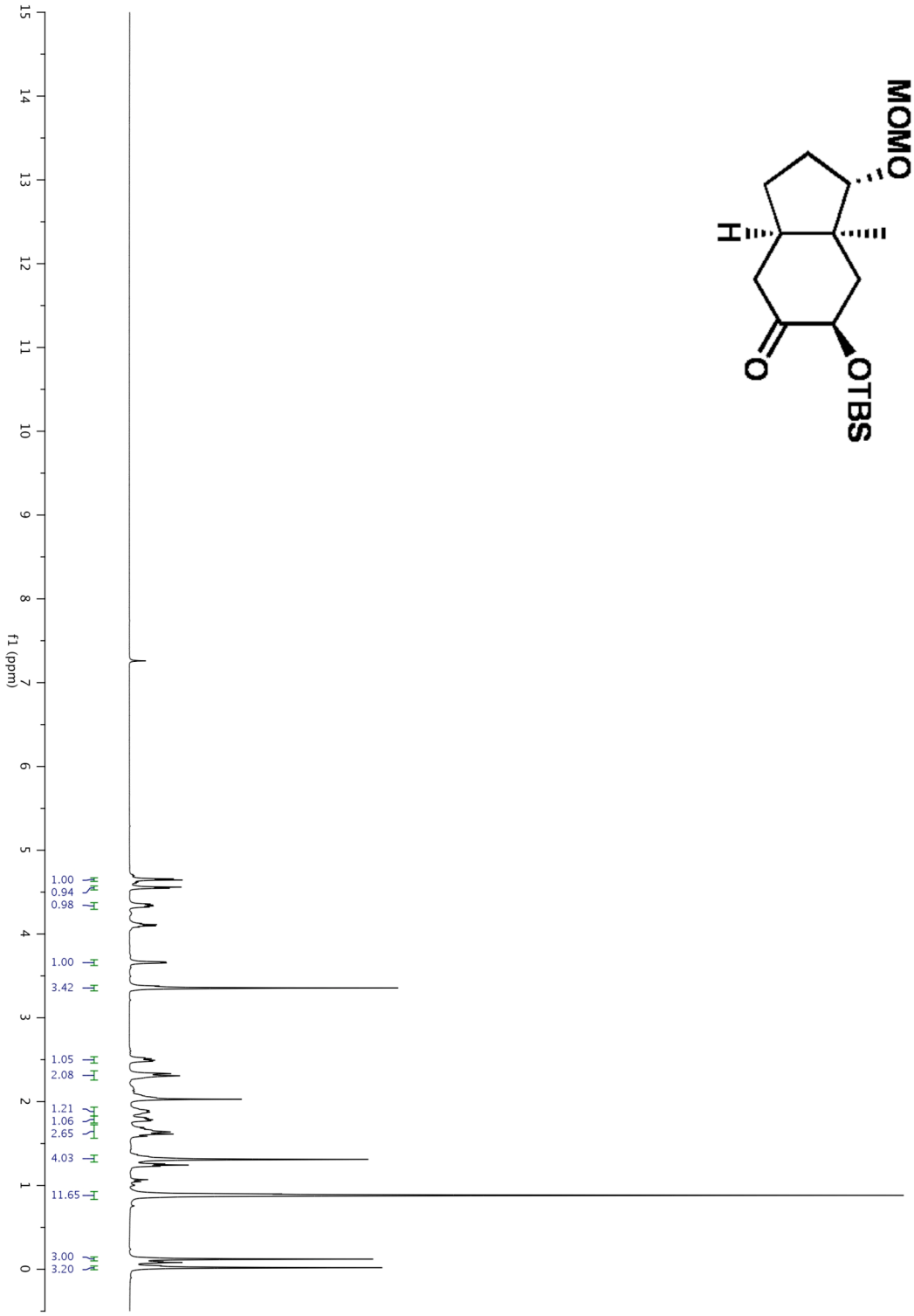
2.9. References and Notes

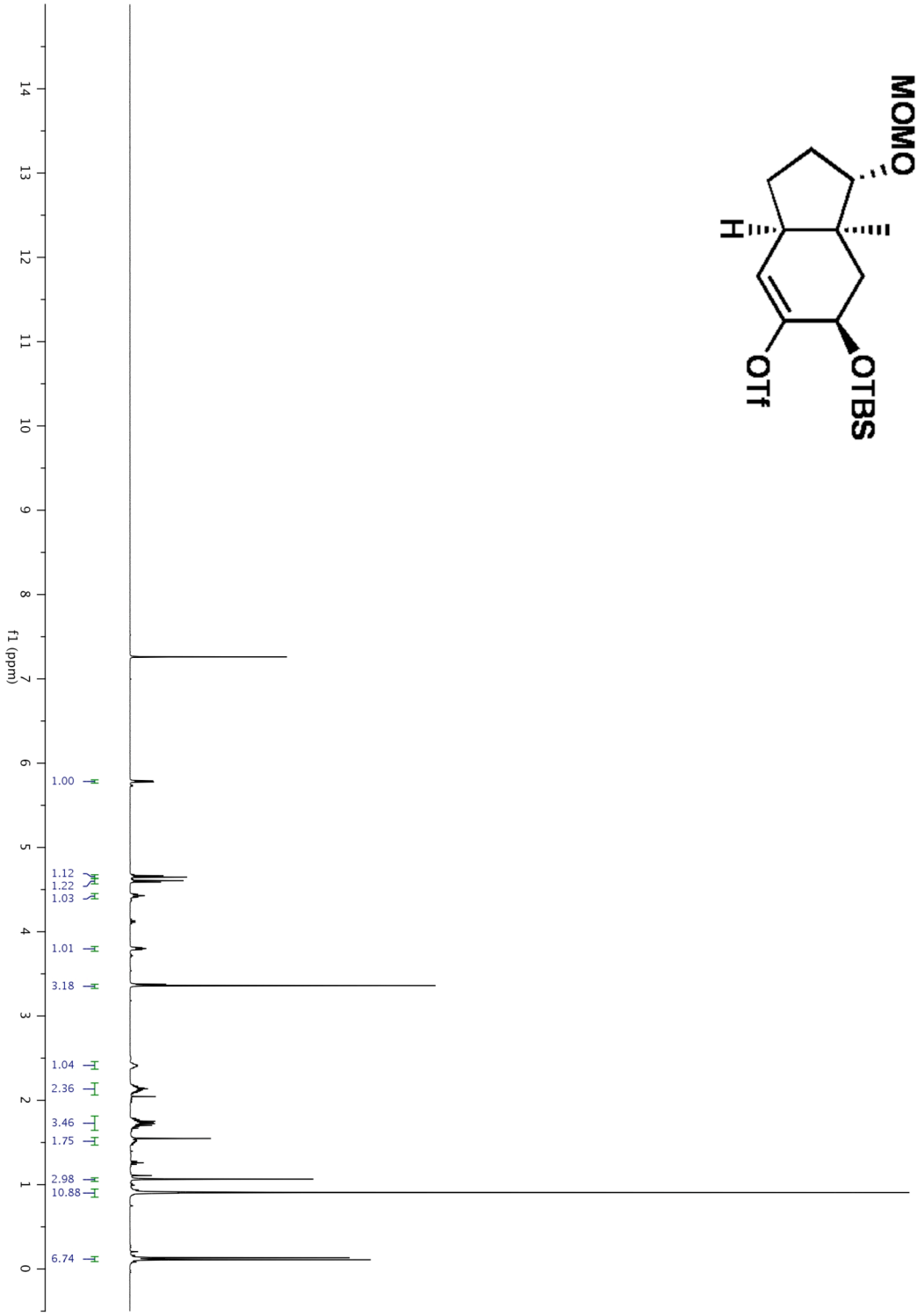
(1) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1990**, *Collect. Vol. VII*, 363.
(2) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1.
(3) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091.
(4) Rubottom, G. M.; Vazquez, M. A.; Pelegrin, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.
(5) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1998**, *Collect. Vol. IX*, 165.
(6) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.
(7) Sheppard, G. S.; Wang, J. Y.; Kawai, M.; Fidanze, S. D.; BaMaung, N. Y.; Erickson, S. A.; Barnes, D. M.; Tedrow, J. S.; Kolaczkowski, L.; Vasudevan, A.; Park, D. C.; Wang, G. T.; Sanders, W. J.; Mantei, R. A.; Palazzo, F.; Tucker-Garcia, L.; Lou, P. P.; Zhang, Q.; Park, C. H.; Kim, K. H.; Petros, A.; Olejniczak, E.; Nettesheim, D.; Hajduk, P.; Henkin, J.; Lesniewski, R.; Davidsen, S. K.; Bell, R. L. *J. Med. Chem.* **2006**, *49*, 3832.
(8) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508.
(9) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
(10) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.
(11) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575.
(12) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.
(13) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.
(14) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.
(15) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
(16) Ollivier, C.; Bark, T.; Renaud, P. *Synthesis-Stuttgart* **2000**, 1598.
(17) Grainger, R. S.; Innocenti, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3445.
(18) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002.

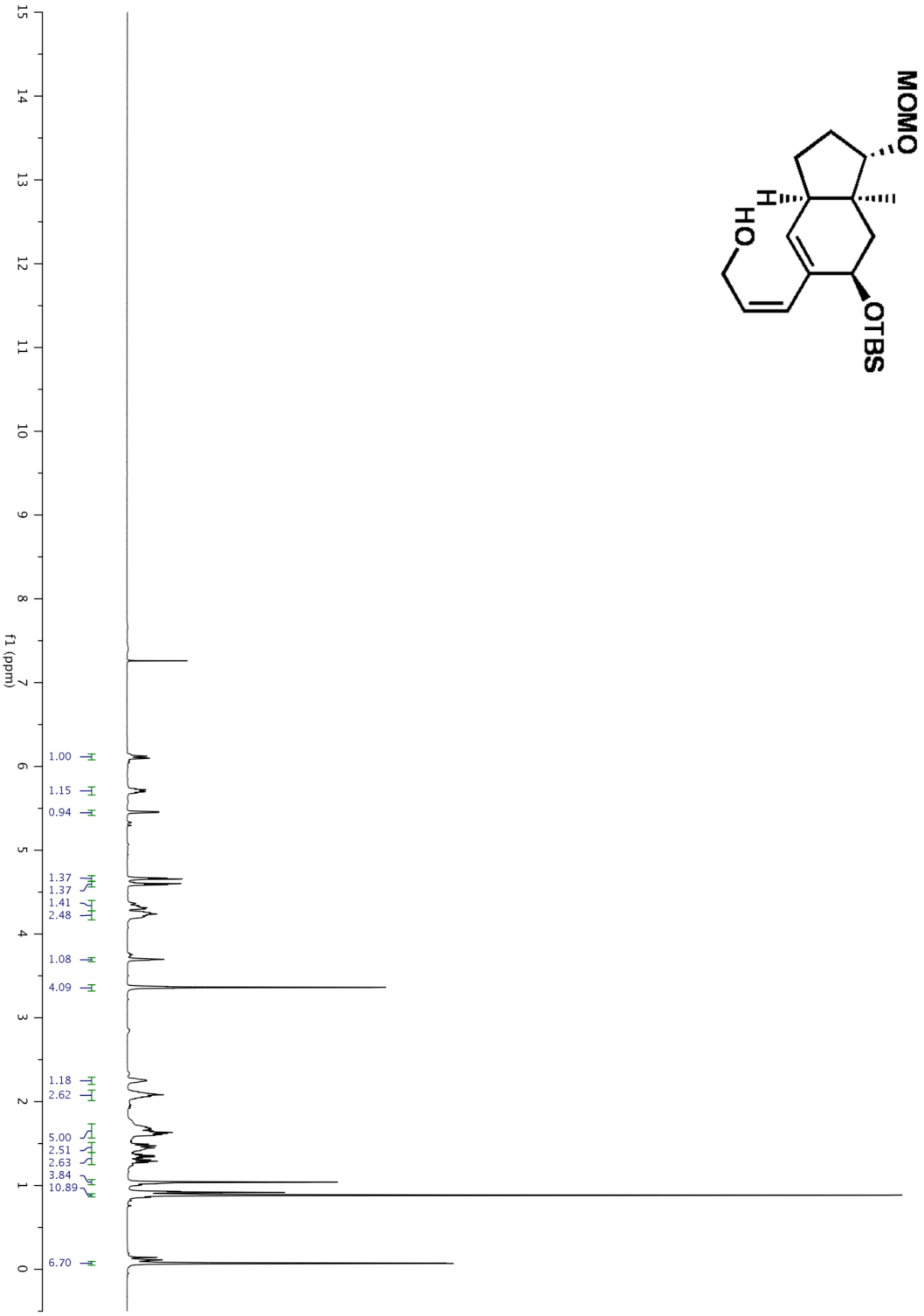
Appendix 1
Spectra Relevant to Chapter 2

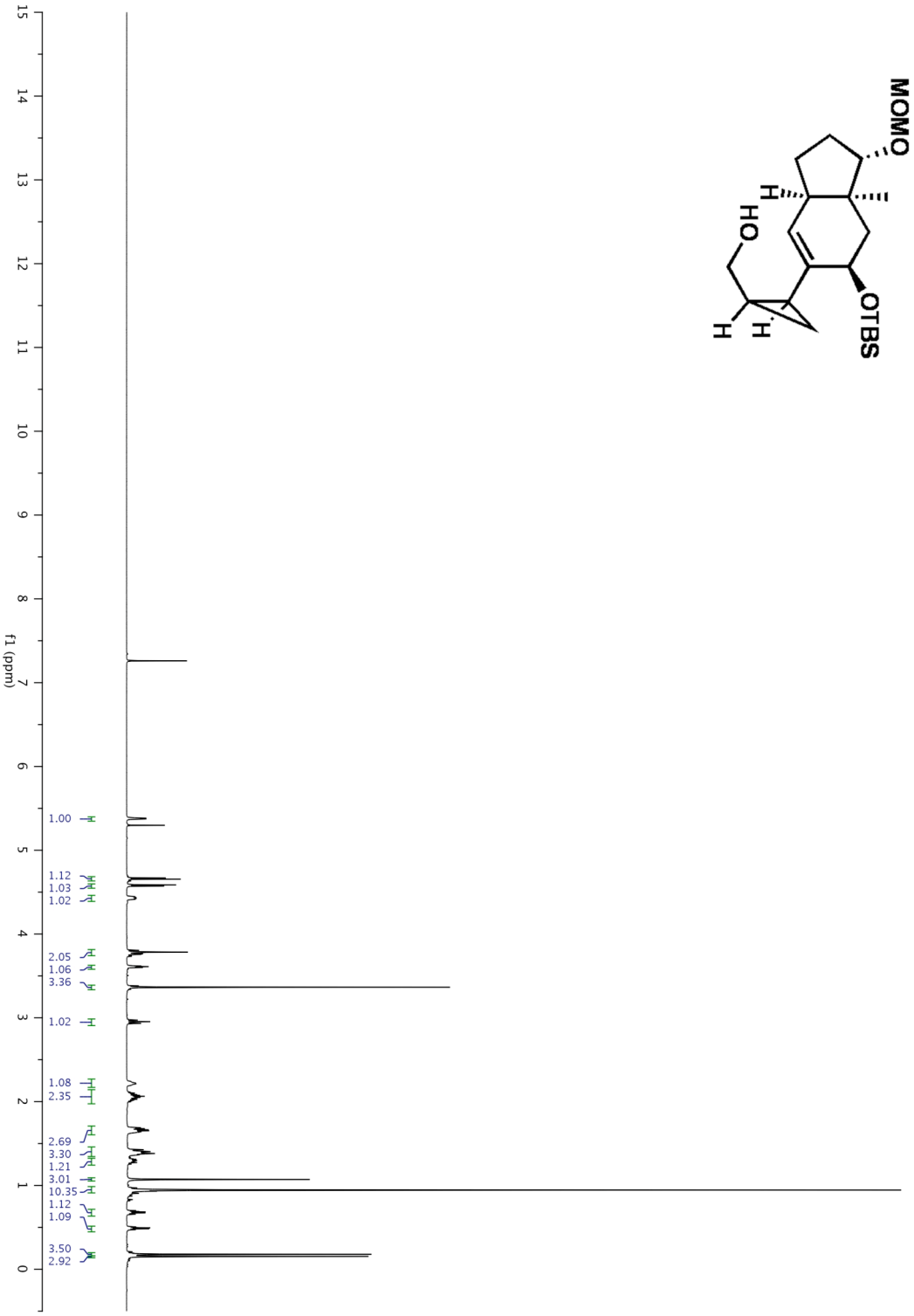

MOMO
OH
O
f1 (ppm)
1.00
3.63
1.16
1.70
3.47
1.76
1.26
1.91
2.29
2.03
4.11

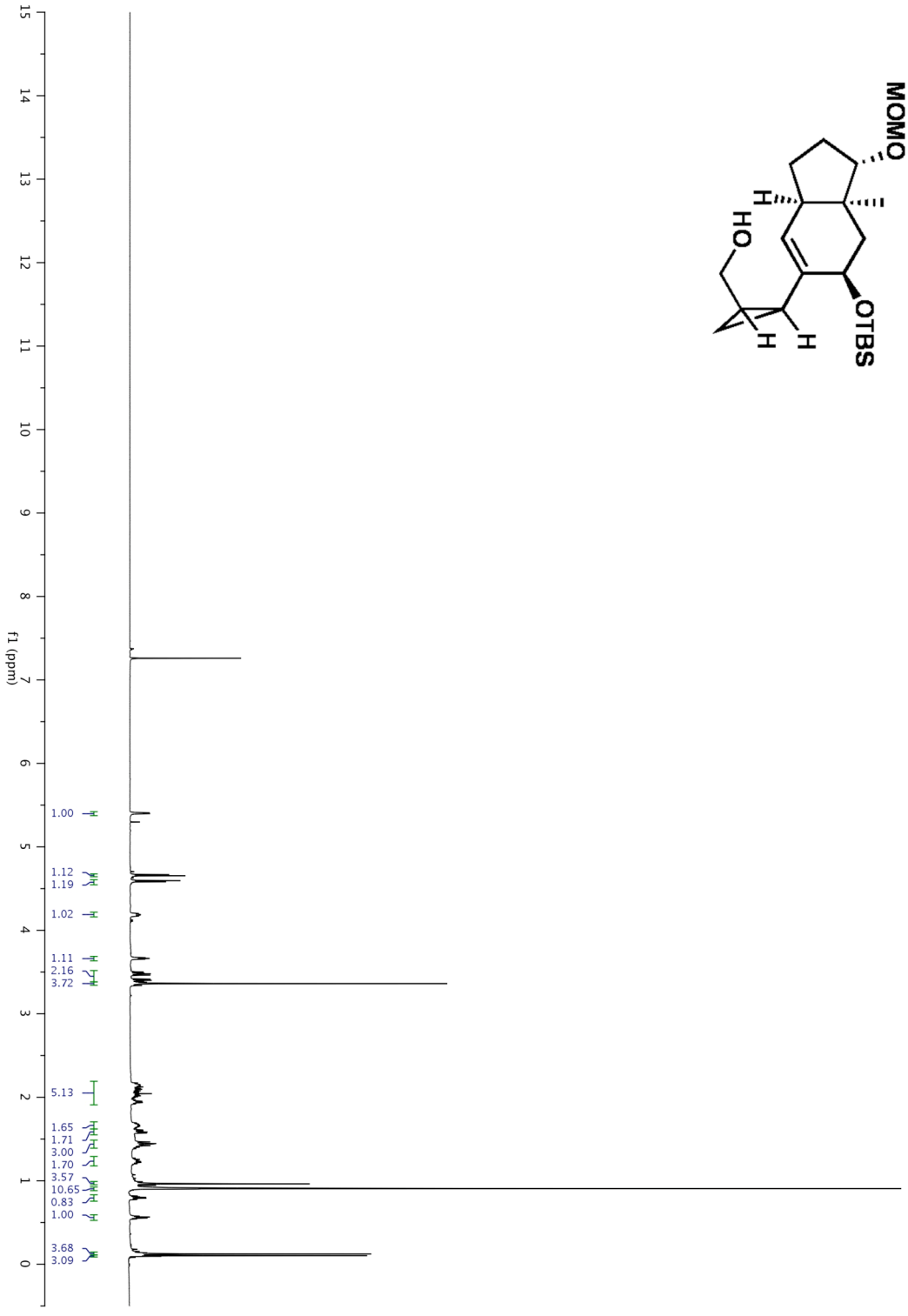

MOMO
OTBS
O
f1 (ppm)
1.00
2.14
1.05
1.07
3.10
1.09
2.09
1.11
2.18
3.10
9.35
3.08
3.11

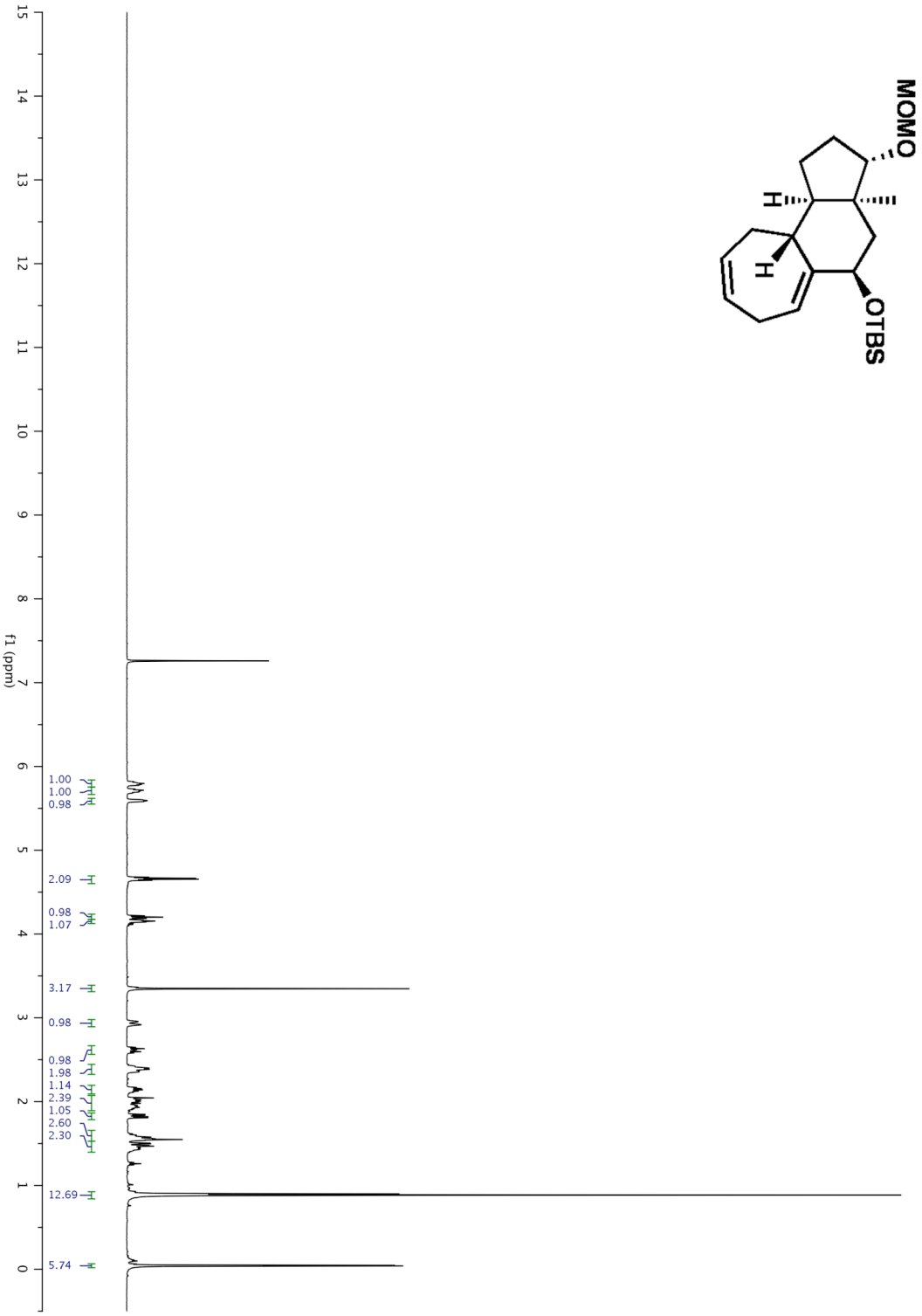

MOMO
H
O
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
0.94
0.98
1.00
3.42
1.05
2.08
1.21
1.06
2.65
4.03
11.65
3.00
3.20

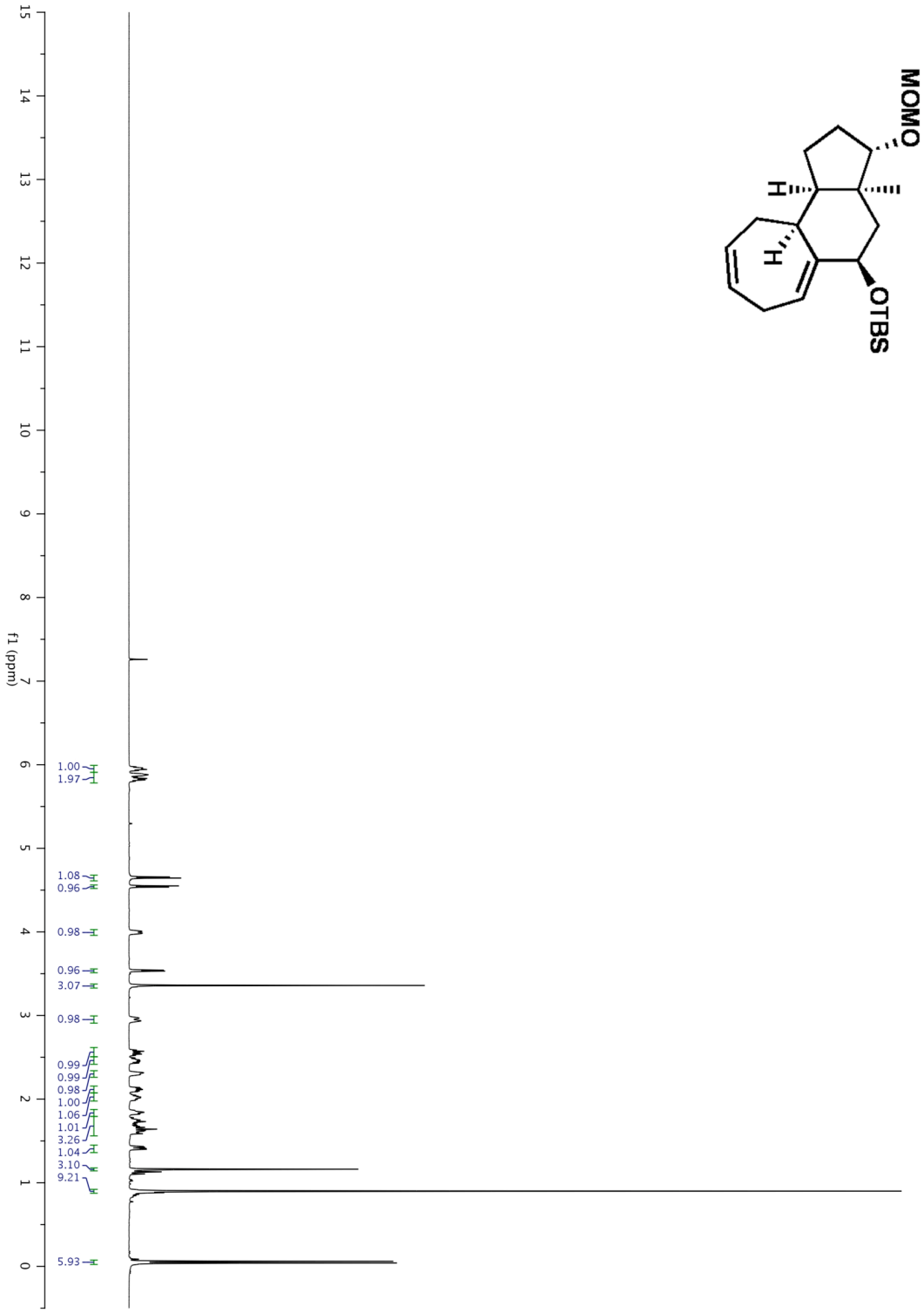

MOMO
H
OTf
OTBS
f1 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.00
1.12
1.22
1.03
1.01
3.18
1.04
2.36
3.46
1.75
2.98
10.88
6.74

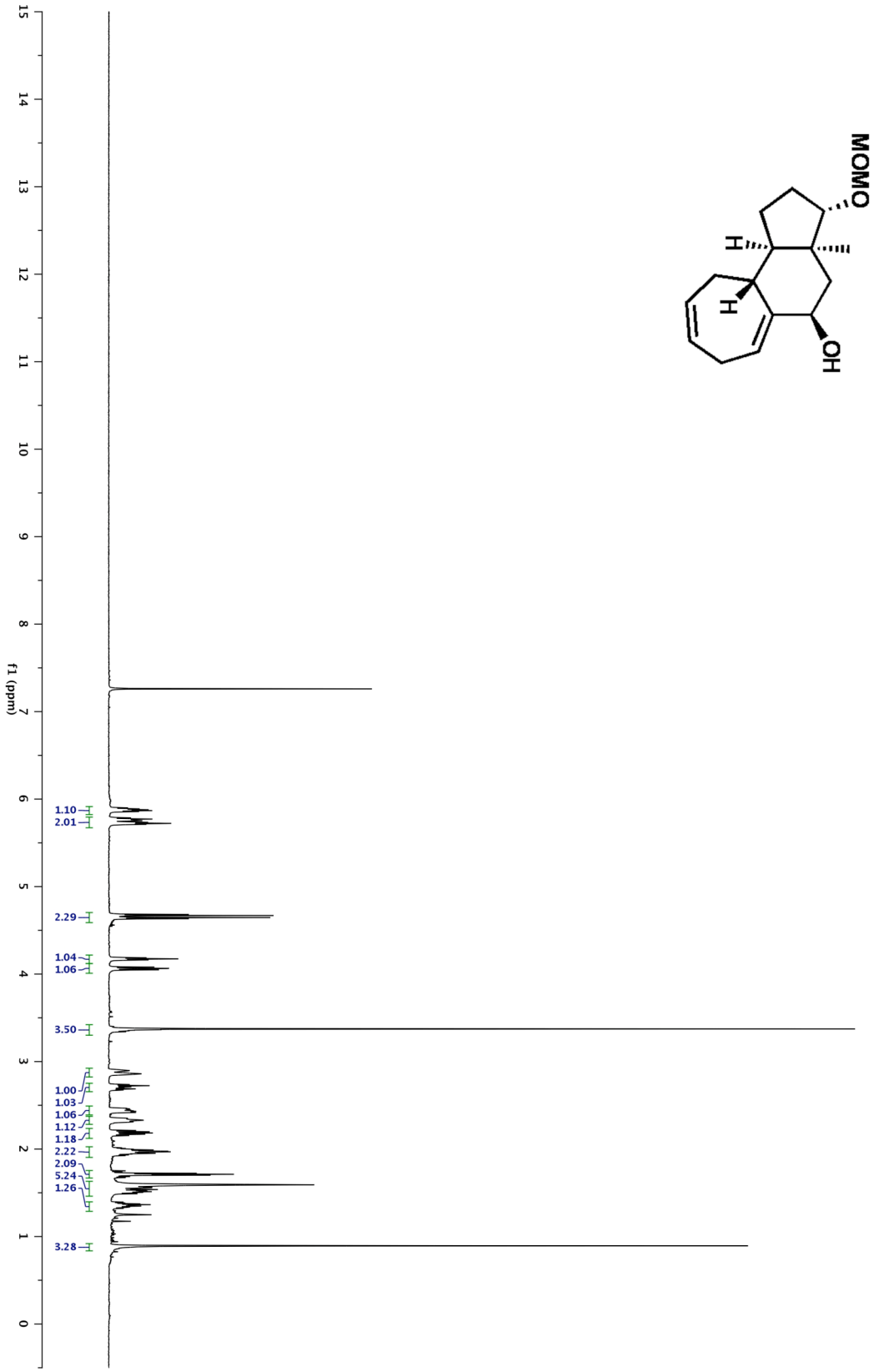

MOMO
H
HO
OTBS
f1 (ppm)
1.00
1.15
0.94
1.37
1.37
1.41
2.48
1.08
4.09
1.18
2.62
5.00
2.51
2.63
3.84
10.89
6.70

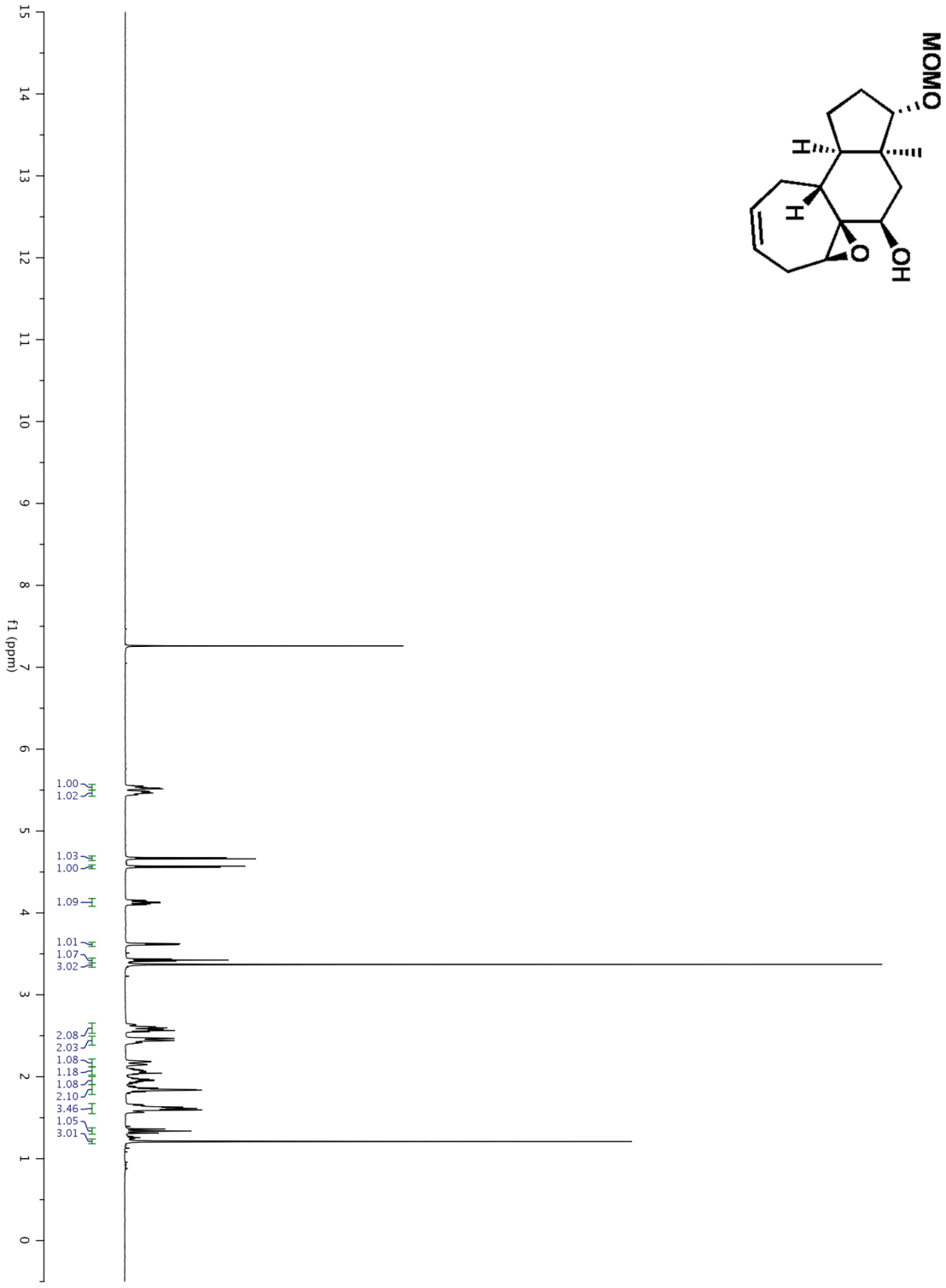

MOMO
H
OH
H
H
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.12
1.03
1.02
2.05
1.06
3.36
1.02
1.08
2.35
2.69
3.30
1.21
3.01
10.35
1.12
1.09
3.50
2.92

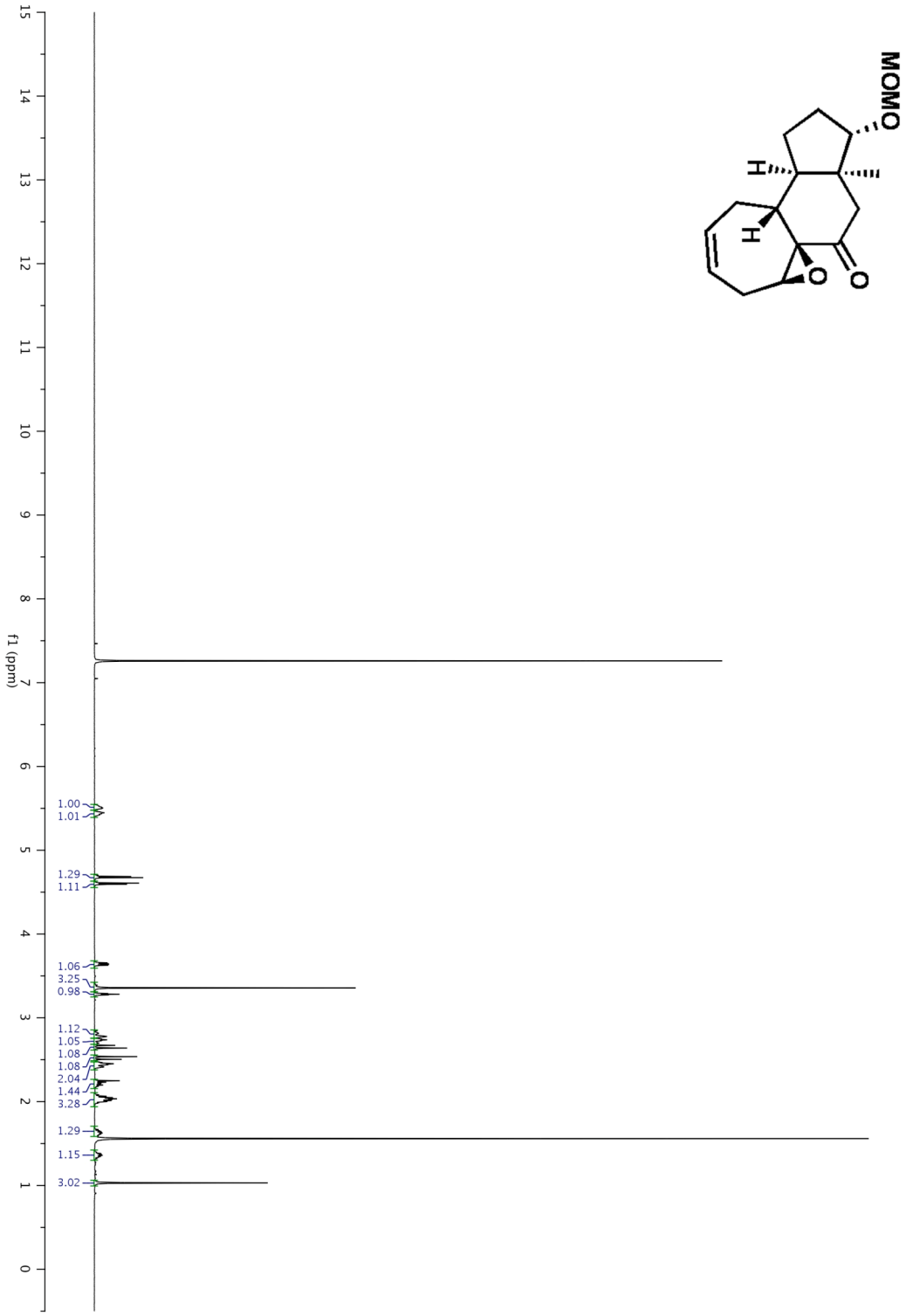

MOMO
H
HO
H
H
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.12
1.19
1.02
1.11
2.16
3.72
5.13
1.65
1.71
3.00
1.70
3.57
10.65
0.83
1.00
3.68
3.09

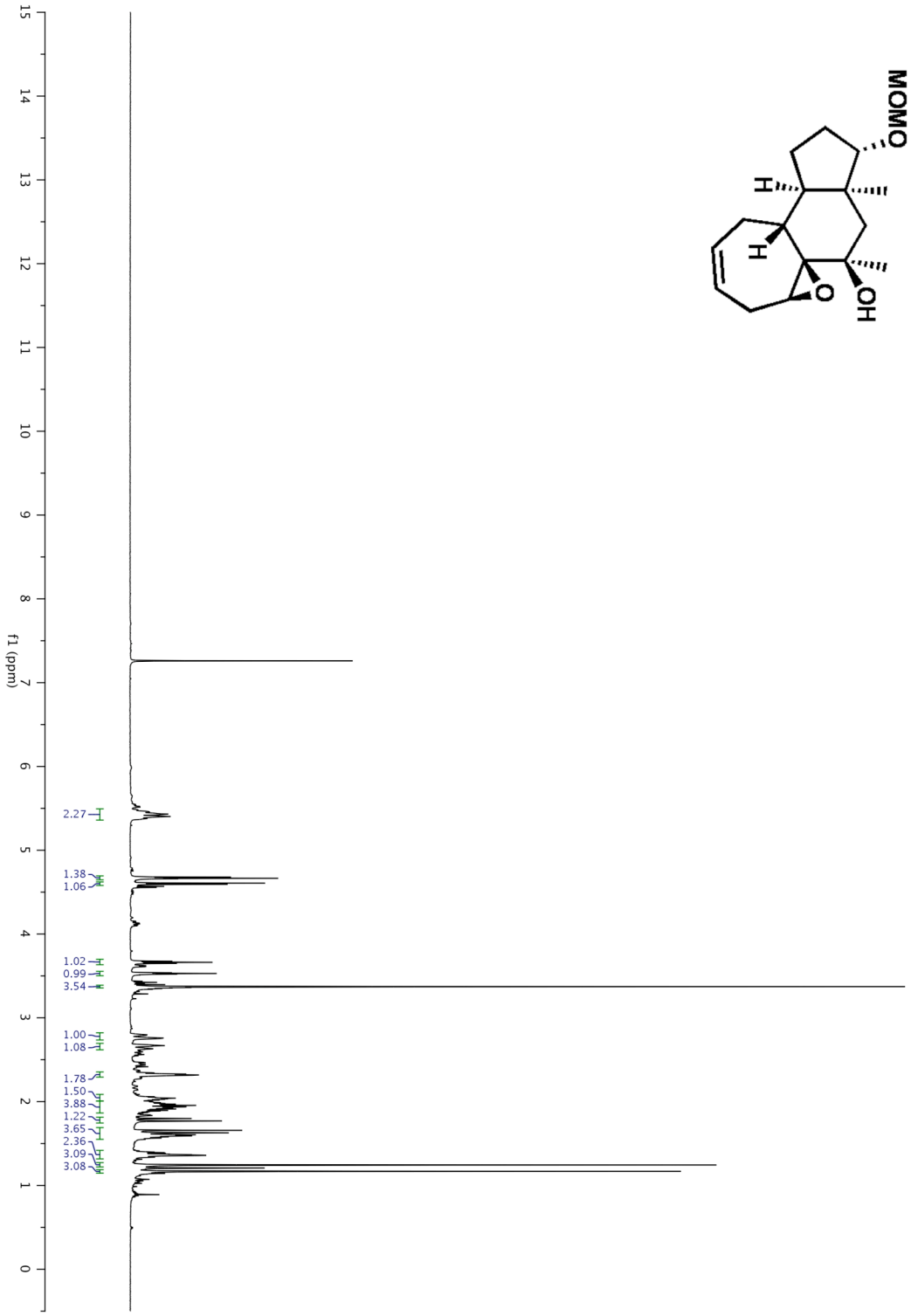

MOMO
H
H
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.00
0.98
2.09
0.98
1.07
3.17
0.98
0.98
1.98
1.14
2.39
1.05
2.60
2.30
12.69
5.74

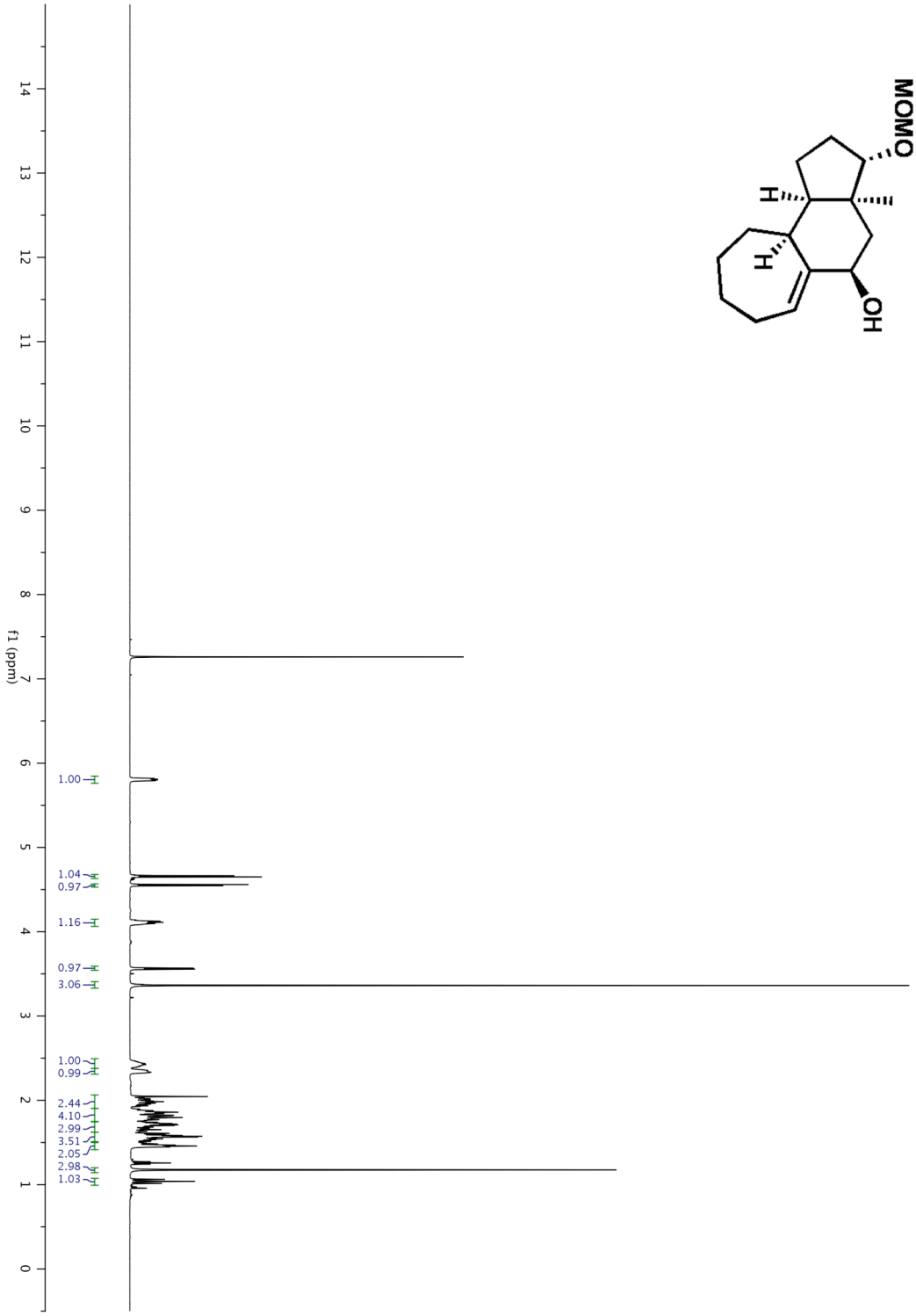

MOMO
H
H
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.97
1.08
0.96
0.98
0.96
3.07
0.98
0.99
0.99
0.98
1.00
1.06
1.01
3.26
1.04
3.10
9.21
5.93

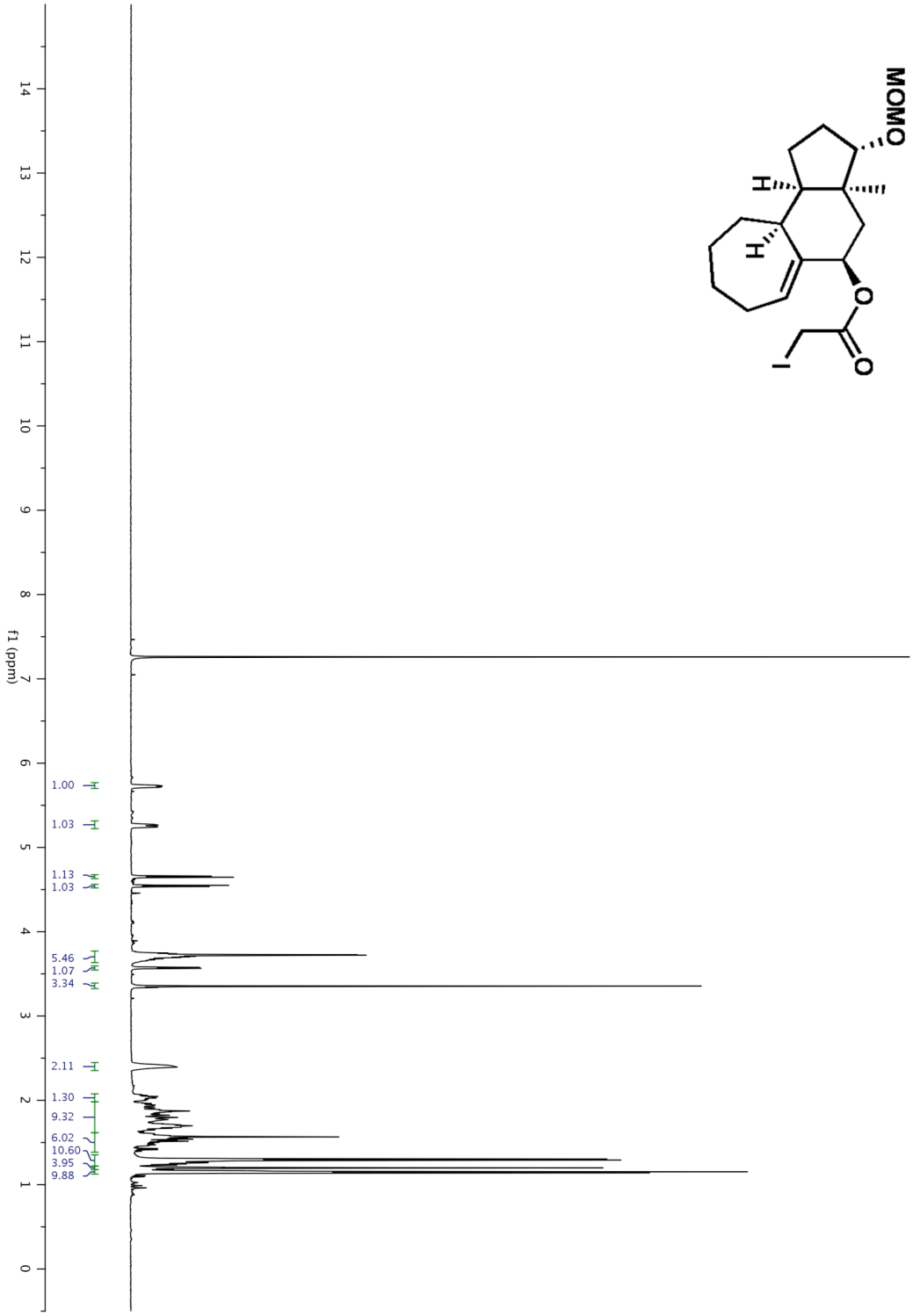

MOMO
H
H
OH
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.10
2.01
2.29
1.04
1.06
3.50
1.00
1.03
1.06
1.12
1.18
2.22
2.09
5.24
1.26
3.28

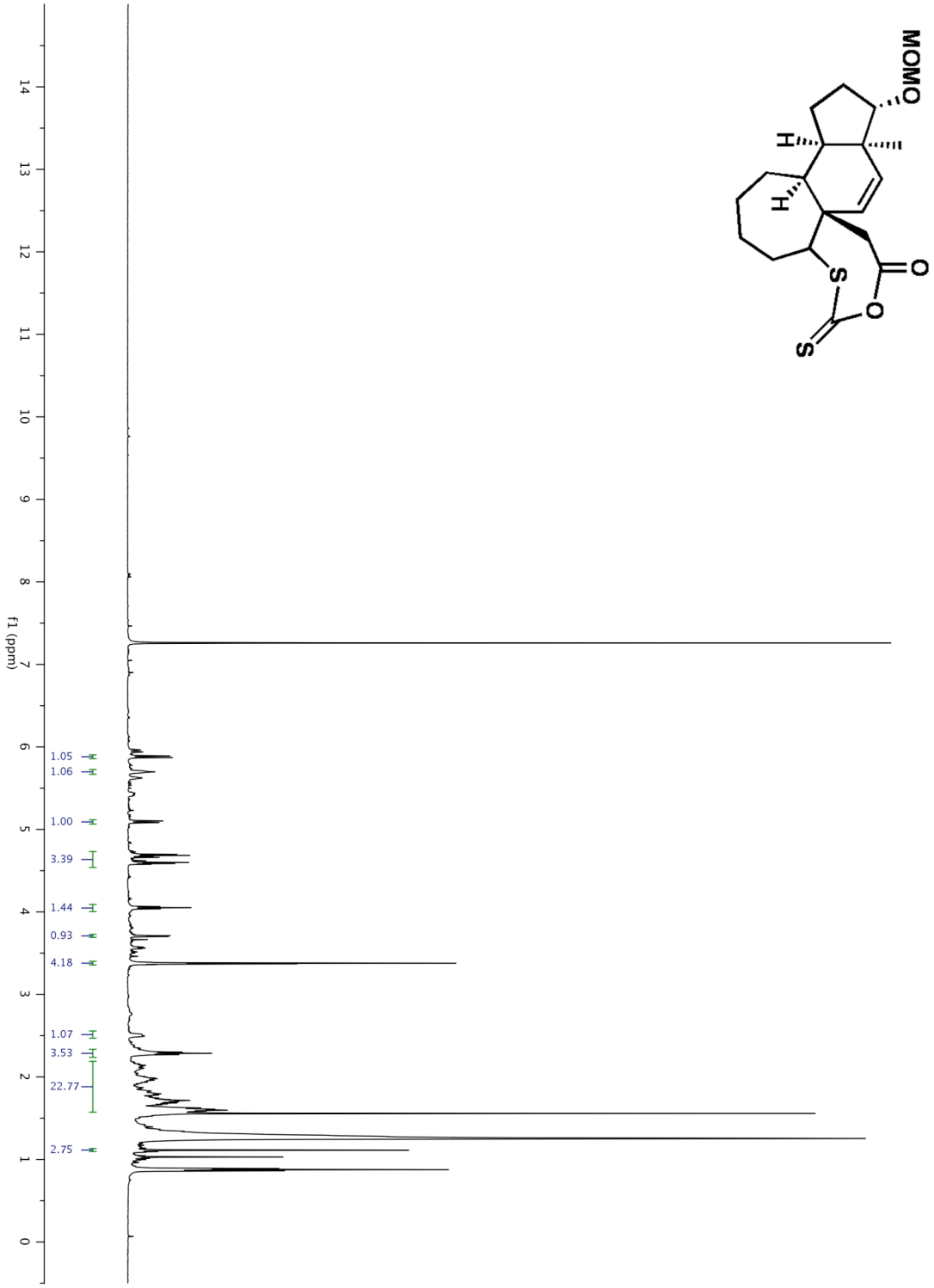

MOMO
H
H
O
OH
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.02
1.03
1.00
1.09
1.01
1.07
3.02
2.08
2.03
1.08
1.18
1.08
2.10
3.46
1.05
3.01

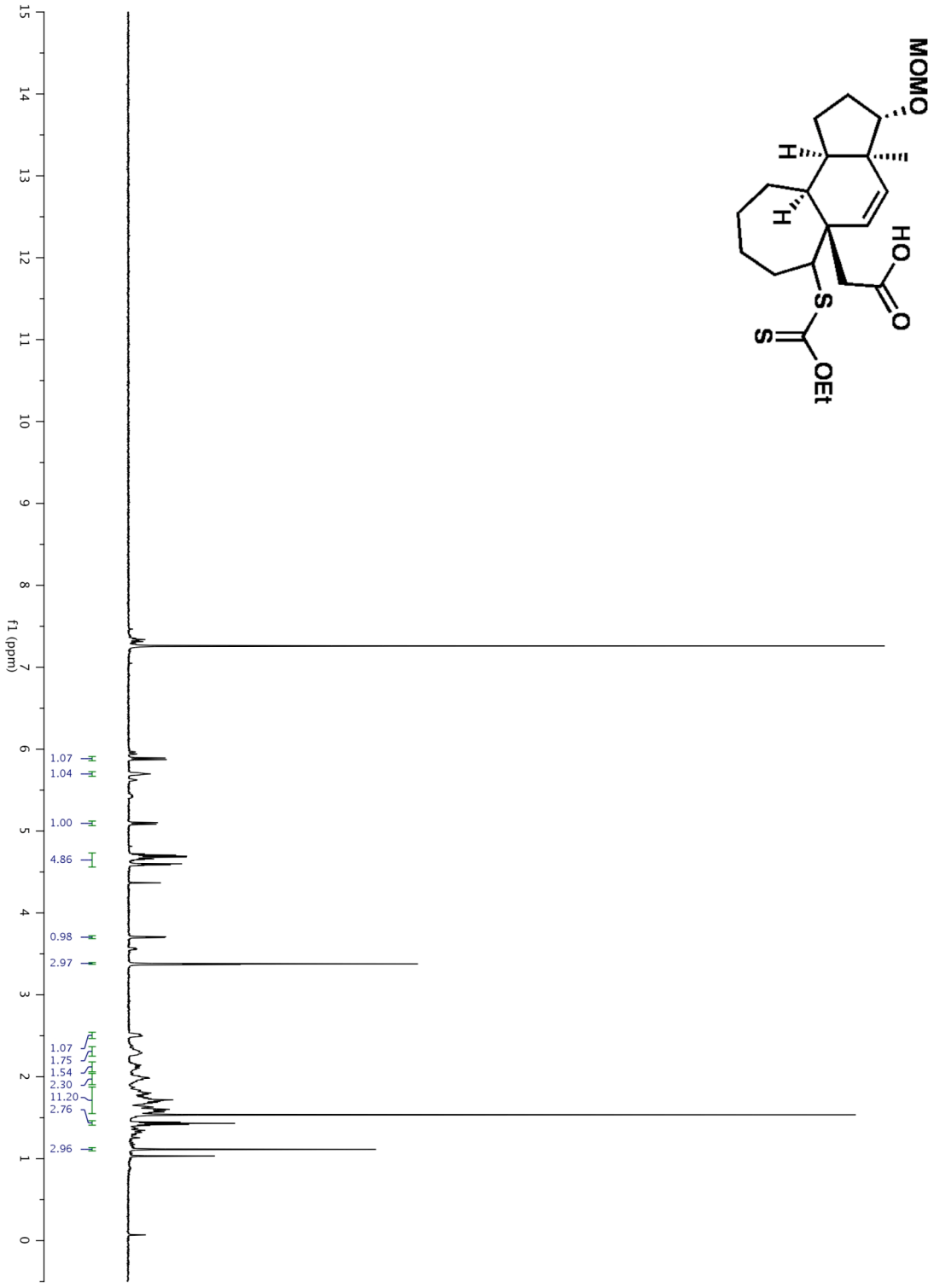

MOMO
H
H
O
O
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.01
1.29
1.11
1.06
3.25
0.98
1.12
1.05
1.08
1.08
2.04
1.44
3.28
1.29
1.15
3.02


MOMO
H
H
O
OH
f1 (ppm)
2.27
1.38
1.06
1.02
0.99
3.54
1.00
1.08
1.78
1.50
3.88
1.22
3.65
2.36
3.09
3.08


MOMO
H
H
OH
f1 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.00
1.04
0.97
1.16
0.97
3.06
1.00
0.99
2.44
4.10
2.99
3.51
2.05
2.98
1.03


MOMO
H
H
O
O
I
f1 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.00
1.03
1.13
1.03
5.46
1.07
3.34
2.11
1.30
9.32
6.02
10.60
3.95
9.88


MOMO
H
H
S
S
O
O
f1 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.05
1.06
1.00
3.39
1.44
0.93
4.18
1.07
3.53
22.77
2.75


MOMO
H
H
HO
O
S
S
OEt
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.07
1.04
1.00
4.86
0.98
2.97
1.07
1.75
1.54
2.30
11.20
2.76
2.96

Chapter 3
Second Generation Rhodium-Carbenoid Approach to the Tricyclic Core

3.1. Introduction

Our initial strategy fell short of selectively targeting the cyanthiwigin diterpenes, thus we sought a highly diastereoselective cyclopropanation reaction to achieve our goal of developing a general approach to the cyanthiwigin and cyathane families of natural products. The rhodium-mediated decomposition of diazo reagents drew our attention as a potential contender for this role.[1] If the rhodium-carbenoid cyclopropanation proved to have excellent stereoselectivity with our substrate, we realized we also had the opportunity to carry out a resolution en route to the cyanthiwigin and cyathane diterpenes.

3.2. Divergent Reactions on Racemic Mixtures

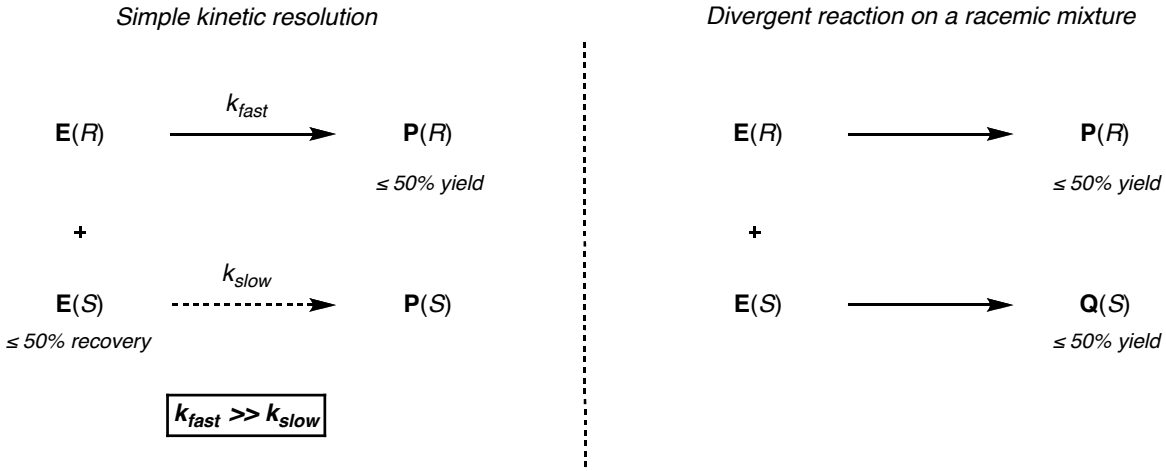
A resolution is "the separation of a racemic mixture into its individual component enantiomers," as defined by Anslyn and Dougherty.[2] Resolutions have been performed since the mid-19th century, and began after Pasteur's discovery of chirality. Pasteur performed the first physical resolution by separating the enantiomers of tartrate under the microscope based on their different crystal forms. In later work, Pasteur also carried out the first simple kinetic resolution, whereby he fed *Penicillium glaucum* racemic ammonium tartrate, and found that he was left with enantioenriched starting material, since the fungus metabolized a single enantiomer of the ammonium tartrate.[3]

Simple kinetic resolutions rely on a difference in reaction rates between enantiomers to obtain enantioenriched material. A chiral, non-racemic agent reacts with one enantiomer (e.g., E(*R*), Fig. 3.2.1) more quickly than with the antipode (e.g., E(*S*)). The selectivity factor (*s*) is defined as the ratio of the rates of these two reactions (eq 1). With no selectivity ($s = 1$), a racemic mixture of products would be formed. In an ideal scenario, with a large rate difference

$$s = k_{fast} / k_{slow} \qquad \textbf{(1)}$$

(e.g., $s \geq 200$), one could obtain enriched product in a 50% yield, as well as enriched starting material in 50 % recovery. A disadvantage of this strategy is that to obtain high yields of each compound (~50%) with excellent enantioenrichment (≥ 95% *ee*), extremely high selectivity factors ($s \geq 200$) are required, which are difficult to achieve.[4]

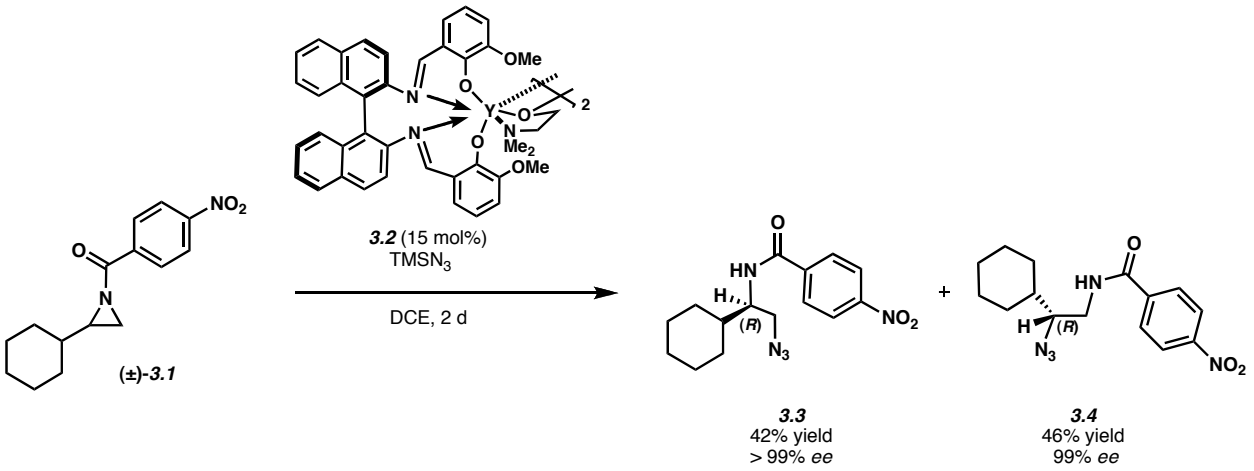
Figure 3.2.1. Simple kinetic resolution versus a divergent reaction on a racemic mixture.



One way to avoid the necessity for exquisite selectivity factors is to use a divergent reaction on a racemic mixture (divergent RRM) approach.[3,5] In this strategy, both enantiomers react with a chiral reagent at similar rates to form separable, non-enantiomeric products (e.g., P(*R*) and Q(*S*), Fig. 3.2.1). With excellent reagent control, both products can be formed in high yields (up to 50%) and enantiomeric enrichment. Unlike simple kinetic resolutions, the relative rates do not matter as long as there is complete reagent control.[3] It is important to note that this definition of divergent RRMs encompasses a variety of transformations that do not necessarily involve a kinetic resolution (e.g., Scheme 4.3.3). Of the reactions that do employ kinetic resolutions, there are three general categories of divergent RRMs: regiodivergent, structurally divergent and stereodivergent.

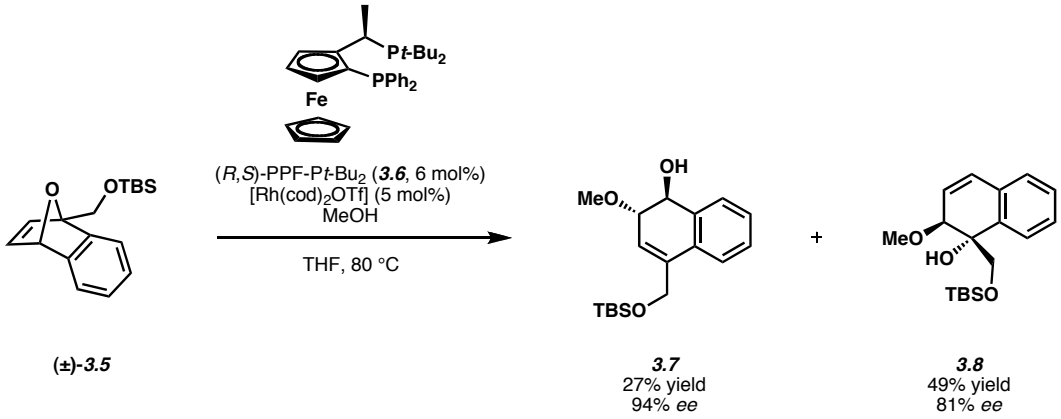
Employment of a regiodivergent RRM provides two enriched, regioisomeric products. A variety of reaction modalities fit into this category. For example, using a chiral yttrium-salen complex (**3.2**, Scheme 3.2.1), Parquette and RajanBabu were able to effect the opening of aziridines (e.g., **3.1**) to form enantioenriched 1,2-diamine regioisomers (**3.3** and **3.4**).[6] The (*R*)-enantiomer of **3.1** is attacked at the methylene by trimethylsilylazide yielding diamine derivative **3.3**, whereas the (*S*)-enantiomer undergoes reaction at the chiral center with inversion to afford regioisomer **3.4**.

Scheme 3.2.1. Regiodivergent opening of aziridines by Parquette and RajanBabu.[6]



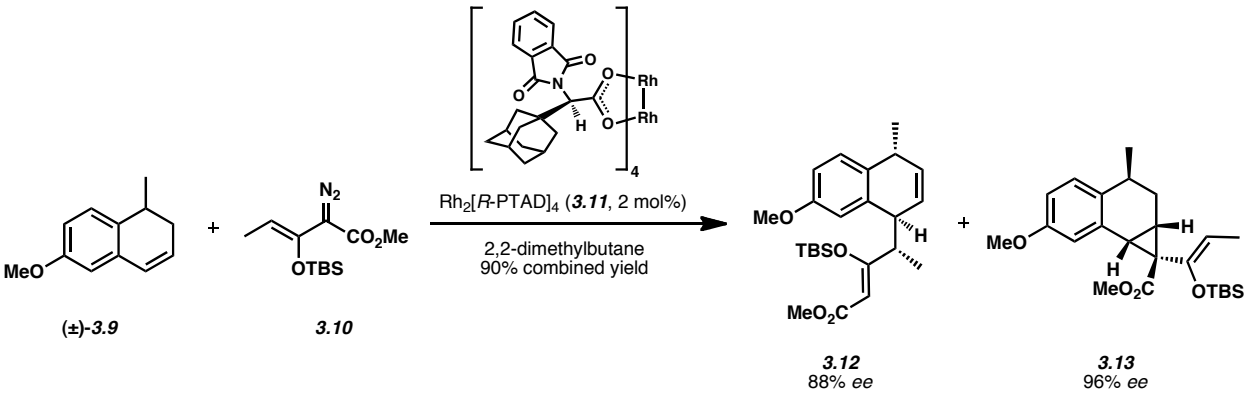
Lautens and coworkers demonstrated a rhodium-catalyzed regiodivergent RRM for the synthesis of differentially disubstituted 1,2-dihydronaphthalene products (Scheme 3.2.2).[7] In the presence of ferrocene ligand **3.6**, rhodium inserts into oxabicycle **3.5** regioselectively, followed by the addition of a nucleophile (e.g., methanol), to form two enriched hydroxy-dihydronapthalene substrates (**3.7** and **3.8**).

Scheme 3.2.2. Lautens' regiodivergent hydroxy-dihyronaphthalene synthesis.[7]



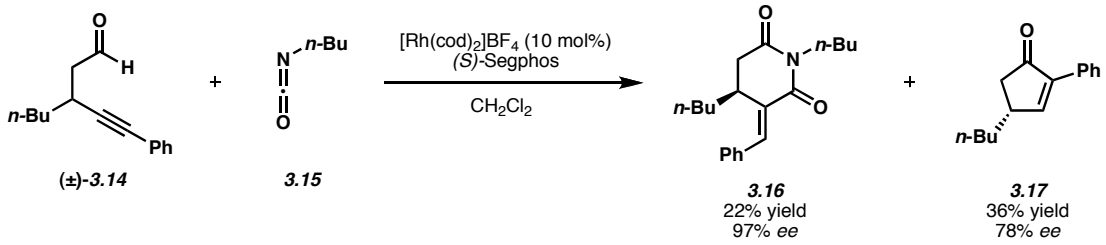
In a structurally divergent RRM, two different products are formed from the racemic starting material. The products do not have to be isomers, but often are, as in an example by Davies (Scheme 3.2.3).[8] The rhodium carbenoid formed from diazoacetate **3.10** reacts with a single enantiomer of dihydronapthalene **3.9** via C-H insertion/Cope rearrangement to form siloxy enoate **3.12** in 88% *ee*. The antipode is cyclopropanated to form fused tricycle **3.13** in 96% *ee*.

Scheme 3.2.3. Structurally divergent reaction of dihydronaphthalenes by Davies.[8]



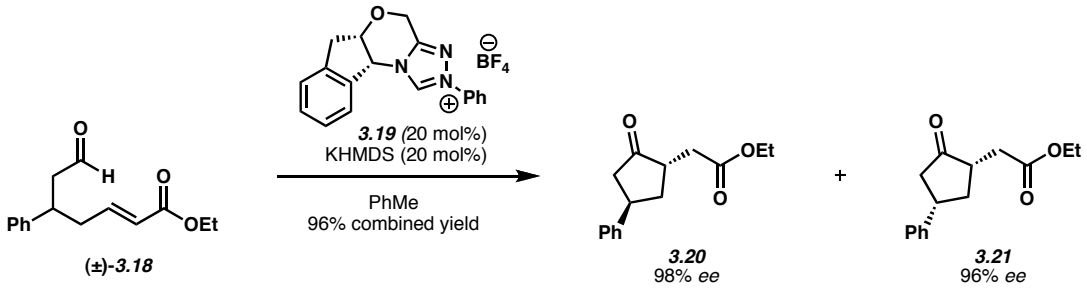
An example of employing a structurally divergent RRM to form non-isomeric products from **3.14** and **3.15** was carried out by Tanaka and coworkers (Scheme 3.2.4).[9] After insertion by a rhodium catalyst into the aldehydic C-H bond, the (*S*)-enantiomer of **3.14** undergoes a [4+2] annulation with **3.15** to form 2-alkylideneglutarimide **3.16**, whereas the (*R*)-enantiomer of **3.14** reacts intramolecularly to form cyclopentenone **3.17**.

Scheme 3.2.4. Tanaka's structurally divergent reactions of 4-alkynals.[9]



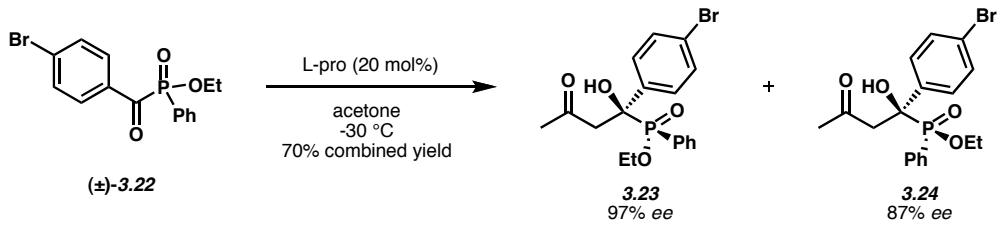
A stereodivergent RRM strategy generally utilizes a racemic starting material possessing resident stereocenters. In the divergent step, a new stereocenter is made via reagent control independent of the resident stereocenters. The products formed are diastereomers and must be easily separable if the method is to be useful. In practice, this aspect can be difficult to achieve. For example, Rovis demonstrated a stereodivergent RRM to form disubstituted cyclopentanones via a Stetter reaction (Scheme 3.2.5).[10] Each diastereomer (**3.20** and **3.21**) was produced in high yield and enantioenrichment, however the products were inseparable, limiting the utility of the resolution.

Scheme 3.2.5. Stereodivergent Stetter reaction by Rovis.[10]



Separation difficulties also plagued Zhao and coworkers in their synthesis of α-hydroxyphosphinates (Scheme 3.2.6).[11] Although the proline-catalyzed aldol reaction of racemic phosphinates (e.g., **3.22**) with acetone was successful, the products were generally formed as mixtures that were inseparable by flash chromatography. However, substrates **3.23** and **3.24** could be separated through recrystallization.

Scheme 3.2.6. Zhao's stereodivergent approach to α-hydroxyphosphinates.[11]

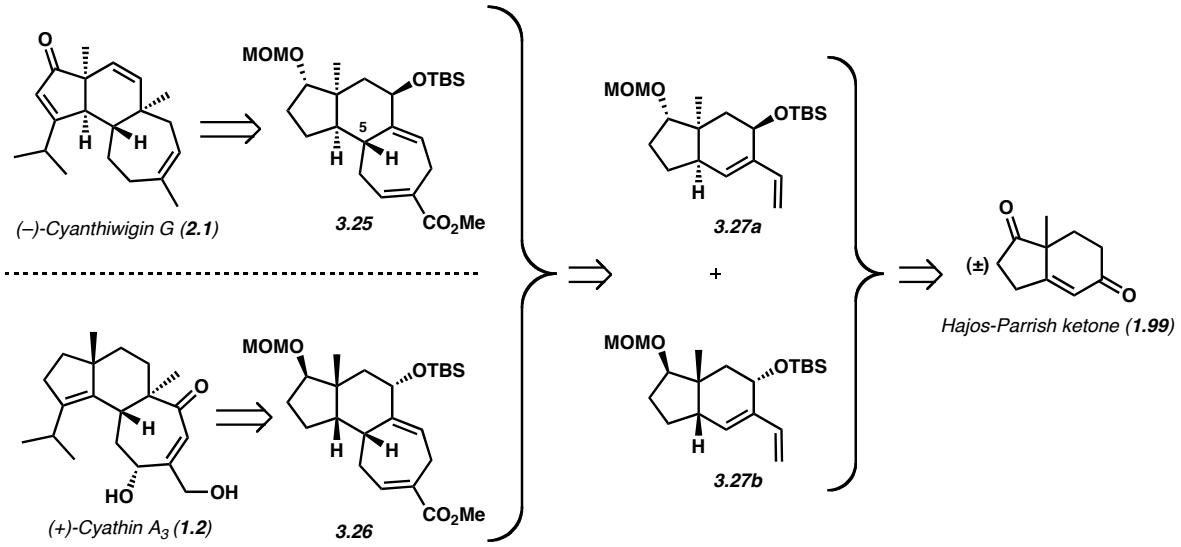


Despite potential separation issues, stereodivergent RRMs are a powerful way to resolve intermediates with resident stereocenters. It is this approach that we intended to utilize in our strategy toward the cyanthiwigins and cyathanes.

3.3. Alternative Retrosynthesis

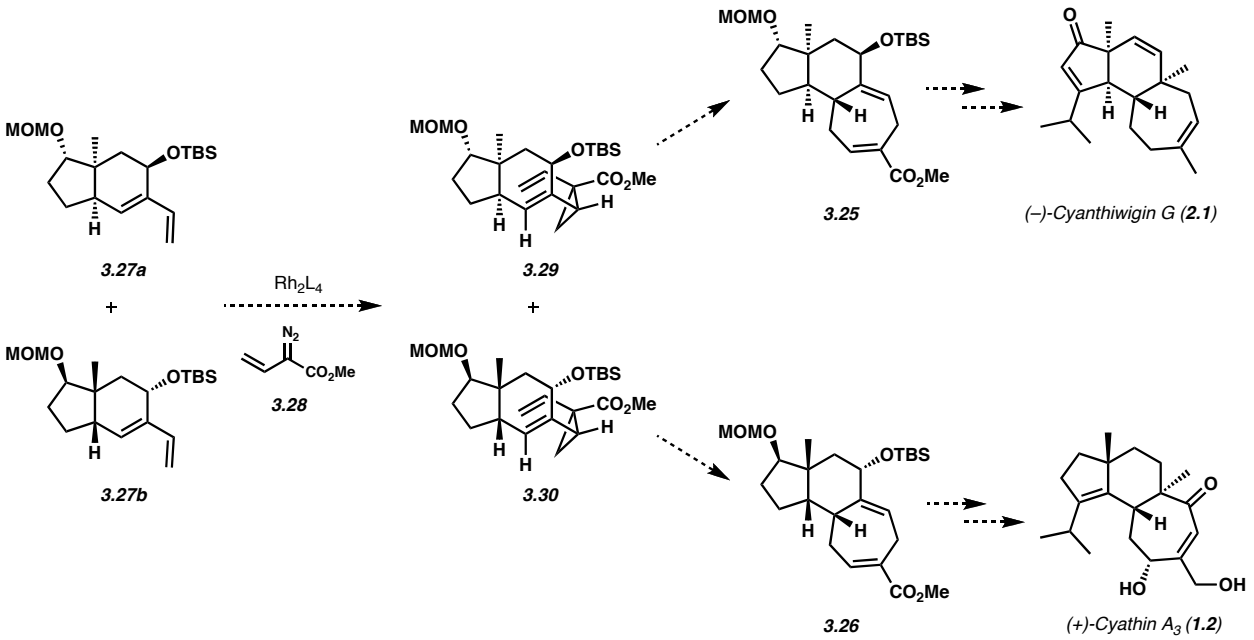
In our second-generation approach, which was to take advantage of stereodivergent RRM, we envisioned the naturally-occurring enantiomers of cyanthiwigin G (**2.1**) and cyathin A_3 (**1.2**) arising from pseudoenantiomeric tricycles **3.25** and **3.26**, which share a common stereocenter at C5 (Scheme 3.3.1). The seven-membered ring could be constructed from racemic diene **3.27** using a stereodivergent RRM. Finally, the diene could be derived from the racemic Hajos-Parrish ketone (**1.99**).

Scheme 3.3.1. Second-generation retrosynthesis of the cyanthiwigin and cyathane diterpenoids.



Our previous strategy highlighted the importance of a diastereoselective cyclopropanation to be able to target both the cyanthiwigin and cyathane families of natural products. We therefore turned to the rhodium-mediated decomposition of a diazo reagent to carry out the cyclopropantion. Davies and others have shown that this process can be exquisitely stereoselective.[1,12-14] In our system, with excellent reagent control, we would be able to cyclopropanate from a single face of the racemic diene **3.27**, for example the α-face as shown in Scheme 3.3.2. Cope rearrangement would lead to two enantioenriched diastereomers (**3.25** and **3.26**), overall effecting a resolution via a stereodivergent RRM.

Scheme 3.3.2. Key stereodivergent cyclopropanation.



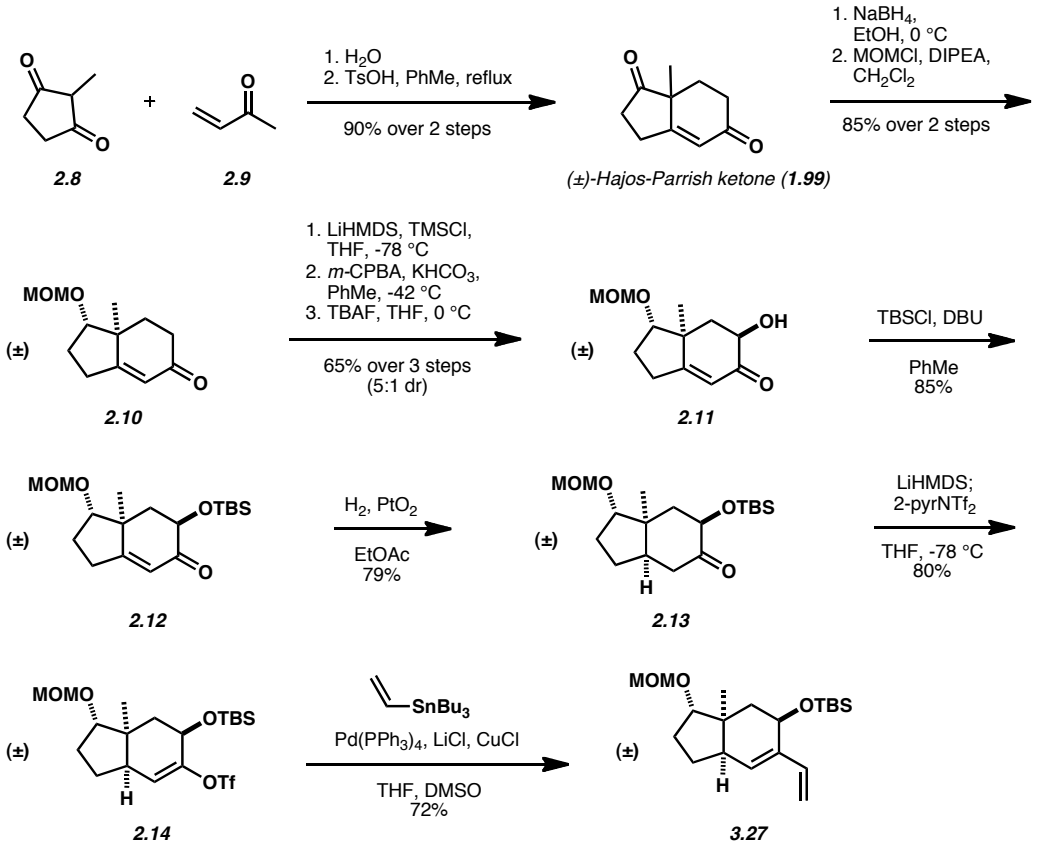
Our second-generation strategy has several benefits. First, each product of the stereodivergent RRM can be utilized toward the total synthesis of a naturally occurring antipode of a member of the cyanthiwigin (e.g., **2.1**) and cyathane (e.g., **1.2**) natural products. The use of both products avoids one of the classic drawbacks to a resolution: generally only a single product of a resolution is desired, and the other must be discarded, or at best, recycled. It is also an improvement over our initial strategy, which only targeted the naturally-occurring cyanthiwigins and the unnatural enantiomer of the cyathanes (or vice versa). With the current plan, we can now synthesize both natural or both unnatural antipodes. Additionally, the new route is more flexible due to the late-stage determination of the natural or unnatural enantiomeric series through catalyst choice at the cyclopropanation step, rather than making the decision based on the enantioenriched Hajos-Parrish ketone (see Chapter 2.2).

However, because the diene (**3.27**) is derived from the Hajos-Parrish ketone, we also have easy access to enriched diene (**3.27a** or **3.27b**) by starting from the corresponding enantioenriched Hajos-Parrish ketone. We therefore have the option of targeting only the cyanthiwigins (e.g., **3.27a** to **2.1**) or only the cyathanes (e.g., **3.27b** to **1.2**), committing all of the material to the desired pathway. Finally, the synthesis is streamlined by installing the second vinyl group in the cyclopropanation step, avoiding an additional oxidation and olefination sequence. The ester installed in the cyclopropanation can be transformed into the requisite functionality for the desired natural product (e.g., a methyl group for the cyanthiwigins; see **3.25** to **2.1**).

3.4. Construction of the Tricycle

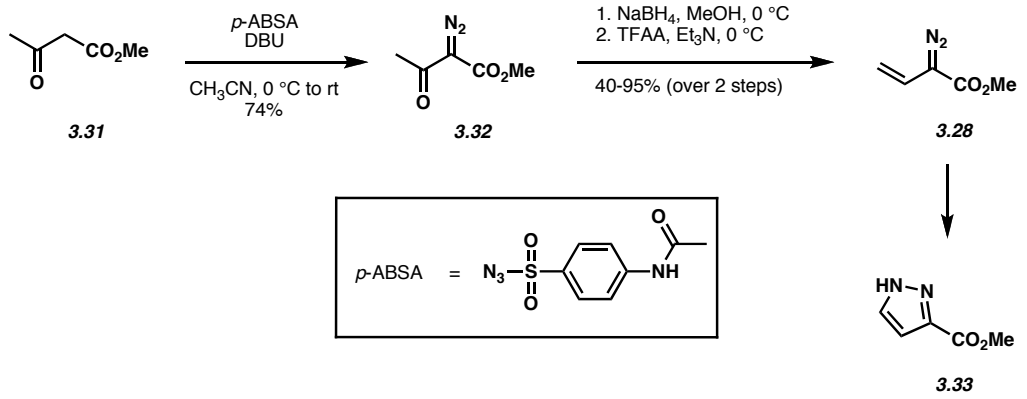
Synthesis of the diene (**3.27**, Scheme 3.4.1) proceeded similarly to the previous route to dienol **2.6** (see Chapter 2.3). Racemic Hajos-Parrish ketone (**1.99**) was synthesized via a Robinson annulation of 2-methyl-1,3-cyclopentanedione (**2.8**) and methyl vinyl ketone (**2.9**).[15] Reduction of the ketone in **1.99** and protection of the resulting hydroxyl group as a methoxymethyl ether[16] was followed by a Rubottom oxidation[17] to afford α-hydroxy enone **2.11**. After the hydroxyl group was protected as the silyl ether, enone **2.12** was reduced, and transformed to enol triflate **2.14**. Finally, a Corey-modified Stille reaction[18] coupled the bicycle to vinyl tributyltin to furnish the desired racemic diene (**3.27**).

Scheme 3.4.1. Construction of diene **3.27**.



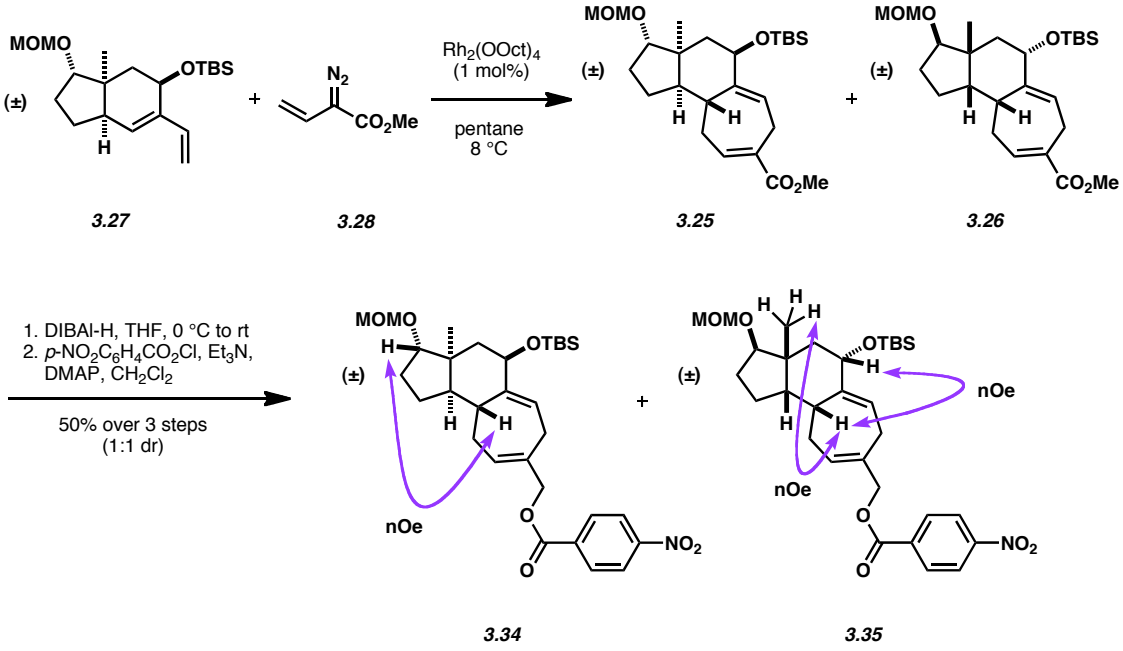
Next, the vinyl diazoacetate[19] (**3.28**, Scheme 3.4.2) to be used in the cyclopropanation was prepared. Starting from methyl acetoacetate (**3.31**), a diazo transfer with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[20] yielded keto-diazoacetate **3.32**. Sodium borohydride reduction of ketone **3.32** and elimination of the resultant hydroxyl group using trifluoroacetic anhydride (TFAA) in triethylamine gave vinyl diazoacetate **3.28**. The vinyl diazoacetate (**3.28**) was freshly made before each use, as it readily cyclized to pyrazole **3.33** over time or with exposure to heat, particularly when stored neat. A solution of the reagent is more stable, and can be kept intact in a 4 °C freezer for several days.

Scheme 3.4.2. Synthesis of vinyl diazoacetate **3.28**.



To test the key cyclopropanation/Cope rearrangement sequence, we first employed an achiral catalyst, dirhodium octanoate, to promote diazo decomposition. The resulting diastereomeric tricycles (**3.25** and **3.26**, Scheme 3.4.3) were more unstable as compared to the previous tricyclic system (e.g., **2.2**, Scheme 2.3.2), presumably due to the enoate now present in the cycloheptadiene, and were more prone to decomposition. We consequently reduced the ester with diisobutylaluminum hydride (DIBAl-H), and protected the primary alcohol as the *p*-nitrobenzoate (**3.34** and **3.35**). NOESY analysis confirmed the identity of the cyanthiwigin (**3.34**) and cyathane (**3.35**) tricycles.

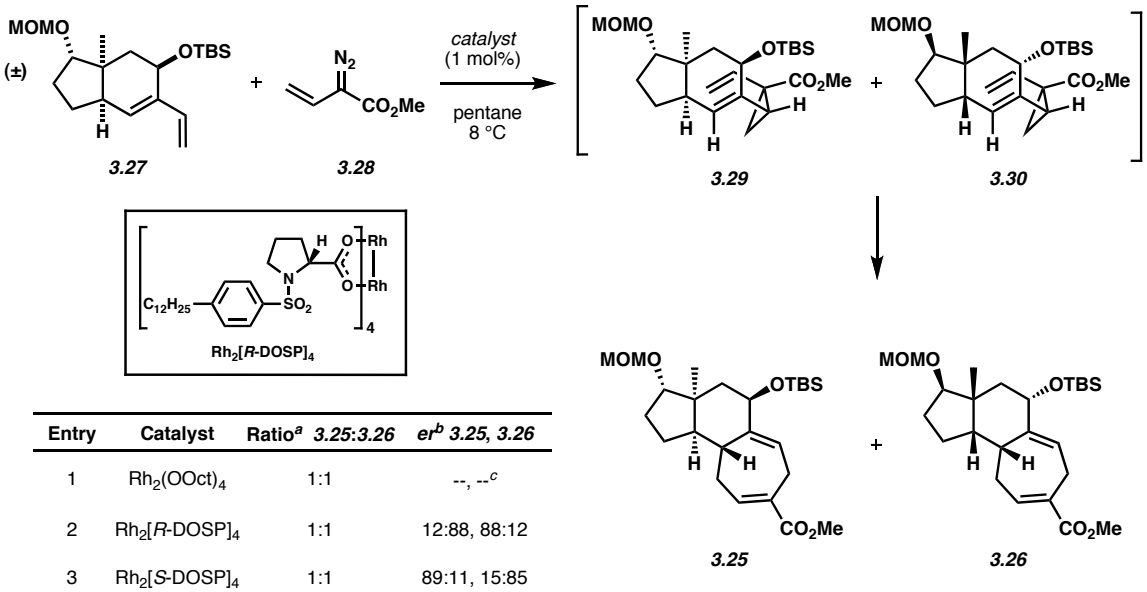
Scheme 3.4.3. Synthesis of the cyanthiwigin and cyathane cores.



We were pleased that the achiral catalyst formed a 1:1 diastereomeric ratio of products (entry 1, Scheme 3.4.4), as this implied that there was little inherent substrate selectivity in the cyclopropanation step, unlike our first-generation system. Hopeful that minimal substrate

control would translate into good reagent control, we employed the Davies chiral Rh_2[DOSP]$_4$ catalysts[21,22] in the cyclopropanation reaction. Good reagent control was achieved, producing the enantioenriched tricycles in enantiomeric ratios of 85:15 and higher. Importantly, switching from Rh_2[*R*-DOSP]$_4$ (entry 2) to Rh_2[*S*-DOSP]$_4$ (entry 3) changed the preference for the enantiomer formed, giving access to the unnatural series of the natural products, and demonstrating the viability of the approach. Considering the complexity of diene **3.27**, which contains multiple resident stereocenters, and the difficulties encountered with the initial dienol system (**2.6**; see Chapter 2.4), the results were very encouraging.

Scheme 3.4.4. Stereodivergent cyclopropanation to furnish enantioenriched cyanthiwigin and cyathane cores.

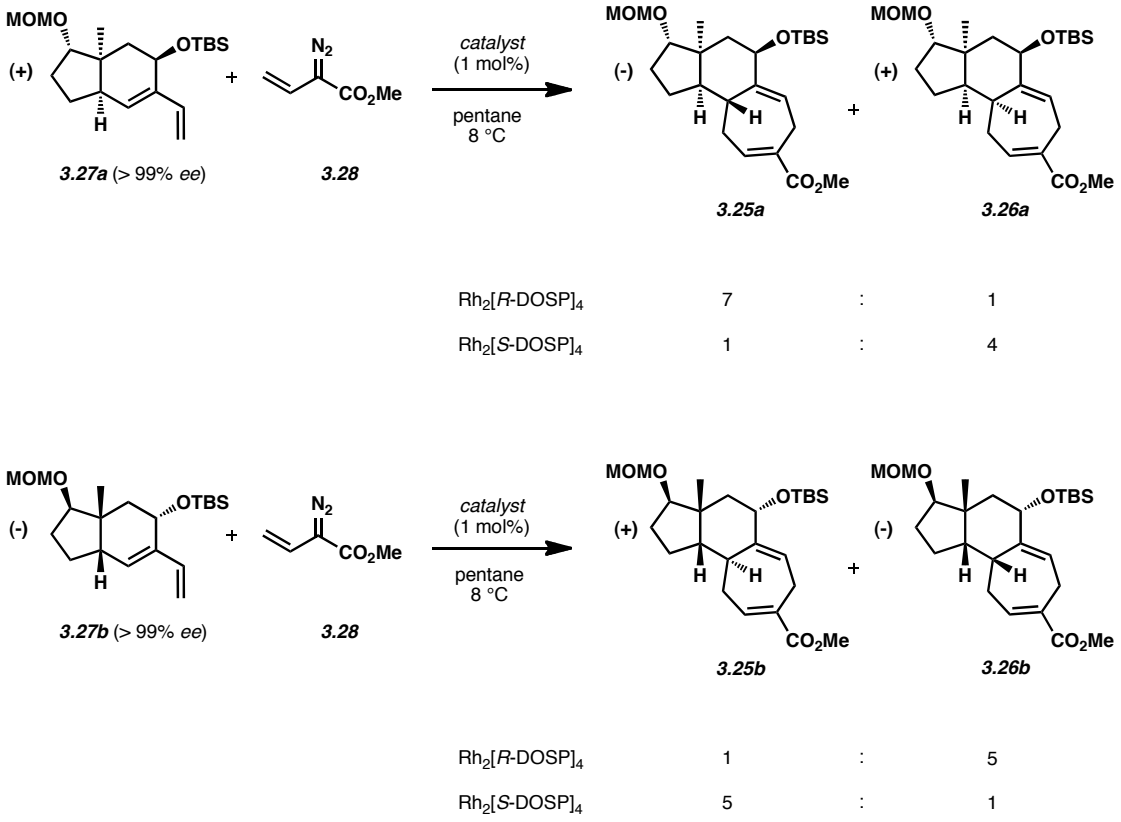


Entry	Catalyst	Ratio[a] *3.25*:*3.26*	*er*[b] *3.25*, *3.26*
1	$Rh_2(OOct)_4$	1:1	--, --[c]
2	Rh_2[*R*-DOSP]$_4$	1:1	12:88, 88:12
3	Rh_2[*S*-DOSP]$_4$	1:1	89:11, 15:85

[a] Determined by ^{1}H NMR; [b] Determined on reduced and protected tricycle by HPLC using Chiralcel OD-H column, 2.0% 2-propanol in hexane; [c] On multiple runs there was no enrichment within error (± 1.5%).

To deconvolute the selectivity of the cyclopropanation, we prepared each enantiomer of the diene (**3.27a** and **3.27b**) from (+)- or (-)-Hajos-Parrish ketone, respectively (Scheme 3.4.5). The selectivity of the cyclopropanation was more transparent starting from enantioenriched diene, as only two stereoisomers were possible in this scenario, rather than four in the racemic case. With perfect reagent control, only a single stereoisomer would be formed. The modest selectivity observed in the resolution translated into diastereomeric ratios ranging from 4:1 to 7:1. On the basis of the previous dienol studies (see Chapter 2.5), we knew that the *t*-butyldimethylsilyl ether on the B-ring could be playing a role in the selectivity of the reaction, perhaps being the source of the moderate diastereoselectivity observed in the cyclopropanation step. However, with optimization, the stereoselectivity of the reaction may be improved, which will lead to the production of a single product in this reaction, or two highly enriched diastereomers when starting from the racemic diene (see Chapter 3.6).

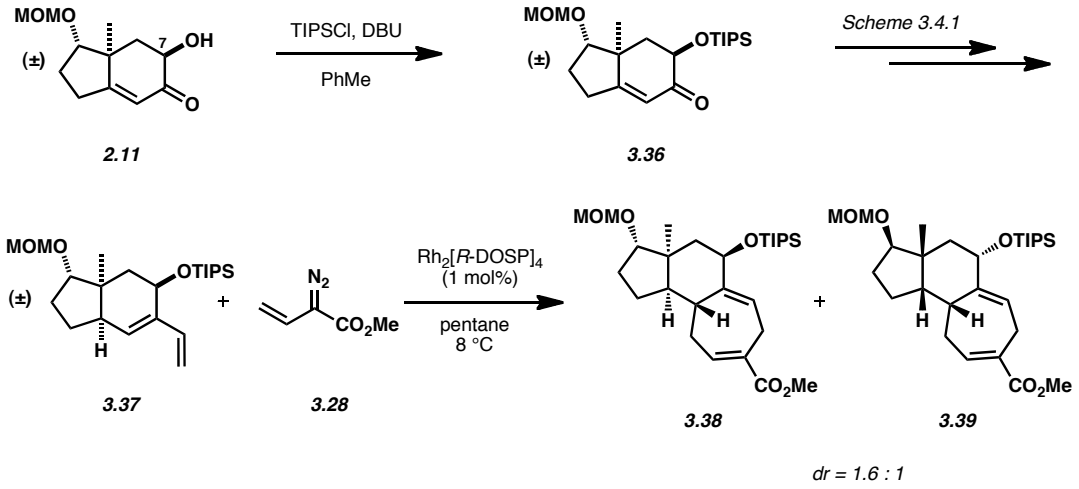
Scheme 3.4.5. Cyclopropanation of enantioenriched dienes **3.27a** and **3.27b**.



3.5. Substrate Studies on the Key Cyclopropanation/Cope Rearrangement

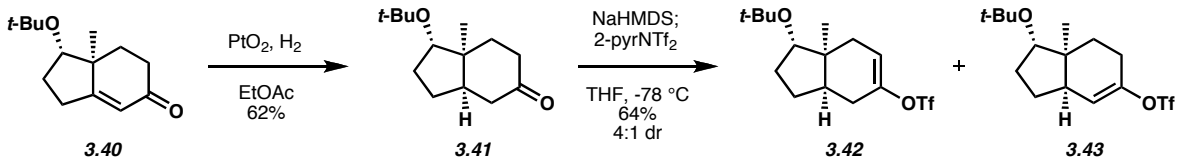
To probe the hypothesis that the B-ring substituent was negatively affecting reagent control, we first employed a bulkier protecting group to form the triisopropylsilyl ether analog of the diene (**3.37**, Scheme 3.5.1) to determine if the bulkier substituent on the B-ring would lead to more pronounced substrate control. We synthesized TIPS analog **3.36**, employing TIPSCl after the Rubottom oxidation, and then carried forward the material in an identical manner to the TBS substrate (see Scheme 3.4.1). In the rhodium-mediated cyclopropanation, we did observe increased substrate control. The formation of tricycle **3.38** was favored, presumably because cyclopropanation from the α-face avoids steric interactions with the TIPS group, whereas production of tricycle **3.39** is the result of the mismatched case.

Scheme 3.5.1. Synthesis of TIPS-analog **3.37** and subsequent cyclopropanation/Cope rearrangement.



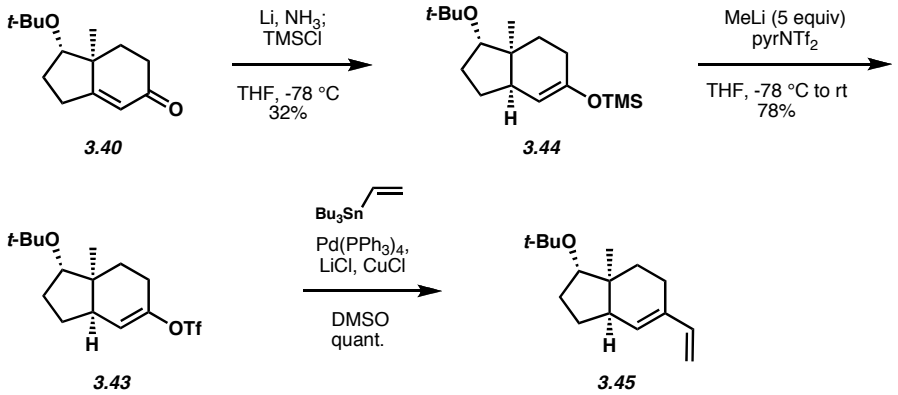
As the silyl ether at C7 appeared to be eroding reagent control, we hypothesized that a substrate lacking substitution on the B-ring would be more amenable to complete reagent control. Starting from Hajos-Parrish ketone derivative **3.40**, we pursued an analogous synthesis of the target diene, first reducing to the ketone (**3.41**), and then trapping as the enol triflate (**3.42** and **3.43**) after kinetic deprotonation (Scheme 3.5.2). Unfortunately, the deprotonation suffered from poor regioselectivity, leading to a 4:1 mixture of enol triflates, favoring undesired regioisomer **3.42**.

Scheme 3.5.2. Poor regioselectivity in the formation of enol triflate **3.43**.



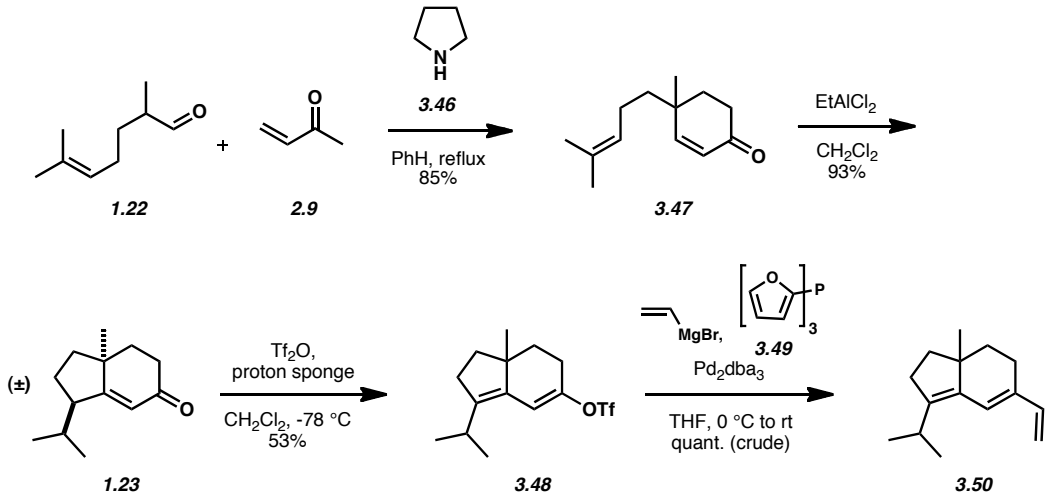
To obtain desired enol triflate **3.43**, we pursued a Birch reduction of **3.40**, followed by trapping in situ as the trimethylsilyl enol ether (**3.44**, Scheme 3.5.3). The desired lithium enolate could be regenerated with methyl lithium, and then trapped as the enol triflate (**3.43**). While de Meijere and coworkers[23] reported yields of 84% for the Birch reduction followed by trapping as the silyl enol ether to form bicycle **3.44**, in our hands we only obtained low yields for the step. The difficulties include removing excess ammonia after the reduction (to prevent reaction with the trimethylsilyl chloride), without quenching the lithium enolate. With the isolated product (**3.44**), we were able to regenerate the lithium enolate with methyl lithium under rigorously anhydrous conditions and form the desired regioisomer of the enol triflate (**3.43**). The Corey-modified Stille coupling[18] with vinyl tributyltin proceeded without event to furnish desired diene **3.45**.

Scheme 3.5.3. Synthesis of diene **3.45** with an unsubstituted B-ring.



Additionally, we wanted to probe the effect of steric bulk on the A-ring on the selectivity of the rhodium-mediated cyclopropanation step. A triene like **3.50** (Scheme 3.5.4) was also desirable since it would incorporate a completed A-ring appropriate for the majority of the cyathane diterpenes (see Chapter 1). Although the isopropyl group seems rather distal to the alkene, we wanted to confirm that it would not interfere in the diastereoselectivity of the cyclopropanation step. Following the precedent of Snider[24,25] to form enol triflate **3.48**, we started with the Robinson annulation of melonal (**1.22**) with methyl vinyl ketone (**2.9**) in the presence of pyrrolidine (**3.46**). Treatment with ethyl aluminum dichloride promoted cyclization to bicycle **1.23**. Triflic anhydride in the presence of proton sponge furnished enol triflate **3.48**. We initially utilized the Corey-modified Stille coupling[18] to access triene **3.50**. However, removal of excess stannane byproduct from the nonpolar triene proved challenging. Additionally, the triene was unstable to silica chromatography. We consequently moved to Kumada cross-coupling conditions,[26] which yielded the desired triene cleanly without the need for flash chromatography.

Scheme 3.5.4. Construction of diene **3.50** with a substituted A-ring.



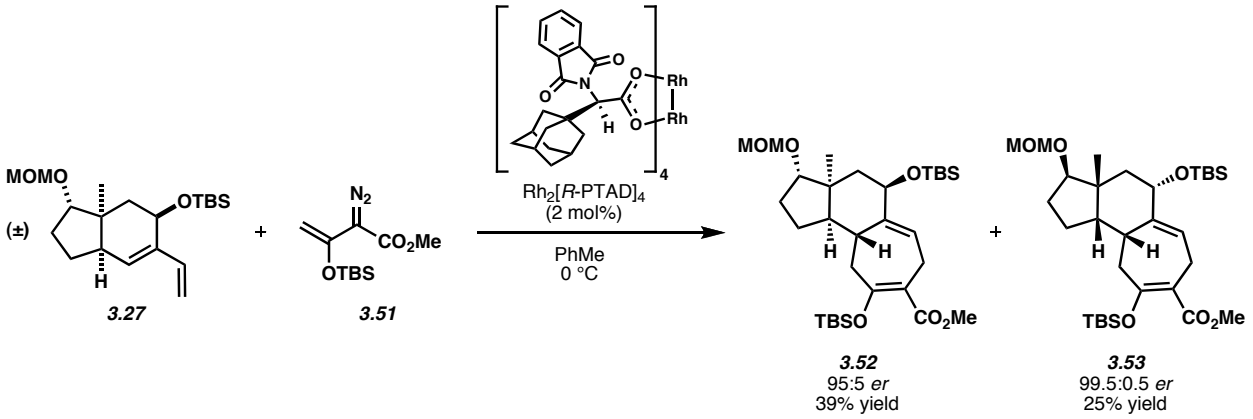
With both unsubstituted B-ring diene **3.45** and bulky A-ring triene **3.50** in hand, we plan to test these substrates under the $Rh_2[DOSP]_4$-mediated cyclopropanation conditions. We will

see whether we obtain better reagent control using diene **3.45**, leading to higher enantioenrichment and better yields of the resultant tricycle. Addtionally, we will determine whether the isopropyl group on the A-ring of triene **3.50** impacts the reaction.

3.6. Catalyst and Diazo Substrate Studies on the Key Cyclopropanation/Cope Rearrangement

In addition to changing the diene, one can optimize the reaction by exploring different diazo substrate and catalyst combinations. In collaboration with the Davies group, we have examined the use of Rh_2[*R*-PTAD]$_4$ with silyl enol ether diazoacetate **3.51** (Scheme 3.6.1).[27] This catalyst system delivered superior selectivity, returning tricycles **3.52** and **3.53** with 95:5 and 99.5:0.5 enantiomeric ratios, respectively. This route will provide access to more highly enantioenriched tricycles, which will be utilized in the syntheses of the cyanthiwigin and cyathane natural products.

Scheme 3.6.1. Rh_2[PTAD]$_4$-catalyzed stererodivergent RRM.



3.7. Conclusion

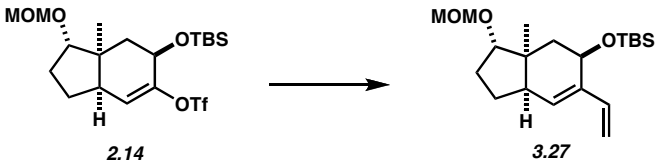
Using a rhodium-mediated cyclopropanation, we were able to successfully target both the cyanthiwigin and cyathane tricyclic cores. With good reagent control, we effected a resolution of our racemic diene **3.27** to form each tricycle (**3.25** and **3.26**) in enantioenriched form. Starting with enantioenriched diene, we can also selectively target either the cyanthiwigin or the cyathane natural products. We further investigated the key transformation through the examination of a variety of substrates, as well as different diazo reagent and catalyst combinations, and found that the Rh_2[PTAD]$_4$ catalyst in combination with silyl enol ether diazoacetate **3.51** provides more effective reagent control, furnishing the cores of the cyanthiwigins and cyathanes in high enantiomeric ratios.

3.8. Experimental Contributions

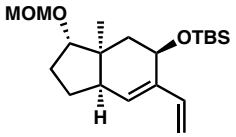
Yajing Lian (Davies group, Emory University) optimized the Rh_2[PTAD]$_4$-catalyzed reaction of **3.27** (Scheme 3.6.1). Laura C. Miller performed the rest of the research detailed in the chapter.

3.9. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Dichloromethane (DCM), toluene (PhMe) and triethylamine (Et_3N) were distilled over calcium hydride. Pentane was dried over 4 Å MS, and sparged with nitrogen. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125 and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$: δ = 7.26 for ^1H NMR and δ = 77.0 for ^{13}C NMR; C_6D_6: δ = 7.15 for ^1H NMR and δ = 128.39 for ^{13}C NMR). Data for ^1H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley. Enantiomeric ratios (*er*'s) were determined on a Shimadzu VP Series or an Agilent 1100 Chiral HPLC. A polarimeter with a sodium lamp was used to determine specific rotations and concentrations are reported in g/dL.

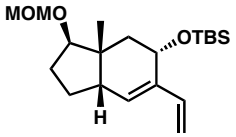


Diene ((±)-3.27): The reaction was run in an identical manner as that to form **2.6**, using vinyltributyltin instead of **2.15** (See Chapter 2.8). Flash chromatography (gradient of hexanes to 20:1 hexanes/EtOAc) afforded **3.27** as a clear oil in 72% yield. $\mathbf{R_f}$ 0.64 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.85 (d, *J* = 3.7 Hz, 1H), 5.31 (d, *J* = 17.7 Hz, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.44 (t, *J* = 6.6 Hz, 1H), 3.78 (t, *J* = 4.8 Hz, 1H), 3.36 (s, 3H), 2.24 (dd, *J* = 12.6, 7.3 Hz, 1H), 2.14-1.99 (m, 2H), 1.73-1.40 (m, 4H), 1.01 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.2, 136.3, 129.6, 112.6, 95.7, 85.6, 66.8, 55.3, 44.6, 44.0, 41.3, 30.4, 29.2, 26.0, 20.7, 18.2, -3.7, -4.6; **IR** (film) ν_{max} 1642, 1620, 1253, 1045 cm^{-1}; **HRMS** (EI+) calcd for $[C_{20}H_{36}O_3Si]^+$: *m/z* 352.2434, found 352.2431.



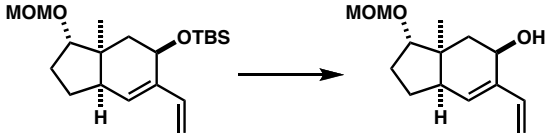
3.27a

Diene ((+)-3.27a): The enriched diene was prepared identically to (±)-**3.27**, but starting with (+)-Hajos-Parrish ketone. $[\alpha]_D$ = +16.7 (c = 0.088, $CHCl_3$).



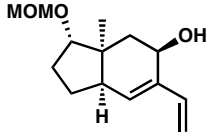
3.27b

Diene ((-)-3.27b): The enriched diene was prepared identically to (±)-**3.27**, but starting with (-)-Hajos-Parrish ketone. $[\alpha]_D$ = -0.7 (c = 0.11, $CHCl_3$).



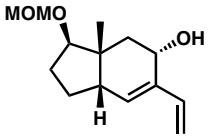
3.27 *3.54*

Allylic Alcohol (3.54): Diene **3.27** (10.4 mg, 0.0295 mmol) was dissolved in THF (0.95 mL). To the solution was added 4 Å MS, and TBAF (0.11 mL, 1 M in THF, 0.11 mmol). The reaction mixture was stirred at room temperature for 12 hours, at which time it was filtered through Celite. Saturated aq. NH_4Cl was added to the filtrate and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4 and concentrated. The crude alcohol was purified by flash chromatography (80:20:1 hexanes/EtOAc/NEt_3) affording **3.54** as a clear oil (4.4 mg, 63% yield). $\mathbf{R_f}$ 0.18 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.28 (dd, *J* = 17.8, 11.1 Hz, 1H), 5.68 (s, 1H), 5.37 (d, *J* = 17.8 Hz, 1H), 5.09 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H), 4.55 (t, *J* = 4.5 Hz, 1H), 4.19 (t, *J* = 7.4 Hz, 1H), 3.39 (s, 3H), 2.34-2.26 (m, 1H), 2.19-2.08 (m, 1H), 2.08-1.98 (m, 1H), 1.87 (dd, *J* = 14.4, 4.0 Hz, 1H), 1.75 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.70-1.60 (m, 1H), 1.46-1.33 (m, 1H), 0.99 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.4, 135.5, 135.1, 112.8, 96.4, 83.3, 63.6, 55.3, 44.3, 42.2, 38.6, 29.1, 27.1, 21.2; **IR** (film) ν_{max} 3452, 1642, 1603, 1043 cm^{-1}; **HRMS** (EI+) calcd for $[C_{14}H_{22}O_3]^+$: *m/z* 238.1569, found 238.1564.



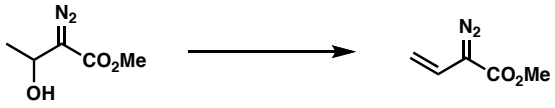
3.54a

Allylic Alcohol (3.54a): Prepared from (+)-**3.27a**. 99% *ee* by HPLC using a Chiralcel AD-H column, 1 mL/min, 2.0% ethanol in hexane, t_R = 28.9 (major) and 30.8 (minor) min, UV 230 nm.



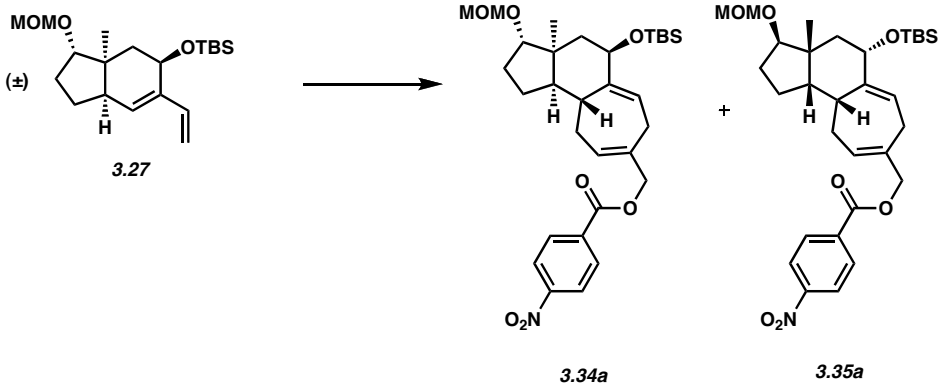
3.54b

Allylic Alcohol (3.54b): Prepared from (-)-**3.27b**. > 99% *ee* by HPLC using a Chiralcel AD-H column, 1 mL/min, 2.0% ethanol in hexane, t_R = 30.6 (major) min, UV 230 nm.



3.55 *3.28*

Vinyl diazoacetate[28] (3.28): To a solution of crude hydroxy diazoacetate **3.55**[19] (0.10 g, 0.70 mmol) in 2.15 mL Et_3N at 0 °C was added trifluoroacetic anhydride (0.11 mL, 0.84 mmol) over 30 min. The reaction mixture was stirred for an additional 3 h at 0 °C. At that time, the reaction mixture was poured onto ice. Keeping the organic fraction on ice, the aqueous layer was extracted with cold CH_2Cl_2 (3 x 4 mL). The combined organic layer was dried over Na_2SO_4 and carefully concentrated, with ice in the rotary evaporator bath. The crude product was purified via column chromatography (10:1 pentane/Et_2O) and the yellow/orange band was collected. Following careful concentration (in both concentrations some of the product is lost), vinyl diazoacetate **3.28** was obtained as a yellow oil in a 95% yield (84 mg) and was used immediately. Spectral data agreed with that reported for the compound.[19]



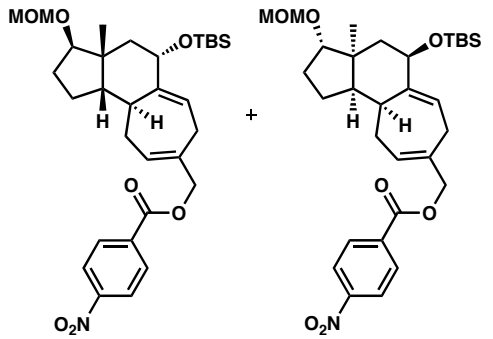
3.27 *3.34a* *3.35a*

***p*-Nitrobenzoate Tricycles (3.34a** and **3.35a): Representative Procedure:** A solution of diene **3.27** (20.4 mg, 0.0533 mmol) and Rh_2[*R*-DOSP]$_4$ (1.1 mg, 0.0058 mmol) in pentane (0.3 mL) was placed in a cold room (8 °C). Vinyl diazoacetate **3.28**[19] (24.0 mg, 0.188 mmol) in 0.60 mL pentane was added over 3 h via syringe pump. After the addition was complete, the reaction was stirred for an additional 20 h at 8 °C. The mixture was filtered through a plug of deactivated neutral alumina with Et_2O, concentrated and subsequently diluted with THF (0.5 mL) and cooled to 0 °C. DIBAl-H (0.380 mL, 1.0 M in PhMe, 0.380 mmol) was added dropwise, and the reaction mixture was allowed to return to room temperature over one hour. An aq. solution of potassium sodium tartrate (Rochelle's salt, 15 mg in 1.0 mL of H_2O) was added, and the reaction was stirred vigorously for 1 h. After dilution with H_2O (1 mL), the solution was extracted with

Et_2O (3 x 3 mL), and the combined organic layers were washed with brine. The solution was dried over Na_2SO_4 and concentrated. The crude material was diluted with CH_2Cl_2 (1.4 mL). DMAP (1.0 mg, 0.0082 mmol), 4-nitrobenzoyl chloride (35.7 mg, 0.192 mmol) and Et_3N (40.0 μL, 0.287 mmol) were added to the reaction mixture. After 8 h, the reaction mixture was diluted with H_2O (1 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were washed sequentially with a saturated aq. $NaHCO_3$ solution (1 mL) and brine (1 mL). The crude mixture was dried over Na_2SO_4 and concentrated to give a yellow oil. Flash chromatography (gradient of 30:1 hexanes/EtOAc to 20:1 hexanes/EtOAc) afforded **3.34a** and **3.35a** as clear oils (50% combined yield over 3 steps); 1.04:1 dr (**3.34a**: **3.35a**).

3.34a: $\mathbf{R_f}$ 0.48 (4:1 hexanes/EtOAc); 12:88 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.4 (minor) and 18.1 (major) min, UV 254 nm; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 5.90 (t, *J* = 6.7 Hz, 1H), 5.62 (t, *J* = 5.5 Hz, 1H), 4.77 (d, *J* = 12.2 Hz, 1H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.67 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 4.25 (t, *J* = 8.2 Hz, 1H), 4.13 (t, *J* = 4.8 Hz, 1H), 3.35 (s, 3H), 2.99 (d, *J* = 14.8 Hz, 1H), 2.76 (dd, *J* = 17.9, 6.5 Hz, 1H), 2.45-2.40 (m, 1H), 2.36 (t, *J* = 9.8 Hz, 1H), 2.21 (td, *J* = 14.4, 7.3 Hz, 1H), 2.08-1.91 (m, 2H), 1.87 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.63-1.43 (s, 4H), 0.88 (s, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.5, 150.5, 145.7, 137.6, 135.7, 130.7, 129.0, 123.5, 119.6, 96.7, 84.5, 74.9, 70.4, 55.2, 49.2, 43.2, 42.3, 37.0, 29.1, 28.3, 27.8, 25.9, 25.2, 23.5, 18.2, -4.6, -4.7,; **IR** (film) ν_{max} 1727, 1608, 1531, 1347, 1271, 1102, 1046 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{31}H_{45}NO_7Si]^+$(M+Li)$^+$: *m/z* 578.3125, found 578.3126.

3.35a: $\mathbf{R_f}$ 0.42 (4:1 hexanes/EtOAc); 88:12 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.6 (major) and 14.9 (minor) min, UV 254 nm; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 5.99-5.90 (m, 2H), 4.75 (s, 2H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.54 (d, *J* = 6.7 Hz, 1H), 3.99 (d, *J* = 10.3 Hz, 1H), 3.54 (d, *J* = 5.6 Hz, 1H), 3.36 (s, 3H), 3.14 (d, *J* = 16.7 Hz, 1H), 2.62 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.53-2.47 (m, 1H), 2.39-2.30 (m, 1H), 2.18-2.10 (m, 1H), 2.07-1.95 (m, 1H), 1.87 (s, 1H), 1.75 (dd, *J* = 21.2, 12.3 Hz, 1H), 1.66-1.61 (m, 3H), 1.43 (dd, *J* = 12.4, 4.3 Hz, 1H), 1.16 (s, 3H), 0.88 (s, 9H), 0.021 (s, 3H), 0.018 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.5, 150.5, 141.8, 139.7, 135.7, 130.7, 128.6, 123.5, 117.4, 95.1, 85.7, 70.5, 69.7, 55.5, 49.7, 46.0, 42.9, 36.0, 30.3, 28.6, 26.5, 25.9, 24.6, 19.2, 18.4, -4.9, -5.0; **IR** (film) ν_{max} 1727, 1608, 1530, 1347, 1271, 1100, 1036 cm^{-1}; **HRMS** (FAB+) calcd for $[LiC_{31}H_{45}NO_7Si]^+$ (M+Li)$^+$: *m/z* 578.3125, found 578.3138.

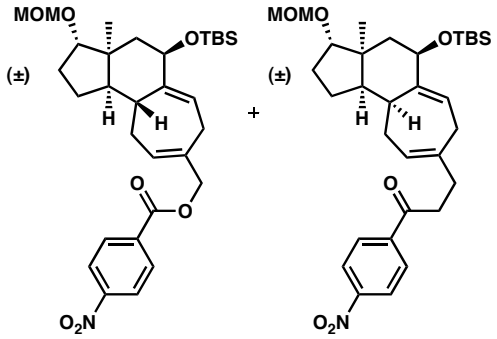


3.34b *3.35b*

***p*-Nitrobenzoate Tricycle (3.34b** and **3.35b):** Prepared analogously to **3.34a** and **3.35a**, but with Rh_2[*S*-DOSP]$_4$; 1.05:1 dr (**3.34b**: **3.35b**).

3.34b: 89:11 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.5 (major) and 18.4 (minor) min, UV 254 nm.

3.35b: 15:85 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.6 (minor) and 14.9 (major) min, UV 254 nm .

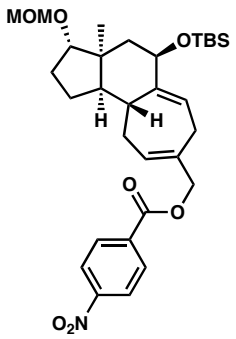


3.34 *3.35*

***p*-Nitrobenzoate Tricycle (3.34** and **3.35):** Prepared analogously to **3.34a** and **3.35a**, but with $Rh_2(OOct)_4$; 1:1.3 dr (**3.34** : **3.35**).

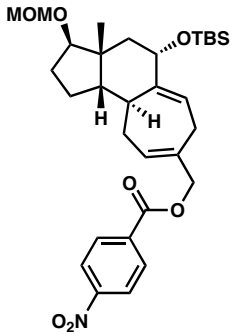
3.34: 51:49 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.6 (major) and 18.6 (minor) min, UV 254 nm.

3.35: 50:50 *er* by HPLC using a Chiralcel OD-H column, 0.5 mL/min, 2.0% 2-propanol in hexane, t_R = 13.2 (major) and 14.3 (minor) min, UV 254 nm .



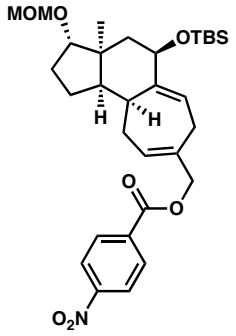
3.34a

***p*-Nitrobenzoate Tricycle ((-)-3.34a):** Prepared from (+)-**3.27a**. $[\alpha]_D$ = -6.5 (c = 0.067, $CHCl_3$).



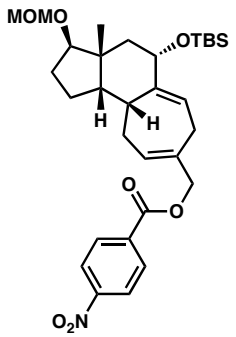
3.34b

***p*-Nitrobenzoate Tricycle ((+)-3.34b):** Prepared from (-)-**3.27b**. $[\alpha]_D$ = +8.3 (c = 0.089, $CHCl_3$).



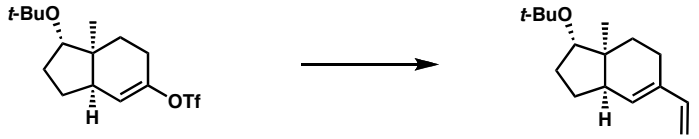
3.35b

***p*-Nitrobenzoate Tricycle ((+)-3.35b):** Prepared from (+)-**3.27a**. $[\alpha]_D$ = +49.7 (c = 0.039, $CHCl_3$).



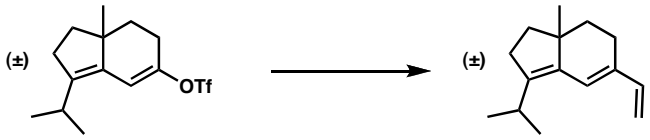
3.35a

***p*-Nitrobenzoate Tricycle ((-)-3.35a):** Prepared from (-)-**3.27b**. $[\alpha]_D$ = -37.4 (c = 0.10, $CHCl_3$).



3.43 *3.45*

Simplified B-Ring Diene (3.45): The reaction was run in an identical manner as that to form **3.27**, using vinyltributyltin and diene **3.43**.[23] Flash chromatography (gradient of hexanes to 20:1 hexanes/EtOAc) afforded **3.45** as a clear oil in a quantitative yield. $\mathbf{R_f}$ 0.58 (9:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.64 (d, *J* = 4.0 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 3.57 (t, *J* = 6.9 Hz, 1H), 2.25-2.17 (m, 1H), 2.17-2.09 (m, 1H), 2.09-1.92 (m, 2H), 1.76-1.59 (m, 3H), 1.59- 1.47 (m, 2H), 1.44-1.26 (m, 3H), 1.15 (s, 9H), 0.94 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 140.0, 134.0, 133.5, 110.1, 76.7, 72.5, 44.7, 42.3, 32.9, 29.9, 28.7, 27.8, 26.8, 21.0, 20.7, 13.6; **IR** (film) ν_{max} 2925, 2924, 1463 cm^{-1}.



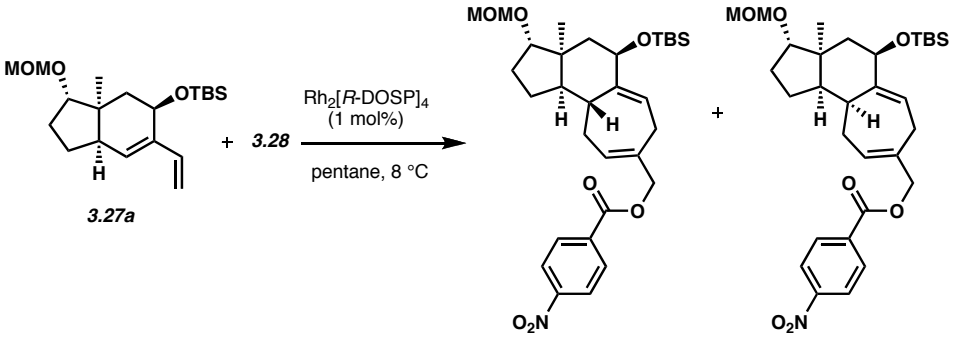
3.48 *3.50*

Triene (3.50): To a solution of enol triflate **3.48**[25] (82.6 mg, 0.255 mmol) in 0.4 mL THF was added 0.51 mL vinylmagesium bromide (1.0 M in THF, 0.51 mmol) at 0 °C. A solution of Pd_2dba_3 (4.7 mg, 5.1 x 10^{-3} mmol) and tri-2-furylphosphine (5.4 mg, 0.023 mmol) in THF (0.24 mL) was added dropwise via syringe. The reaction was allowed to return to room temperature over 40 min, at which time an additional portion of catalyst (8.0 mg, 8.7 x 10^{-3} mmol) and ligand (7.9 mg, 0.034 mmol) was added. After stirring at room temperature for 17 h, the reaction was cooled to 0 °C and quenched with water (1 mL). The aqueous layer was extracted with pentane (3 x 2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to afford triene **3.50** in a quantitative yield (52 mg). $\mathbf{R_f}$ 0.65 (9:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, C_6D_6) δ 6.52 (dd, *J* = 17.4, 10.7 Hz, 1H), 6.36 (s, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.02 (d, *J* = 10.7 Hz, 1H), 2.81-2.73 (m, 1H), 2.44-2.36 (m, 1H), 2.32-2.18 (m, 3H), 1.72-1.67 (m, 2H), 1.50-1.38 (m, 2H), 1.00-0.92 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.6,

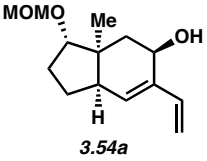
140.8, 138.7, 136.1, 123.3, 111.8, 45.6, 39.7, 36.3, 29.4, 27.3, 23.3, 22.2, 22.1, 21.7; **IR** (film) ν_{max} 2959, 2927, 1462, 1109 cm^{-1}.

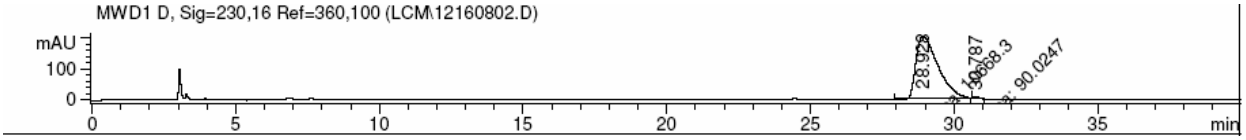
Characterization of 3.34 and 3.35:

The determination of the absolute stereochemistry was deduced using enantioenriched **3.27** along with the Rh_2[*R*-DOSP]$_4$ and Rh_2[*S*-DOSP]$_4$ catalysts. The respective *p*-nitrobenzoates were then isolated, and the optical rotation and chiral HPLC retention time determined. For an example, see the scheme below. The absolute stereochemistry of (-)-**3.34a** and (+)-**3.35b** could be determined by the known absolute stereochemistry of (+)-Hajos-Parrish ketone.



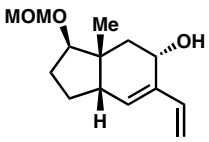
HPLC Traces:



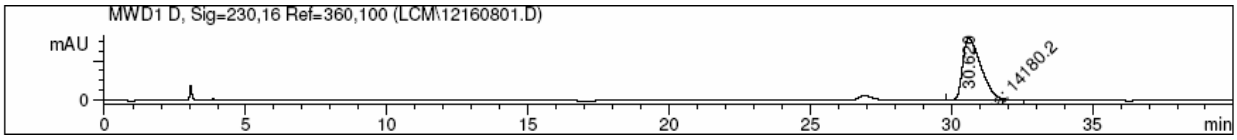


Signal 4: MWD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.928	MM	0.8800	1.06683e4	202.05759	99.1632
2	30.787	MM	0.2015	90.02467	7.44653	0.8368
Totals :				1.07584e4	209.50412	

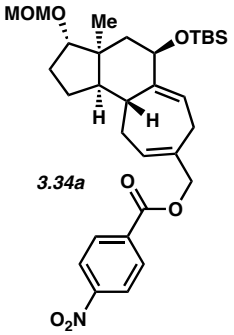


3.54b

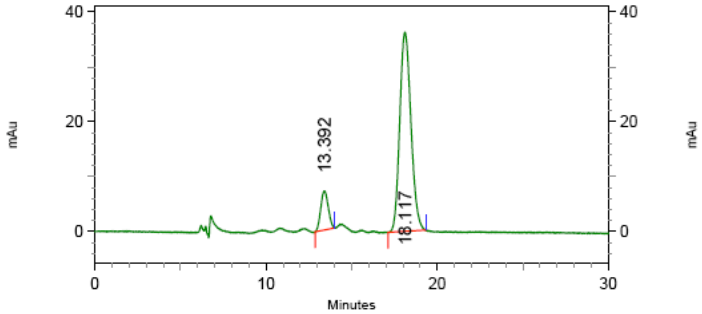


Signal 4: MWD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.620	MM	0.7565	1.41802e4	312.41635	100.0000
Totals :				1.41802e4	312.41635	

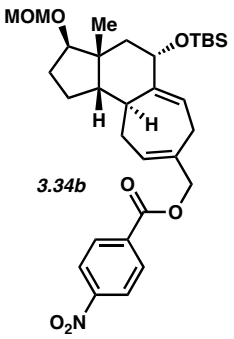


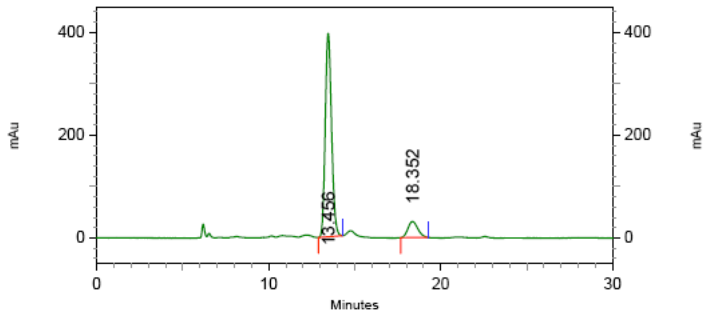
3.34a



2: 254 nm, 4 nm Results

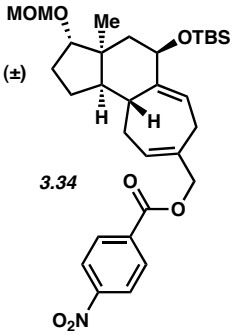
Retention Time	Area	Area Percent
13.392	215936	11.593
18.117	1646730	88.407

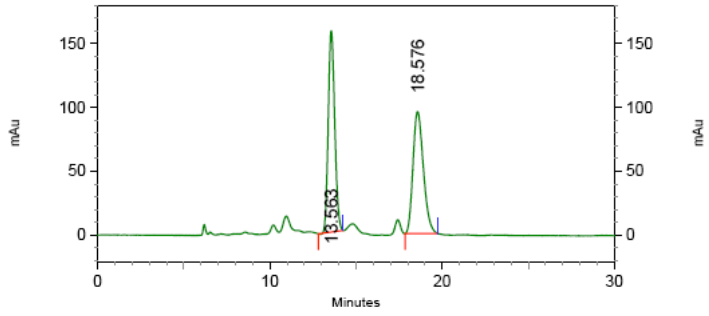




2: 254 nm, 4 nm Results

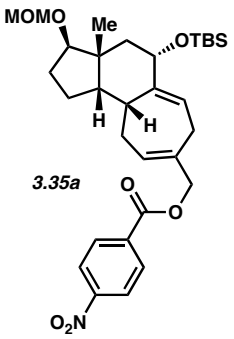
Retention Time	Area	Area Percent
13.456	10119498	88.989
18.352	1252085	11.011

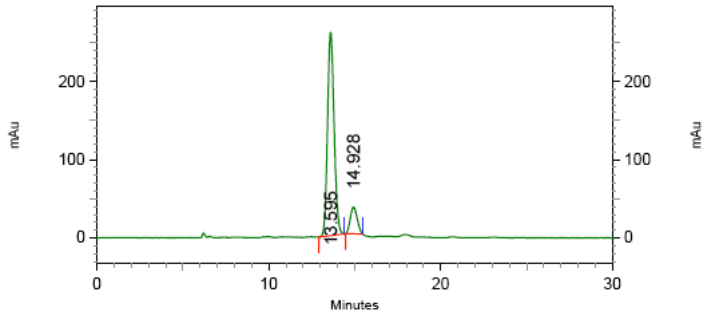




2: 254 nm, 4 nm Results

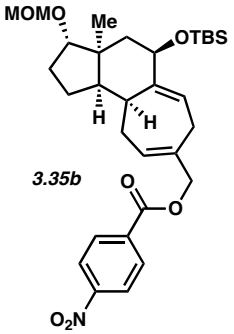
Retention Time	Area	Area Percent
13.563	4132557	50.765
18.576	4008065	49.235

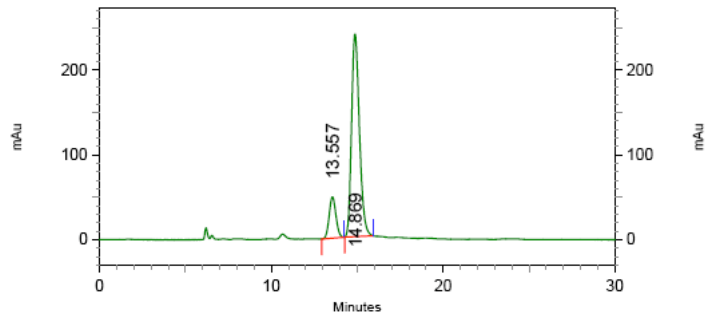




2: 254 nm, 4 nm Results

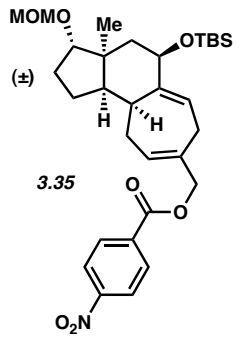
Retention Time	Area	Area Percent
13.595	6908620	87.864
14.928	954218	12.136

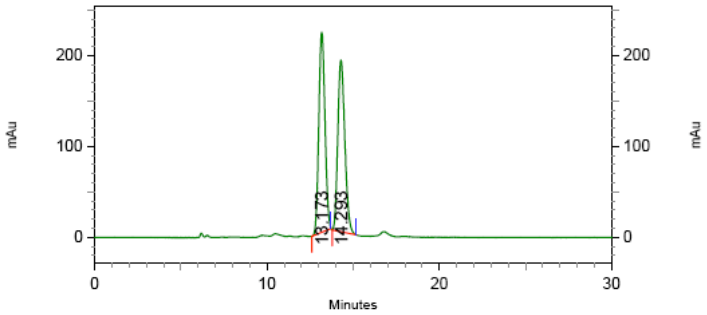




2: 254 nm, 4 nm Results

Retention Time	Area	Area Percent
13.557	1333969	14.864
14.869	7640499	85.136





2: 254 nm, 4 nm Results

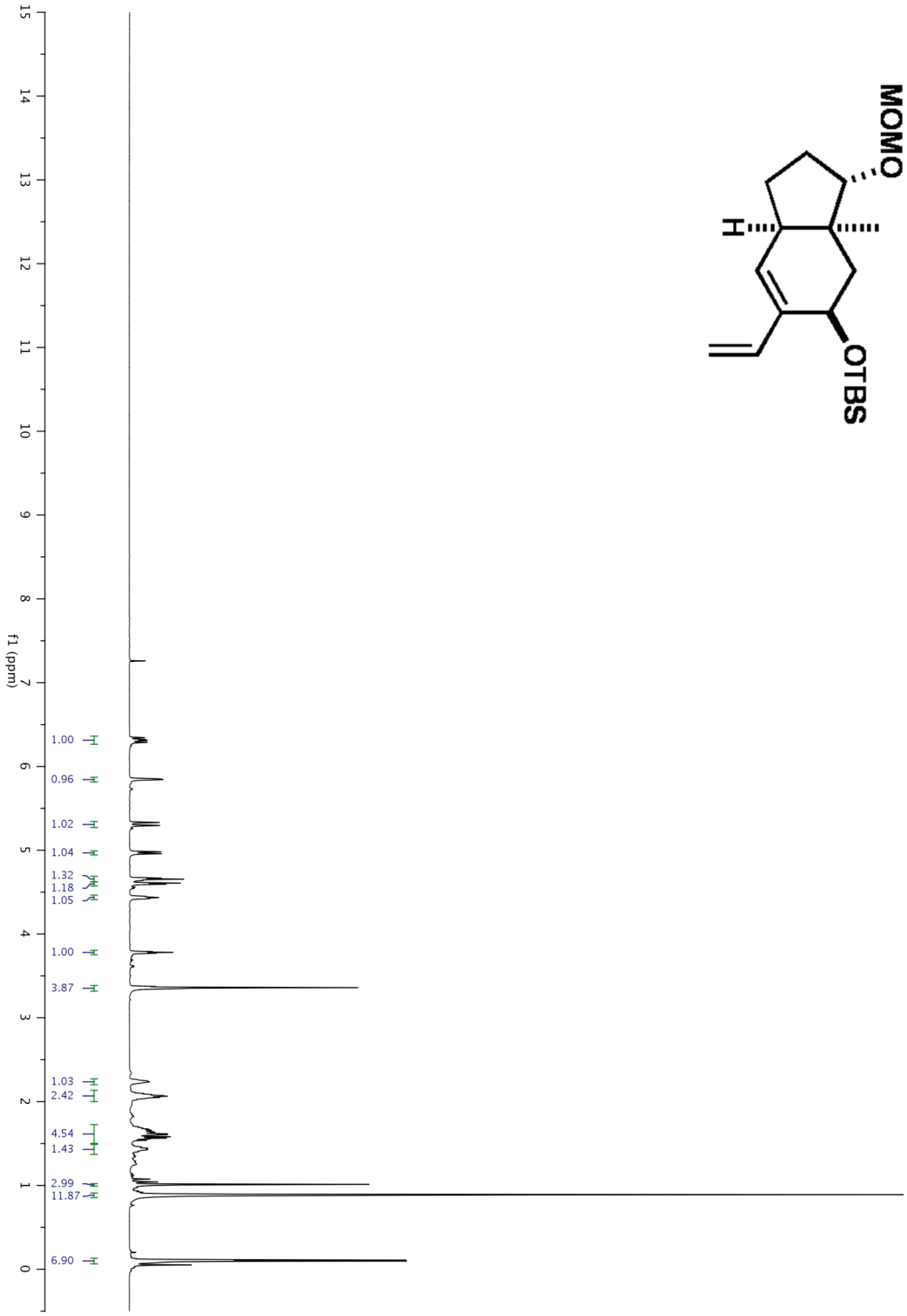
Retention Time	Area	Area Percent
13.173	5427320	50.360
14.293	5349756	49.640

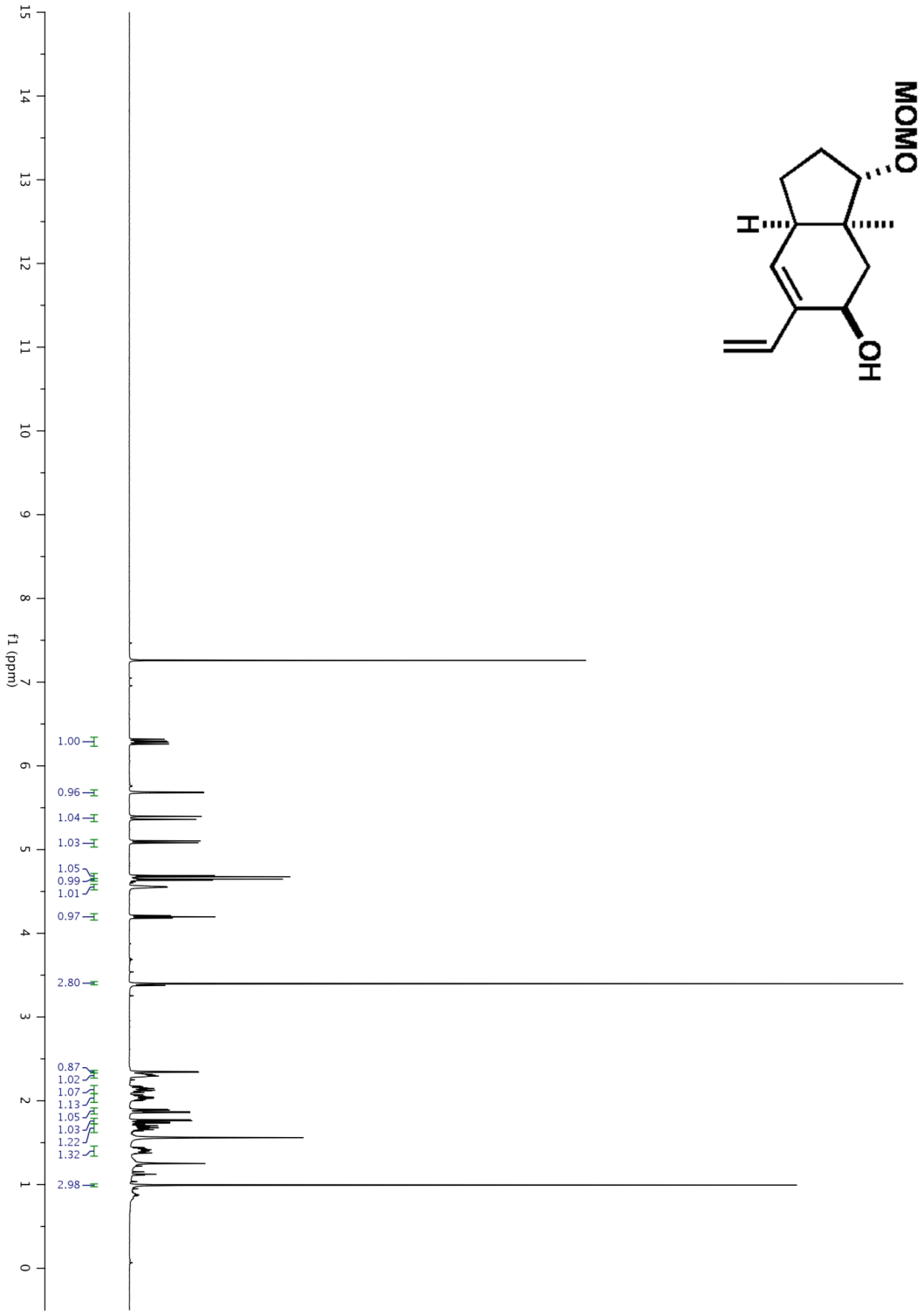
3.10. References and Notes

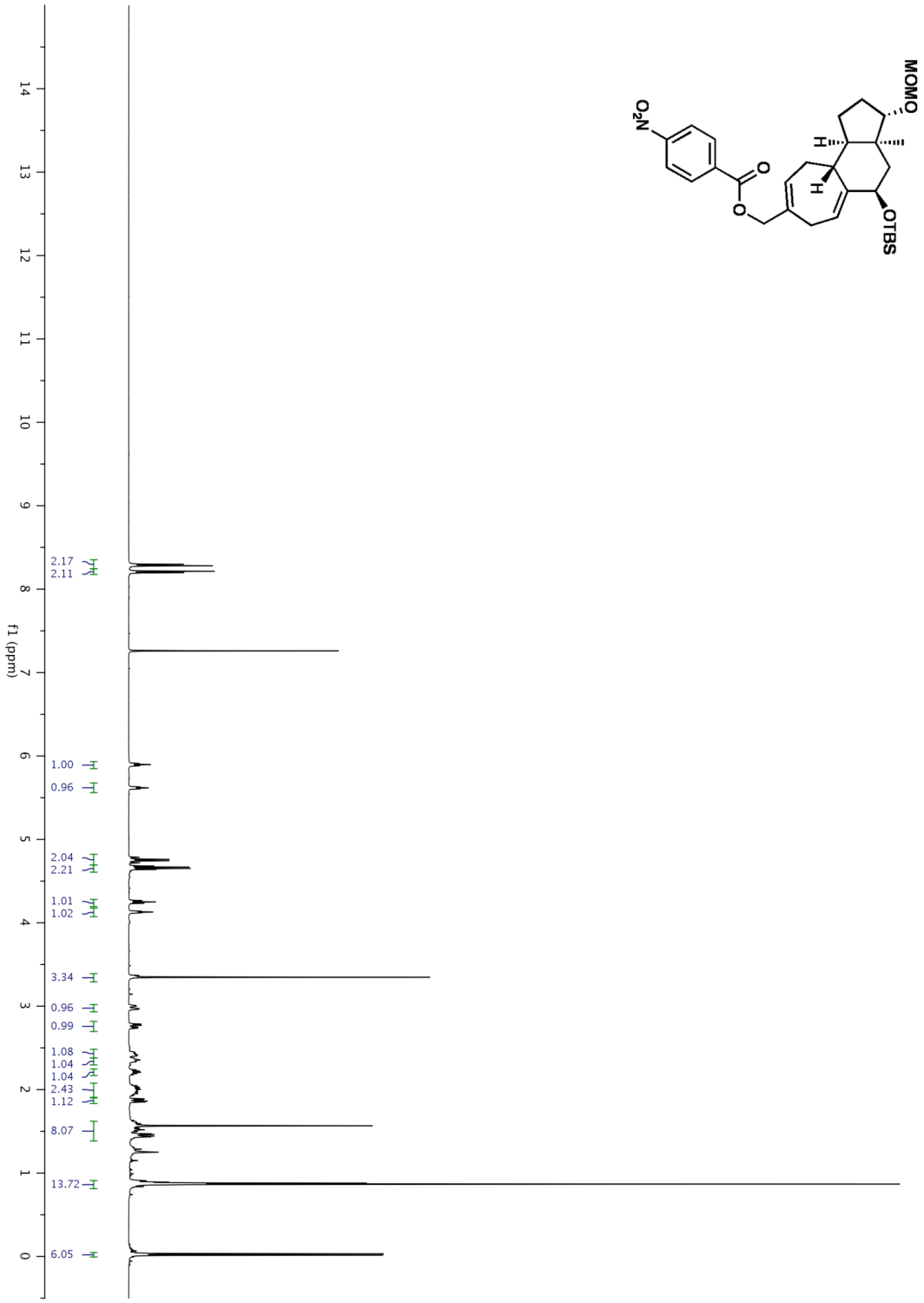
(1) Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009**, *38*, 3061.
(2) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, 2006.
(3) Vedejs, E.; Jure, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3974.
(4) Kagan, H. B.; Fiaud, J. C. In *Top. Stereochem.*; Eliel, E. L., Fiaud, J. C., Eds.; Wiley: New York, 1988; Vol. 18, p 249.
(5) Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231.
(6) Wu, B.; Parquette, J. R.; RajanBabu, T. V. *Science* **2009**, *326*, 1662.
(7) Webster, R.; Boing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444.
(8) Nadeau, E.; Ventura, D. L.; Brekan, J. A.; Davies, H. M. L. *J. Org. Chem.* **2010**, *75*, 1927.
(9) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 2734.
(10) Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368.
(11) Samanta, S.; Perera, S.; Zhao, C. G. *J. Org. Chem.* **2010**, *75*, 1101.
(12) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
(13) Davies, H. M. L.; Walji, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1733.
(14) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021.
(15) Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1990**, *Collect. Vol. VII*, 363.

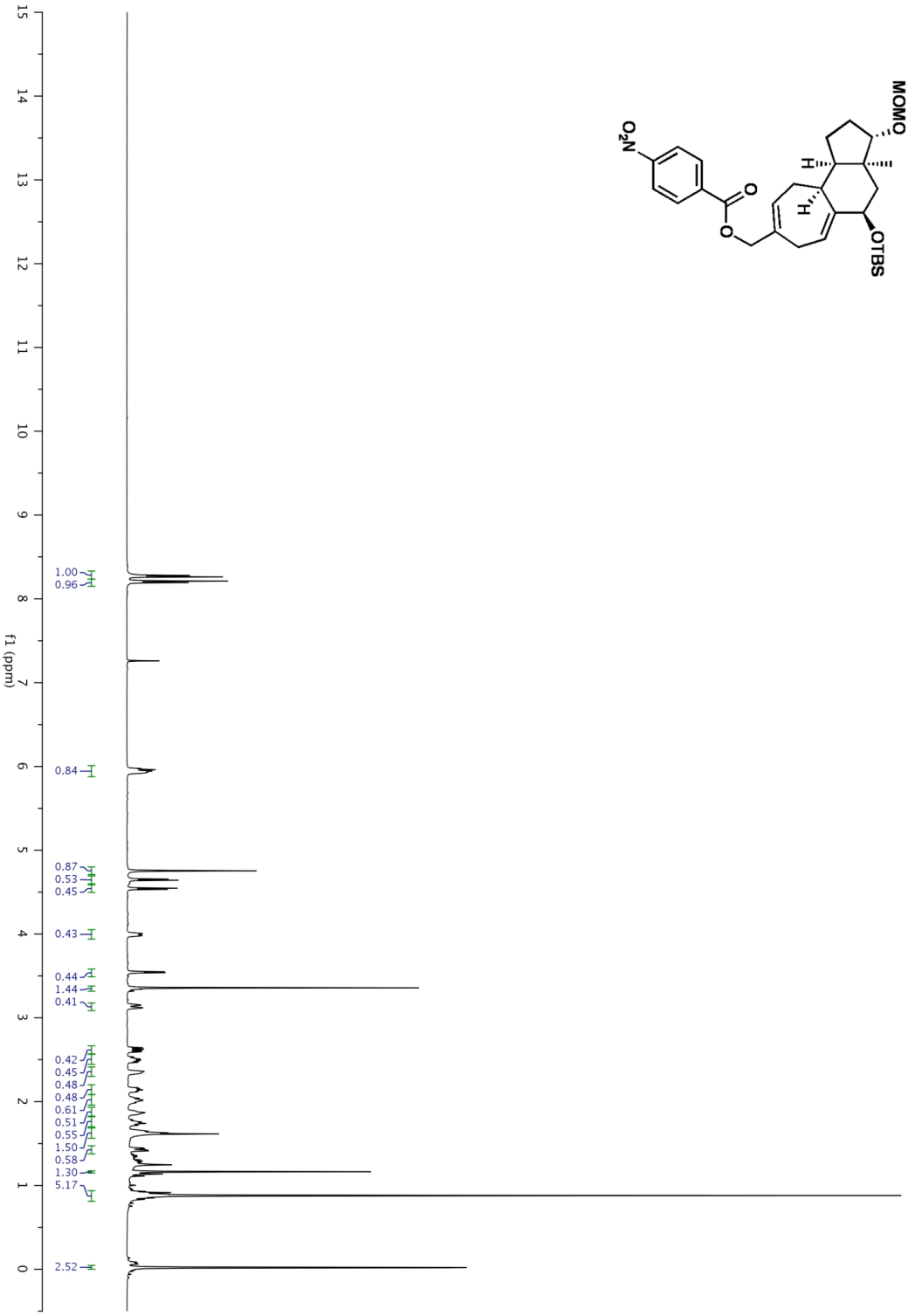
(16) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091.
(17) Rubottom, G. M.; Vazquez, M. A.; Pelegrin, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.
(18) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
(19) Davies, H. M. L.; Hougland, P. W.; Cantrell, W. R. *Synth. Commun.* **1992**, *22*, 971.
(20) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(21) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
(22) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.
(23) Sunnemann, H. W.; Hofmeister, A.; Magull, J.; de Meijere, A. *Chem. Eur. J.* **2007**, *13*, 3739.
(24) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951.
(25) Snider, B. B.; Vo, N. H.; O'Neil, S. V.; Foxman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 7644.
(26) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.
(27) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437.
(28) Davies, H. M. L.; Hansen, J., Personal Communication.

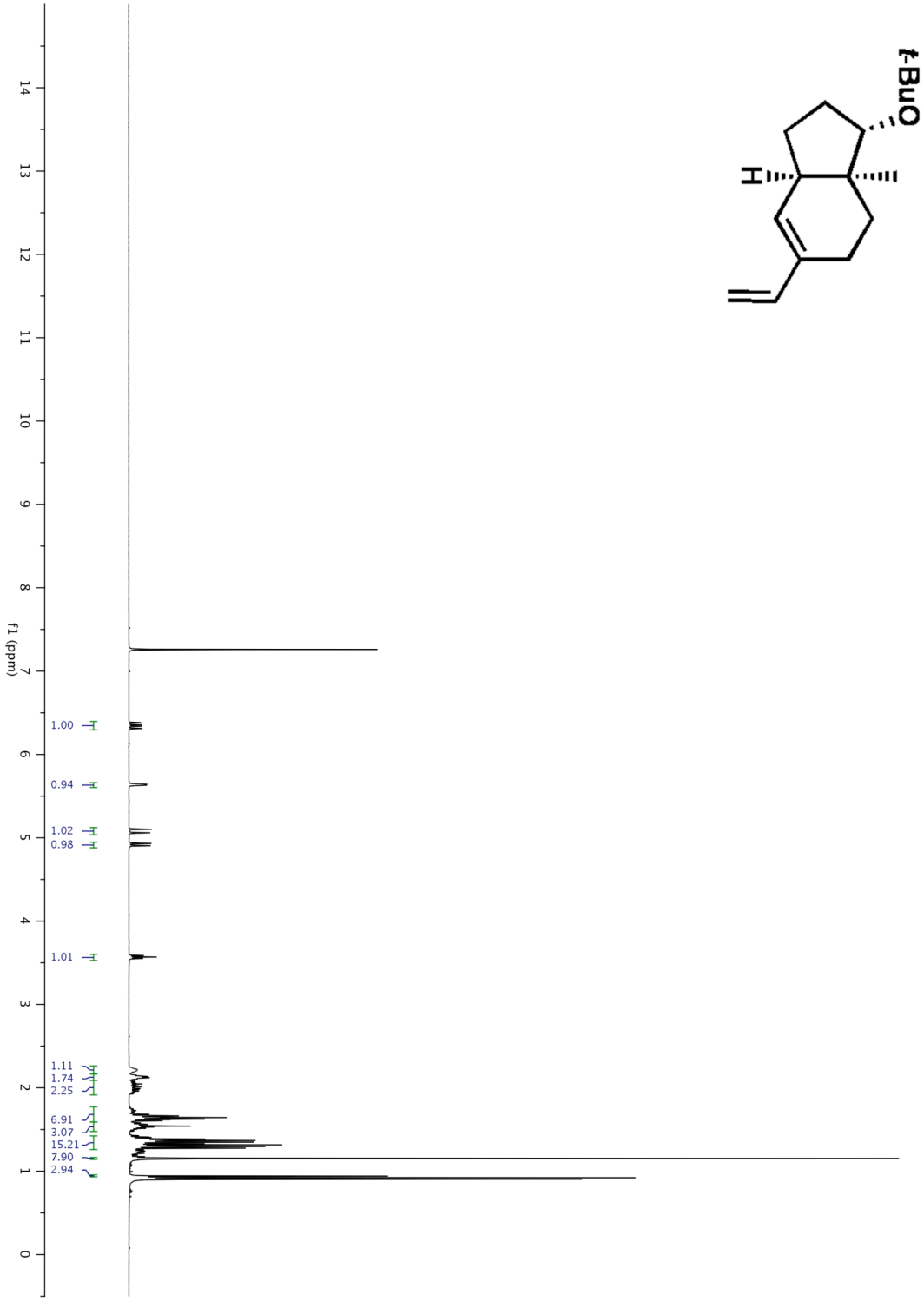
Appendix 2
Spectra Relevant to Chapter 3

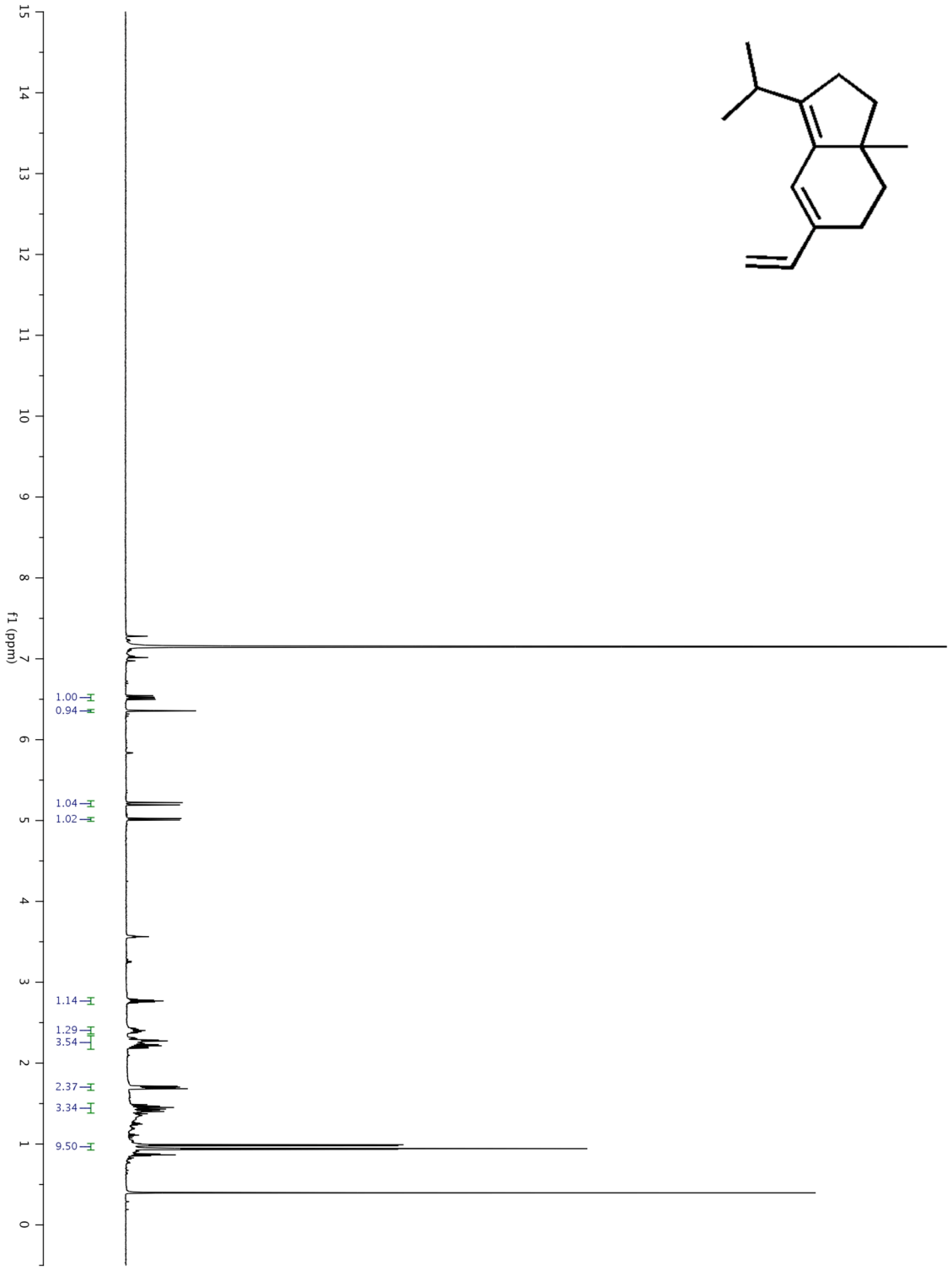

MOMO
H
OTBS
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
0.96
1.02
1.04
1.32
1.18
1.05
1.00
3.87
1.03
2.42
4.54
1.43
2.99
11.87
6.90


MOMO
H
OH
f1 (ppm)
1.00
0.96
1.04
1.03
1.05
0.99
1.01
0.97
2.80
0.87
1.02
1.07
1.13
1.05
1.03
1.22
1.32
2.98


f1 (ppm)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
2.17
2.11
1.00
0.96
2.04
2.21
1.01
1.02
3.34
0.96
0.99
1.08
1.04
1.04
2.43
1.12
8.07
13.72
6.05
O2N
O
O
H
H
MOMO
OTBS


MOMO
OTBS
O2N
H
H
O
O
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
0.96
0.84
0.87
0.53
0.45
0.43
0.44
1.44
0.41
0.42
0.45
0.48
0.48
0.61
0.51
0.55
1.50
0.58
1.30
5.17
2.52


t-BuO
H
f1 (ppm)
1.00
0.94
1.02
0.98
1.01
1.11
1.74
2.25
6.91
3.07
15.21
7.90
2.94


f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
0.94
1.04
1.02
1.14
1.29
3.54
2.37
3.34
9.50

Chapter 4
Studies Toward the Installation of the Second All-Carbon Quaternary Center

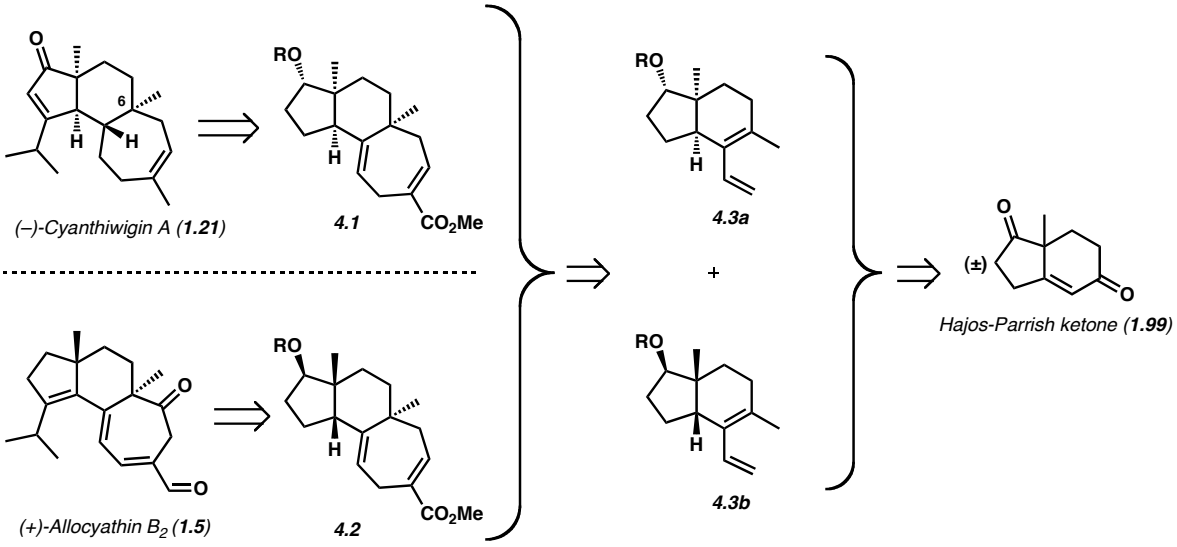
4.1. Introduction

A remaining challenge in our synthesis of the cyathane core is the stereoselective installation of the second all-carbon quaternary center. All-carbon quaternary centers are a classic and on-going challenge in organic synthesis.[1] We thought it would be possible to install the second all-carbon quaternary center during the [*3*,*3*] sigmatropic rearrangement of the divinylcyclopropane substrate, which would provide a stereoselective method to construct this important stereocenter in the cyanthiwigin and cyathane natural products.

4.2. Toward the Installation of the Second All-Carbon Quaternary Center

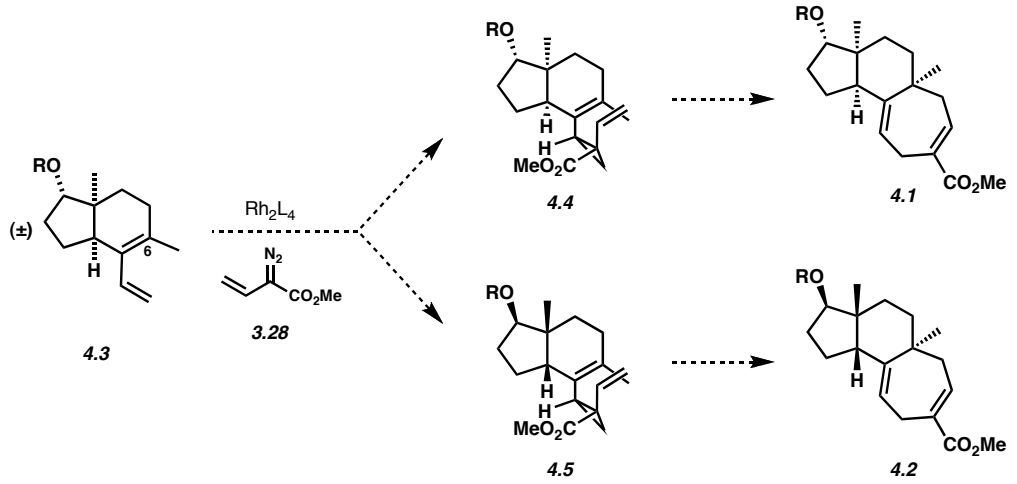
In our third-generation retrosynthesis of the cyanthiwigins and cyathanes, we reasoned that cyanthiwigin A (**1.21**) and allocyathin B_2 (**1.5**) could be constructed from simplified tricycles **4.1** and **4.2**, which possess both all-carbon quaternary centers. The tricycles **4.1** and **4.2** in turn could be derived from racemic diene **4.3**. Finally, diene **4.3** could arise from the Hajos-Parrish ketone (**1.99**).

Scheme 4.2.1. Third-generation retrosynthetic analysis of the cyanthiwigins and cyathanes.



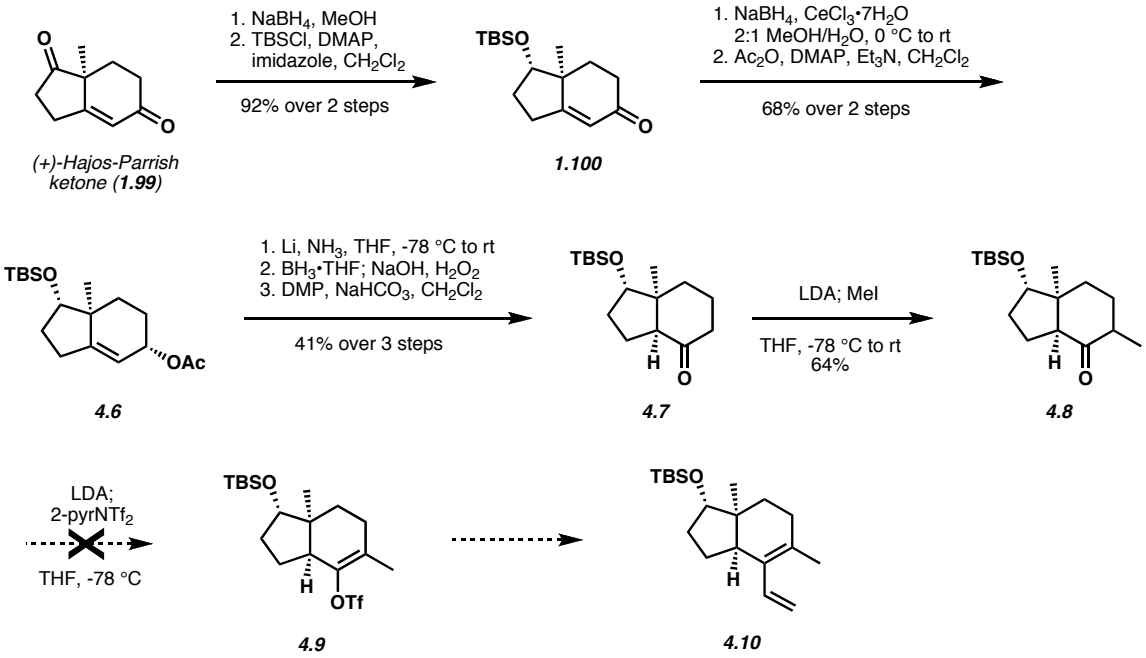
In diene **4.3**, the methyl group at C6 is in place prior to the cyclopropanation step (Scheme 4.2.2). The cyclopropanation/Cope rearrangement step now installs the second all-carbon quaternary center. In addition, the C6 stereocenter should be set diastereoselectively if good reagent control is obtained in the cyclopropanation step. For example, cyclopropanation from the β-face as shown in Scheme 4.2.2 would result in placing the C6 methyl group on the α-face of the tricycle (**4.1** and **4.2**). If successful, this stategy would constitute a powerful method to install the angular methyl group of C6.

Scheme 4.2.2. Stereodivergent RRM to install the C6 all-carbon quaternary center.



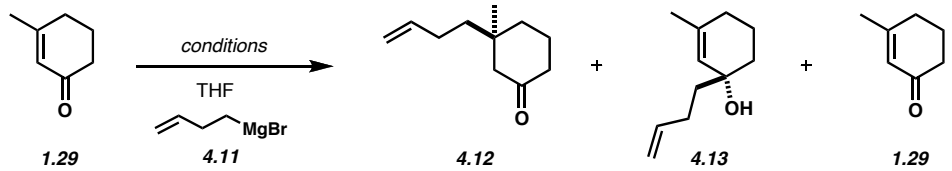
We initiated the synthesis of the target diene with the selective reduction of the Hajos-Parrish ketone (**1.99**), followed by silyl ether formation to furnish **1.100**. Acetate **4.6** was obtained via Luche reduction of enone **1.100** and acetylation.[2] Classical Birch reduction conditions efficiently cleaved the acetate, and a hydroboration/oxidation sequence gave access to ketone **4.7**.[2,3] Kinetic deprotonation of bicycle **4.7** with lithium diisopropylamide (LDA) and subsequent trapping with methyl iodide provided **4.8** as an inconsequential mixture of diastereomers. Unfortunately, the triflation step proved challenging, as we were unable to form enol triflate **4.9** via treatment with LDA followed by Comins' reagent.[4]

Scheme 4.2.3. Attempted synthesis of diene **4.10**.



Because of the difficulties associated with triflation of **4.8**, we pursued the desired diene motif in an alternative bicycle. Nearly all of the cyathane natural products possess a $\Delta^{2,3}$ A-ring with a C3 isopropyl group. Following the route developed by Tori[5] (Scheme 4.2.4; *c.f.* Chapter 1.4), we intended to construct cross-conjugated triene **4.19** with an A-ring functionalized for the cyathane diterpenoids. The first step of the sequence is the conjugate addition of homoallyl Grignard (**4.11**) into 3-methylcyclohexenone (**1.29**). Unfortunately, in our hands using the reported conditions (entry 1, Table 4.2.1), the reaction not only failed to reach completion, but also produced the 1,2-addition product (**4.13**) in amounts ranging from 1 : 0.2 **4.12**/**4.13** to 1 : 2.3 **4.12**/**4.13**. Decreasing the temperature only exacerbated the formation of 1,2-addition product **4.13** (entries 2 and 3). Concerned that our copper source was compromised, we utilized freshly-prepared copper(I) bromide-dimethylsulfide[6] or commercial copper(I) iodide with added dimethyl sulfide (entries 4 and 5) as the copper(I) source, but neither modification furnished an improved product distribution. Treatment with trimethylsilyl chloride (entry 6) helped to stem

Table 4.2.1. Conjugate addition conditions to form cyclohexanone **4.12**.



1.29 ***4.11*** ***4.12*** ***4.13*** ***1.29***

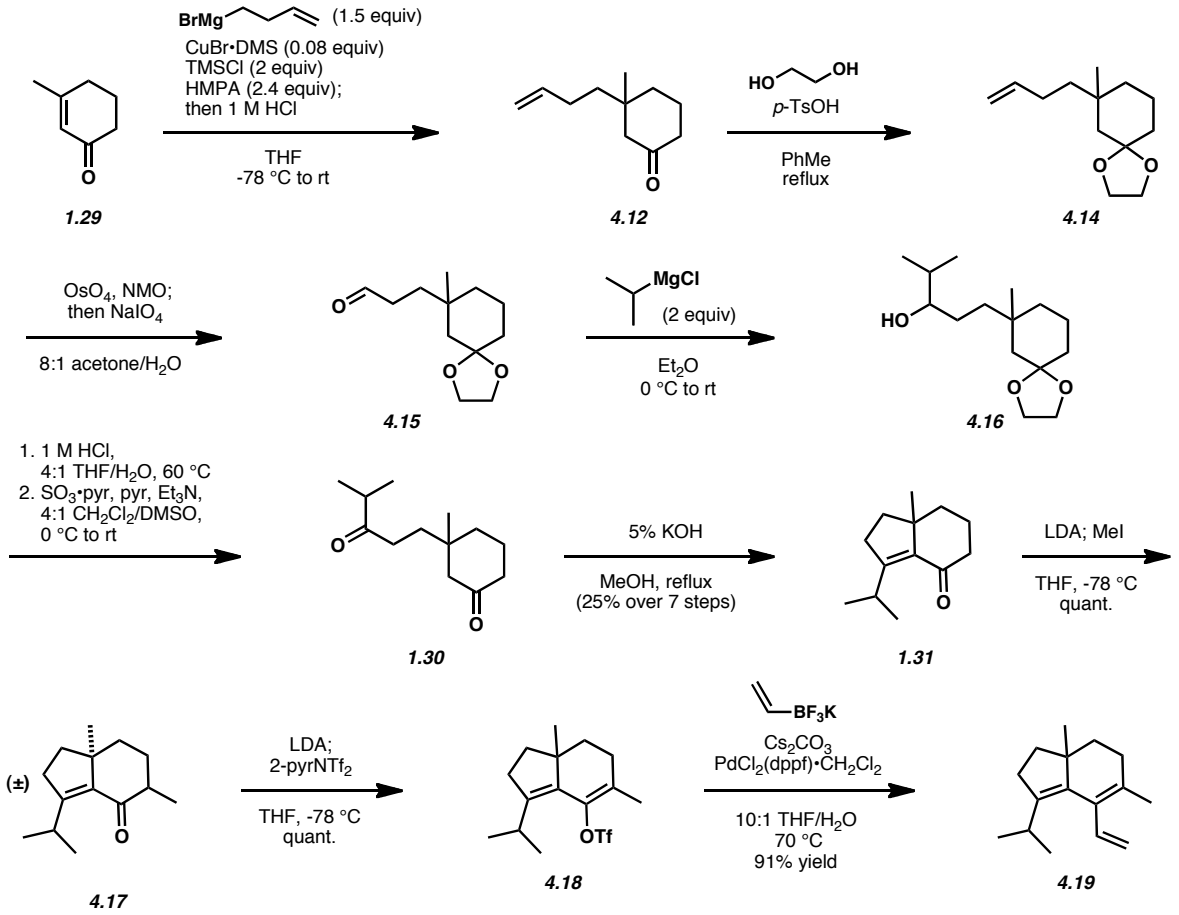
Entry	Conditions	Result (*4.12 : 4.13 : 1.29*)
1	CuBr•DMS[a] (0.6 equiv) ***4.11*** (3 equiv), -30 °C 2 h to 6 h	1 : 0.2 : 0.2
2	CuBr•DMS[a] (0.6 equiv) ***4.11*** (3 equiv), -42 °C 5 h	1 : 1 : 0
3	CuBr•DMS[a] (0.6 equiv) ***4.11*** (3 equiv), -78 °C 3 h	1 : 9 : 6
4	CuBr•DMS[b] (0.6 equiv) ***4.11*** (3 equiv), -30 °C 3 h	1 : 8 : 7
5	CuI (0.15 equiv) DMS (2 equiv) ***4.11*** (1.1 equiv), -78 °C 3 h	1 : 30 : 60
6	CuI•2 LiCl (0.05 equiv) TMSCl (2 equiv) ***4.11*** (1.1 equiv), -42 °C 3 h	1 : 0 : 12
7	CuBr•DMS (0.08 equiv) TMSCl (2 equiv) HMPA (2.4 equiv) ***4.11*** (1.5 equiv), -78 °C to rt 12 h; then 1 M HCl	1 : 0 : 0

[a] Acros; [b] Freshly prepared.

the formation of 1,2-addition product **4.13**, but the reaction failed to reach completion.[7] The addition of hexamethylphosphoramide (HMPA) to the reaction mixture along with the trimethylsilyl chloride (entry 7) was instrumental in facilitating the exclusive formation of 1,4-addition product **4.12** in a quantitative yield.[8]

Ketal protection of ketone **1.29** proceeded without event, but the oxidative cleavage of terminal alkene **4.14** to provide **4.15** was more problematic (Scheme 4.2.4). After ozonolysis, the decomposition of the secondary ozonide to the aldehyde under reductive conditions was challenging. Reduction using zinc with acetic acid[5] was ineffective in our hands, resulting in isolation of the secondary ozonide. Dimethylsulfide was a more efficient reductant, but when the reaction was run in methanol,[9] the dimethyl acetal of aldehyde **4.15** was isolated. Although running the reaction in dichloromethane solved this issue, we ultimately turned to a dihydroxylation/oxidation sequence as a more convenient and reliable route to aldehyde **4.15**. 1,2-Addition of isopropylmagnesium chloride furnished alcohol **4.16**.

Scheme 4.2.4. Synthesis of cross-conjugated triene **4.19**.

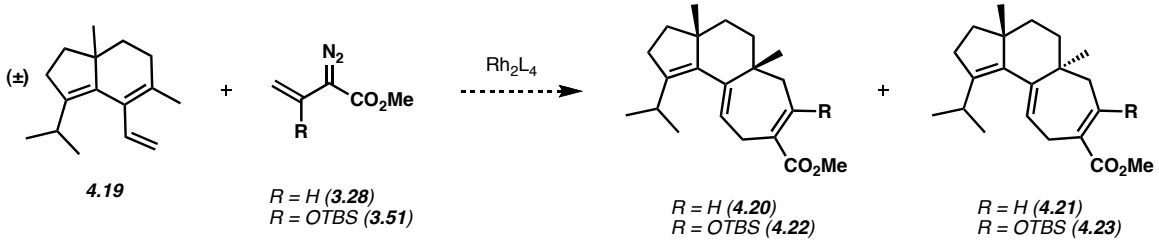


Though a Jones oxidation directly furnished diketone **1.30** from **4.16**,[5] we found that stepwise sequence beginning with the removal of the ketal followed by a Doering oxidation was more scalable. Diketone **1.30** underwent an intramolecular aldol condensation to form volatile enone **1.31**. Alkylation and triflation gave dienol triflate **4.18**. Initially, a Kumada coupling[10]

with vinylmagnesium bromide was pursued to form target bicycle **4.19**, but the desired product (**4.19**) was obtained in a 56% yield, along with unreacted starting material. Corey-modified Stille conditions[11] were successfully used to push the reaction to completion. However stannane byproducts were difficult to separate from cross-conjugated triene **4.19**, limiting the reaction's usefulness. In the end, a Suzuki coupling with potassium vinyltrifluoroborate[12] proved to be a superior approach, furnishing racemic bicycle **4.19** in 90% yield. It should be noted that each enantiomer of ketone **4.12** has been prepared previously using an asymmetric conjugate addition, so enantioenriched bicycle **4.19** should be similarly accessible.[13,14]

With target bicycle **4.19** in hand, we proceeded to test the key cyclopropanation/Cope rearrangement step (Scheme 4.2.5). We first investigated the use of vinyl diazoacetate **3.28**[15] with the $Rh_2[DOSP]_4$[16,17] catalysts. Despite our best efforts, the major product of the reaction was the starting bicycle. Diazoacetate **3.28** is sensitive to cyclization, forming the pyrazole at elevated temperatures (see Scheme 3.4.2). We therefore pursued the use of the $Rh_2[PTAD]_4$[18] catalysts with the more robust silyl enol ether diazoacetate **3.51**. Unfortunately, we were unable to isolate the desired cycloheptadiene (**4.22** or **4.23**) or the intermediate divinylcyclopropane from the rhodium(II)-catalyzed cyclopropanations conducted at a variety of temperatures. After computational modeling of cross-conjugated triene **4.19**, it became clear that the terminal alkene was nestled between the isopropyl substituent on the A-ring and the methyl group on the B-ring. Thus, the steric encumbrance of the alkene is likely a cause of the difficulties encountered in the cyclopropanation step.

Scheme 4.2.5. Attempted cyclopropanation of cross-conjugate triene **4.19**.



4.19

*R = H (**3.28**)*
*R = OTBS (**3.51**)*

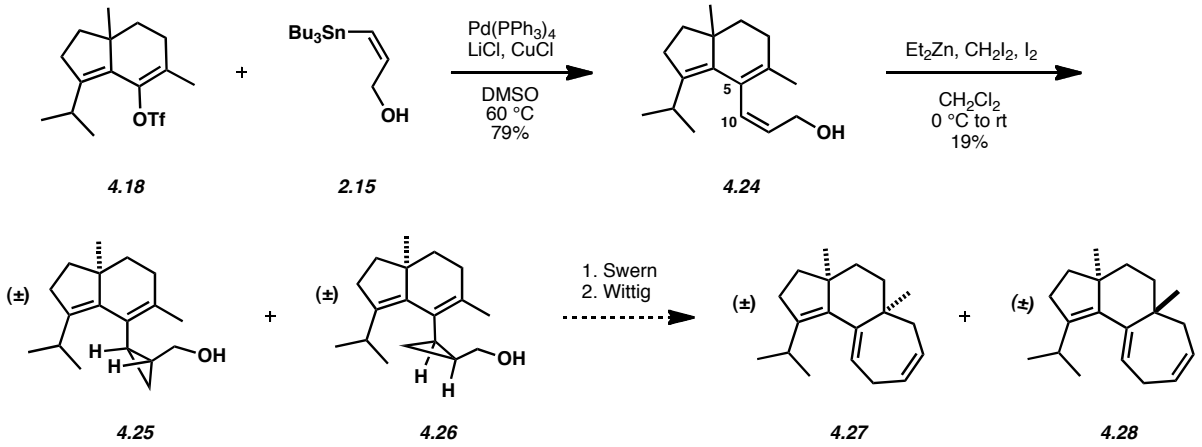
*R = H (**4.20**)*
*R = OTBS (**4.22**)*

*R = H (**4.21**)*
*R = OTBS (**4.23**)*

Because of this roadblock, we revisited our original strategy for the preparation of the tricycle (see Chapter 2). We reasoned that perhaps the appropriate allylic alcohol (**4.24**, Scheme 4.2.6) could help to direct a Simmons-Smith cyclopropanation to furnish cyclopropanols **4.25** and **4.26**, which in turn could be advanced to tricycles **4.27** and **4.28** after oxidation and olefination. Utilizing the previously synthesized stannane **2.15**,[19,20] a Corey-modified Stille coupling[11] furnished cross-conjugated trienol **4.24** in 79% yield. Simmons-Smith cyclopropanation[21] using diethylzinc and diidomethane in toluene at 45 °C was unsuccessful. The Denmark cyclopropanation conditions[22] only furnished small amounts of the cyclopropanols **4.25** and **4.26**. These results support the hypothesis that the alkene is sterically hindered, as do the NMR data, where broadening of the alkene peaks are observed, presumably due to slow rotation about C5-C10 bond in a sterically-congested environment. In order to selectively target the cyanthiwigins or the cyathanes, an asymmetric cyclopropation would be required. Considering the low yields of cyclopropanols **4.25** and **4.26** obtained, we doubted that dienol **4.24** could accommodate the additional steric bulk required in an asymmetric cyclopropanation,

for example using the Charette dioxaborolanes.[23] Combined, these factors limited the utility of this route.

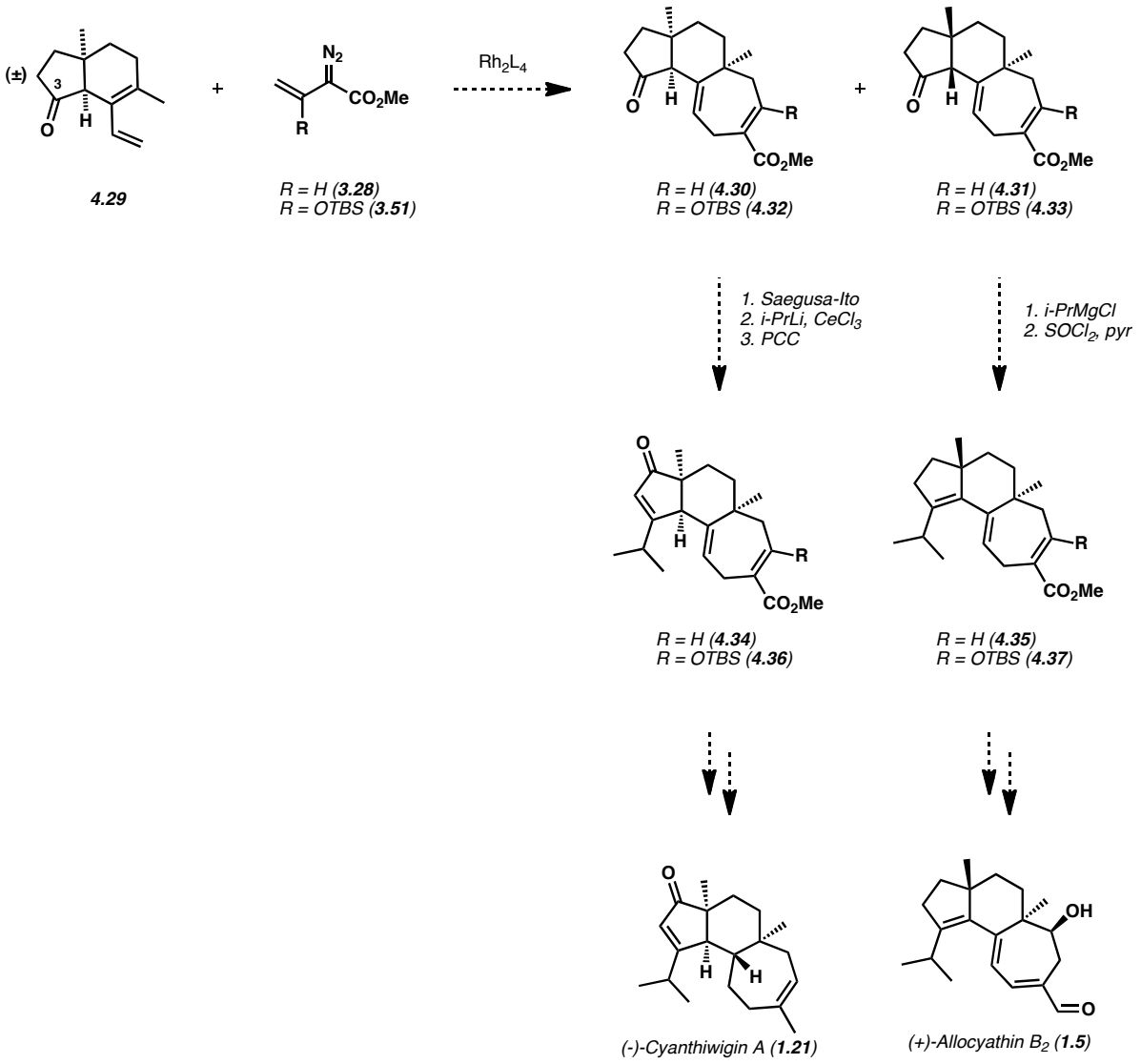
Scheme 4.2.6. Efforts toward the construction of tricycles **4.27** and **4.28**.



4.3. Future Directions

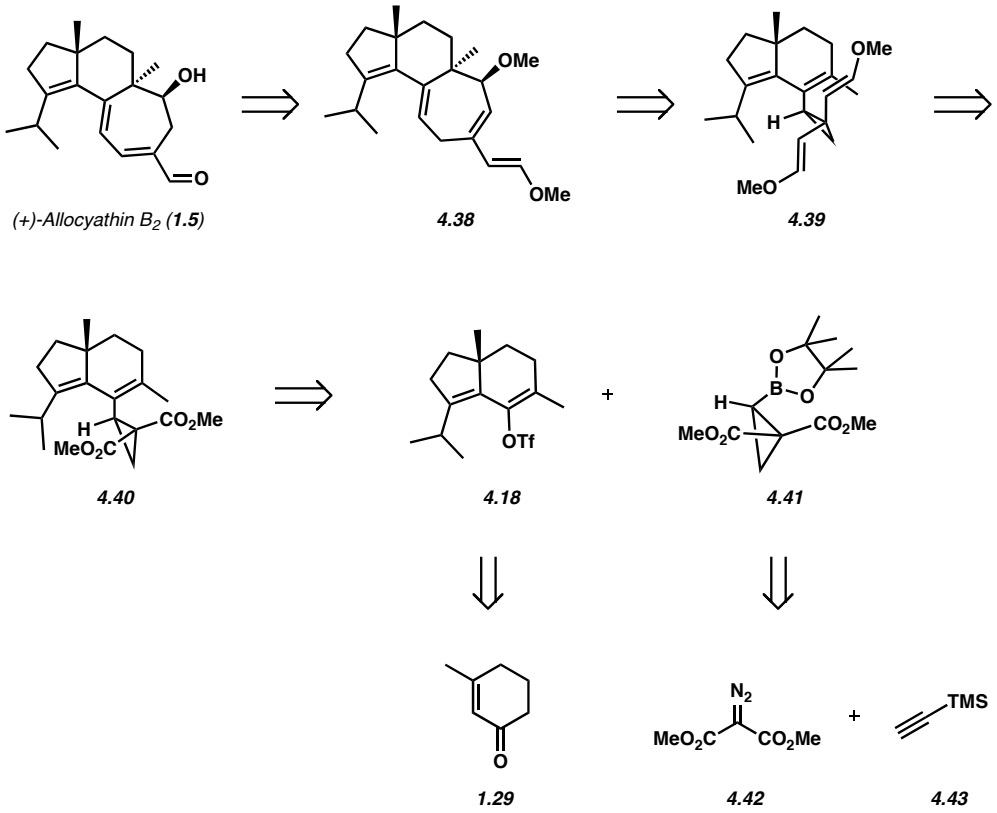
A key difficulty in the quest to install the second all-carbon quaternary center via the divinylcyclopropane Cope rearrangement was the isopropyl group on the A-ring, which appears to severely hinder the cyclopropanation step. To address this challenge, we would like to target diene **4.29** (Scheme 4.3.1). A ketone is at C3 on the A-ring of diene **4.29**, rather than the C3 isopropyl group of diene **4.19**, hopefully decreasing the steric encumbrance of the terminal alkene group. After a successful cyclopropanation/Cope rearrangement sequence, the appropriate A-ring functionalities could be installed on the cyanthiwigin core (**4.30** or **4.32**) and the cyathane core (**4.31** or **4.33**), respectively. A Saegusa-Ito oxidation could install an enone and, following the precedent of Phillips,[24] a 1,2-addition of isopropyllithium followed by an allylic transposition with pyridinium chlorochromate could furnish the completed A-ring (**4.34** or **4.36**) for cyanthiwigin A (**1.21**). Alternatively, a 1,2-addition of isopropylmagnesium chloride into ketone **4.31** or **4.33** followed by the elimination of the tertiary alcohol using the Nakada protocol[25] could provide the completed A-ring (**4.35** or **4.37**) for allocyathin B_2 (**1.5**). The flexibility afforded by this route is superior to the previous prefunctionalized A-ring substrate **4.19**, where more extensive functional group manipulation would be necessary to prepare the cyanthwigin A-ring.

Scheme 4.3.1. Proposed utilization of versatile diene **4.29** in the synthesis of the cyanthiwigin and cyathane natural products.



Alternatively, we could use a related prefunctionalized A-ring substrate to access allocyathin B_2 (**1.5**, Scheme 4.3.2). The natural product could be constructed from closely-related tricycle **4.38**. The seven-membered ring could be formed from divinylcyclopropane **4.39**. We postulated that Cope precursor **4.39** could arise from diester **4.40**, which in turn could be derived from a union of enol triflate **4.18** and cyclopropyl boronate **4.41**. We have already built enol triflate **4.18** from 3-methylcyclohexenone (**1.29**), and Gevorgyan has reported the synthesis of enantioenriched boronate **4.41** from diazoacetate **4.42** and trimethylsilylacetylene (**4.43**).[26]

Scheme 4.3.2. Retrosynthesis of (+)-allocyathin B_2 via a cross-coupling approach.



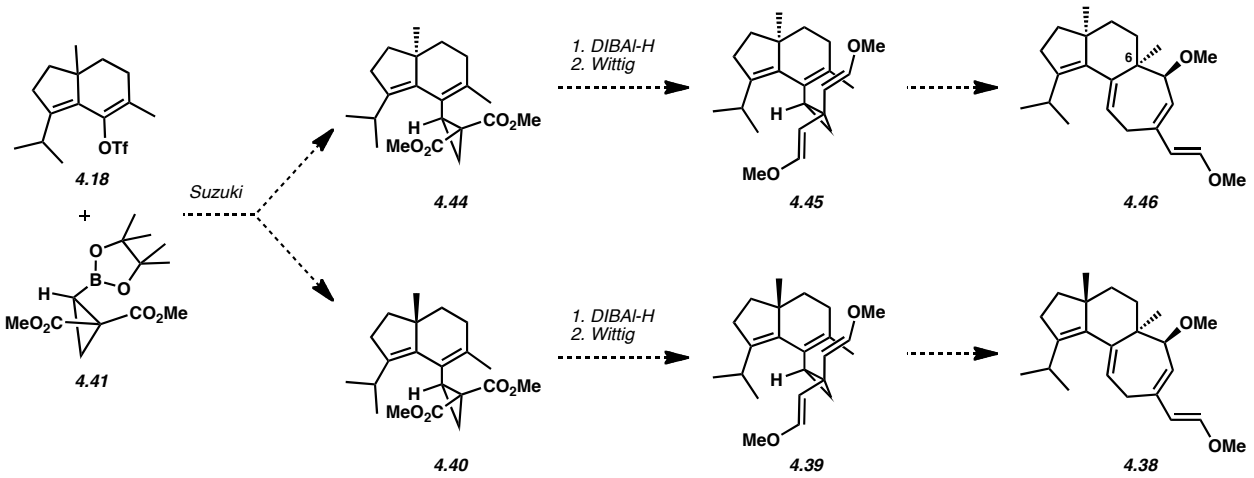
*(+)-Allocyathin B_2 (**1.5**)* ***4.38*** ***4.39***

4.40 ***4.18*** ***4.41***

1.29 ***4.42*** ***4.43***

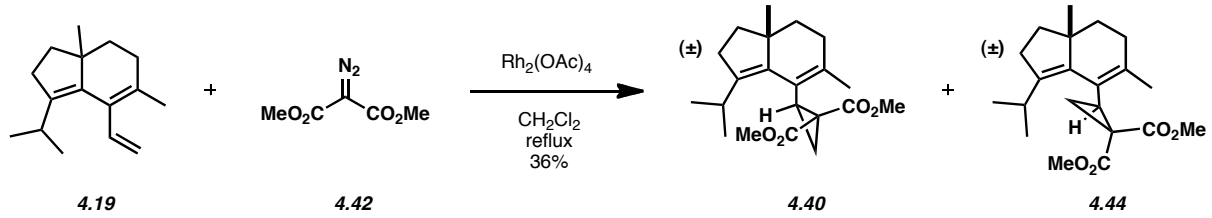
In this route, we prefunctionalize the boronate fragment **4.41** via enantioselective hydroboration across a cyclopropene. The Suzuki coupling becomes the sterically demanding step, rather than the rhodium(II)-mediated cyclopropanation, and should be able to accommodate higher reaction temperatures to drive the reaction to completion. If we utilize racemic dienol triflate **4.18** (Scheme 4.3.3), the stereodivergent RRM will not utilize a kinetic resolution, it will simply couple an enantioenriched boronate (**4.41**) to racemic triflate **4.18** to furnish two enantioenriched cyclopropanes (**4.44** and **4.40**). Each diester could then undergo further manipulations to form a dialdehyde, and then divinylcyclopropanes **4.45** and **4.39** after Wittig olefination. Only one of the methyl enol ethers should be in the proper *cis* orientation to undergo the [*3,3*] sigmatropic rearrangement to form tricycles **4.46** and **4.38**, stereoselectively installing the all-carbon quaternary center at C6. The desired cyanthiwigin and cyathane targets should be accessible from advanced tricycles **4.46** and **4.38**, respectively.

Scheme 4.3.3. Proposed stereodivergent Suzuki coupling to afford enantioenriched cyanthiwigin (**4.46**) and cyathane (**4.38**) cores.



To explore preliminary chemistry in this route, we sought to access racemic diesters **4.40** and **4.44**. When cross-conjugated triene **4.19** was subjected to diazoacetate **4.42**[27] in the presence of rhodium(II) acetate in refluxing dichloromethane, cyclopropanes **4.40** and **4.44** were isolated (Scheme 4.3.4). This result was surprising, considering our earlier difficulties in carrying out cyclopropanations of any kind on this type of substrate (see Chapter 4.2). Although diazoacetate **4.42** is known to be particularly difficult to use as a reagent in asymmetric cyclopropanations,[28] the formation of cyclopropanes **4.40** and **4.44** demonstrates that the rhodium-mediated cyclopropanation of bicycle **4.19** is possible. As such, we also need to revisit the cyclopropanation of this substrate with $Rh_2[PTAD]_4$ as well as other rhodium(II) sources.

Scheme 4.3.4. Cyclopropanation of cross-conjugated triene **4.19**.



4.4. Conclusion

We have developed a new approach to install the second all-carbon quaternary center of the cyanthiwigin and cyathane natural products via a Cope rearrangement. Starting from 3-methylhexenone (**1.29**), we have been able to construct two cross-conjugated trienes (**4.19** and **4.24**). Although both of these substrates proved to be sterically hindered, making cyclopropanation difficult, we have been able to successfully cyclopropanate each bicycle (see Schemes 4.2.6 and 4.3.4). We have also devised a strategy to install the bulky isopropyl group after formation of the tricyclic core of the cyanthiwigin and cyathane diterpenoids, as well as a route that installs the cyclopropane via a Suzuki coupling. These strategies should provide

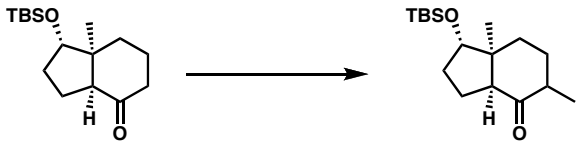
powerful methods to stereoselectively install the second all-carbon quaternary center at the ring fusion position of the cyanthiwigin and cyathane diterpenoids.

4.5. Experimental Contributions

Laura C. Miller carried out the research detailed in Chapter 4.

4.6. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) was dried over alumina under a nitrogen atmosphere in a GlassContour solvent system. Dichloromethane (DCM) was distilled over calcium hydride. Pentane was dried over 4 Å MS, and sparged with nitrogen. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 23 °C refer to oil bath temperature, which was controlled by an OptiCHEM temperature modulator. Thin layer chromatography was performed using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. SiliCycle Silica-P silica gel (particle size 40-63 μm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVB-400, DRX-500, AV-500 and AV-600 MHz spectrometers with ^{13}C operating frequencies of 100, 125, 125 and 150 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$: δ = 7.26 for ^{1}H NMR and δ = 77.0 for ^{13}C NMR; C_6D_6: δ = 7.15 for ^{1}H NMR and δ = 128.39 for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), br (broad). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley.



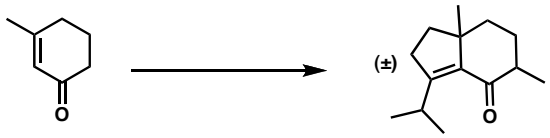
4.7 *4.8*

α-Methyl Ketone (4.8): To a solution of diisopropylamine (0.060 mL, 0.46 mmol) in 3 mL THF at 0 °C was added 0.17 mL *n*-BuLi (2.5 M in hexanes, 0.42 mmol) dropwise. The reaction mixture was stirred at 0 °C for 20 minutes, and was then cooled to -78 °C. A solution of ketone **4.7**[2,3] (0.102 mg, 0.355 mmol) in 0.5 mL THF was added dropwise to the reaction mixture. After stirring for 1.5 h at -78 °C, methyl iodide (0.040 mL, 0.73 mmol) was added dropwise. The reaction was maintained at -78 °C for an additional 30 min, and was then stirred at room temperature for 30 min. Saturated aq. NH_4Cl solution (3 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layer was washed with brine (3 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The

crude yellow oil obtained was purified via flash chromatography (gradient of 20:1 hexanes/EtOAc to 9:1 hexanes/EtOAc) to afford a combined 69 mg of both diastereomers of **4.8** as a yellow oil (64% combined yield, 1:1 dr).

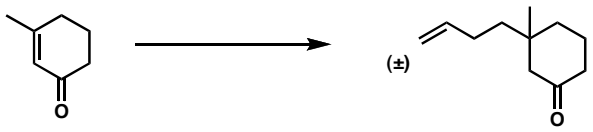
4.8a: $\mathbf{R_f}$ 0.49 (9:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.64 (t, *J* = 8.5 Hz, 1H), 2.40-2.25 (m, 3H), 1.95-1.73 (m, 3H), 1.73-1.59 (m, 2H), 1.51-1.35 (m, 2H), 1.05-0.98 (m, 6H), 0.86 (s, 9H), 0.00 - -0.05 (d, *J* = 2.8 Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 213.3, 73.3, 56.3, 50.3, 44.3, 31.8, 31.1, 29.1, 25.7, 22.5, 17.9, 17.9, 14.7, -4.4, -5.1.

4.8b: $\mathbf{R_f}$ 0.42 (9:1 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.71 (dd, *J* = 5.4, 2.5 Hz, 1H), 2.64-2.51 (m, 2H), 2.28-2.16 (m, 1H), 2.09-1.97 (m, 1H), 1.96-1.79 (m, 2H), 1.70-1.52 (m, 2H), 1.45-1.35 (m, 1H), 1.31-1.22 (m, 1H), 1.03 (d, *J* = 6.6 Hz, 3H), 1.00 (s, 3H), 0.87 (s, 9H), 0.04-0.00 (m, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.4, 80.8, 57.0, 40.4, 33.2, 31.4, 31.4, 26.2, 25.8, 25.7, 19.8, 18.0, 14.9, -4.6, -5.0; **IR** (film) ν_{max} 2956, 2930, 1705 cm^{-1}; **HRMS** (EI+) calcd for $[C_{17}H_{32}O_2Si]^+$: *m/z* 296.2172, found 296.2169.



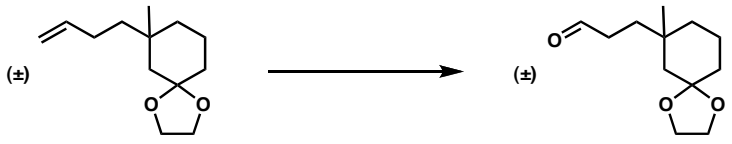
1.29 *4.17*

The procedures of Tori[5] were largely followed to synthesize bicycle **4.17** from 3-methylcyclohexenone (**1.29**). The steps where alternative conditions were used are described below.



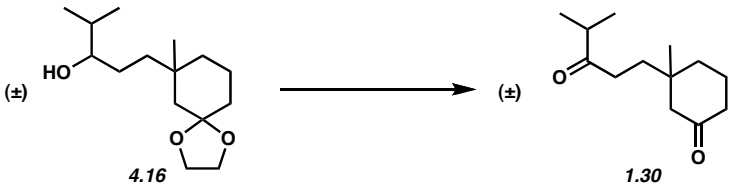
1.29 *4.12*

Cyclohexanone (4.12): To a solution of homoallylmagnesium bromide (25.1 mL, 2.9 M in THF, 72.7 mmol) in 70 mL THF at -78 °C was added 0.80 g CuBr•DMS (3.9 mmol) and 20.5 mL HMPA (116 mmol). After 5 min, a solution of 3-methylcyclohexenone (**1.29**, 5.0 mL, 49 mmol) and trimethylsilyl chloride (12.5 mL, 97.0 mmol) in 50 mL THF was added over 30 min. The reaction mixture was stirred at -78 °C for an additional 2 hours, and then allowed to return to room temperature overnight (12 h). 1 M HCl (35 mL) was added, and the resulting mixture was stirred for an hour at room temperature before separating the layers. The aqueous layer was extracted with ether (2 x 75 mL). The combined organic layer was washed sequentially with water (6 x 350 mL), saturated aq. $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL). The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure to afford 8.0 g of **4.12** as a pale yellow oil that was carried on crude. $\mathbf{R_f}$ 0.52 (7:3 hexanes/EtOAc). The spectral data agreed with that reported for cyclohexanone **4.12**.[5]



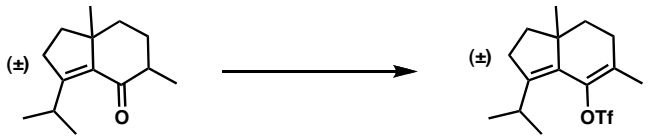
4.14 *4.15*

Aldehyde (4.15): Crude alkene **4.14** (7.74 g, 36.8 mmol) was dissolved in an 8:1 mixture of acetone/water (50 mL). N-methylmorpholine (9.49 g, 81.0 mmol) and osmium tetroxide (0.61 mL, 2.5% wt/vol in *t*-BuOH, 0.050 mmol) were added, and the reaction mixture was stirred at room temperature until the dihydroxylation was complete (18 h). The reaction mixture was diluted with 260 mL acetone and 30 mL water. Sodium periodate (25.9 g, 0.121 mol) was added and the reaction was stirred for 19 h at room temperature. After dilution with 400 mL Et_2O, the organic layer was separated and washed with saturated aq. Na_2SO_3 (200 mL), saturated aq. $NaHCO_3$ (200 mL) and brine (200 mL). The solution was dried over Na_2SO_4 and concentrated to afford 5.76 g of a pale yellow oil which was used directly in the next reaction. $\mathbf{R_f}$ 0.45 (7:3 hexanes/EtOAc). The spectral data were consistent with that reported for aldehyde **4.15**.[5]



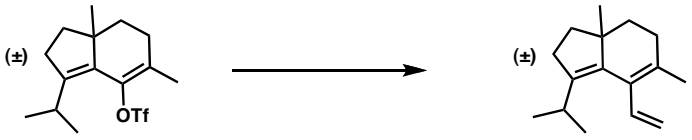
4.16 *1.30*

Diketone (1.30): To a reaction flask equipped with a reflux condensor was added a solution of crude alcohol **4.16** (6.34 g, 24.7 mmol) in a 4:1 mixture of THF/H_2O (50 mL). Following the addition of 1 M HCl (19 mL), the reaction mixture was stirred at 60 °C for 3 h. After cooling to 0 °C, a saturated aq. $NaHCO_3$ solution (25 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (2 x 75 mL) and the combined organic layer was washed with brine (25 mL). The solution was dried over $MgSO_4$ and concentrated under reduced pressure to afford hydroxy ketone **4.47** as a yellow oil (5.3 g). The crude hydroxy ketone (5.3 g, 24 mmol) was dissolved in a 4:1 mixture of CH_2Cl_2/DMSO (120 mL). Et_3N (16 mL, 0.11 mol), pyridine (12 mL, 0.15 mol) and SO_3•pyr (6.8 g, 43 mmol) were added to the stirred reaction mixture at 0 °C, which was allowed to return to room temperature over 21 h. The reaction was poured onto water (75 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic layers were washed sequentially with water (3 x 150 mL), 10% aq. $CuSO_4$ solution (150 mL) and brine (150 mL). The solution was dried over Na_2SO_4 and concentrated to afford 4.76 g of diketone **1.30** as a yellow oil. The crude material was taken onward to the next step. $\mathbf{R_f}$ 0.62 (6:4 hexanes/EtOAc). The spectral data were consistent with that reported for diketone **1.30**.[5]



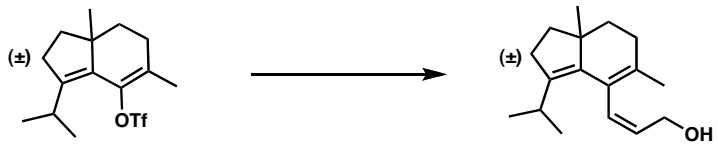
4.17 *4.18*

Enol Triflate (4.18): *n*-BuLi (0.91 mL, 2.3 mmol) was added dropwise to a solution of diisopropylamine (0.33 mL, 2.4 mmol) in THF (18 mL) at 0 °C. After stirring at 0 °C for 20 min, the reaction was cooled to -78 °C. A solution of enone **4.17** (0.39 g, 1.9 mmol) in 2.5 mL THF was added dropwise. The reaction mixture was stirred at -78 °C for 1.5 h, at which time a solution of 2-pyrNTf$_2$[4] (0.76 g, 2.1 mmol) in 2.5 mL THF was added. The reaction was stirred at -78 °C for 1.5 h, then warmed to 0 °C and quenched with a saturated aq. $NaHCO_3$ solution (10 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated. The crude material was purified via column chromatography (98:2 hexanes/Et_3N) to give enol triflate **4.18** as a pale yellow oil in quantitative yield (0.64 g). $\mathbf{R_f}$ 0.72 (9:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.436-3.33 (m, 1H), 2.37-2.27 (m, 1H), 2.22-2.14 (m, 1H), 2.06-1.96 (m, 1H), 1.67-1.54 (m, 4H), 1.35-1.28 (m, 2H), 1.28-1.18 (m, 2H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.00-0.96 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.39, 140.00, 130.60, 129.24, 120.76, 118.21, 49.48, 38.80, 37.28, 32.33, 29.81, 28.17, 22.33, 21.94, 20.71; **IR** (film) ν_{max} 2927, 1417, 1209 cm^{-1}; **HRMS** (EI+) calcd for $[C_{15}H_{21}F_3O_3S]^+$: *m/z* 338.1164, found 338.1170.



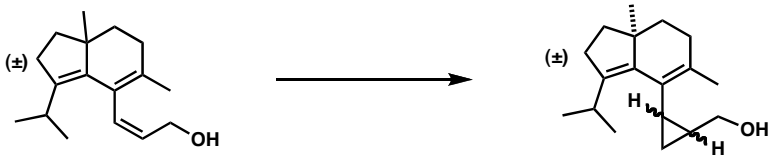
4.18 *4.19*

Triene (4.19): To a Schlenk flask was added potassium vinyltrifluoroborate (0.20 g, 1.5 mmol), cesium carbonate (1.4 g, 4.4 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (97 mg, 0.13 mmol) and enol triflate **4.18** (0.46 g, 1.4 mmol) in a 10:1 THF/water solution (33 mL). The reaction mixture was sparged with nitrogen for 15 minutes, then sealed and stirred at reflux for 18 h. The reaction mixture was poured onto water (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated. Column chromatography (10:1 pentane/Et_2O) afforded triene **4.19** as a pale yellow oil in 91% yield (0.26 g). $\mathbf{R_f}$ 0.80 (9:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, C_6D_6) δ 6.55 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.22-5.10 (m, 2H), 3.42-3.33 (m, 1H), 2.49-2.38 (m, 1H), 2.35-2.25 (m, 1H), 2.15-2.04 (m, 1H), 2.03-1.94 (m, 1H), 1.76-1.67 (m, 4H), 1.60-1.47 (m, 3H), 1.03 (s, 3H), 1.01 (d, *J* = 3.0 Hz, 3H), 1.00 (d, *J* = 3.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.6, 137.3, 137.1, 133.4, 129.8, 116.6, 46.9, 38.7, 38.0, 32.0, 29.1, 28.0, 22.7, 22.2, 21.1, 20.5; **IR** (film) ν_{max} 3082, 2923, 1621, 1449, 913 cm^{-1}; **HRMS** (EI+) calcd for $[C_{16}H_{24}]^+$: *m/z* 216.1878, found 216.1873.



4.18 *4.24*

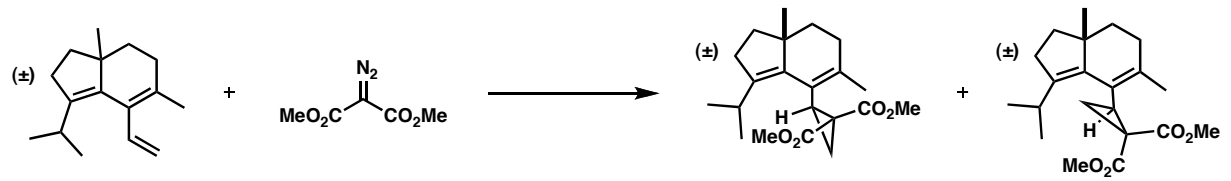
Allylic alcohol (4.24): To a flame dried Schlenk flask was added lithium chloride (0.48 g, 11 mmol) and the salt was flame-dried under vacuum until the solid was free-flowing (around 1 min). After cooling under a nitrogen atmosphere, $Pd(PPh_3)_4$ (0.21 g, 0.19 mmol) and copper(I) chloride (0.46 g, 9.5 mmol) were added and the Schlenk was evacuated and refilled with nitrogen four times. A solution of enol triflate **4.18** (0.64 g, 1.9 mmol) and stannane **2.15** (1.0 g, 2.9 mmol) in DMSO (16 mL) was added to the reaction mixture. After sparging with nitrogen for 15 min, the Schlenk was sealed and the reaction mixture was stirred at 60 °C for 12 h. After cooling, the reaction mixture was diluted with Et_2O (35 mL) and washed with a 5:1 brine/5% NH_4OH solution (15 mL). The aqueous layer was extracted with Et_2O (2 x 35 mL). The combined organic layer was washed with water (2 x 20 mL) and brine (2 x 20 mL). The solution was dried over $MgSO_4$ and concentrated under reduced pressure. Pure allylic alcohol **4.24** was obtained as a pale yellow oil (0.37 g, 79% yield) after flash chromatography (gradient of hexanes to 9:1 hexanes/EtOAc). $\mathbf{R_f}$ 0.30 (4:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, C_6D_6) δ 6.14 (br s, 1H), 5.69-5.57 (m, 1H), 4.13- 3.84 (br m, 2H), 3.48 (br s, 1H), 2.48- 2.33 (m, 1H), 2.31-2.21 (m, 1H), 2.19-2.06 (m, 1H), 1.99-1.85 m, 1H), 1.74-1.38 (m, 7H), 1.05-0.81 (m, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 140.7, 135.9, 133.0, 131.3, 129.6, 125.6, 60.2, 45.8, 38.3, 36.7, 30.6, 28.4, 27.8, 26.8, 21.7, 20.4, 17.5; **IR** (film) ν_{max} 3337, 2922, 1444, 1020 cm^{-1}; **HRMS** (EI+) calcd for $[C_{17}H_{26}O]^+$: *m/z* 246.1984, found 246.1991.



4.24 *4.48*

Cyclopropanol (4.48): To flask A was added allylic alcohol **4.24** (12 mg, 0.047 mmol). Flask A was evacuated and refilled 3 times with nitrogen and then CH_2Cl_2 (0.3 mL) was added. Diethylzinc (0.04 mL, 1.95 M in CH_2Cl_2, 0.078 mmol) was added to flask A at 0 °C, and the reaction mixture was stirred for 10 min at 0 °C. To flask B was added iodine (44 mg, 0.17 mmol) in 0.8 mL CH_2Cl_2. Diethylzinc (0.045 mL, 1.95 M in CH_2Cl_2, 0.088 mmol) was added to flask B at 0 °C and the reaction mixture was stirred for 10 min at that temperature. To a solution of diiodomethane (0.013 mL, 0.16 mmol) in 2 mL CH_2Cl_2 in flask C was added diethylzinc at 0 °C (0.08 mL, 1.95 M in CH_2Cl_2, 0.16 mmol), and the reaction mixture was stirred for 5 min at 0 °C. The contents of flask A were added to flask B at 0 °C over 30 s. After stirring for 2 min at 0 °C, the contents of flask B were added to flask C over 30 s. The reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature over 12 h. The reaction was quenched with 1 M NaOH (2 mL) solution at 0 °C. After separation, the aqueous layer was extracted with

CH_2Cl_2 (2 x 5 mL). The combined organic layer was washed with brine (2 mL), dried over $MgSO_4$ and concentrated. Column chromatography (gradient of 20:1 hexanes/EtOAc to 9:1 hexanes/EtOAc) furnished cyclopropanol **4.48** as a single diastereomer (2.3 mg, 19% yield). $\mathbf{R_f}$ 0.34 (4:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 3.53-3.44 (m, 2H), 3.18-3.10 (m, 1H), 2.46- 2.37 (m, 1H), 2.37- 2.30 (m, 1H), 2.29-2.20 (m, 1H), 2.03-1.96 (m, 1H), 1.85 (s, 3H), 1.79 (dd, *J* = 9.6, 3.8 Hz, 1H), 1.72-1.66 (m, 1H), 1.65-1.59 (m, 1H), 1.58-1.44 (m, 2H), 1.29-1.23 (m, 1H), 1.19-1.12 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.00-0.96 (m, 6H), 0.34-0.28 (m, 1H); **HRMS** (EI+) calcd for $[C_{18}H_{28}O]^+$: *m/z* 260.2140, found 260.2148.



4.19 *4.42* *4.40* *4.44*

Cyclopropanes (4.40 and **4.44):** To a refluxing solution of triene **4.19** (14 mg, 0.065 mmol) and $Rh_2(OAc)_4$ (1.7 mg, 3.8 x 10^{-3} mmol) in 0.3 mL CH_2Cl_2 was added a solution of diazoacetate **4.42**[27] (20 mg, 0.13 mmol) in CH_2Cl_2 (0.16 mL) over 2 h via syringe pump. Following addition, the reaction mixture was stirred at reflux for a further 30 min. After cooling, the reaction mixture was passed through a plug of silica with CH_2Cl_2 and concentrated. The crude product was purified by flash chromatography (gradient of hexanes to 30:1 hexanes/EtOAc) to furnish 8.2 mg of cyclopropanes **4.40** and **4.46** as a mixture of diastereomers in 36% yield. $\mathbf{R_f}$ 0.45 (9:1 hexanes/EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.77 (s, 1H), 3.63 (s, 1H), 3.14-3.05 (m, 1H), 2.42-2.31 (m, 1H), 2.30-2.22 (m, 1H), 2.16-2.06 (m, 1H), 2.05-1.96 (m, 1H), 1.86-1.81 (m, 1H), 1.76 (s, 3H), 1.72-1.62 (m, 1H), 1.59-1.42 (m, 2H), 1.28-1.23 (m, 1H), 1.02-0.93 (m, 6H), 0.90-0.86 (m, 2H), 0.81 (s, 3H); **IR** (film) ν_{max} 2954, 1738, 1730, 1325, 1280, 1213, 1130 cm^{-1}; **HRMS** (ESI) calcd for $[C_{21}H_{29}O_4]^+$: *m/z* 345.2060, found 345.2061.

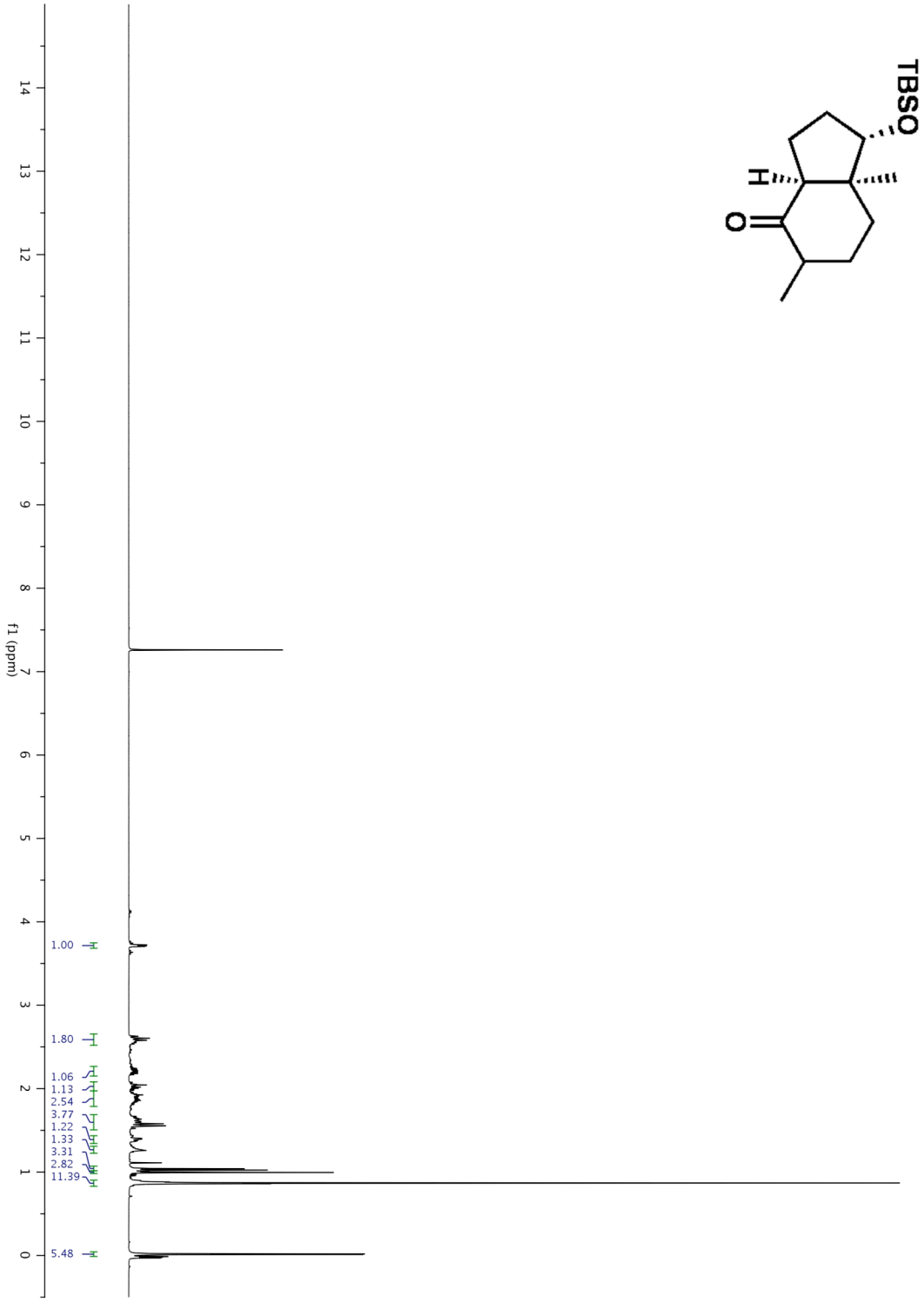
4.7. References and Notes

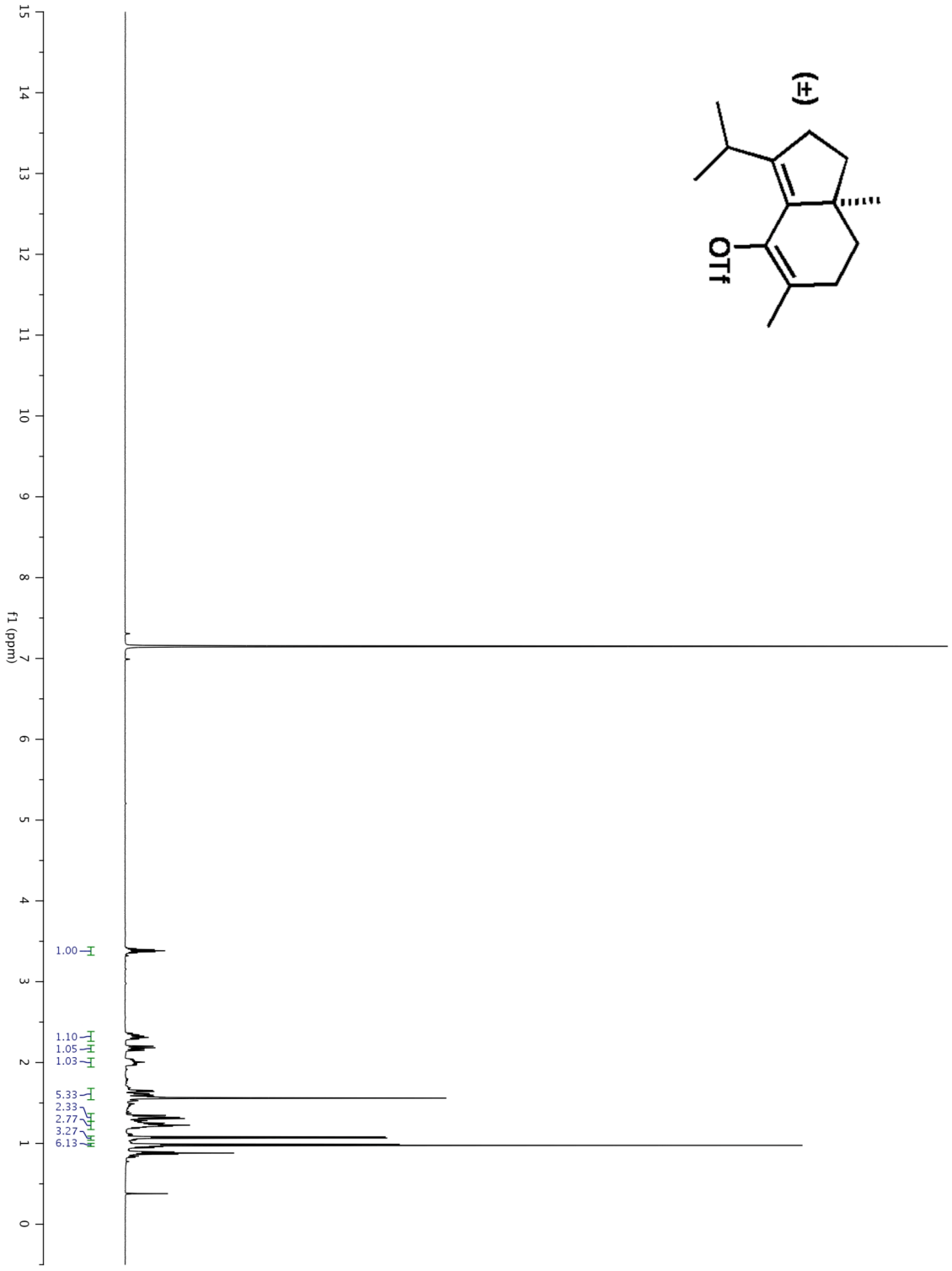
(1) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473.
(2) Fernandez, B.; Perez, J. A. M.; Granja, J. R.; Castedo, L.; Mourino, A. *J. Org. Chem.* **1992**, *57*, 3173.
(3) Lepage, O.; Stone, C.; Deslongchamps, P. *Org. Lett.* **2002**, *4*, 1091.
(4) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. *Org. Synth.* **1998**, *Collect. Vol. IX*, 165.
(5) Tori, M.; Toyoda, N.; Sono, M. *J. Org. Chem.* **1998**, *63*, 306.
(6) Park, I. H.; So, M. S.; Park, K. H. *Bull. Kor. Chem. Soc.* **2007**, *28*, 1515.
(7) Martinez-Solorio, D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 189.
(8) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.
(9) Hart, D. J.; Lai, C.-s. *Synlett* **1989**, 49.
(10) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030.
(11) Han, X. J.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
(12) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107.

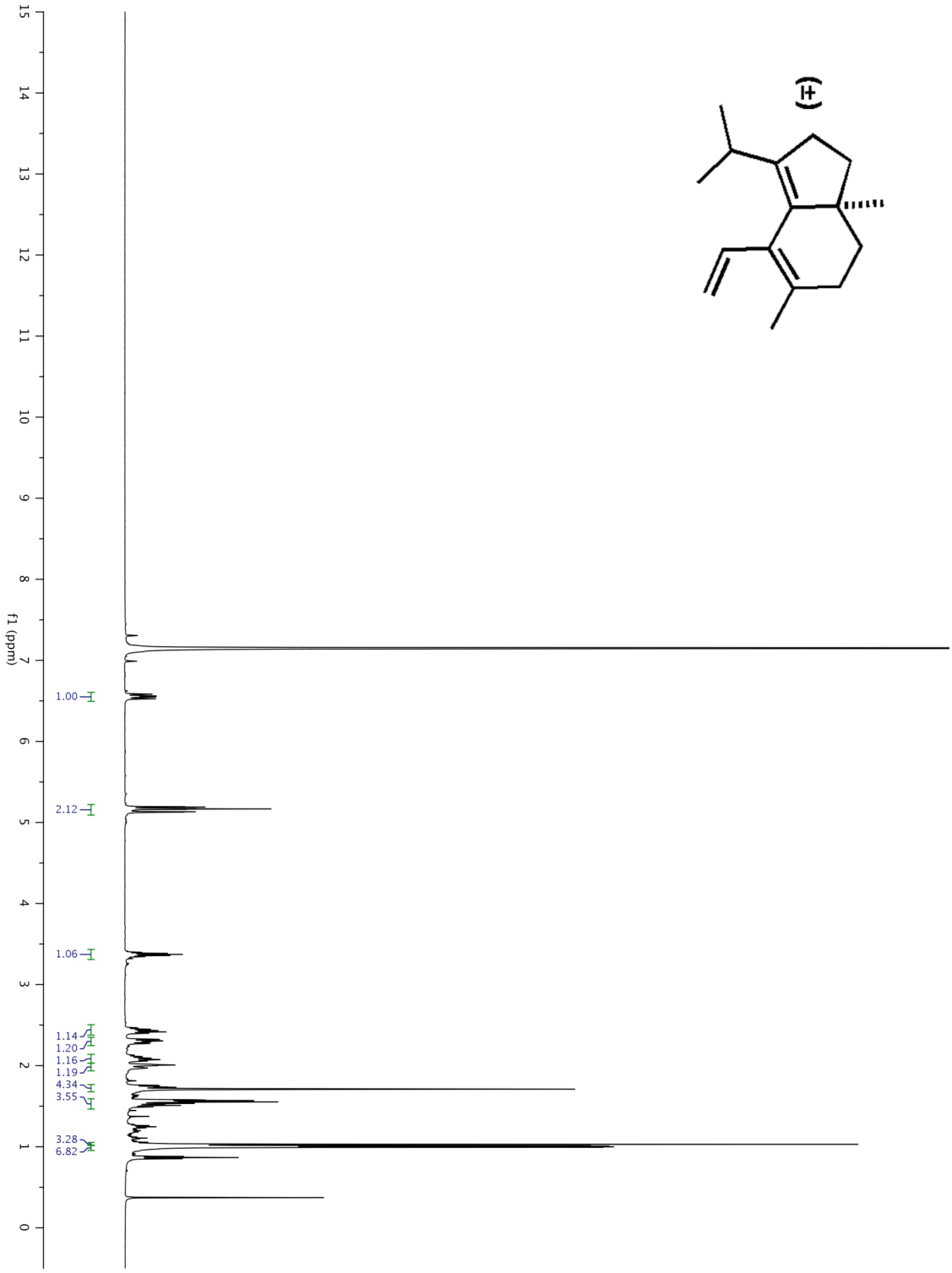
(13) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416.
(14) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. Eur. J.* **2007**, *13*, 9647.
(15) Davies, H. M. L.; Hougland, P. W.; Cantrell, W. R. *Synth. Commun.* **1992**, *22*, 971.
(16) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.
(17) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
(18) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437.
(19) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.
(20) Sheppard, G. S.; Wang, J. Y.; Kawai, M.; Fidanze, S. D.; BaMaung, N. Y.; Erickson, S. A.; Barnes, D. M.; Tedrow, J. S.; Kolaczkowski, L.; Vasudevan, A.; Park, D. C.; Wang, G. T.; Sanders, W. J.; Mantei, R. A.; Palazzo, F.; Tucker-Garcia, L.; Lou, P. P.; Zhang, Q.; Park, C. H.; Kim, K. H.; Petros, A.; Olejniczak, E.; Nettesheim, D.; Hajduk, P.; Henkin, J.; Lesniewski, R.; Davidsen, S. K.; Bell, R. L. *J. Med. Chem.* **2006**, *49*, 3832.
(21) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.
(22) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584.
(23) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.
(24) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334.
(25) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897.
(26) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198.
(27) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(28) Doyle, M. P.; Davies, S. B.; Hu, W. H. *Org. Lett.* **2000**, *2*, 1145.

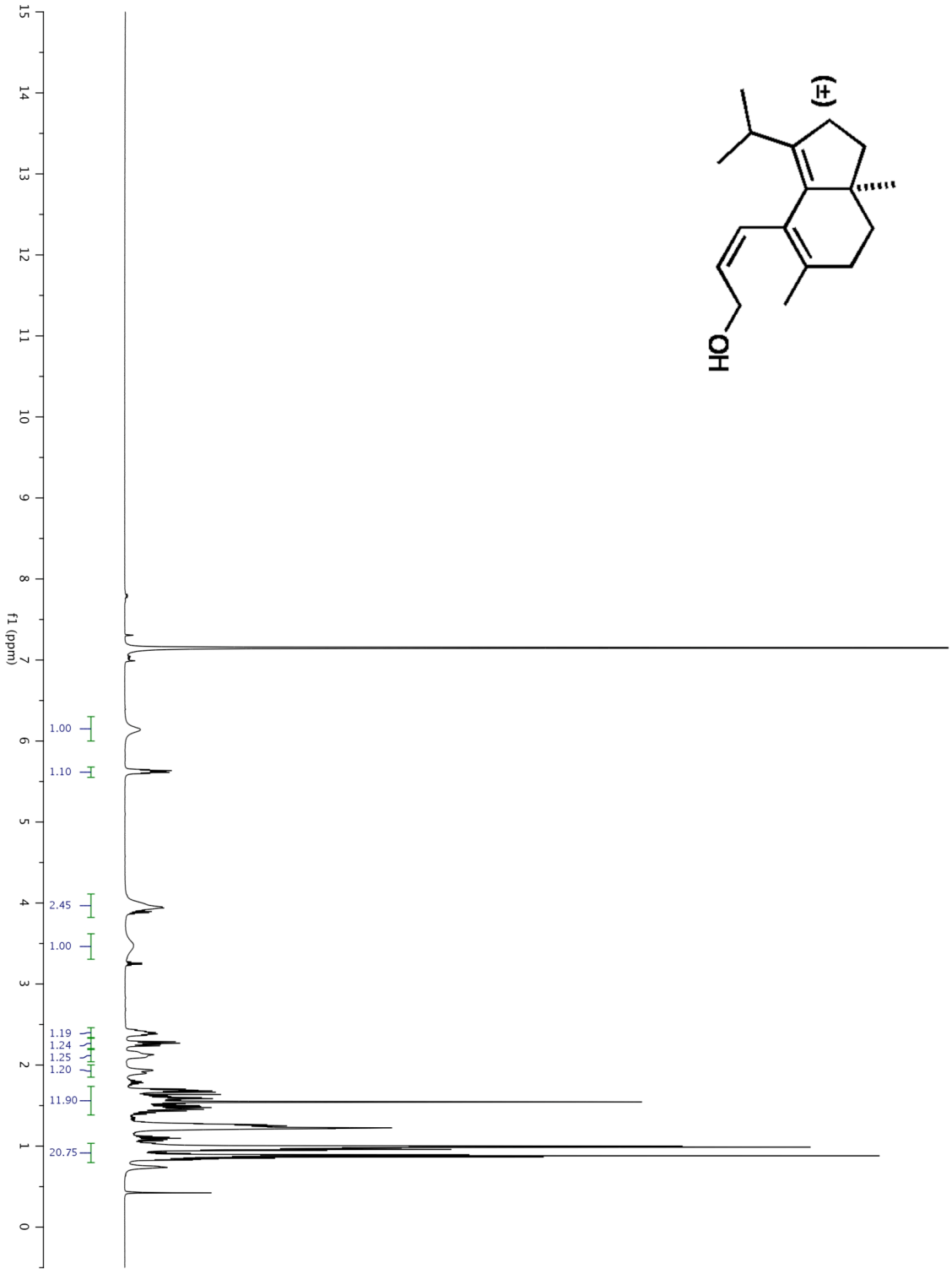
Appendix 3
Spectra Relevant to Chapter 4

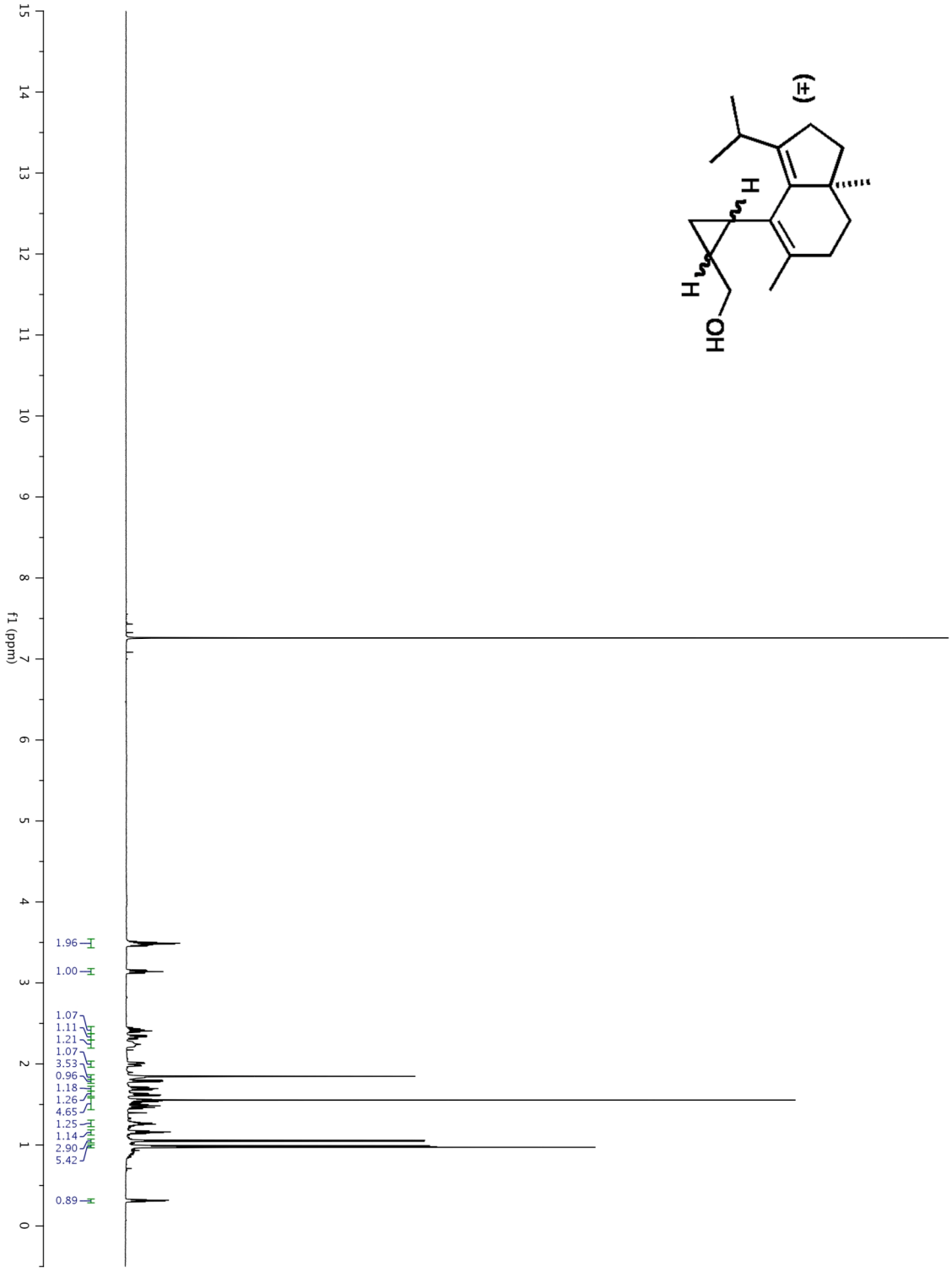

TBSO
H
O
f1 (ppm)
1.00
2.81
2.94
2.04
1.99
5.54
8.50
5.31

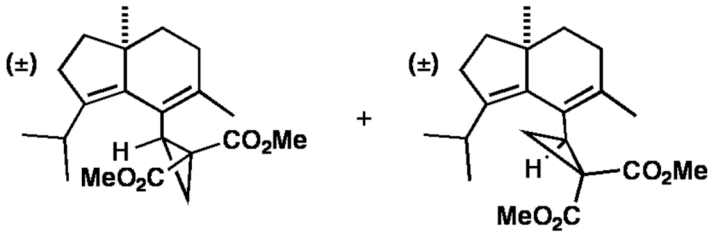

TBSO
H
O
f1 (ppm)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
1.00
1.80
1.06
1.13
2.54
3.77
1.22
1.33
3.31
2.82
11.39
5.48

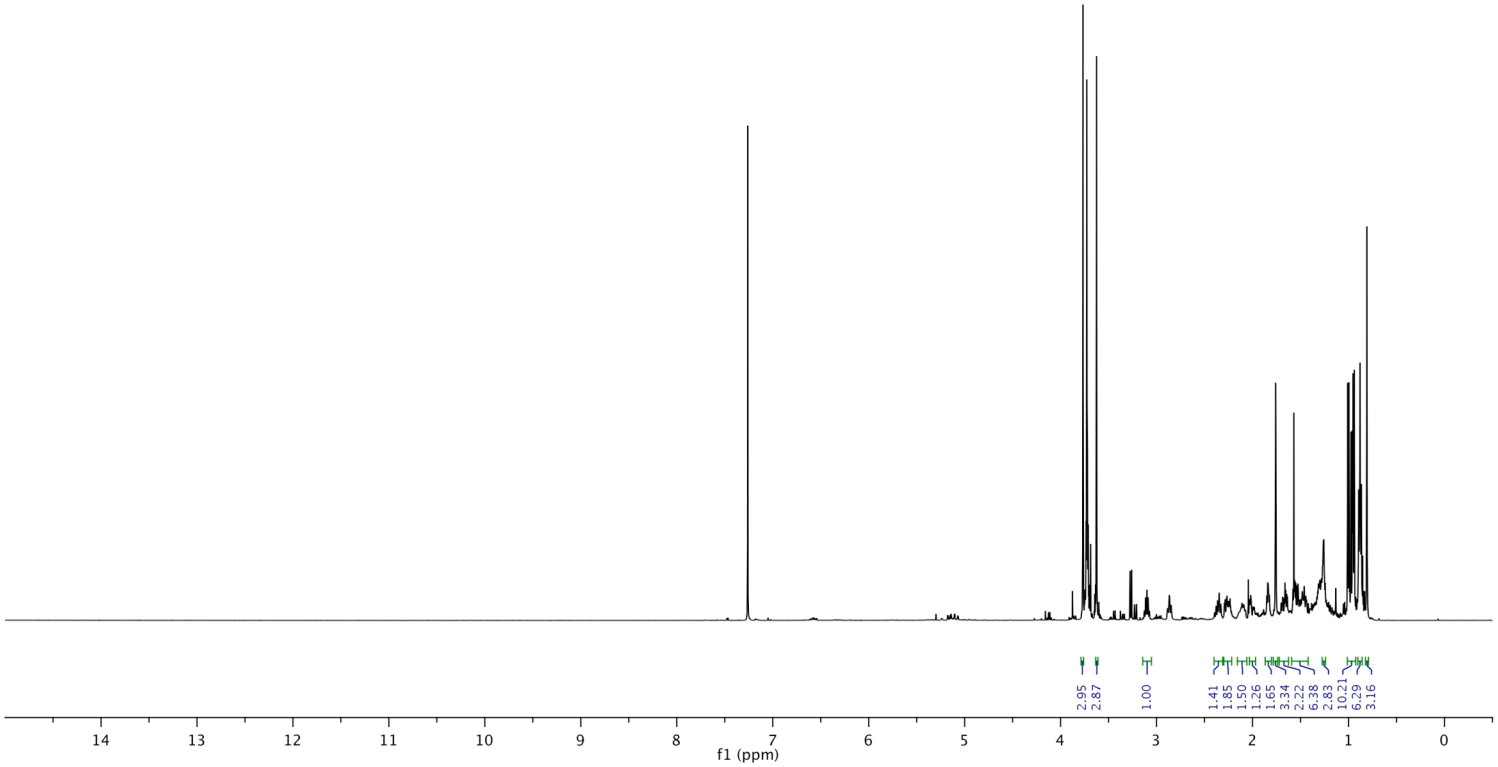

(±)
OTf
f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.00
1.10
1.05
1.03
5.33
2.33
2.77
3.27
6.13


f1 (ppm)
1.00
2.12
1.06
1.14
1.20
1.16
1.19
4.34
3.55
3.28
6.82


f1 (ppm)
1.00
1.10
2.45
1.00
1.19
1.24
1.25
1.20
11.90
20.75
OH


f1 (ppm)
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
1.96
1.00
1.07
1.11
1.21
1.07
3.53
0.96
1.18
1.26
4.65
1.25
1.14
2.90
5.42
0.89
(±)
H
H
HO


(±)
H
MeO2C
CO2Me
+
(±)
H
CO2Me
MeO2C


2.95
2.87
1.00
1.41
1.85
1.50
1.26
1.65
3.34
2.22
6.38
2.83
10.21
6.29
3.16
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)