Studies Toward the Total Synthesis of Maoecrystal V

A thesis presented

by

Paul John Krawczuk

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Dedication

This thesis is dedicated to my family:
William Krawczuk, Mary Krawczuk,
Linda Krawczuk and Mark Krawczuk
Acknowledgements

Thanks to all of my Baran Labmates over the years. I have had the honor of working with some extremely intelligent and hard working people who have inspired me, taught me volumes about chemistry and kept me feeling humble. Despite all of the hard work, we have had a lot of fun and I will fondly remember my time in the Baran Lab forever. I am sure that I would do it all over again. Take care and best wishes to all of you.

I also would like to thank my family for being understanding and accepting my decision to come to California to obtain my PhD. You have all been extremely supportive and loving even though you have missed me immensely over the years. I love you all very much.

I also would like to give special thanks to Phil for giving another guy from the “Schuster lab” a chance to do total synthesis at TSRI. Thanks for everything Phil. I can truly say that I worked for a living legend in chemistry. May you continue to make new discoveries, conquer the unconquerable and to inspire generations of chemists in the future.

Finally I would like to thank Emily for being so wonderful and supportive. You are amazing! You have made the end of my graduate career the best part of the experience. Thank you for everything! Now I only hope that I can return the favor. I love and cherish you and I look forward to our bright future together!
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List of Abbreviations

Ac = acetyl
acac = acetylacetonate
AIBN = azobis(iso-butyronitrile)
b = broad
BHT = butylated hydroxytoluene = 2,6-bis(1,1-dimethylethyl)-4-methylphenol
BRSM = based on recovered starting material
n-BuLi = n-butyllithium
CAN = ammonium cerium nitrate
cat. = catalyst or catalytic
Cy = Cyl = cyclohexyl
d = doublet
dba = dibenzylideneacetone
DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL = di-iso-butylaluminum hydride
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene
o-DCB = ortho-dichlorobenzene
DCM = dichloromethane (CH$_2$Cl$_2$)
DEAD = diethylazodicarboxylate
DMAP = (4-dimethylamino)pyridine
DMDO = dimethyldioxirane
DMF = N,N'-dimethylformamide
DMP = Dess–Martin periodinane
DMPU = 1,3-dimethyltetrahydropyrimidin-2(1H)-one
DMS = dimethyl sulfide
DMSO = dimethylsulfoxide
ESI-TOF = electrospray ionization-time of flight
esp = (α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)
EDC = 1-ethyl-3-[3-(dimethylamino)propyl]carbo diimide
EtOAc = ethyl acetate
hv = UV irradiation
HRMS = high resolution mass spectrometry
HMDS = hexamethyldisilazide
HPMA = hexamethylphosphoramide
IBX = ortho-iodoxybenzoic acid
IR = infrared
imid = imidazole
NaHMDS = sodium hexamethyldisilazide
KHMD S = potassium hexamethyldisilazide
Koser’s Reagent = hydroxy(tosyloxy)iodobenzene
LCMS = liquid chromatography mass spectrometry
LDA = lithium diisopropylamide
LAH = lithium aluminum hydride
LHMDS = lithium hexamethyldisilazide
LTA = lead(IV)acetate (Pb(OAc)₄)
LRMS = low resolution mass spectrometry
L-Selectride = lithium tri-(sec-butyl)borohydride

m = multiplet

$m$-CPBA = meta-chloroperoxybenzoic acid

MMPP = magnesium monoperoxyphthalate

mp = melting point

MOM = methoxy methyl ether

Ms = methanesulfonyl

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

NMR = nuclear magnetic resonance

OPP = pyrophosphate

[O] = oxidant

PhH = benzene (C$_6$H$_6$)

PhMe = toluene (C$_7$H$_8$)

PIDA = phenyliodine diacetate

PIFA = iodosobenzene bis(trifluoroacetate)

PMA = phosphomolybdic acid

PTLC = preparative thin layer chromatography

Pyr = pyridine (C$_5$H$_5$N)

$p$-ABSA = para-acetamidobenzenesulfonyl azide

SET = single electron transfer

q = quartet

s = singlet
t = triplet

tBuMePhos = 2-Di-tert-butylphosphino-2'-methylbiphenyl

TBS = tert-butyldimethylsilyl

TBSOTf = tert-butyldimethylsilyltrifluoromethane sulfonate

TEA = triethylamine (Et$_3$N)

TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical

Tf = trifluoromethanesulfonate

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

p-TsOH = para-toluenesulfonic acid

THF = tetrahydrofuran (C$_4$H$_8$O)

TLC = thin layer chromatography

TMS = trimethylsilyl

TMSI = iodo(trimethyl)silane

TMSOTf = trimethylsilyl trifluoromethanesulfonate

Ts = para-toluenesulfonyl
ABSTRACT

In 2004, Li and coworkers reported the isolation of the complex diterpenoid maoecrystal V, from the leaves of the Chinese medicinal herb *Isodon eriocalyx*, whose structure was verified by x-ray crystallographic analysis. It possesses a unique architecture, with five highly congested rings and seven stereocenters, two of which are adjacent all carbon quaternary centers located in its interior. In addition to the complex structure of this natural product, it also has promising biological activity, showing selective cytotoxicity towards the HeLa tumor cell line at low concentration (IC$_{50}$=40 nM), and low toxicity towards other cell lines tested. For these reasons maoecrystal V has attracted significant attention from the synthetic community. Herein we report on many of the strategies that we have pursued towards the total synthesis. One of these strategies culminated in the stereoselective synthesis of the complete carbon skeleton of the natural product. The hallmarks of this strategy are the arylation of a substituted cyclohexane ring, followed by an oxidative dearomatization, and finally by an intramolecular Diels–Alder reaction in order to construct the [2.2.2]bicyclooctane moiety.
Chapter 1

Maoecrystal V:

Isolation and Background
Section 1.1: Isolation, Proposed Biosynthesis and Biological Properties

The *Isodon* genus, of the *Labiatae* family, is comprised of about 150 different species that are found ubiquitously, but are more abundant in tropical and subtropical Asia.\(^1\) Plants from these species have been used for centuries as medicinal agents in traditional Chinese medicine. This genus has long been recognized as a plentiful source of diterpenoid natural products, many of which are biologically active. It has been estimated that over 600 diterpenoid natural products have been isolated from these sources, most of which are *ent*-kauranoids.\(^1\) Maoecrystal V was isolated exclusively from the leaves of *Isodon eriocalyx*, in the midst of a campaign toward the identification of new bioactive molecules.\(^2\)

*Isodon eriocalyx* is specifically used in its crude plant form as both an antibacterial agent as well as an anti-inflammatory treatment.\(^3\) It is used for indications such as sore throat, inflammation, influenza, hypertension (high blood pressure) and dermatophytosis (ringworm). One of the major terpene constituents of this plant is the natural product eriocalyxin B, which is a proposed intermediate in the biosynthetic hypothesis put forth by Han and coworkers for maoecrystal V (1.1, Figure 1.1).\(^3\) This biosynthesis combined with the proposed biosynthesis of the *ent*-kaurene skeleton is shown in Figure 1.2.

This biosynthesis begins with geranylgeranyl pyrophosphate (1.2) which, under the action of the cyclase enzyme *ent*-copalyl diphosphate synthase, is cyclized first to
make a trans-decalin rings system of ent-copalyl diphosphate which is subsequently cyclized by an ent-kaurene synthase to give the ent-kaurene tetracyclic core of the eriocalyxin family of natural products. This core structure is then heavily oxidized by various cytochrome enzymes to eventually give eriocalyxin B (1.5), along with many other related natural products of varying oxidation patterns. After an enzymatic vicinal cis-diol cleavage, epi-eriocalyxin A (1.6) is formed. This intermediate natural product can once again be enzymatically modified by decarbonylation (or perhaps the aldehyde moiety is first oxidized to the carboxylic acid and decarboxylated) to give cationic species 1.7 that can be intercepted by water to generate a secondary alcohol. Next, the tertiary carbon on the bicycle is enzymatically oxidized triggering a carbocation initiated ring shift, to yield another tertiary carbocation shown as the “hypothetical intermediate” 1.7 which can be intercepted by the proximal secondary alcohol, thus forming the tetrahydrofuran ether found in the maoecrystal V. The overall sequence results in a highly oxidized 19-carbon terpenoid that is one carbon fewer than its geranylgeranyl pyrophosphate starting material due to the decarbonylation (or decarboxylation).
Maoecrystal V has been considered by its isolation chemists to be “the most modified naturally occurring ent-kauranoid isolated to date”.\(^1\)

To lend some credence to their biosynthetic hypothesis, the isolation chemists reference the following acid-catalyzed rearrangement of compounds 1.8 and 1.9 to compound 1.10 and 1.11 respectively demonstrated by McPhail and coworkers.\(^5\) It was found that by treating tetracycle 1.8 or 1.9 with sulfuric acid in chloroform at room temperature that a [1,2]-carbon shift would take place giving [2.2.2]bicycle 1.10 or 1.11 respectively. It was noted that with no oxygen containing substituent on C9 of the [3.2.1]bicycle, the [2.2.2]bicycle did not form, due to the lack of anchimeric assistance as shown in the intermediate structure of Figure 1.3.

It was during a continuous search to isolate bioactive components from the *Isodon* genus that Han-Dong Sun and coworkers isolated maocystal V in approximately 1994.\(^2\) They isolated this new structure from the methanolic extracts of 11.9 kilograms of dried and powdered leaves. After chromatographic purification, they isolated 5 milligrams of maocystal V. They did not publish their findings until 2004 due to the uncertainty in its structural assignment. A tentative structure (1.12, Figure 1.4) was put forth, which contained an oxetane ring that was mostly in accord with the NMR and MS data and by

\[\text{Figure 1.3 Demonstration of potential conversion of a [3.2.1]bicycle to a [2.2.2]bicycle.}\]

\[
\begin{align*}
1.8, R & = H \\
1.9, R & = Ac
\end{align*}
\]

\[
\begin{align*}
1.10, R & = H, 8\% \\
1.11, R & = Ac, 96\%
\end{align*}
\]
comparison to other known *ent*-karuanoids. However, the *ent*-kauranoid family of natural products is vast and contains members with many different oxidation states at various sites, as well as various cleavage patterns. Knowing this, the isolation chemists hesitated to publish the structure until they obtained a crystal structure of the newly isolated compound. It was not until about 10 years later that they were able to grow a single crystal suitable for X-ray crystallographic analysis. It was at this point that they realized that their originally proposed structure was actually incorrect and thus the real structure 1.1 of maoecrystal V was obtained.

Maoecrystal V was evaluated for cytotoxicity against five different human tumor cell lines K562 (leukemia), A549 (lung cancer), BGC-823 (gastric cancer), CNE (throat cancer) and HeLa (cervical cancer).\(^2\) It was found that during these studies that maoecrystal V was selectively cytotoxic against HeLa cells (IC\(_{50}\) = 0.02\(\mu\)g/mL), while being virtually non-toxic towards any of the other four cell lines (IC\(_{50}\) = 1.47 \(\times\) 10\(^4\) \(\mu\)g/mL or greater). Compared to the standard chemotherapy treatment of *cis*-platin (IC\(_{50}\) = 0.99\(\mu\)g/mL) maoecrystal V was found to be active at lower concentration. Due to this selective cytotoxicity it could be possible that maoecrystal V, or its derivatives, could be viable chemotherapeutic agents.

\(^{1}\)Figure 1.4 Originally proposed structure and correct structure as confirmed by crystallography

\(^{2}\)Originally proposed structure of maoecrystal V (1.12) actual structure confirmed by X-ray crystallographic analysis (1.1)
Section 1.2: Progress by others in the field

As stated before maoecrystal V has attracted much attention from other groups in the field of total synthesis. To date several groups have published studies toward the total synthesis of maoecrystal V and there has been one total synthesis. In addition to the peer-reviewed manuscripts discussed here, there have been a number of doctoral dissertations on the topic of studies toward the total synthesis. Only the key transformations towards the total synthesis of maoecrystal V will be discussed.

The first report on any synthesis effort to be published was from the group of Professor Zhen Yang. This publication caused controversy in our laboratory because one of the authors on this paper, Dr. Chuang-chuang Li, had been a postdoctoral fellow in our laboratory and my colleague Dr. Niklas Schöne and I had discussed our synthetic efforts with Dr. Li on several occasions. At the time we only perceived his questions as scientific inquiry and we discussed our work freely, as we often do with our laboratory colleagues. As a further testament to Dr. Li’s questionable activities concerning research, while he was employed in the Baran Lab working on the total synthesis of cortistatin A, he was simultaneously overseeing a total synthesis effort towards the same molecule with his group in China.

The Yang group’s study towards maoecrystal V began with an arylation of β-keto ester 1.13 using an aryl lead species. They next reduced the ester moiety and deprotected the phenol to provide primary alcohol 1.16. This alcohol was then converted to the acrylate ester 1.17. The hemiketalized phenol of 1.17 was then dearomatized using Pb(OAc)₄, and this was followed by an intramolecular Diels–Alder reaction that provided bicycle 1.18. From this point they hydrogenated the olefin of the bicycle and performed
a samarium(II) iodide reduction of the α-acetoxy group to yield 1.20.

As a comparison to our, at that time unpublished results, I have prepared a table (Figure 1.6) of comparisons between the two groups’ work. We had access to the contents of their notebooks (they were scanned and sent to us by Yang’s Group) and we were able to compare the exact dates in this manner. Shortly after the Yang group published their work, we prepared a manuscript for publication with our work that was closely paralleled by their work, to protect our own research effort, and so that the community could see that there was some form of intellectual property theft.7

It was our intent to let this scenario be judged by the community and thus we included the following note in our communication: “During this period one of the corresponding authors of the preceding letter was employed as a postdoctoral associate (C.-C. Li) in this laboratory: Gong J, Lin G, Li C-C, Yang Z Org. Lett. 2009, DOI: 10.1021/ol9014392. This work was reported in an NIH proposal (received 8/11/2008 and reviewed on 10/9/2008 by the BCMB-B study section) and a final report to the DFG (submitted: 7/17/2009).”
<table>
<thead>
<tr>
<th>Transformation from Yang Group</th>
<th>Transformation from Baran Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure 1" /> March, 2009</td>
<td><img src="image2.png" alt="Chemical Structure 2" /> November, 2007</td>
</tr>
<tr>
<td><img src="image3.png" alt="Chemical Structure 3" /> March, 2009</td>
<td><img src="image4.png" alt="Chemical Structure 4" /> January, 2008</td>
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<td><img src="image5.png" alt="Chemical Structure 5" /> March, 2009</td>
<td><img src="image6.png" alt="Chemical Structure 6" /> January, 2008</td>
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<tr>
<td><img src="image7.png" alt="Chemical Structure 7" /> March, 2009</td>
<td><img src="image8.png" alt="Chemical Structure 8" /> February, 2008</td>
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<tr>
<td><img src="image9.png" alt="Chemical Structure 9" /> March, 2009</td>
<td><img src="image10.png" alt="Chemical Structure 10" /> February, 2008</td>
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<td><img src="image11.png" alt="Chemical Structure 11" /> April, 2009</td>
<td><img src="image12.png" alt="Chemical Structure 12" /> February, 2008</td>
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<td><img src="image13.png" alt="Chemical Structure 13" /> April, 2009</td>
<td><img src="image14.png" alt="Chemical Structure 14" /> February, 2008</td>
</tr>
<tr>
<td><img src="image15.png" alt="Chemical Structure 15" /> June, 2009</td>
<td><img src="image16.png" alt="Chemical Structure 16" /> March, 2008</td>
</tr>
</tbody>
</table>

*Figure 1.6 Comparison of the studies towards papers published by the Yang group and the Baran group.*
It is our opinion that by publicly acknowledging this act of plagiarism and intellectual theft, that future researchers will be more careful and vigilant so that they do not become victims of the same crime. It is also my expectation that those who may have low enough moral standards to consider this sort of transgression will realize that they will be caught and that there will be consequences.

The next paper that appeared in the literature was from the Danishefsky group. Their overall strategy is the merger of an aromatic ring and a 1,3-dicarbonyl compound via a palladium-catalyzed coupling and use of a Birch reduction to provide 1.26. In their strategy they initially began with an arylation of 4,4-dimethylcyclohexane-1,3-dione 1.21 with aryl bromide 1.22. From here they synthesized tributyltin ether 1.24 in 6 steps. This compound was then treated with $n$-BuLi in order to effect a [2,3]-Wittig rearrangement to provide alcohol 1.25. The aromatic ring of 1.25 was then reduced using lithium in ammonia followed by isomerization with HCl to provide 1.26, which they next esterified to yield ester 1.27. Formation of silyl enol ether 1.28 gave the desired Diels–Alder precursor, which upon heating to 180 °C, followed by silyl deprotection gave bicycle 1.29. Unfortunately this bicycle results from the incorrect facial selectivity during the Diels–Alder cycloaddition and does not match the bicycle needed for Maoecrystal V.

Figure 1.7 Danishefsky group's study towards maoecrystal V.
The Danishefsky group published a follow up to this paper in 2011 where they chose to begin with a symmetrical Diels–Alder precursor so there would be no issue with facial selectivity. To begin they joined the lithium enolate of ester 1.30 with vinylogous acid chloride 1.31. To this resulting enone they performed a two-step reduction and allylic oxidation to furnish alcohol 1.33. After esterification and silyl ether formation they produced a meso Diels–Alder substrate that cannot give an incorrect bicycle due to its symmetry. The Diels–Alder reaction proceeded smoothly to afford the bicycle, which was treated with TBAF to produce the ketone and to eliminate phenylslufinic acid yielding unsaturated lactone 1.35. This lactone was then epoxidized using nucleophilic epoxidation conditions to give the α,β-epoxy lactone. The epoxide was then regioselectively opened using magnesium iodide to give an iodohydrin, which was subsequently reduced with Bu$_3$SnH in the presence of AIBN to give alcohol 1.36. Directed m-CPBA epoxidation of the olefin proximal to the tertiary alcohol yielded the cyclization precursor which was treated with p-TsOH to generate tetrahydrofuran 1.37. Unfortunately, the epoxide opening resulted in the wrong epimer needed for maecrystal V. In order to overcome this difficulty they developed a seven-step route which involves: thioketalization of the ketone, desulfurization and olefin reduction, oxidation to the
ketone, reduction again to the opposite alcohol, followed by mesylation, elimination, epoxidation of the vinyl ether and finally epoxidation and opening to give ketone 1.38. Though very creative, this route still had many unsolved problems that would be necessary for elaboration to the natural product.

Then Nicolaou/Chen group published their route to maocrystal V core structures in 2009.10 Their strategy also included a dearomatization reaction as well as an intramolecular Diels–Alder reaction to furnish the [2.2.2]bicycle. The synthesis commenced with a decarboxylative Heck coupling to furnish β-aryl enone 1.41. From here the doubly-protected resorcinol was deprotected using BBr3. Mono alkylation using MOMCl and sodium hydride provided free phenol 1.42. This phenol was then alkylated using a previously reported alkyl bromide, which served as a precursor for the dienophile. After alkylation of the pyrrolidine moiety with iodomethane, E1cb elimination of the ammonium salt yielded vinyl ether 1.43. Silyl enol ether formation afforded a diene, which could undergo the desired intramolecular Diels–Alder reaction to give [2.2.2]bicycle 1.44 after deprotection of the silyl group with HCl. This bicycle was subsequently oxidatively dearomatized using PIFA in methanol to give the dienone 1.45. Hydrogenation of this intermediate yielded a mixture of the aromatized structure and saturated compound 1.46. The stereochemical configuration next to the tetrahydrofuran ring did not match that found in the natural product.
This was a result of delivery of the hydrogen from the incorrect face of the olefin. Next the ester was hydrolyzed with NaOH to provide crude acid 1.47 that was treated with chloroiodomethane in the presence of potassium tert-butoxide and 18-crown-6. This sequence provided first a halo ester that further alkylated the enolate to provide lactone 1.48. Unfortunately there was an undesired side reaction that took place as well under these conditions that installed an exocyclic methylene on the other side of the ketone as a result of alkylation and β-elimination. Presumably this reaction could be optimized to prevent this side reaction from occurring. This structure and two other intermediates synthesized in a similar manner were screened for biological activity and it was found that compound 1.48 had moderate cytotoxicity (GI$_{50}$ between 3.6-6.7µm) toward four different human tumor cell lines. In follow up work, Professor Chen and coworkers began with intermediate 1.45 from their previous work. In this publication they were seeking a strategy to invert the configuration of the tetrahydrofuran ring and established a way to introduce the requisite geminal dimethyl group where a dimethoxy...
ketal previously existed previously. Diol 1.49 was obtained in four steps, which was then hydrogenated with palladium on carbon and hydrogen to provide 1.50, with the correct stereocenter for the tetrahydrofuran ring presumably due to direction by the allylic alcohol. At this point the remaining ketone was methylenated to give olefin 1.51. This olefin was next cyclopropanated to add the additional carbon necessary for the geminal dimethyl group. After a Dess–Martin periodinane oxidation provided the diketone, the cyclopropane was hydrogenated open to yield the advanced maoecrystal V structure 1.53.

Another study towards the lactone fused to the bicyclic portion of maoecrystal V appeared in the literature in 2010 from Singh and coworkers in India.\textsuperscript{12} They utilized a similar oxidative dearomatization, intramolecular Diels–Alder cycloaddition approach.
Beginning with protected phenol 1.54 they installed an acrylate ester and removed the acetonide to give diol 1.55. Upon treatment with aqueous sodium periodate an oxidative dearomatization was realized to give an unisolable intermediate that either homodimerized or gave the desired [2.2.2]bicycle. It was found that if the homodimerized cycloadduct was heated to 140 °C it would undergo a retro-Diels–Alder to yield the same intermediate and react in the desired way to provide bicycle 1.56. From here the epoxide in bicycle 1.56 was reductively cleaved open with zinc and ammonium chloride in aqueous methanol. The resulting alcohol 1.57 was subjected to Jones’ oxidation conditions which led to a subsequent decarboxylation at 100 °C to give the truncated bicycle 1.58 that was ultimately reduced with hydrogen in the presence of palladium on carbon to give bicyclic lactone 1.59. This was a decent approach to a small fragment of the molecule yet it borrows heavily from strategies used by others and leaves no possibility for elaboration to the natural product.

The group of Professor Regan Thomson and coworkers put forth their synthesis of the carbocyclic core of maoecrystal V in 2010 as well.13 Their approach was quite different in terms of strategy using an intramolecular Nazarov reaction to bring the two six membered rings of the natural product together and an intermolecular Diels–Alder reaction with nitroethylene to construct the [2.2.2]bicycle. Starting with 3,3-dimethylcyclohexanone they first performed a Rubottom oxidation/TBS protection to form compound 1.60. With this ketone they performed a Horner–Wadsworth–Emmons reaction to generate an unsaturated Weinreb amide that they immediately reacted with 2-lithio-1,3-cyclohexadiene to give enone 1.61. This was the precursor for their Nazarov cyclization which proceeded with iron(III) chloride to yield cyclopentenone 1.62. After
reduction of the ketone with DIBAL-H, which they found was necessary for the cycloaddition to take place, the diene portion of the molecule underwent a Diels–Alder reaction with nitroethylene to provide bicycle 1.63, as a single stereoisomer, which was confirmed by X-ray analysis. To elaborate further, the nitro group was epimerized using KOH, and a Jones’ oxidation restored the ketone functionality. Silyl ether formation followed by a Rubottom oxidation with \( m \)-CPBA provided alcohol 1.65. Hydrogenation of the enone with hydrogen and palladium on carbon led to the undesired formation of cyclopropane species 1.66. Nonetheless this intermediate was further elaborated through an oxidative cleavage performed with methanolic periodic acid, which was subsequently reduced with sodium borohydride to provide lactone 1.67, whose structure was confirmed by X-ray analysis. This strategy shows promise for the eventual elaboration to the natural product.

The Trauner group also published their results towards the total synthesis of maoecrystal V in 2010. Their approach began by synthesizing the bicycle, elaborating it to install the “center” of the molecule and finally leaving the A-ring construction for the end. Their synthesis commenced with 2-cyclohexen-1-one, which they first alkylated
and then performed a Sakurai allylation to generate olefin compound 1.68. This olefin was then subjected to ozonolysis/ozonide reduction with dimethylsulfide to yield the corresponding aldehyde, which was then subjected to treatment with HCl which caused an intramolecular aldol reaction thus constructing bicycle 1.69. Diastereoselective addition of trimethylsilyl lithium acetylide gave tertiary alcohol 1.70. Treatment of this alcohol with sodium hydride caused a transesterification to give the lactone, which was subsequently subjected to Lindlar reduction conditions to provide olefin 1.71. At this point they desired to do a double aldol with the enolate of the lactone and formaldehyde to form 1.74, however this product was only obtained in small amount, so in order to overcome this difficulty a stepwise approach was investigated. Using carefully controlled conditions the first aldol with formaldehyde was successful providing alcohol 1.72. This alcohol was then oxidized to the aldehyde (which existed in its enol form exclusively) using Dess–Martin periodinane. They were unable to conduct another aldol reaction on this substrate, so they elected to reduce the aldehyde with sodium borohydride to provide the primary alcohol, which they could successfully perform the aldol reaction with and give the diol. At this point another ozonolysis/ozonide reduction with dimethylsulfide provides the advanced structure 1.74. This compound provides an
excellent starting point for the completion of the synthesis of the natural product, there are several functional handles available for construction of the A-ring, and elaboration of the bicycle to that desired in the natural product.

The next paper to be published on maoecrystal V was that of its total synthesis by Yang and coworkers. Many of the steps in this strategy closely mirror those in their prior communication. As before a lead mediated arylation brought together keto-ester 1.75 and aryl lead species 1.76. At this point the reduction of the bis-neopentyl ketone was explored. It was found that with LAH 12% of the desired diastereomer could be obtained, along with 72% of the undesired. A workaround that they found for this was

\[
\begin{align*}
1.75 \quad \text{CO}_2\text{Me} & \quad \text{OMOM} \\
\text{pyridine, CHCl}_3 & \quad \text{Bu}_4\text{N})\text{BH}_4 \\
1.76 \quad \text{CO}_2\text{Me} & \quad \text{OMOM} \\
\text{Lindlar Reduction} & \quad \text{DBU, PhMe, 100ºC} \\
1.80 \quad \text{OAc} & \quad \text{OAc} \\
\text{Bu}_3\text{SnH, TEMPO, PhH, reflux} & \quad \text{DBU, PhMe, 100ºC} \\
1.82 \quad \text{Br} & \quad \text{OAc} \\
\text{NBS, (PhCO}_2\text{)}_2 & \quad \text{CCl}_4, \text{ reflux} \\
1.83 \quad \text{OAc} & \quad \text{OH} \\
\text{Zn, AcOH, THF, H}_2\text{O} & \quad \text{DBU, PhMe, 100ºC} \\
1.84 \quad \text{OH} & \quad \text{OH} \\
\text{Sml}_2, \text{THF, MeOH} & \quad \text{DBU, PhMe, 100ºC} \\
\end{align*}
\]

Figure 1.14 Yang group's total synthesis of maoecrystal V.
the use of tetrabutylammonium borohydride, a reagent which the authors claim forms a cationic-π interaction between the aromatic ring and the ammonium salt to deliver the hydride from the top face of the ketone as drawn, to provide the desired alcohol in 65% yield along with returned starting material. The methyl ester was then reduced to primary alcohol 1.78. From this point a phosphonate ester was coupled onto the primary alcohol that was further transformed into the α-diazo-phosphonate ester. This would be used to generate a carbene that would undergo O–H insertion. Indeed when the diazo compound 1.79 was heated with rhodium(II) acetate the desired O–H insertion took place providing seven-membered ring 1.80. The phosphonate next served as a precursor for the Horner–Wadsworth–Emmons reaction that took place with paraformaldehyde using potassium tert-butoxide as base. With the requisite dienophile in hand, the phenol was deprotected and oxidatively dearomatized using lead(IV) acetate. The Diels–Alder cycloaddition then took place after heating the precursor to 140 °C to yield bicycle 1.81. All that remained now for the completion of the natural product was functional group manipulation. The method for allylic oxidation was not very straightforward and required four steps to arrive at the desired enone. Initially the site was functionalized by an allylic bromination using NBS under radical conditions initiated by benzoyl peroxide. This preinstalled bromine was then used to generate an allylic radical by use of tributyltin hydride in the presence of TEMPO as trapping agent to generate adduct 1.83. The N–O bond of the TEMPO was then reductively cleaved to ultimately lead to the allylic alcohol. At this point the α-acetoxy group on the bicycle was removed as before using samarium(II) iodide to furnish 1.84. In this instance it provided exclusively the wrong epimer at C16 that would later need to be epimerized. The bicyclic olefin was then
chemoselectively reduced using Lindlar’s catalyst to provide intermediate 1.85, which was oxidized using Dess–Martin periodinane to yield ketone 1.86. Ultimately the final step to complete the total synthesis was the epimerization of the methyl group at C16, which was accomplished by using DBU in toluene at 100 °C, thus completing the first total synthesis of maoecrystal V. This synthesis was far from ideal and there is much room for improvement in efficiency and also in diastereoselectivity in making this complicated molecule.

The last approach that was published just this year (2011) comes from the laboratory of Professor Armen Zakarian.16 The main features of this synthetic effort are a rhodium catalyzed C–H functionalization, an oxidative dearomatization and an intramolecular Diels–Alder to form the bicycle. Their synthesis began with the small aromatic natural product sesamol (1.87), which they first alkylated using Mitsunobu conditions to give the corresponding aryl ether. The aromatic ring was next ortho-metalated with n-BuLi, followed by transmetalation to the organozinc using zinc(II) chloride. This metalated species was then reacted with methyl chlorooxoxoacetate to give α-keto-ester 1.88. This compound was further converted to the α-diazo-ester by action of tosylhydrazide to make the hydrazone, then DBU to form the diazo group. A rhodium(II) acetate mediated carbene formation led to C–H insertion into the methylene adjacent to the aromatic ether with good diastereoselectivity. Dihydrobenzofuran 1.90 was then deprotonated with LHMDS and alkylated with iodomethane in the presence of diethyl zinc and DMPU to provide 1.91 as a mixture of diastereomers. From here the ester was reduced and the 1,3-benzodioxole was regioselectively mono-deprotected using
methyl magnesium bromide to install an ethyl group on one alcohol and leave the free phenol on the other, which is presumably controlled by chelation of the magnesium to the primary alcohol. This phenol was dearomatized using PIFA to afford diethoxy-protected ortho-quinone 1.93, which served as the diene component of a Diels–Alder reaction. Several different dienophiles were installed on the primary alcohol at this point such as vinyl sulfone to form 1.94 and acrylate to form 1.96. When both of these were heated up to 90 °C and 160 °C respectively the desired cycloadducts 1.95 and 1.97 were obtained.

During this study towards the total synthesis of maoecrystal V, a method for formation of the [2.2.2]bicycle fused to the tetrahydrofuran ring, with proper stereochemistry, was established. There are many other issues that need to be solved, but this serves as a nice entry into the maoecrystal V arena.

Figure 1.15 Zakarian group's studies toward maoecrystal V.
Section 1.3: References


Chapter 2

Early Approaches
Section 2.1: Retrosynthetic Analysis: Oxidative Coupling

During the course of this project it was our belief that a strong starting point would ensure a smooth and successful endgame. It was for this reason that we examined many diverse retrosyntheses that ultimately lead us in the direction of our more refined routes. Below is an outline of the routes attempted for construction of the core of maoecrystal V. All will not be discussed for the sake of brevity and the routes that will be discussed were chosen due to their overall importance of the evolution of our strategy. Throughout the course of this research the use of reduction/oxidation manipulations and protecting groups was intentionally kept to a minimum to improve efficiency.

Figure 2.1 Overall summary of routes attempted towards maoecrystal V.
Our initial retrosynthesis of Maoecrystal V (2.1), where we sought to use an oxidative coupling disconnection, began with a simplification of the A-ring by removal of the enone moiety to simply leave a substituted cyclohexene ring. This would be advantageous due to the reactivity and instability of carrying an enone through an entire total synthesis. It was envisioned that this could be easily installed via an allylic oxidation on olefin 2.2. The tetrahydrofuran ring would come from the reduction of a hemiketal, that in a forward sense, would form with the A-ring ketone and the tertiary alcohol found in bicycle 2.2. This alcohol would be installed by performing a Rubottom oxidation on the silyl enol ether formed from lactone 2.3. With simplified structure 2.3 in hand the key intramolecular Diels–Alder reaction was planned to construct the bicycle and the lactone simultaneously and set the stereochemistry for the rest of the endeavor.

![Diagram](https://example.com/diagram.png)

**Figure 2.2** Initial retrosynthesis for the construction of maocrysal V.

To generate Diels–Alder precursor 2.4 we imagined that a silyl enol ether of enone 2.5 would provide the desired diene, and an esterification with the primary alcohol and acryloyl chloride would yield the ester. The hydroxymethyl group found in 2.5 would result from a formylation of the corresponding ketone. An oxidative coupling of the
lithium enolates of ketone 2.7 and enone 2.6 was planned for construction of the 1,4-diketone moiety.

At the time that we were developing this strategy, our lab was interested in further developing oxidative coupling methodology. Coworkers in the lab had found that the reaction was fairly general and we wished to apply it to the total synthesis of a complex natural product.\textsuperscript{1,2} The opportunity to use oxidative coupling for the construction of this intermediate stemmed from the realization that there was a 1,4-(dissonant) relationship between the carbonyl compounds in 2.5\textsuperscript{3}. Bonds of this type are notoriously hard to construct relative to the consonant relationships of 1,3- and 1,5-dicarbonyl compounds (Claisen condensation, Michael addition, Aldol reaction and Mannich reaction), due to resistance in the inherent reactivity needed. The use of oxidative enolate coupling has emerged as a way to prevail over this innate reactivity. In order to achieve good conversion to the desired product we planned to use an excess of the commercially available cyclohexenone due to the fact that homocoupling could predominate or lead to a statistical mixture of products from homo- and heterocoupling.

Section 2.2: Execution of the synthesis

To begin this synthesis we wanted to embark with a chiral starting material for the oxidative coupling. After surveying the literature it became obvious that a compound such as 2.10 would be a practical source of chirality. It was well known that symmetrical diketone 2.9 could be desymmetrized asymmetrically with greater then 98% ee using baker’s yeast in order to selectively produce (S)-(+)3-hydroxy-2,2-
dimethylcyclohexanone 2.10, a compound that has shown diverse applications in total synthesis.\textsuperscript{4}

The neopentyl hydroxyl group was protected using TBSOTf and 2,6-lutidine to generate oxidative coupling partner 2.7.\textsuperscript{5} This ketone and cyclohexenone were oxidatively heterocoupled by deprotonating both ketones to generate their lithium enolates and then oxidizing them with diacetoxy iodobenzene. It is presumed that a single electron transfer process occurs to form two α-radical species that combine to form a carbon-carbon bond.\textsuperscript{2} This reaction produces a mixture of inseparable diastereomers that we next attempted to perform an aldol reaction with. When first

![Figure 2.3 Execution of oxidative coupling strategy and attempted hydroxymethylation.](image)

 attempting these reactions we considered that we might be able to treat diketone 2.12 with aqueous base and aqueous formaldehyde to obtain the aldol product. It was expected that if the aldol occurred on the desired ketone of 2.12 it would spontaneously form the hemiketal with the enone carbonyl, generating 2.13, and prevent it from reacting with another equivalent of formaldehyde. Unfortunately under the conditions examined,
we obtained only recovered starting material. In retrospect, it seems as if conditions that would catalyze the forward reaction also would catalyze the retroaldol reaction, leaving this reaction in equilibrium and favoring the starting material.

We next decided to probe the reactivity of the diketone with formation of a silyl enol ether. It was found that treatment with excess TBSOTf and triethylamine only provided the silyl enol ether 2.14 of the enone. This selectivity seems to be the result of steric hindrance generated by the geminal dimethyl group. Since intermediate 2.14 only possessed a single acidic position, it might be possible to quantitatively form the enolate, add formaldehyde and then quench the reaction with acid to perform the aldol without the competing retroaldol. When we again attempted this reaction with various enolates and formaldehyde and were unable to obtain any desired product. The nucleophilic position of the enolate is in fact very sterically hindered and upon forming the desired bond an all-carbon quaternary center would be formed. It is indeed not surprising these attempted aldol reactions afforded no product.

At this point it seemed like any further attempts to form the quaternary center with an aldol reaction were in vain. Even if the desired product was formed, it could reversibly undergo a retroaldol cleavage under the reaction conditions to return the starting material. We decided to attempt the oxidative coupling reaction on a series of ketones with substitution in the α-position that would serve as alcohol surrogates, yet cannot undergo the retroaldol process, in order to obtain the quaternary center directly from oxidative coupling. We set out to make five different substrates, all of made by alkylation of the lithium enolate of ketone 2.7 with the corresponding electrophile.
Unfortunately all attempts (see Figure 2.4) to perform these reactions under the typical oxidative coupling conditions resulted in only homocoupling of the cyclohexenone partner to give 2.26. It seemed apparent that the rate of homodimerization of the enone far exceeded that for heterocoupling, due to the need for formation of a quaternary center in the product, a seemingly unfavorable process. The reactivity of the coupling partners would need to be changed so that a homodimerization would be stopped and cross coupling would take place.

It next dawned on us to explore other oxidative coupling conditions that perhaps did not go through the intermediacy of a lithium enolate so that only cross coupling could take place. We would attempt to use a 1,3-dicarbonyl compound with a single electron oxidant, to produce an electrophilic $\alpha$-radical that would be attacked by a nucleophile such as a silyl enol ether.\(^6\)\(^7\) These couplings were attempted using $\beta$-keto ester 2.24, made by simply treating 2.7 with LDA followed by methyl cyanoformate, and the TBS
enol ether of cyclohexenone. Reactions of this type had some precedence in the literature but in our hands with either cerium(III) chloride or ammonium cerium(IV) nitrate the desired product was not formed.\(^6,^7\)

Since the oxidative coupling route to construct diketone 2.12 was already established we decided to take a different approach to the formation of the quaternary center and attempt an intramolecular alkylation by making use of a silyl tethered primary iodide.\(^8\) Whereas this alkylation was possible on the non-coupled ketone partner 2.28, when the same reaction was attempted on intermediate 2.32 it was unsuccessful probably due to the greater steric repulsion of forming the quaternary center.\(^9\)

Due to difficulty synthesizing the desired quaternary center, either through an aldol, alkylation or directly through an oxidative coupling, we turned our attention to a new strategy.
Section 2.3: Retrosynthetic analysis: 1,3-dipolar cycloaddition

Following the failed attempts at oxidative coupling a completely different approach was attempted. We hypothesized that a 1,3-dipolar cycloaddition of a nitrile oxide onto an α-aryl enone would lead to appropriate functionality for elaboration into the required cis-1,3-diol found in maecrystal V. Starting from the natural product, in a retrosynthetic sense, an oxidation of the A-ring ketone to an enone was the first strategic maneuver that would serve to remove the reactive enone functionality. An etherification of the secondary alcohol in 2.34 onto the olefin of the bicycle was next proposed. Bicyclic intermediate 2.34 was then proposed to come from the intramolecular Diels–Alder cycloaddition shown. This intermediate would arise from a Birch reduction of the aromatic ring followed by olefin isomerization to generate an enone and silylation to give a siloxy-diene. The dienophile for the intramolecular Diels–Alder reaction could be traced back to a propiolic acid moiety, attached via simple esterification. Diol 2.36 would come from a reductive cleavage of substituted isoxazoline 2.37. The isoxazoline
heterocycle is a versatile intermediate due to the fact that many synthetic methods for their conversion into useful functional groups exist.\textsuperscript{11} The isoxazoline would arise from the previously mentioned 1,3-dipolar cycloaddition of a nitrile oxide.\textsuperscript{12} By using a chiral auxiliary as the the R-group on the nitrile oxide we could render the cycloaddition enantioselective. A Suzuki coupling would be used to generate the \( \alpha \)-aryl enone from the simple precursors 2.39 and 2.40.

**Section 2.4: Execution of the forward synthesis**

The forward synthesis proceeded by first forming iodo-enone 2.40. This was done by stirring commercially available enone 2.41 with iodine and pyridine in dichloromethane to give a quantitative yield of the product. Boronic ester 2.42 was formed by ortho-metalation of anisole with \( n \)-BuLi followed by quenching with...
bis(pinacolato)diboron. The Suzuki coupling proceeded without issue in 91% yield by simply using palladium on carbon as the palladium source. In order to have a chiral dipole we began with mannitol, which was protected as the bis-acetonide. This diol was then subjected to oxidative cleavage with sodium periodate and tetrabutylammonium fluoride, to produce an unstable aldehyde that was immediately condensed with hydroxylamine hydrochloride to give oxime 2.46. This oxime was then chlorinated using N-chlorosuccinimide and was subsequently treated with triethylamine to eliminate HCl and form the 1,3-dipole in the presence of α-aryl enone 2.44. The reaction was unsuccessful leaving only returned starting material and most likely dimerized dipole (although it was not isolated). The cycloaddition was attempted again using a dipole derived from dibromoformoxime 2.52 again leading to only returned starting material on related α-aryl enone 2.53. At the time we elected not to pursue this route any further, believing that any dipolar addition we might attempt on this sterically hindered and electron poor olefin would be unsuccessful. At a later point, after further strategies had been attempted and knowledge about the reactivity of this molecule was gained, that we would return to the dipolar cycloaddition strategy.

Section 2.5: Retrosynthetic analysis: tandem reaction

In looking at the structure of maoecrystal V from another vantage point, it seemed as if a tandem vicinal di-functionalization of an enone could be an excellent strategy for
construction of its carbocyclic core. Starting another retrosynthesis from the natural product it seemed logical to remove the two unsubstituted methylenes of the bicycle by using an intermolecular Diels–Alder reaction with an ethylene equivalent. The diene for this cycloaddition would be formed as the silyl enol ether of intermediate 2.55. Selectivity would not pose an issue since it contains only one enolizable carbonyl. The enone functionality would come from oxidation of precursor 2.56 with IBX, a reagent that is capable of oxidizing alcohols to enones in one step.\(^\text{15}\) It is in formation of compound 2.56 that the tandem conjugate addition and epoxide opening was envisioned. It was our hope that under some form of activation that the tertiary alcohol in 2.57 could engage the enone in an oxo-Michael addition, thus generating an enolate that would be capable of an intramolecular attack of the proximal epoxide, to yield the cage core structure 2.56.\(^\text{16}\) This represents a greatly simplifying transformation, leading back to ester 2.57, which could be formed \textit{via} esterification.

Figure 2.8 Tandem conjugate addition/epoxide opening strategy.
Section 2.6: Execution of the forward synthesis

To generate the precursor for esterification commercially available enone 2.41 was subjected to a Baylis–Hillman reaction with aqueous formaldehyde and imidazole as catalyst to construct primary alcohol 2.59.\textsuperscript{17} Constructing acid component 2.62 was more complicated and it took much more experimentation to come to a reasonable synthetic route. Beginning with unsaturated ester 2.60, treatment with \textit{m}-CPBA afforded the epoxide. This epoxide was opened with TMSI in acetonitrile to give the iodohydrin.\textsuperscript{18} The iodide was next eliminated with DBU to provide allylic alcohol 2.61. Hydrolysis of this ester with lithium hydroxide provided the acid coupling partner. When it came time to merge the two fragments together, the typical esterification reagents (EDCI or DCC) provided none of the desired product. It was found however that Mitsunobu conditions could provide desired ester 2.63 in 71\% yield.\textsuperscript{19} Next, oxidation with IBX provided the dienone in acceptable yield. To setup the substrate for the tandem reaction all that was

![Figure 2.9 Attempting the tandem conjugate addition/epoxide opening.](image-url)
needed was a directed epoxidation of the most electron rich olefin. This was accomplished by using magnesium monoperoxyphthalate (MMPP) to give compound 2.57. Many conditions were then attempted for the formation of the desired core structure 2.56, however none were successful. Different modes of reactivity were explored based on literature precedents for related transformations (see Figure 2.9) using reagents such as strong bases, Lewis acids, weak bases, protic acids, radical conditions, palladium catalysis and simple thermal conditions, however decomposition or returned starting material were the only outcomes.

It was rationalized that the combination of the tertiary alcohol being an extremely poor nucleophile and that it needed to add into a very hindered electrophile made the desired reaction very unfavorable. The intramolecular nature of this reaction was not sufficient to allow it to progress as we had hoped and unfortunately this strategy was considered unworkable.
Section 2.7: References


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Section 2.8: Experimental section

General Procedures.

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), triethylamine (TEA), dichloromethane (DCM), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and p-anisaldehyde in ethanol/aqueous H$_2$SO$_4$/CH$_3$CO$_2$H and heat as developing agents. NMR spectra were recorded on a Bruker DRX 600, DRX 500, or an AMX 400 spectrometer and were calibrated using residual solvent as an internal reference (CDCl$_3$: 7.26 ppm for $^1$H NMR and 77.16 ppm for $^{13}$C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, a = apparent. In addition the following abbreviations were used: TMEDA = tetramethylethylenediamine, THF = tetrahydrofuran, EtOAc = Ethyl Acetate, o-DCB = ortho-dichlorobenzene, TFA = trifluoroacetic acid, DBU = 1,8-Diazabicycloundec-7-ene, TLC = thin layer chromatography, rt = room temperature. IR spectra were recorded on a Perkin-Elmer Spetrum BX spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144
melting point apparatus. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

**Compounds 2.8** through **2.10** have been previously reported.⁴

**Compound 2.7** has been previously reported.⁵

**Compound 2.12:**

TBS ketone 2.7 (0.400 g, 1.56 mmol) and freshly distilled cyclohexenone (0.450 g, 4.68 mmol) were mixed together and azeotropically dried with benzene followed by drying on high-vacuum for a minimum of 15 minutes. The flask was backfilled with argon and then dry THF (45 mL) was added and the solution was cooled to −78 ºC. Next freshly prepared 0.5 M LHMDS (1.46 mL, 7.02 mmol) was added slowly and the mixture was stirred at −78 ºC for 5 minutes followed by warming to 0 ºC for 30 minutes. The flask was then cooled to −78 ºC again and diacetoxy iodobenzene (2.26 g, 7.02 mmol), that had been previously dried for 12 hours on high-vacuum, was quickly added as a solid by means of removal of the septum. After stirring for 5 minutes at −78 ºC the cooling bath was removed and the flask was allowed to slowly warm to room temperature. After the reaction had reached room temperature, it was quenched by the addition of saturated aqueous NH₄Cl (50 mL) and EtOAc (50 mL). The reaction was then extracted with EtOAc (3 X 100 mL) and dried with MgSO₄. The solvent was removed *in vacuo* and
subjected to column chromatography to yield 164 mg (30%) of 2.12 as an inseparable mixture of two diastereomers.

2.12: clear oil, TLC (EtOAc/hexanes 1:3): $R_f = 0.5$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): major isomer: 6.92 – 6.95 (m, 1 H), 5.98 – 6.00 (d, $J = 9.9$ Hz, 1 H), 3.51 – 3.54 (m, 1 H), 3.11 – 3.12 (m, 1 H), 2.45 – 2.53 (m, 2 H), 2.36 – 2.40 (m, 2 H), 1.92 – 1.97 (m, 2 H), 1.67 – 1.75 (m, 3 H), 1.20 (s, 3 H), 1.058 (s, 3 H), 0.84 (s, 9 H), 0.03 (s, 3 H), 0.018 (s, 3 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ (ppm): both isomers: 215.2, 214.1, 200.9, 200.4, 150.4, 150.0, 130.1, 130.0, 79.5, 77.5, 52.6, 51.0, 46.0, 45.9, 43.5, 43.4, 30.5, 28.3, 26.7, 26.0, 25.9, 25.9, 25.6, 25.4, 24.5, 22.4, 22.0, 21.6, –3.9, −4.4, −4.8, −4.9; IR (film) $\nu_{\text{max}}$: 2952, 2930, 2857, 1705, 1676, 1472, 1463, 1386, 1255, 1103, 835, 774 cm$^{-1}$; MS ($m/z$): [M+H]$^+$ calcd. for C$_{20}$H$_{34}$O$_3$Si, 351.2; found, 351.0.

**Compound 2.14:**

To a stirred solution of oxidative coupling product 2.12 (0.049g, 0.1450 mmol) in dichloromethane (5 mL) at 0 ºC was added triethylamine (0.021g, 0.211 mmol) followed by TBSOTf (0.045g, 0.169 mmol). The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After the starting material was determined to be consumed by TLC (EtOAc: Hex 1:4 v/v), the reaction was quenched by the addition of saturated aqueous NaHCO$_3$ (5 mL) and Et$_2$O (5 mL). The organic portion was dried with MgSO$_4$ and concentrated *in vacuo*. A rapid column (EtOAc: Hex 1:4 v/v) was run to purify the compound due to its instability on silica to yield 54 mg of 2.14 as a clear oil in 83% yield.
2.14: clear oil, TLC (Et$_2$O/hexanes 1:4): $R_F = 0.8$; $^1$H NMR (600 MHz, CD$_2$Cl$_2$) $\delta$ (ppm):
major isomer: 5.61 – 5.66 (m, 1 H), 5.27 – 5.31 (m, 1 H), 5.13 – 5.16 (m, 1 H), 3.47 –
3.50 (m, 1 H), 2.92 – 2.99 (m, 1 H), 2.51 – 2.58 (m, 1 H), 1.97 – 2.20 (m, 3 H), 1.71 –
1.93 (m, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 0.92 (s, 9 H), 0.86 (s, 9 H), 0.19 (s, 3 H), 0.18
(s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (150 MHz, CD$_2$Cl$_2$) $\delta$ (ppm): both
isomers: 215.2, 214.1, 154.5, 154.4, 126.0, 123.4, 123.0, 120.0, 119.3, 103.2, 103.1, 79.9,
77.9, 53.1, 51.5, 47.6, 47.1, 36.6, 28.7, 26.7, 26.1, 26.1, 25.9, 25.7, 22.9, 22.6, 21.9, 21.8,
21.6, 20.4, 18.8, 18.7, 18.7, –3.3, –4.0, –4.0, –4.0, –4.2, –4.3, –4.5, –4.5; IR (film) $\nu_{\text{max}}$:
3040, 2953, 2929, 2885, 2857, 1707, 1652, 1593, 1472, 1463, 1361, 1252, 1200, 1101,
834, 774 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{26}$H$_{48}$O$_3$Si$_2$, 465.3215; found, 465.3218.

**Iodo enone 2.40** has been previously reported.$^{20}$

**Boronic Ester 2.43** has been previously reported.$^{21}$

**Aryl Enone 2.44**

Iodo enone 2.40 (0.320 g, 1.28 mmol) and boronic ester (0.330 g, 1.41 mmol) 2.43 were
dissolved in 9 mL of 1:1 DME/H$_2$O and solid sodium bicarbonate (0.271 g, 2.56 mmol)
was added. To this solution was added 0.136 g of 10% palladium on carbon and the
solution was heated for 12 hours. After the reaction was judged to be complete by TLC
the mixture was cooled to room temperature and filtered through a pad of Celite with
EtOAc (50 mL). This biphasic mixture was extracted with brine (25 mL) and water (25
mL) and dried with MgSO₄. The crude compound was subjected to column chromatography to provide 0.268 g (91% yield) of product 2.44 as a clear oil.

2.44: clear oil: TLC (EtOAc/hexanes 1:4): \( R_f = 0.4 \); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \) (ppm): 7.27 – 7.30 (t, \( J = 7.8 \) Hz, 1 H), 7.04 – 7.05 (d, \( J = 7.4 \) Hz, 1 H), 6.92 – 6.94 (t, \( J = 7.2 \) Hz, 1 H), 6.88 – 6.89 (d, \( J = 8.2 \)Hz, 1 H), 6.57 (s, 1 H), 3.75 (s, 3 H), 2.60 – 2.62 (t, \( J = 6.8 \) Hz, 2 H), 1.96 – 1.98 (t, \( J = 6.8 \) Hz, 2 H), 1.24 (s, 6 H); \(^{13}\)C NMR (150 MHz, CDCl₃) \( \delta \) (ppm): 197.5, 157.3, 157.2, 136.0, 130.7, 129.3, 126.7, 120.6, 111.1, 55.8, 36.4, 35.1, 33.5, 28.2; IR (film) \( \nu_{\text{max}} \): 3516, 2957, 2864, 2836, 1675, 1589, 1490, 1435, 1352, 1264, 1241, 1141, 1025, 841, 752 cm\(^{-1}\); HRMS (\( m/z \)): [M+H]\(^+\) calcd. for C\(_{15}\)H\(_{18}\)O\(_2\), 231.1379; found, 231.1389.

Oxime 2.46 has been previously reported.\(^{22}\)

Aryl enone 2.53:
Iodo enone 2.40 (1.0 g, 4.0 mmol) and 2-(2-(methoxymethoxy)-3-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.993 g, 4.0 mmol) were dissolved in 10/5/3 : DMF/EtOH/H\(_2\)O 18 mL total. To this solution was added sodium carbonate (0.932 g, 8.8 mmol) and the solution was degassed for 15 minutes, by means of sonication and argon bubbling. To this solution was added Pd(ddpf)Cl\(_2\)•DCM (0.163, 0.2 mmol) and the vial was sealed and warmed to 60 °C for 2 hours until the TLC showed no remaining starting material. The mixture was cooled to room temperature and filtered through a pad of Celite, rinsing with EtOAc (50 mL). This biphasic mixture was extracted with brine (25
mL) and water (25 mL) and dried with MgSO₄. The crude compound was subjected to column chromatography to provide 1.04 g (95% yield) of product 2.53 as a clear oil.

2.53: clear oil: TLC (EtOAc/hexanes 1:4): \( R_f = 0.4 \); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) (ppm): 7.11 – 7.14 (dd, \( J = 1.6, 7.5 \) Hz, 1 H), 6.98 – 7.01 (t, \( J = 7.5 \) Hz, 1 H), 6.89 – 6.91 (dd, \( J = 1.7, 7.4 \) Hz, 3 H), 6.66 (s, 1 H), 4.79 (s, 2 H), 3.48 (s, 3 H), 2.60 – 2.63 (t, \( J = 6.5 \) Hz, 2 H), 2.32 (s, 1 H), 1.95 – 1.99 (t, \( J = 6.8 \) Hz, 2 H), 1.24 (s, 6 H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) (ppm): 197.7, 157.7, 156.2, 135.3, 131.0, 130.8, 130.4, 128.7, 123.5, 77.4, 60.1, 36.2, 35.0, 33.3, 27.9, 16.3; IR (film) \( \nu_{\text{max}} \): 2957, 2926, 2865, 1678, 1460, 1353, 1157, 1070, 976 cm\(^{-1}\); HRMS (m/z): [M+H]\(^+\) calcd. for C\(_{17}\)H\(_{22}\)O\(_3\), 275.1642; found, 275.1637.

Alcohol 2.59 has been previously reported.\(^{23}\)

Ester 2.61 has been previously reported.\(^{18}\)

Ester 2.63:

Carboxylic acid 2.62 (0.275 g, 1.79 mmol), enone 2.59 (0.276 g, 1.79 mmol) and triphenyl phosphine (0.563 g, 2.148 mmol) were combined in a flask and azeotropically dried with benzene, then dried on high-vacuum for a minimum of 15 minutes. The flask was backfilled with argon and dry THF (40 mL) was added to the flask. The flask was cooled to −78 °C and diethyl azodicarboxylate (0.374 g, 2.148 mmol) was added dropwise. After the addition was complete the reaction was allowed to slowly come to room temperature by letting the cooling bath come to this temperature. The reaction was
diluted with ether (50 mL) and 50% aqueous saturated NaHCO$_3$ (100 mL) and extracted with ether (3 X 50 mL). The combined organic fractions were dried with MgSO$_4$ and concentrated in vacuo. The crude product was purified with flash chromatography with EtOAc/Hexanes (1:1) as eluent to obtain the product as a clear oil in 71% yield (0.354 g).

**2.63:** clear oil: TLC (EtOAc/hexanes 1:1): $R_f = 0.6$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 6.63 (s, 1 H), 6.02 – 6.04 (m, 1 H), 5.60 – 5.61 (d, $J = 9.8$ Hz, 1 H) 4.81 (a t, $J = 1.3$ Hz, 2 H), 3.15 (s, 1 H), 2.47 – 2.50 (t, $J = 5.4$ Hz, 2 H), 1.94 – 2.16 (m, 3 H), 1.86 – 1.88 (t, $J = 5.4$ Hz, 2 H) 1.76 – 1.83 (m, 3 H), 1.17 (s, 6 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 197.5, 176.0, 157.5, 132.7, 131.0, 126.5, 71.7, 62.5, 35.8, 34.4, 33.8, 33.0, 27.7, 24.5, 18.3.

**Epoxide 2.57:**

1. To a stirred solution of **2.63** (0.290 g, 1.04 mmol) in DMSO (10 mL) was added catalytic TsOH•H$_2$O (0.040 g, 0.2 mmol). The flask was warmed to 80 °C and IBX (1.46 g, 5.22 mmol) was added in 0.146 g portions every thirty minutes over the course of 10 hours. After the last addition the reaction was allowed to stir for 1 additional hour at 80 °C and was then cooled to room temperature. The reaction mixture was diluted with EtOAc (100 mL) and brine (100 mL) and extracted with EtOAc (3 X 100 mL). The combined organic fractions were dried with MgSO$_4$ and concentrated in vacuo. The resulting residue was chromatographed on silica with EtOAc/Hexanes (2:1) as eluent to afford 0.163 g of intermediate dienone as a colorless oil in 59% yield, with the material balance being recovered as starting material.

**Intermediate Dienone:** clear oil: TLC (EtOAc/hexanes 2:1): $R_f = 0.3$. 

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II. **Intermediate Dienone** (0.53 g, 0.192 mmol), from the previous procedure, was dissolved 1.4 mL of i-PrOH/H₂O (1:1) and treated with MMPP (0.190 g, 0.384 mmol). The solution was stirred for 1 hour at room temperature and then diluted with water (10 mL) and EtOAc (10 mL). The aqueous layer was washed with EtOAc (3 X 20 mL) and the combined organic extracts were dried over MgSO₄. After chromatography with EtOAc/Hex (2:1) the product epoxide was obtained as a clear oil in 38% yield over two steps (0.116 g).

2.57: clear oil; TLC (EtOAc/hexanes 2:1): \( R_f = 0.2 \). \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) (ppm): 6.85 – 6.86 (m, 1 H), 6.82 – 6.85 (m, 1 H), 6.15 – 5.25 (d, \( J = 9.7 \) Hz, 1 H), 4.93 – 4.99 (m, 2 H), 3.37 – 3.38 (m, 1 H), 3.33 – 3.34 (d, \( J = 3.9 \) Hz, 1 H), 3.16 (s, 1 H), 1.97 – 2.22 (m, 1 H), 1.75 – 1.82 (m, 1 H), 1.69 – 1.74 (m, 1 H), 1.59 – 1.65 (m, 1 H), 1.49 – 1.57 (m, 1 H), 1.35 – 1.43 (m, 1 H), 1.25 (s, 6 H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) (ppm): 184.4, 173.4, 156.8, 154.8, 131.6, 127.0, 72.9, 62.5, 55.3, 54.8, 38.3, 32.5, 26.8, 22.9, 15.6.
Appendix to

Chapter 2: Spectra
Chapter 3

Refined Approaches: Overcoming

Quaternary Center Synthesis
Section 3.1: Retrosynthetic Analysis: Radical Coupling

It was now time for us to rethink our strategy once again. We decided to return to the idea of an oxidative coupling. On this attempt we would again make use ammonium cerium(IV) nitrate to generate the stabilized radical of a β-keto aldehyde in the presence of a silyl enol ether with the hope that it would intercept the radical and make a carbon-carbon bond.¹ This strategy would also overcome the problem of homocoupling that we observed in our previous oxidative coupling attempts, due to the difference in reactivity of the two partners. Our retrosynthetic analysis begins with a different simplifying strategy: using the tertiary alcohol to carry out a C–H activation reaction, in order to generate the tetrahydrofuran moiety of the natural product. This transformation eliminates problems such as retroaldol reactions and the need for any oxygen conjugate addition. It is well known that reagents such as PIDA and lead(IV) acetate that are capable of creating oxygen-centered radicals are able to perform these sorts of transformations.² With the tetrahydrofuran ring disconnected, bicycle 3.2 can be thought to arise again from an intramolecular Diels–Alder reaction of an α-hydroxy enoate and a
TBS silyl enol ether. This silyl enol ether could be derived from the corresponding enone using TBSOTf with triethylamine. Ester 3.3 would be formed from the primary alcohol, a result of aldehyde reduction, and an appropriate acid through esterification. At this point we would apply our radical coupling reaction between β-keto aldehyde 3.5 and silyl enol ether 3.6, both of which are available from cheap commercial starting materials.

Section 3.2: Execution of the synthesis: Success and the need for revision

Precedent for the formation of a carbon-carbon bond by formation of a radical of a β-ketoester and attack by an enol ether had been known with manganese(III) acetate and copper(II) acetate as well as with ammonium cerium(IV) nitrate (Figure 3.2 A and B). As discussed previously (Chapter 2) we attempted this reaction and it proved to be unsuccessful. We presumed that the β-keto aldehyde might have a different reactivity owing to its exclusive presence in the enol form as witnessed by NMR. The β-ketoester that we previously attempted this reaction with did not exist in the enol form at all but in fact as a mixture of cis- and trans-epimers. Based on the proposed mechanism, (Figure 3.2 C) the enol form of the β-ketoester is necessary for the compound to be oxidized.

We prepared suitable substrates for this reaction, β-keto aldehyde 3.5 and the TBS silyl...
enol ether of 2-methylcyclohex-2-enone (3.6). They were reacted together in the presence of ammonium cerium(IV) nitrate in methanol with sodium bicarbonate buffer and to our delight we obtained the desired coupled product 3.4. This reaction marked the first time that we successfully constructed the all carbon quaternary center for C10 of maoecrystal V! With intermediate 3.4 we found that we could chemoselectively reduce the aldehyde in the presence of the other two carbonyl groups by using the mild and bulky reagent, lithium tri(tert-butoxy)aluminium hydride, to give the hydroxymethyl unit. This primary hydroxyl group was promptly treated with acryloyl chloride in the presence of triethylamine in dichloromethane to provide ester 3.7.

Following this we were poised to make the precursor for the Diels–Alder reaction. However upon treatment with TBSOTf and triethylamine the silyl enol ether that formed was incorrect isomer 3.8, resulting from γ-deprotonation of the enone rather than the desired α-deprotonation, shown in 3.9. Although diene 3.8 would not be able to react in the Diels–Alder cycloaddition in the desired sense, we realized that it could be aromatized to phenol 3.10 quite easily, by dehydrogenation with palladium on carbon in
the presence of oxygen. Free phenol 3.11 was then formed by deprotection of the TBS-group using TBAF.

Phenols have often served as precursors for dienes either through Birch reductions or through oxidative dearomatization reactions.\(^4\) A Birch reduction did not seem viable in this scenario since there were easily reduced enone and enoate functional groups, so an oxidative dearomatization was attempted. The first oxidants that were screened were PIDA, PIFA, and sodium periodate, none of which gave dearomatization. Lead(IV) acetate in acetic acid was found to be quite effective at dearomatizing the phenol to corresponding acetate derived \textit{ortho}-quinol 3.12.\(^5\) This masked \textit{ortho}-quinol now had an appropriate diene structure to provide the desired bicyclic compound. Indeed upon heating the compound to 165 °C in \textit{ortho}-dichlorobenzene a Diels–Alder cycloadduct was obtained. Upon examination of the NMR it was unclear which diastereomer had formed. Even two dimensional spectroscopy experiments were inconclusive so single crystal X-ray diffraction was employed to determine the structure. Upon growing crystals and submitting them for X-ray analysis it was found that the diene

\begin{center}
\textbf{Figure 3.4} Synthesis of incorrect bicycle structure and its X-ray structure.
\end{center}
had reacted in the undesired manner to provide 3.13 instead of 3.14. The product was the result of undesired facial selectivity, a consequence of the substrate. We next planned to alter the structure to obtain our desired core.

Section 3.3: Revised Retrosynthesis

Now that we had established a way to construct a bicycle, albeit the incorrect one, the route would need revision to make it workable. The carbonyl of the A-ring appeared to be the only functional group that was playing a role in determining the facial selectivity of the product. It was hypothesized that if we used the propensity of the carbonyl to favor the observed selectivity, we could simply move the geminal-dimethyl group next to the carbonyl to obtain the correct carbon framework. Also, by adding an additional functional handle for eventual enone installation this route could be viable.

Since this strategy utilized the intermediacy of a phenol it became fitting to employ an arylation reaction, instead of a radical coupling to install the cyclohexenone

![Diagram of chemical reactions and structures](image-url)
moiety, followed by several steps worth of manipulations to produce a phenol. Barton had pioneered work in arylation of active methylene compounds using guanidine bases with triarylbumuth dichlorides.\textsuperscript{6} It was already established that these reactions were general and capable of forming quaternary centers.

To employ these additions to our revised retrosynthesis we would first remove the carbonyl of \textbf{3.1} via allylic oxidation, thus removing the enone functionality. Next a reductive cleavage would dispose of the acetoxy group resulting from dearomatization. A hemiketal reduction was envisioned for formation of the tetrahydrofuran ring found in \textbf{3.1}. Making these disconnections would lead back to \textbf{3.15}, which could be further simplified by removing the tertiary alcohol using a Rubottom oxidation. The A-ring olefin would arise from elimination of a secondary alcohol, after removal of the TBS protecting group. Bicycle \textbf{3.16} would arise from our newly proposed Diels–Alder cycloaddition. Precursor \textbf{3.17} would result from the dearomatization of the phenol from \textbf{3.18} that would come from the arylation.

Our previously utilized carbonyl compound \textbf{3.21} now became a perfect match for our needs, having a carbonyl next to the geminal-dimethyl group and a chiral OTBS group that could later be converted to the enone. We easily could install an $\alpha$-aldehyde next to the carbonyl group to serve as the hydroxymethyl group after reduction and to allow for the arylation reaction.
Section 3.4 Execution of the synthesis: Construction of the carbon skeleton

Synthesis of the triarylbismuth starting material for this route begins with ortho-cresol, which is protected as its MOM ether 3.23 using dimethoxymethane in the presence of phosphorus(V) pentoxide. The aromatic ring was then ortho-metalated with \( n\)-BuLi followed by addition of bismuth(III) chloride to form triarylbismuth 3.24. The bismuth was next oxidized to form triarylbismuth(V) dichloride using sulfuryl chloride, to form the active arylation species 3.19. To prepare the \( \beta \)-keto aldehyde we first started, as before, with symmetrical ketone 3.25 which was subjected to the baker’s yeast mediated desymmetrization to yield chiral alcohol 3.26. This alcohol was TBS-protected with TBSOTf and 2,6-lutidine to give 3.21. This compound was then formylated with ethyl formate and sodium methoxide produced \textit{in situ} from methanol and sodium hydride to form 3.20.

Now with both coupling partners secured, we were ready for the arylation reaction. After investigating some different conditions it was found that DBU in toluene
at room temperature were the best conditions. The desired product was produced in 67% yield as a mixture of diastereomers (7:3). We proceeded with major diastereomer 3.18, which had a *trans*-relationship between the aryl group and the TBS protected alcohol. Again lithium tri(tert-butoxy)aluminium hydride was used to chemoselectively reduce the aldehyde, in the presence of the ketone, to the hydroxymethyl group of compound 3.27. This newly formed alcohol was then acrylated with acryloyl chloride to provide ester 3.28 (Figure 3.7). The MOM-group was then removed using trifluoroacetic acid in dichloromethane. The resulting phenol spontaneously formed a hemiketal with the proximal ketone to give intermediate 3.29. The formation of the hemiketal was of no consequence since it is in equilibrium with its open form in acidic solution and the reaction solvent for the dearomatization is acetic acid. Lead(IV) acetate was again employed to oxidatively dearomatize the phenol which reacted smoothly to provide a mixture of acetate epimers of compound 3.17. These two epimers could be separated and carried on separately, however it was not a problem to carry these two on together because the epimeric stereocenter would become *sp*²-hybridized at a later stage, losing its stereochemical information.

The critical moment for the Diels–Alder reaction had finally arrived. Diels–Alder precursor 3.17 was heated in the microwave to 165 °C for 1 hour and to our delight we obtained cycloadduct 3.16. The reaction was also tested thermally (without the presence of microwaves) at the same temperature and worked satisfactorily but took a much longer time (over 24 hours). If each diastereomer was carried on separately then the reaction only produced one compound, which was the *endo*-cycloadduct. This was proven to be true by X-ray crystallographic analysis of both diastereomers of 3.16. The cycloadduct
resulting from the minor diastereomer of 3.17, was crystallized directly after purification. Cycloadduct 3.16, resulting from the major diastereomer of 3.17, was first treated with BF$_3$•OEt$_2$ to remove the TBS-group (to give alcohol 3.30) so that a crystal suitable for X-ray analysis could be grown. Thus it was proved that the newly designed intramolecular Diels–Alder provided the correct facial selectivity and delivered the desired cycloadduct.

To further elaborate the bicycle towards maoecrystal V the olefin resulting from the Diels–Alder reaction was hydrogenated using palladium on carbon to give 3.31. The acetoxy-group was then reductively cleaved off using samarium(II) iodide to give a 17:3 diastereomeric ratio of 3.32 to 3.33 in 76% yield.$^{11}$ This reductive cleavage goes through the intermediacy of a samarium enolate that is quenched by the solvent, in this case
methanol, to give the reduced ketone. The structure of both diastereomers of the reduced product was in fact confirmed by X-ray crystallographic analysis of the minor product (3.33), to show that it was the opposite found in maoecrystal V, implying that the major product (3.32) was in fact the desired one. Interestingly if the samarium(II) iodide reduction was carried out on bicycle 3.16 a 1:1 ratio of methyl epimers was obtained.

The desired major diastereomer 3.32 was then carried on by treatment with excess TBSOTf and excess triethylamine in DCM to fortunately give exclusively the silyl ketene acetal (3.34). This compound was relatively stable, but was found to hydrolyze on silica, so it was not purified but used crude with various oxygen transfer reagents as shown in Figure 3.8. A Rubottom oxidation did in fact occur with all the reagents that were screened, although in all cases it gave exclusively the wrong epimer 3.35. The best
yield was obtained by using MMPP as oxidant. This result was not seen as a failure but instead as an opportunity for further exploration and creativity.

We also attempted to replace the TBS group with a mesylate, postulating that the size difference of the protecting group could play a factor in the steric environment or cause a change in overall conformation of the molecule. Upon treating 3.32 with BF₃•OEt₂ as before, we were able to smoothly remove the TBS group to provide the corresponding alcohol. This secondary alcohol was then mesylated with methanesulfonyl chloride and triethylamine to give mesylate 3.36. The silyl enol ether of this mesylated compound was formed and treated with various oxidants (Davis’ oxaziridine gave the best results) to again generate the undesired alcohol diastereomer 3.38, which was confirmed by X-ray crystallography.¹³

The inherent preference of electrophiles to react on the same face as the oxidants screened was further reinforced by the use of various other electrophiles. We observed that when silyl enol ether 3.34 was protonated, either by addition of acid or by adventitious acid in the reaction medium the proton gave the epimer of the starting lactone, resulting from protonation of the enolate from the opposite face (effectively giving the exo-cycloadduct). This indicated to us that any electrophile that we attempted
to react with the silyl enol ether would approach from that face since, for all intents and purposes, a proton is the smallest electrophile.

We sought to use this preference to install a leaving group by reacting the silyl enol ether with bromine, to make the corresponding bromide, an intermediate that would have allowed for displacement by an oxygen nucleophile. The only product that was isolated from this reaction however, was unsaturated lactone 3.39, presumably from bromination and subsequent elimination. Incorrect alcohol diastereomer 3.35 was next subjected to mesylation conditions, however the mesylate group suffered the same fate as the brominated intermediate: to eliminate and give identical unsaturated lactone 3.39. Additionally we thought that perhaps the lithium enolate of lactone 3.16 would display different reactivity with triplet oxygen due to its diradical nature and be able to react in the desired fashion. Any attempts to react this substrate with a strong base such as LDA and oxygen lead to decomposition.

Another variation of the Diels–Alder reaction strategy was to try using dienophiles with substitution in the α-position. Since these substrates were difficult to prepare, due to the fact that the ester was either difficult to form or could not survive the

![Diagram showing reactions and structures](image-url)

*Figure 3.10 A: Using different dienophiles; B: Using pyruvate as dienophile; C: Attempted retroaldol-aldol; D: Attempted ketone reduction.*
necessary deprotection or dearomatization conditions, the only substrates we could prepare were the α-methoxy acrylate 3.41a (R = OMe) and the α-bromo acrylate 3.41b (R = Br). We hoped that these would participate in the Diels–Alder cycloaddition in the same way that the acrylate had previously to give the endo-product. Upon heating these sensitive substrates under the typical conditions, they decomposed without providing any trace of cycloaddition product. Forming pyruvate ester 3.43 proved feasible, however it did not participate in a Diels–Alder cycloaddition. We had hoped that it would tautomerize to the α-hydroxy-acrylate and react as a dienophile to provide the desired hydroxy-bicycle 3.44. Instead the ester was cleaved and deformylation took place.

Incorrect hydroxy-bicycle 3.35 was revisited with the hope that treating it with base or acid would cause it to undergo a retroaldol reaction to give a macrocyclic intermediate that would invert the ketone and reclose in an aldol reaction to give 3.45. These attempts were also unsuccessful and usually provided complex rearrangement products. Finally bicycle 3.31 was reduced with sodium borohydride with the expectation that one or both of the ketones would be reduced, to perhaps create an opportunity for a directed C–H functionalization. Unexpectedly the outcome of the reaction was solely reduction of the lactone in 3.31 to lactol 3.46, even under forcing conditions.

We decided that the Rubottom oxidation reaction required further investigation and perhaps modifying the substrate control by changing some of its functionality would encourage different diastereoselectivity. In order to modify the substrate it was decided to rearrange some of the steps of the endgame and remove the TBS group and eliminate the resulting alcohol to give olefin 3.47 as shown in Figure 3.11.
This did not prove to be as straightforward as had been hoped. The TBS group was smoothly removed by using BF$_3$•OEt$_2$ to provide alcohol 3.48. This alcohol was mesylated to give mesylate 3.36. It was upon attempted elimination with DBU that an unexpected attack of the bicyclic ketone to displace the mesylate, in an S$_{n}$2 fashion, took place to provide caged structure 3.49. Attempted elimination of the enol oxygen to give the desired product was unsuccessful. Repeating this elimination reaction, under neutral conditions, by simply heating the mesylate in DMSO also provided the same product (3.49). It was due to this inability to eliminate the secondary alcohol that a revised route to the desired olefin was investigated.

In considering a new route to the olefin we were hoping to find a more scalable procedure so that we could obtain larger quantities of the later intermediates. A successful route that we utilized involved a Suzuki coupling to merge the aromatic ring with the cyclohexyl ring followed by a conjugate reduction and trap with formaldehyde to generate the quaternary center. We began with ketone 3.21 and in a three step sequence brominated it with phenyltrimethyl ammonium perbromide (PTAB) to generate...
the α-bromide followed by elimination with lithium carbonate and lithium bromide in refluxing DMF to give the corresponding enone. This enone was next iodinated with iodine in pyridine to give α-iodo enone 3.50. This enone was found to participate quite well with pinacol-borate 3.51 to form α-aryl enone 3.52 under standard Suzuki coupling conditions. We next performed a conjugate reduction of the enone with L-Selectride to
form the enolate, which was then trapped with formaldehyde to give primary alcohol 3.27, as a mixture of two diastereomers. This compound was an intermediate that had been synthesized previously using bismuth arylation chemistry. It also demonstrated that an aldol reaction with a lithium enolate could form an all carbon quaternary center on this substrate, provided that a stabilizing phenyl ring was present on the enolate.

To make use of α-aryl enone 3.52 to generate the olefin target, we treated it with TBAF to remove the TBS group and to our surprise the TBAF simply acted as a base and eliminated the -OTBS group off in a single step. The conjugate reduction was then attempted followed by trapping with formaldehyde and again the reaction proceeded as desired giving exclusively 1,4-reduction with none of the potential 1,2- or 1,6-reduction, to yield alcohol 3.54. This intermediate was next carried through seven steps of the chemistry previously discussed (e.g. esterification, deprotection, dearomatization, Diels–Alder, samarium reduction, hydrogenation, and silyl enol ether formation) without any difficulty. We could now test the hypothesis that the OTBS group was causing the incorrect selectivity during the Rubottom oxidation. Unfortunately only undesired diastereomer 3.62 was once again obtained.
Intermediate primary alcohol 3.54 (Figure 3.14) was further studied for potential early stage reduction, with the intent of using the A-ring alcohol as a directing group for a late stage C–H functionalization. Upon treatment of 3.54 with lithium aluminum hydride (and with all other hydride sources screened) we obtained a new alcohol from reduction of the ketone. At the time we were unsure of the exact structure, as we did not know the stereochemical outcome of the reaction, yet we continued on with the material while attempting to grow a crystal for X-ray analysis. The X-ray revealed that the ketone had in fact been reduced to give the undesired alcohol diastereomer. In addition, the MOM group had migrated from the phenol to the primary alcohol, which was later determined to be inconsequential. The next step was esterification with acryloyl chloride to give phenolic ester 3.64. Upon deprotection of the MOM group the acrylate group underwent a transesterification with the primary alcohol to give ester 3.65. The phenol was then dearomatized using lead(IV) acetate to provide the dienone precursor for the Diels–Alder reaction. It was at this time that we obtained crystal structure of alcohol 3.63 and we realized that we had obtained the wrong alcohol diastereomer from the reduction and that the MOM group shift had shifted. Having established the structure of the dienone derived from 3.65 by NMR we were fairly confident about the fact that the acrylate had undergone a transesterification to give the desired ester. Despite the fact that the wrong alcohol diastereomer was obtained, we elected to go through with the Diels–Alder with the expectation that perhaps the alcohol could later be inverted or displaced or used in some other creative way to form the tetrahydrofuran ring. Upon heating the substrate to 150 ºC we obtained new cycloadduct 3.66. The NMR showed what appeared to be a Diels–Alder product however it did not show the expected spectrum. An X-ray structure
was obtained, which revealed that the A-ring alcohol formed a hemiketal structure with the bicyclic ketone after the cycloaddition. In the process the acetate group was cleaved off to give the corresponding tertiary alcohol of cycloadduct 3.66. At this point any further pursuit of this early reduction route seemed unfeasible.

In a final attempt to obtain the desired alcohol diastereomer compound 3.54 was revisited and elaborated as before to bicycle 3.60. This compound was heated with benzeneseleninic anhydride, a reagent known for installing tertiary alcohols adjacent to ketones, for an attempted oxygenation. The results were indeed very surprising! We had in fact obtained the desired alcohol diastereomer and it formed the hemiketal as predicted (and desired), however the alcohol of the hemiketal engaged the bicyclic ketone to form another hemiketal as shown in compound 3.67. These results paralleled those found in the Figure 3.14 with the Diels–Alder product. Additionally the bicyclic methyl group was oxidized and then cleaved to leave a carbonyl in its place. A proposed mechanism is shown below in Figure 3.16.
It is initially believed that the bicyclic ketone enolizes and the enol carbon attacks the selenium of the benzeneseleninic anhydride, causing an elimination of benzeneseleninic acid. This intermediate undergoes an intramolecular syn-elimination to provide enone 3.70.\(^1\) This enone next undergoes oxidative cleavage by the benzeneseleninic anhydride. This is proposed as the first intermediate, due to the fact that if the reaction is stopped prematurely 1,2-diektone 3.71 is the major product. The next step that could occur is enolization of the lactone, which now attacks another equivalent of benzeneseleninic anhydride, with the enol oxygen and eliminates benzeneseleninic acid. This intermediate then undergoes a [2,3]-sigmatropic rearrangement that occurs from the top face of the enol, as drawn, leading to the desired alcohol isomer (3.75) after cleavage of the oxygen-selenium bond. From this point there are two successive hemiketal formation events to finally lead to product 3.67. Product 3.67 does in fact possess the connectivity for the desired tetrahydrofuran ring system.
needed in maoecrystal V, but it was obtained with the concessions of methyl group cleavage and the second ketalization reaction, making this reaction or intermediate synthetically useless (but structurally intriguing!). The reaction was also preformed on the -OTBS containing substrate 3.32, with the same results. It was believed that formation of the desired alcohol diastereomer would always lead to the same double ketalization event and therefore any strategy that utilized this plan was not usable for our synthetic campaign.

Section 3.5 Dipolar cycloaddition Retrosynthesis

In looking back at ideas from our previous efforts towards the total synthesis of maoecrystal V, the dipolar cycloaddition idea seemed to be the most intelligent and powerful plan. It was attractive because it used the cycloaddition to ensure a cis-relationship between the 1,3-diol intermediate from our previous retrosynthesis (Chapter 2, Figure 2.6). Our previous attempts involved formation of the nitrile oxide dipole and

![Figure 3.17 Revisiting cycloaddition via use of arylation.](image)
its subsequent reaction with an $\alpha$-aryl enone. This provided no product, which we reasoned, was most likely due to the imposing steric environment of the reacting olefin. It might be possible to conduct the dipolar cycloaddition on the enone and then install the desired aryl ring to intercept the identical intermediate. Working backwards from maoecrystal V we would remove the enone functionality as before with an IBX oxidation and break the bicyclic ring system with an intramolecular Diels–Alder reaction to go back to 3.77. Diene 3.77 would arise from an oxidative dearomatization of a phenol, such as 3.78. The dienophile moiety would be tethered to a vinyl ether so that the tetrahydrofuran would form during the Diels–Alder reaction, thus avoiding difficulties with carbonyl reduction that we encountered previously. This could be synthesized by some type of etherification reaction between the secondary alcohol and the acrylate of 3.78. A diazotization reaction followed by nucleophilic displacement with the desired acid would provide ester 3.78 from primary amine 3.79. Amino alcohol 3.79 would arise from complete reduction of bromo-isoxazoline 3.80 using Raney nickel.20 At this point in the retrosynthesis, our previously planned intermediate would be intercepted. The plan to form it however has changed in that cycloadduct 3.81 would be arylated using the same triaryloubismuth dichloride reagent that we previously employed. In order to form cycloadduct 3.81 we would use dibromoformoxime with base in the presence of enone 3.82.21

Section 3.6 Progress to date and future directions

This strategy began with first testing the 1,3-dipolar cycloaddition. We were pleased to find that 4,4-dimethyl-2-cyclohexenone (3.82) reacted with the bromo-nitrile
oxide generated *in situ* from dibromoformoxime to form **3.81**. The conditions that were found to work best were: sodium bicarbonate as base, toluene at reflux, with slow addition of dibromoformoxime. This compound could be purified on silica gel, however it was found to be incompatible with bases such as triethylamine, DBU or anything more basic as they caused aromatization to isoxazole **3.83**. Also upon standing at ambient temperature under an air atmosphere it was found to slowly oxidize to isoxazole **3.83**. Fortunately if this compound was deprotonated at −78 °C in degassed tetrahydrofuran, it could be arylated using NaHMDS and triarylbismuth dichloride **3.19**, prepared previously, to provide tricycle **3.84** in 39% yield.

Our next step was to reduce the bromo-isoxazoline to the amino-alcohol. We attempted a number of different conditions for this reduction, some of them well precedent, others not. None of these reductions led to the desired product and most often resulted in loss of the aromatic ring, presumably *via* a hydride shift, to form isoxazole **3.83**. During the use of TiCl₃ (solution in 3 M HCl) for the attempted reduction, the only product that we observed was the deprotection of the MOM-ether to provide hemiketal **3.80**. This was a serendipitous finding because when this hemiketal

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**Figure 3.18** Formation of cycloadduct, arylation and attempted reduction.
was subjected to Raney nickel under a hydrogen atmosphere amino-alcohol 3.79 (Figure 3.19) was obtained.\textsuperscript{20b} In addition nitrile 3.86 was also formed, but it was found that it could be resubjected to the reaction conditions to furnish more amine 3.79. Upon trying the same reduction with lithium aluminum hydride, we obtained the over reduced product triol-amine 3.85. Deprotection of 3.84 was then repeated using 1 M HCl in dioxane to provide hemiketal 3.80. Now that we had a reliable way to construct amino-alcohol 3.79, we focused on forming an ester from the amine. The initial attempt we made was simply to form an acetate ester from the primary amine. The standard conditions that we followed used aqueous sodium nitrite with the carboxylic acid acting both as the acid catalyst for diazotization and nucleophile, in acetonitrile.

This variety of reaction is known using acetic acid on much simpler amine substrates or intramolecularly, so it was unclear how successful the reaction would be.\textsuperscript{21,22} We were pleased to find that we indeed formed acetate ester 3.87 using standard conditions. The acetate could be easily cleaved off of this substrate with potassium carbonate in methanol to give diol 3.88.
We then set out to test the reaction on various carboxylic acids to determine the scope of acids tolerable with our substrate that would also be useful for elaboration (Figure 3.20). From the acids tested we found that acetic acid, acrylic acid, 2-methoxyacrylic acid and diethylphosphono acetic acid worked well and propionic acid, pyruvic acid and 2-bromoacrylic acid did not. The acids that did not participate well in the reaction are quite unstable and prone to polymerization on their own so perhaps it is not surprising that they did not work well. Those acids that did work only did so in modest yield, most likely to skeletal rearrangements that can take place after diazotization. These reactions did however provide enough material to carry out additional investigations.

Ester 3.91 was synthesized because it allows for synthesis of a vinyl ether through a three step sequence of diazo transfer, O–H insertion and Horner–Wadsworth–Emmons

![Figure 3.20 Synthesis of various esters via diazotization and examples that were unsuccessful.](image-url)
olefination, which has been well documented in the literature. With our substrate we were able to perform this sequence (Figure 3.21) however the product (3.96) that we obtained was the result of O–H insertion into the hemiketal alcohol, instead of the secondary alcohol (3.97) as desired. This was a problem that we were unable to overcome with catalyst control, trying various rhodium sources (same product), copper sources (no reaction was obtained with any copper source) and Lewis acids (decomposition).

We elected to try to synthesize a methoxy ketal from the existing hemiketal to act as a protecting group for the tertiary alcohol of 3.91. Subjecting ester 3.91 to any acidic conditions caused the same outcome each time, a fragmentation to cleave open the six membered ring and a dehydration to aromatize to benzofuran 3.99 as shown in Figure 3.22. Since the hemiketal alcohol proved to be the more reactive than the secondary alcohol during attempted O–H insertion, we thought that perhaps we could mono-protect it using electrophilic reagents. Treatment with TMSOTf provided silylation of both
alcohols to give 3.101 and treatment with acetic anhydride provided acetylation of both alcohols to give 3.102, with no selectivity.

An earlier protection of the hemiketal as the methoxy ketal was then investigated. By treating hemiketal 3.80 (Figure 3.23) with toluenesulfonic acid in methanol/trimethyl orthoformate at reflux we could obtain ketal 3.103. This ketal could be subjected to either Raney nickel or LAH to obtain the amino-alcohol 3.104. This intermediate, differing only by a single methyl group, was then subjected to the identical reaction conditions as described before for diazotonation and esterification, however no product was obtained. It seems as if the additional, albeit minor, steric bulk added by the methoxy ketal was enough to interfere with this reaction from proceeding as it had before.

Simultaneously with these studies, we investigated forming vinyl ether 3.106 (Figure 3.24) using acrylate ester 3.78 and α-methoxy acrylate ester 3.90. In order to use acrylate ester 3.78 we envisioned a Wacker oxidation where the secondary alcohol would serve as the nucleophile in place of water in the typical Wacker oxidation. Even though
Wacker oxidations of electron poor olefins, such as acrylates, usually provide 1,3-dicarbonyl compounds, it was proposed that the intramolecularity may allow for attack to give the desired product.\textsuperscript{24} To our dismay none of the desired product was detected in the reaction mixture.

Another set of conditions found that had potential to form the ether was the use of iodine with silver(I) nitrate, which presumably forms an iodonium species that can be attacked by the oxygen nucleophile and provide the olefin after iodide elimination.\textsuperscript{25} Under these conditions the starting material decomposed providing no trace of product.

Turning our attention next to \(\alpha\)-methoxy acrylate ester \textbf{3.90} we subjected to two different sets of palladium catalysis were attempted based on promising literature precedent.\textsuperscript{26} Unfortunately both of these reactions failed on our substrate.
Since we were unable to form desired vinyl ether 3.106 prior to the Diels–Alder cycloaddition it was hypothesized that an alcohol directed C–H functionalization could be used to create the tetrahydrofuran. This is the current synthetic route being pursued towards the total synthesis of maocryystal V in our laboratory. This route begins with ester 3.78, synthesized previously, which is subjected to dearomatization conditions to give dienone 3.107. This substrate was then heated under our standard Diels–Alder conditions, as low as 110 °C up to 165 °C. Under these conditions it appears that the Diels–Alder took place, but then the A-ring fragmented to give aldehyde compound 3.108 through the mechanism show. As a way to overcome this, we acetylated the secondary alcohol of dienone intermediate 3.107 to afford diacetate 3.109. When this substrate was heated to 140 °C it underwent the desired Diels–Alder reaction to provide bicycle 3.110 (tentatively assigned, potentially the undesired isomer 3.111, see Figure 3.25). The facial selectivity of this reaction has not yet been determined but efforts are underway to determine which diastereomer has formed.
If we have formed the desired isomer 3.110, the completion of the total synthesis should be straightforward. Hydrogenation of tentatively assigned bicycle 3.110 worked in quantitative yield to provide 3.112. Samarium(II) iodide reduction of the α-acetoxy group of the bicycle should proceed without difficulty, due to the homology to previously successful reactions. Removal of the acetate group (if it is not removed by the samarium(II) iodide) from 3.113 with neutral conditions (e.g. KCN in ethanol) should provide the desired secondary alcohol 3.114 that will be the substrate for C–H functionalization to form 3.115. This will be the most challenging reaction remaining. There are precedents for reactions of this type that form tetrahydrofuran rings intramolecularly. Typically these conditions make use of light, a halogen and either hypervalent iodine (such as PIDA, PIFA and Kosser’s reagent) or lead(IV) acetate.

A few examples follow in Figure 3.27. In Figure 3.27-A Roscher and Shaffer used bromine along with silver(I) oxide to perform a C–H activation on the tertiary carbon of 3.116, over the potential primary carbon, to provide more substituted
tetrahydrofuran ring 3.117 selectively in quantitative yield.\textsuperscript{27a} Shown in Figure 3.27-B is an example from the Paquette group.\textsuperscript{27b} Terpenoid 3.118 is treated with PIDA along with iodine and light to perform a related C–H activation to form tetrahydrofuran 3.119 in excellent yield. In the example shown in Figure 3.27-C Corey and coworkers treated advanced Ginkolide B intermediate 3.120 with lead(IV) acetate, iodine and light to provide strained tetrahydrofuran 3.121, which for their purposes was the undesired product.\textsuperscript{27c} Their desired product was that of C–H activation of the ether bearing carbon to generate the acetal. Finally in Figure 3.27-D Burton and coworkers formed

cis-tetrahydrofuran 3.123 by treatment of rigid steroid scaffold 3.122 with PIDA, iodine and light.\textsuperscript{27d} What is notable in Figure 3.27-C and D is that ether formation occurred without inversion, meaning that these transformations did not simply occur by intermediacy of an alkyl halide, followed by displacement.

After the formation of the tetrahydrofuran ring, an oxidation of the A-ring ketone of 3.115 to the enone is all that will remain. IBX is a reagent known to perform this oxidation reaction and it should selectively oxidize the most sterically accessible ketone preferentially giving the A-ring enone and completing the synthesis of maoecrystal V.\textsuperscript{28}
If the C–H functionalization pathway does not go as planned, the potential for other types of etherifications exist. For example lactone 3.114 (Figure 3.28) could be oxidized to its unsaturated form to provide bicycle 3.124. From here the ether could be formed by an electrophile-initiated cyclization such as iodoetherification or selenoetherification. This activating element would then need to be removed reductively to provide desired tetrahydrofuran 3.115. The cyclization may also be possible with palladium catalysis. If the olefin of bicycle 3.124 proves to be too electron poor to participate in the intended reactions, the lactone carbonyl could be reduced to the lactol to render the olefin electron rich. After the cyclization event, the lactol could simply be reoxidized to lactone 3.115 and the total synthesis would be completed by IBX oxidation to give maoecrystal V.

One final topic to be discussed is the enantioselective synthesis of maoecrystal V using the route disclosed here. If cycloadduct 3.81 (Figure 3.29) could be made as a single enantiomer then the remainder of the synthesis would be enantiospecific. Perhaps a catalyst will be found to allow for the direct enantioselective 1,3-dipolar cycloaddition.
that we have shown from 3.81 to 3.82. As of now this reaction does not exist, so a few alternatives are proposed.

As discussed in Chapter 2 the use of a chiral nitrile oxide could allow for some control of stereochemistry in the cycloaddition. After the cycloaddition the R-group could be removed to give 3.127, which could be arylated as before. As an alternative strategy enone 3.82 could be reduced stereoselectively to give the known chiral allylic

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\text{Figure 3.29 Proposed methods for an enatioselective synthesis maecrystal V.}
\]
alcohol 3.128. The cycloaddition would then be preformed on this alcohol, which would potentially give rise a single diastereomer, or the diastereomers could be separated if they are produced. Enantiopure 3.129 could then be oxidized under mild conditions to give pure 3.81. Finally, the isoxazole 3.83 could be stereoselectively reduced to give the 3.81 by means of a chiral hydride source or transfer hydrogenation with enantiocontrol by the ligands.33

If none of these plans are successful perhaps another variation or perhaps a completely different strategy could lead to future efforts for the rapid and efficient construction of this challenging molecule.
3.7 Conclusion and distribution of credit

Working on this molecule for approximately the last six years has been an extremely challenging and demanding. Much of the success, and the failure, comes down to luck. For every bad result, I have had an equally good result. Even though I was unsuccessful at completing the total synthesis, I feel that I was extremely successful in forming the carbon skeleton and learning volumes of chemistry along the way. There are many other strategies that I worked on that I was not able to include here due to time restrictions; however my notebooks should be available in the Baran laboratory for the sake of prosperity.

I have worked in collaboration with Dr. Niklas Schöne, Jun (Cindy) Shi and professor Phil Baran. Everything I have discussed in this thesis was experimental work that I directly carried out. Dr. Schöne and I worked together for 1 year (September 2007 – September 2008) on the synthesis of the maocrystal V core with reactions involving: radical coupling, bismuth arylation, dearomatization, intramolecular Diels–Alder chemistry and attempted Rubottom oxidations. Jun Shi joined the project at the end of 2009 after the publication of our initial approach. I have not reported any of her work directly. For those interested in her achievements on the project please see chapter 3 of her thesis.
Section 3.8: References


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Section 3.9: Experimental section

General Procedures.

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), triethylamine (TEA), dichloromethane (DCM), and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and p-anisaldehyde in ethanol/aqueous H$_2$SO$_4$/CH$_3$CO$_2$H and heat as developing agents. NMR spectra were recorded on a Bruker DRX 600, DRX 500, or an AMX 400 spectrometer and were calibrated using residual solvent as an internal reference (CDCl$_3$: 7.26 ppm for $^1$H NMR and 77.16 ppm for $^{13}$C NMR). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, a = apparent. In addition the following abbreviations were used: TMEDA = tetramethylethylenediamine, THF = tetrahydrofuran, EtOAc = Ethyl Acetate, o-DCB = ortho-dichlorobenzene, TFA = trifluoroacetic acid, DBU = 1,8-Diazabicycloundec-7-ene, TLC = thin layer chromatography, rt = room temperature. IR spectra were recorded on a Perkin-Elmer Spectruum BX spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points (m.p.) are uncorrected and were recorded on a Fisher-Johns 12-144.
melting point apparatus. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

**Aldehyde 3.4:**

To a solution of keto aldehyde 3.5 (1.11 g, 7.30 mmol) and silyl enol ether 3.6 (3.28, 14.6 mmol) in methanol (70 mL) was added sodium bicarbonate (2.70 g, 36.5 mmol). To this solution was added a solution of ammonium cerium nitrate (8.00 g, 14.6 mmol) in methanol (50 mL) at 0 ºC, under a nitrogen atmosphere. The solution decolorizes to clear almost immediately. After the addition is complete the reaction is quenched by the addition of saturated aqueous sodium bicarbonate (100 mL) and EtOAc (100 mL). The aqueous layer is extracted with EtOAc (3 X 100 mL) and dried over MgSO₄. After filtration concentration *in vacuo*, the residue is purified using flash chromatography with EtOAc/Hexanes (1:4) to yield 0.380 g of product for a yield of 20%. Due to the instability of this compound, it was difficult to purify well on silica and was only partly purified to be used in the next reaction.

3.4: clear oil; TLC (EtOAc:hexanes 1:4 v/v): \( R_F = 0.3 \); \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \) (ppm): 9.56 (s, 1 H), 6.65 – 6.67 (m, 1 H), 6.56 – 6.58 (m, 1 H), 6.01 – 6.03 (m, 1 H), 3.45 – 3.49 (m, 1 H), 2.32 – 2.33 (m, 2 H), 2.25 – 2.27 (m, 1 H), 1.68 (d, \( J = 1.9 \), 3 H), 1.65 – 1.67 (m, 1 H), 1.19 – 1.24 (m, 2 H), 1.11 (s, 3 H), 0.96 (s, 3 H).
Ester 3.7:

I. To a stirred solution of aldehyde 3.4 (0.204 g, 0.784 mmol) in THF (3.9 mL), under a nitrogen atmosphere, at −78 ºC, was added a 1.0 M solution of lithium tri-(tert-butoxy)aluminum hydride (0.94 mL, 0.940 mmol). The solution was stirred for about 30 minutes at −78 ºC at which point TLC indicated that the starting material had been completely consumed. The reaction was quenched by the addition of a pH 7 phosphate buffer (5 mL) at −78 ºC at which point the reaction mixture became frozen. The flask was then removed from the cooling bath and allowed to come to room temperature. Saturated aqueous Rochelle’s salt (5 mL) and brine (5 mL) was then added followed by EtOAc (25 mL). The aqueous layer was extracted with EtOAc (4 X 25 mL) and the combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo to give an oily residue. This material was purified on silica gel using EtOAc/Hexanes (gradient from 1:4 to 1:3) to yield 53% of the product intermediate alcohol (0.109 g).

**intermediate alcohol**: clear oil; TLC (EtOAc:hexanes 1:1 v/v): \( R_f = 0.5 \); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) (ppm): 6.68 (ddd, \( J = 1.5, 2.8, 4.2 \) Hz, 1 H), 6.54 (dd, \( J = 1.8, 10.2 \) Hz, 1 H), 5.94 (d, \( J = 10.2 \) Hz, 1 H), 3.84 (dd, \( J = 1.8, 11.6 \) Hz, 1 H), 3.62 (dd, \( J = 4.2, 14.6 \) Hz, 1 H), 3.44 (t, \( J = 11.3 \) Hz, 1 H), 2.61 (dd, \( J = 1.9, 11.1 \) Hz, 1 H), 2.36 – 2.49 (m, 2 H), 2.10 – 2.09 (m, 1 H), 1.80 (d, \( J = 14.2 \) Hz, 1H), 1.65 (dt, \( J = 1.3, 2.4, 2.4 \) Hz, 3 H), 1.41 (dd, \( J = 1.9, 14.3 \) Hz, 1 H), 1.08 (s, 3 H), 1.07 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) (ppm): 203.0, 200.1, 156.1, 145.0, 135.9, 125.9, 65.4, 51.9, 48.6, 39.7, 32.5, 32.2, 30.8, 26.4, 23.0, 16.0.

II. To a stirred solution of **intermediate alcohol** from the previous step (0.315 g, 1.2 mmol) in DCM (8 mL) at 0 ºC, was added triethylamine (0.194 g, 1.92 mmol) followed
by acryloyl chloride (0.120 g, 1.32 mmol), under a nitrogen atmosphere. Once the starting material was determined to be consumed by TLC (EtOAc/Hexanes 1:3), the reaction was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with EtOAc (3 X 25 mL). The mixture was chromatographed quickly on silica gel using EtOAc/Hexanes (1:1) to provide 31% of ester 3.7 (0.118 g) as a clear oil.

**3.7**: clear oil; TLC (EtOAc:hexanes 1:1 v/v): \( R_F = 0.6 \); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm): 6.67 (bs, 1 H), 6.56 (m, 1 H), 6.41 (d, \( J = 17.5 \) Hz, 1 H), 6.11 (dd, \( J = 10.5, 17.3 \) Hz, 1 H), 6.0 (d, \( J = 10.2 \) Hz, 1 H), 5.85 (d, \( J = 10.7 \) Hz, 1 H), 4.37 (d, \( J = 11.8 \) Hz, 1 H), 4.19 (d, \( J = 11.8 \) Hz, 1 H), 3.57 (dd, \( J = 4.0, 14.9 \) Hz, 1 H), 2.36 – 2.50 (m, 2 H), 2.03 – 2.11 (m, 1 H), 2.00 (d, \( J = 14.3 \) Hz, 1 H), 1.76 (m, 2 H), 1.71 (s, 3 H), 1.17 (s, 3 H), 1.16 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) (ppm): 199.2, 198.5, 165.6, 155.7, 144.3, 134.7, 131.6, 128.1, 125.7, 67.0, 52.8, 47.2, 38.5, 32.9, 32.2, 29.8, 26.7, 23.7, 16.1.

**Silyl Enol Ether 3.8:**

To a stirred solution of ester 3.7 (0.014 g, 0.0442 mmol) in DCM (0.2 mL) at 0 °C was added triethylamine (0.067 g, 0.66 mmol) followed by TBSOTf (0.012 g, 0.049 mmol) under a nitrogen atmosphere. The cooling bath was removed after the addition and the solution was allowed to stir for 1 hour until the starting material was consumed as based on TLC analysis. Once the reaction was complete it was quenched by the addition of saturated aqueous sodium bicarbonate (2 mL) and diluted with DCM (2 mL). The aqueous fraction was extracted further with DCM (3 X 2 mL) and the combined organic fractions were dried with MgSO\(_4\) and concentrated \textit{in vacuo}. The resulting residue was
subjected to purification on silica gel using EtOAc/Hexanes (1:5) as eluent to provide 0.028 g of silyl enol ether 3.8 in 63% yield.

3.8: clear oil; TLC (EtOAc:hexanes 1:5 v/v): $R_F = 0.8$; $^1\text{H}$ NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 6.40 (d, $J = 17.3$ Hz, 1 H), 6.14 (dd, $J = 10.4, 17.4$ Hz, 1 H), 5.85 (d, $J = 10.4$ Hz, 1 H), 5.75 (dd, $J = 2.6, 9.5$ Hz, 1 H), 5.63 (q, $J = 10.1, 10.2$ Hz, 2 H), 5.43 (dd, $J = 4.6, 9.5$ Hz, 1 H), 4.37 (d, $J = 11.8$ Hz, 1 H), 4.24 (d, $J = 11.8$ Hz, 1 H), 2.95 – 3.13 (m, 1 H), 2.10 – 2.35 (m, 2 H), 1.77 (d, $J = 14.1$ Hz, 1 H), 1.67 (d, $J = 2.5$ Hz, 3 H), 1.34 (d, $J = 14.2$ Hz, 1 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.86 (s, 9 H), 0.22 (s, 3 H), 0.02 (s, 3 H).

Aromatized ring 3.10:

To a solution of silyl enol ether 3.8: clear oil (0.017 g, 0.041 mmol) in toluene was added 10% palladium on carbon (0.031 g, 0.029 mmol) and the reaction was heated in a sealed vial at 140 ºC overnight under an oxygen atmosphere. TLC analysis indicated that the starting material had been completely consumed after this time (very little change in $R_F$, however when stained with anisaldehyde the TLC plate reveals that the starting material which is maroon in color has converted to a new spot that is blue in color). The cooled solution was passed through a Celite pad and concentrated in vacuo to yield 0.017 g of 3.10 as a clear oil in 99% yield. The material was used without further purification.

3.10: clear oil; TLC (EtOAc:hexanes 1:5 v/v): $R_F = 0.8$; $^1\text{H}$ NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.01 (d, $J = 7.3$ Hz, 1 H), 6.94 (d, $J = 7.5$ Hz, 1 H), 6.74 (t, $J = 7.5$ Hz, 1 H), 6.36 (d, $J = 16.9$ Hz, 1 H), 6.13 (dd, $J = 10.4, 17.3$ Hz, 1 H), 5.81 (d, $J = 10.4$ Hz, 1 H), 5.63 (d, $J = 3.5$ Hz, 2 H), 4.37 (d, $J = 11.3$ Hz, 1 H), 4.26 (d, $J = 11.3$ Hz, 1 H), 2.18 (s, 3 H), 1.89 (s, 2 H), 1.03 (s, 3 H), 0.87 (s, 9 H), 0.79 (s, 3 H), 0.27 (s, 3 H), 0.06 (s, 3 H).
Phenol 3.11:
TBS phenol 3.10 (0.013 g, 0.030 mmol) was dissolved in THF (1 mL). A 1 M TBAF solution in THF (0.060 mL, 0.059 mmol) was added dropwise and the reaction mixture was stirred for 30 minutes at which point TLC indicated that the reaction was complete. At this time the reaction was diluted with EtOAc (4 mL) and water (4 mL). The aqueous layer was extracted with EtOAc (3 X 5 mL) and the combined organic extracts were dried using MgSO$_4$ followed by concentration in vacuo. The material was purified using silica gel chromatography using ether/hexanes (1:1) to provide 88% of phenol 3.11 (0.008 g).

3.11: clear oil; TLC (Et$_2$O:hexanes 1:1 v/v): $R_F = 0.3$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 6.95 (dd, $J = 7.5$, 13.0 Hz, 2 H), 6.76 (t, $J = 7.5$ Hz, 1 H), 6.23 (d, $J = 17.3$ Hz, 1 H), 5.99 (dd, $J = 10.4$, 17.3 Hz, 1 H), 5.75 (dd, $J = 10.1$, 22.0 Hz, 2 H), 5.65 (d, $J = 10.2$ Hz, 1 H), 4.44 (d, $J = 11.3$ Hz, 1 H), 4.33 (d, $J = 11.4$ Hz, 1 H), 3.69 (s, 1 H), 2.17 (s, 3 H), 1.96 (d, $J = 14.4$ Hz, 1 H), 1.80 (d, $J = 14.2$ Hz, 1 H), 1.06 (s, 3 H), 0.78 (s, 3 H).

Dienone 3.12:
To a room temperature stirred solution of phenol 3.11 (0.005 g, 0.016 mmol) in acetic acid (0.3 mL) was added lead(IV)acetate (0.011 g, 0.025 mmol). The solution was stirred for about 30 minutes and TLC (EtOAc/hexanes 1:1) showed complete conversion to the dienone. The reaction was quenched with water (1 mL) and EtOAc (1 mL). The organic layer was separated, dried (MgSO$_4$), and evaporated in vacuo to give a residue (0.0035 g, 59% yield) that was used without purification in the next step.
3.12: yellow oil; TLC (EtOAc:hexanes 1:1 v/v): $R_F = 0.2$.

**Diels–Alder product 3.13:**

Crude dienone 3.12 (0.0032 g, 0.0086 mmol), from the previous step, was dissolved in o-DCB, under an argon atmosphere, and BHT (0.009 g, 0.042 mmol) was added as a radical inhibitor. The solution was heated to 165 ºC for 2 hours in the microwave reactor, followed by cooling to room temperature. The o-DCB was removed by means of a 100% hexanes column. The column was loaded with the reaction mixture and eluted until TLC indicated that the o-DCB was completely eluted, followed by flushing with 100% EtOAc until the product had been eluted. The crude mixture was purified using preparatory-TLC using ether/hexane as eluent (2:1) to obtain the Diels–Alder product 3.13 (0.0019 g, 60% yield) as a pale yellow foam. The product was crystallized from cyclohexane/ether to yield a crystal suitable for X-ray analysis.

3.13: clear oil; TLC (Et₂O:hexanes 2:1 v/v): $R_F = 0.1$; $^1$H NMR (600 MHz, CDCl₃) $\delta$ (ppm): 6.58 – 6.76 (m, 2 H), 6.11 (dd, $J = 1.5$, 8.5 Hz, 1 H), 6.00 (d, $J = 10.1$ Hz, 1 H), 4.66 (d, $J = 12.2$ Hz, 1 H), 4.47 (dd, $J = 6.3$, 9.9 Hz, 1 H), 4.33 (d, $J = 12.2$ Hz, 1 H), 3.88 (dd, $J = 2.9$, 5.8 Hz, 1 H), 2.32 (d, $J = 14.2$ Hz, 1 H), 2.26 (ddd, $J = 3.1$, 9.9, 13.2 Hz, 1 H), 2.07 (s, 3 H), 1.93 (ddd, $J = 2.7$, 6.3, 13.6 Hz, 1 H), 1.80 (dd, $J = 1.9$, 14.2 Hz, 1 H), 1.25 (s, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H). X-ray structure.

**Triaryl bismuth 3.24:**

$n$-BuLi (34.6 mL, 2.29 $M$ in hexanes, 79.2 mmol) was added with stirring at 0 ºC to TMEDA (9.90 mL, 66.0 mmol). After stirring for 10 min at 0 ºC 1-(methoxymethoxy)-2-
methylbenzene (10.04 g, 66.0 mmol) (3.23) was added. The mixture solidified and was shaken for homogeneity. The mixture was occasionally shaken at rt for 1 h and a solution-suspension of BiCl₃ (6.87 g, 21.8 mmol) in THF (43.6 mL) was added at −78 °C. The obtained mixture was shaken to obtain a homogenous suspension, which was slowly warmed to rt. After stirring for 1 h at rt water (50 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (3 x 200 mL). The combined organic phases were washed with diluted brine (500 mL), dried with Na₂SO₄ and filtered, successively, over Celite® and a silica gel plug with CH₂Cl₂ as eluent, before concentrating. The oil was triturated with pentane (100 mL). The resulting solid was filtered and dried under vacuum to give triaryl bismuth compound 3.24 (7.88 g, 55%) as an off-white solid, which was pure enough for further reactions. An analytically pure sample was obtained via chromatography on silica gel (85:15 to 80:20 hexanes/EtOAc).

3.24: off-white solid; m.p. = 80 – 83 °C; TLC (EtOAc:hexanes 15:85 v/v): \( R_F = 0.25 \); \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) (ppm): 7.41 (dd, \( J = 7.3, 1.3 \) Hz, 1 H), 7.16 (dd, \( J = 7.3, 0.7 \) Hz, 1 H), 7.00 (dd, \( J = 7.3, 7.3 \) Hz, 1 H), 4.92 (s, 2 H), 3.48 (s, 3 H), 2.31 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) (ppm): 159.4, 149.8, 137.2, 131.5, 130.4, 127.9, 99.7, 57.5, 17.5; IR (film) \( \nu_{\text{max}} \) 3044, 2929, 2826, 1447, 1420, 1389, 1251, 1219, 1193, 1154, 1125, 1063, 962, 926, 835, 773 cm\(^{-1}\); HRMS (m/z): [M+Na\(^+\)] calcd. for C\(_{27}\)H\(_{33}\)BiO\(_6\), 685.1973; found, 685.1969.

**Compound 3.19:**

To a solution of 3.24 (15.2 g, 22.9 mmol) in CH₂Cl₂ (115 mL) at 0 °C was added freshly distilled SO₂Cl₂ (1.93 mL, 24.0 mmol). After warming to rt and concentrating, the oil
was triturated with pentane. The resulting solid was filtered and dried under vacuum to give dichlorotriarylbismuth compound 3.19 (15.2 g, 90%) as a pale yellow solid, which was pure enough for further reactions. An analytically pure sample was obtained via chromatography on silica gel (85:15 to 80:20 hexanes/EtOAc).

3.19: off-white solid; TLC (Et₂O:hexanes 1:1): \( R_F = 0.25 \); m.p. = 132 – 134 °C; \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) (ppm): 8.11 (dd, \( J = 1.0, 7.8 \) Hz, 1 H), 7.36 (dd, \( J = 1.0, 7.4 \) Hz, 1 H), 7.30 (dd, \( J = 7.8, 7.4 \) Hz, 1 H), 5.17 (s, 2 H), 3.32 (s, 3 H), 2.50 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) (ppm): 156.9, 155.4, 135.1, 132.2, 131.0 126.1, 100.4, 56.9, 18.6; IR (film) \( \nu_{\text{max}} \) 3053, 2928, 2828, 1591, 1459, 1391, 1258, 1197, 1159, 1071, 927, 834, 764, 730 cm\(^{-1}\); HRMS (m/z): was not obtained for this compound, due to its instability.

Compounds 3.21, 3.25, 3.26 are known.⁹

**Compound 3.20:**
NaH (4.97 g, 60% in mineral oil, 124 mmol) was suspended in a solution of 3.21 (9.65 g, 37.6 mmol) and ethyl formate (21.2 mL, 263 mmol) in toluene (188 mL). MeOH (1.52 mL, 37.6 mmol) was added dropwise, which initiated the reaction. The reaction mixture was kept at rt for 12 h, whereupon the reaction mixture solidified. Water (25 mL) was added cautiously followed by EtOAc (100 mL), 3 \( M \) HCl (100 mL) and brine (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL) and the combined organic phases were washed with brine (200 mL), dried with Na₂SO₄ and concentrated. The residue was taken up in 90:10 hexanes/EtOAc, filtered through a plug of silica gel (using also 90:10 hexanes/EtOAc) and concentrated to give 3.20 (8.35 g, 78%) as a colorless oil.
3.20: colorless oil; TLC (Et₂O:hexanes 1:9 v/v): \( R_F = 0.47 \); \([\alpha]_D^{20} = -3.8^\circ (c = 6.5, DCM)\); \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\) \( \delta 8.58 (d, J = 3.5 \text{ Hz}, 1 \text{ H}), 3.60 (dd, J = 2.6, 8.1 \text{ Hz}, 1 \text{ H}), 2.46 - 2.51 (m, 1 \text{ H}), 2.23 - 2.29 (m, 1 \text{ H}), 1.78 - 1.80 (m, 1 \text{ H}), 1.71 - 1.74 (m, 1 \text{ H}), 1.17 (s, 3 \text{ H}), 1.15 (s, 3 \text{ H}), 0.88 (s, 9 \text{ H}), 0.06 (s, 3 \text{ H}), 0.05 (s, 3 \text{ H}); \(^{13}\text{C NMR (150 MHz, CDCl}_3\) \( \delta 190.8, 186.0, 106.3, 74.8, 43.7, 27.1, 25.9, 25.1, 21.2, 20.0, 18.2, -4.1, -4.9; IR (film) \( \nu_{\text{max}} \) 2953, 2930, 2885, 2857, 1638, 1583, 1472, 1463, 1360, 1251, 1103, 1080, 886, 833 cm\(^{-1}\); HRMS (m/z): [M+H\(^+\)] calcd. for C\(_{15}\)H\(_{28}\)O\(_3\)Si, 285.1880; found, 285.1883.

**Compound 3.18:**

To a suspension of freshly prepared 3.19 (19.1 g, 26.0 mmol) in toluene was added 3.20 (7.06 g, 24.8 mmol) all at once. After stirring at rt for 10 min DBU, (4.63 mL, 31.0 mmol) was quickly added dropwise and the reaction mixture was stirred for 12 h at rt. The mixture was successively filtered over a Celite\(^\circledR\) plug and then a silica gel plug, with EtOAc as eluent, before concentrating. Chromatography on silica gel (98:2 hexanes/EtOAc) furnished the two diastereomers 3.18 (major) (4.92 g, 46%) and 3.18 (minor) (2.24 g, 21%) as colorless oils.

3.18 (major): colorless oil; TLC (EtOAc: hexanes 1:4 v/v): \( R_F = 0.47 \); \([\alpha]_D^{20} = -52.5^\circ (c = 6.0, DCM)\); \(^1\text{H NMR (500 MHz, CDCl}_3\) \( \delta 9.63 (s, 1 \text{ H}), 7.15 (d, J = 7.5 \text{ Hz}, 1 \text{ H}), 7.00 (t, J = 7.7, 1 \text{ H}), 6.77 (d, J = 7.6 \text{ Hz}, 1 \text{ H}), 4.80 (s, 2 \text{ H}), 3.86, (dd, J = 3.4, 8.7, 1 \text{ H}), 3.54 (s, 3 \text{ H}), 2.53 - 2.58 (m, 1 \text{ H}), 2.34 (s, 3 \text{ H}), 2.01 - 2.06 (m, 1 \text{ H}), 1.94 - 1.98 (m, 1 \text{ H}), 1.85 - 1.89 (m, 1 \text{ H}), 1.12 (s, 3 \text{ H}), 1.00 (s, 3 \text{ H}), 0.90 (s, 9 \text{ H}), 0.07 (s, 3 \text{ H}), 0.06 (s, 3 \text{ H}); \(^{13}\text{C NMR (150 MHz, CDCl}_3\) \( \delta 211.2, 198.6, 153.8, 133.6, 132.0, 131.7, 125.7, \ldots\)
124.5, 98.7, 76.8, 68.0, 57.4, 53.2, 27.2, 27.0, 25.9, 23.1, 21.0, 18.2, 18.0, −4.0, −4.8; IR (film) νmax 3707, 3681, 3665, 2951, 2863, 1731, 1691, 1472, 1055, 1033, 1012, 836 cm⁻¹; HRMS (m/z): [M+Na]⁺ calcd. for C₂₄H₃₈O₅Si, 457.2381; found, 457.2379.

3.18 (minor): colorless oil; TLC (EtOAc: hexanes 1:4 v/v): Rf = 0.31; [α]D²⁰: +87.5° (c = 2.3, DCM); ¹H NMR (500 MHz, CDCl₃) δ 9.58 (s, 1 H), 7.11 (d, J = 7.4Hz, 1 H), 7.0 (t, J = 7.7Hz, 1 H), 6.91 (d, J = 7.7Hz, 1 H), 4.70 (s, 2 H), 3.79 (dd, J = 1.5, 5.5Hz, 1 H), 3.51 (s, 3 H), 2.37 – 2.45 (m, 2 H), 2.32 (s, 3 H), 2.20 – 2.26 (m, 1 H), 1.77 – 1.82 (m, 1 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ¹³C NMR (150 MHz, CDCl₃) δ 213.0, 196.8, 153.9, 136.6, 131.3, 131.1, 129.2, 125.1, 96.6, 77.5, 70.2, 57.6, 53.0, 28.3, 26.2, 26.0, 22.5, 18.3, 17.6 −4.2, −4.9; IR (film) νmax 3707, 3681, 3665, 2981, 2966, 2951, 2937, 2864, 1725, 1690, 1472, 1055, 1032, 1012, 836 cm⁻¹; HRMS (m/z): [M+Na]⁺ calcd. for C₂₄H₃₈O₅Si, 457.2381; found, 457.2378.

Compound 3.27:

To a stirred solution of 3.18 (major) (4.92 g, 11.3 mol) in THF (56.6 mL) at −78 °C was added Li(‘BuO)₃AlH (13.6 mL, 1 M in THF, 13.6 mmol) dropwise down the side of the reaction vessel. The reaction mixture was stirred for 30 min at −78 °C until complete conversion was detected by TLC. Then, an aq. pH 7 buffer solution (20 mL, 1 M, NaH₂PO₄, Na₂HPO₄) was added dropwise at −78 °C and the mixture was allowed to reach rt. Saturated aq. Rochelle's salt solution (40 mL) was added and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with 50:50 saturated aq. Rochelle's salt solution/brine (200 mL), dried with Na₂SO₄ and
concentrated. Chromatography on silica gel with 90:10 hexanes/EtOAc furnished 3.27 (3.54 g, 72%) as a colorless oil.

3.27: colorless oil; TLC (EtOAc: hexanes 1:4 v/v): $R_F = 0.34$; $[\alpha]_D^{20} + 12.4^\circ$ (c = 10, DCM); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.23 (d, $J = 7.8$ Hz, 1 H), 7.13 (d, $J = 6.7$ Hz, 1 H), 7.06 (t, $J = 7.6$ Hz, 1 H), 4.86 (d, $J = 5.5$ Hz, 1 H), 4.77 (d, $J = 5.5$ Hz, 1 H), 3.84 (dd, $J = 4.8$, 11.6 Hz, 1 H), 3.65 – 3.67 (m, 1 H), 3.53 (s, 3 H) 3.20 (dd, $J = 9.6$, 11.6 Hz, 1 H), 2.87 (dd, $J = 4.8$, 9.6 Hz, 1 H), 2.59 (m, 1 H), 2.30 (s, 3 H), 2.23 – 2.26 (m, 1 H), 2.00 – 2.06 (m, 1 H), 1.56 – 1.61 (m, 1 H), 1.08 (s, 3 H), 0.90 (s, 3 H), 0.87 (s, 9 H), – 0.02 (s, 3 H), –0.03 (s, 3 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 215.6, 155.2, 134.1, 131.8, 131.3, 124.6, 124.0, 99.2, 79.2, 70.2, 57.4, 56.7, 52.5, 26.4, 26.2, 26.0, 23.9, 22.8, 18.2, 17.9, –4.3, –4.9; IR (film) $\nu_{\text{max}}$ 3521, 2953, 2930, 2886, 2857, 1691, 1472, 1462, 1389, 1256, 1163, 1103, 1090, 1074, 960, 936, 835, 775 cm$^{-1}$; HRMS (m/z): [M+Na]$^+$ calcd. for C$_{24}$H$_{40}$O$_5$Si, 459.2537; found, 459.2534.

**Compound 3.28:**

To a stirred solution of 3.27 (3.54 g, 8.11 mmol), DMAP (35 mg, 284 µmol) and $i$Pr$_2$EtN (6.70 mL, 40.5 mmol) in CH$_2$Cl$_2$ (40.5 mL) at –78 °C was added acryloyl chloride (1.97 mL, 24.3 mmol) dropwise down the wall of the reaction vessel. The reaction mixture was then stirred for 10 min until complete conversion was detected by TLC. Then MeOH (1.64 mL, 40.5 mmol) was added dropwise down the glass wall to quench excess acid chloride. The reaction mixture was warmed to rt and filtered through a plug of silica gel, which was packed with hexanes and washed with 85:15 hexanes/EtOAc. Silica gel
chromatography with 85:15 hexanes/EtOAc furnished 3.28 (2.75 g, 69%) as a colorless oil.

3.28: colorless oil; TLC (Et₂O: hexanes 1:5 v/v): \( R_F = 0.32; [\alpha]_D^{20} + 52.4^\circ \) (c = 10.2, DCM); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.21 (d, \( J = 7.8 \), 1 H), 7.12 (d, \( J = 7.4 \), 1 H), 7.00 (t, \( J = 7.6 \), 1 H), 6.25 (d, \( J = 17.3 \), 1 H), 5.97 (dd, \( J = 10.4 \), 17.3, 1 H), 5.72 (d, \( J = 10.5 \), 1 H), 4.92 (d, \( J = 5.5 \), 1 H), 4.83 (d, \( J = 5.5 \), 1 H), 4.42 (d, \( J = 11.4 \), 1 H), 4.31 (d, \( J = 11.4 \), 1 H), 3.66 (s, 1 H), 3.53 (s, 3 H), 2.55 (br d, \( J = 14.4 \), 1 H), 2.30 (s, 3 H), 2.22 (dt, \( J = 4.2 \), 13.3Hz, 1 H), 2.02 – 2.08 (m, 1 H), 1.57 – 1.61 (m, 1H), 1.08 (s, 3H), 0.87 (s, 9H), 0.85 (s, 3 H), –0.02 (a s, 6 H); \(^1\)C NMR (150 MHz, CDCl₃) \( \delta \) 210.8, 165.9, 155.3, 132.8, 131.8, 131.5, 130.5, 128.5, 125.0, 124.0, 99.1, 79.0, 69.8, 57.3, 54.5, 52.2, 27.9, 26.3, 26.0, 24.0, 23.0, 18.2, 17.8, –4.4, –4.9; IR (film) \( \nu_{\text{max}} \) 2955, 2930, 2886, 2857, 1728, 1698, 1461, 1405, 1258, 1183, 1164, 1075, 962, 835 cm⁻¹; HRMS (m/z): [M+Na]^+ calcd. for C\(_{27}\)H\(_{42}\)O\(_6\)Si, 513.2643; found, 513.2641.

**Compound 3.29:**

To a solution of 3.28 (2.75 g, 5.60 mmol) in CH\(_2\)Cl\(_2\) (56 mL) at 0 °C was added TFA (2.08 mL, 28.0 mmol) quickly dropwise. After 30 min, a solution of Et\(_3\)N (3.88 mL, 28.0 mmol) in CH\(_2\)Cl\(_2\) (23.3 mL) was added quickly dropwise. The reaction mixture was filtered through a plug of silica gel, which was then washed with CH\(_2\)Cl\(_2\). Silica gel chromatography with 95:5 hexanes/EtOAc furnished 3.29 (1.63 g, 65%) as a white foam.

3.29: white foam; TLC (EtOAc: hexanes 1:9 v/v): \( R_F = 0.40; [\alpha]_D^{20} + 47.7^\circ \) (c = 10.4, DCM); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.06 (d, \( J = 7.4 \) Hz, 1 H), 6.98 (d, \( J = 7.5 \) Hz, 1 H), 6.80 (t, \( J = 7.5 \) Hz, 1 H), 6.43 (d, \( J = 17.3 \) Hz, 1 H), 6.17 (dd, \( J = 10.4 \), 17.3 Hz, 1
H), 5.87 (d, J = 10.5 Hz, 1 H), 4.74 (d, J = 11.6 Hz, 1 H), 4.50 (d, J = 11.6 Hz, 1 H),
3.66 (dd, J = 4.0, 9.3 Hz, 1 H), 3.15 (s, 1 H), 2.23 (s, 3 H), 2.06 – 2.11 (m, 1H), 1.63–
1.71 (m, 1 H), 1.51–1.56 (m, 1 H), 1.37–1.43 (m, 1 H), 1.16 (s, 3 H), 1.13 (s, 3 H), 0.92
(s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\) \(\delta\) 166.1, 154.3, 134.6,
131.3, 129.9, 128.4, 121.2, 120.8, 120.7, 113.3, 75.1, 66.2, 51.0, 44.2, 30.1, 26.8, 26.0,
22.2, 18.2, 17.8, 15.2, –4.0, –4.8; IR (film) \(\nu_{\text{max}}\) 3376, 2954, 2929, 2886, 2875, 2875,
1727, 1698, 1636 1472, 1460, 1405, 1257, 1181, 1162, 1073, 980, 958, 934, 834, 773 cm\(^{-1}\);
HRMS (m/z): [M+Na\(^+\)] calcd. for C\(_{25}\)H\(_{38}\)O\(_5\)Si, 469.2381; found, 469.2379.

**Compound 3.17:**

To a stirred solution of 3.29 (1.41 g, 3.16 mmol) in AcOH (75.8 mL) was added
Pb(OAc\(_4\)) (2.33 g, 5.26 mmol) all at once at rt. After stirring for 15 min complete
conversion was detected by TLC. The reaction mixture was diluted with EtOAc (300 mL)
and H\(_2\)O (200 mL) was added and stirring was continued for 30 min. The aqueous phase
was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with
brine (200 mL), dried with Na\(_2\)SO\(_4\) and concentrated. Residual AcOH was removed
under high vacuum. Silica gel chromatography with 80:20 hexanes/EtOAc furnished 3.17
(major) (932 mg, 58%) and 3.17 (minor) (391 mg, 23%) as off-white foams.

3.17 (major): off-white foam; TLC (EtOAc: hexanes 1:4 v/v): \(R_F = 0.01; [\alpha]_D^{20} = + 20.5^\circ\)
(c = 3.5, DCM); \(^1\)H NMR (500 MHz, CDCl\(_3\) \(\delta\) 6.95 (dd, J = 2.1, 5.6 Hz, 1 H), 6.38 (d, J
= 17.3 Hz, 1 H), 6.23 – 6.28 (m, 2 H), 6.09 (dd, J = 10.5, 17.3 Hz, 1 H), 5.82 (d, J = 10.4
Hz, 1 H), 4.52 (d, J = 11.5 Hz, 1 H), 4.25 ( d, J = 11.5 Hz, 1 H), 3.92 (dd, J = 2.8, 8.1
Hz, 1 H), 2.07 – 2.13 (m, 1 H), 2.05 (s, 3 H), 1.90 – 1.97 (m, 1 H), 1.75 – 1.82 (m, 1 H),
1.34 (s, 3 H), 1.16 (s, 3 H), 1.07 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 211.0, 197.7, 169.1, 165.9, 142.0, 139.4, 137.6, 131.3, 128.3, 121.5, 79.2, 76.9, 66.9, 53.3, 51.9, 26.8, 26.5, 25.9, 24.7, 24.0, 22.0, 20.4, 18.2, –4.1, –4.8; IR (film) $\nu_{\text{max}}$ 2955, 2929, 2885, 2855, 1726, 1673, 1645, 1462, 1406, 1368, 1249, 1191, 1104, 982, 835, 775 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{27}$H$_{40}$O$_7$Si, 505.2616; found, 505.2618.

3.17 (minor): off-white foam; TLC (EtOAc: hexanes 1:4 v/v): $R_F = 0.03$; $\left[\alpha\right]_{D}^{20} = –64.2^\circ$ (c = 3.5, DCM); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.96 (d, $J = 6.2$ Hz, 1 H), 6.42 (d, $J = 17.3$ Hz, 1 H), 6.26 (dd, $J = 6.5$, 9.6 Hz, 1 H), 6.20 (d, $J = 9.5$ Hz, 1 H), 6.12 (dd, $J = 10.4$, 17.3 Hz, 1 H), 5.87 (d, $J = 10.4$ Hz, 1 H), 4.57 (d, $J = 11.9$ Hz, 1 H), 4.32 (d, $J = 11.9$ Hz, 1 H), 4.03 (dd, $J = 3.5$, 10.3 Hz, 1 H), 2.10 (s, 3 H), 1.83 – 1.95 (m, 2 H), 1.76 – 1.80 (m, 1 H), 1.34 (s, 3 H), 1.19 (s, 3 H), 1.09 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 214.4, 197.5, 170.0, 165.8, 141.6, 141.0, 136.0, 131.9, 128.0, 121.6, 79.8, 75.7, 65.2, 53.0, 51.8, 27.9, 27.3, 26.0, 24.1, 23.6, 21.5, 20.7, 18.2, –3.9, –4.7; IR (film) $\nu_{\text{max}}$ 2954, 2930, 2885, 2855, 1734, 1675, 1472, 1406, 1370, 1250, 1179, 1102, 1073, 983, 835, 774 cm$^{-1}$; HRMS (m/z): [M+H]$^+$ calcd. for C$_{27}$H$_{40}$O$_7$Si, 505.2616; found, 505.2618.

**Compound 3.16 (major):**

The microwave vial reaction vessel was first treated with hexamethyldisilazane (1 mL) sealed and heated to reflux for 2 min. The vial was cooled, rinsed with acetone and dried under high vacuum. In the sealed pretreated vial, equipped with a magnetic stir bar, was added 3.17 (major) (466 mg, 923 µmol) and BHT (203 mg, 923 µmol). The vial was
capped and evacuated on high vacuum followed by backfilling with argon. To the vial
was then added o-DCB (18.5 mL) and it was heated using a microwave apparatus to 165
°C for 60 min. The reaction mixture was directly loaded on a silica gel column. The
column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and
the eluent was switched to 80:20 hexanes/EtOAc. Furnishing 3.16 (major) (733 mg,
79%) as a white foam.

3.16 (major): white foam; TLC (EtOAc: hexanes 1:1 v/v): R<sub>f</sub> = 0.16; [α]<sub>D</sub><sup>20</sup>: −72.0° (c =
8.5, DCM); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.59 (t, <i>J</i> = 7.3 Hz, 1 H), 6.03 (d, <i>J</i> = 8.4 Hz,
1 H), 4.53 (d, <i>J</i> = 12.2 Hz, 1 H), 4.35 (dd, <i>J</i> = 5.44, 9.63 Hz, 1 H), 4.21 (d, <i>J</i> = 12.2 Hz,
1 H), 3.91 (dd, <i>J</i> = 3.0, 9.5 Hz, 1 H), 3.85 – 3.86 (m, 1 H), 2.15 – 2.19 (m, 1 H), 2.09 (s,
3 H), 2.02 – 2.05 (m, 1 H), 1.90 – 1.95 (m, 2 H), 1.76 – 1.88 (m, 2 H), 1.54 (s, 3 H) 1.29
(s, 3 H), 1.09 (s, 3 H), 0.91 (s, 9 H), 0.10 (a s, 6 H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ
216.4, 200.3, 173.1, 170.0, 139.9, 125.7, 78.8, 74.8, 72.5, 60.4, 52.3, 45.9, 39.3, 28.2,
26.9, 26.0, 25.1, 24.6, 22.0, 21.5, 21.3, 18.2, −4.0, −4.8 ; IR (film) ν<sub>max</sub> 2953, 2931, 2886,
2857, 1736, 1697, 1472, 1370, 1233, 1117, 1105, 1085, 1004, 837, 774 cm<sup>−1</sup>; HRMS
(<i>m/z</i>): [M+H]<sup>+</sup> calcd. for C<sub>27</sub>H<sub>40</sub>O<sub>7</sub>Si, 505.2616; found, 505.2618.

Compound 3.16 (minor):

The preparation of 3.16 (minor) was identical to the procedure for the preparation of 3.16
(major). Compound 3.17 (minor) (391 mg, 775 µmol) was used as starting material,
BHT (171 mg, 775 µmol) and o-DCB (15.5 mL). After chromatography 3.16 (minor)
(270 mg, 69%) was obtained as a white solid.

3.16 (minor): white solid; m.p. = 205 – 207 °C; TLC (EtOAc: hexanes 1:1 v/v): R<sub>f</sub> =
0.16; \([\alpha]_D^{20}: -40.1^\circ (c = 7.8, \text{DCM})\); \(^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \delta 6.52 (d, J = 6.5, 8.2 Hz, 1 \text{ H}), 6.10 (d, J = 8.1 \text{ Hz, } 1 \text{ H}), 4.36 (d, J = 12.1 \text{ Hz, } 1 \text{ H}), 4.28 (d, J = 12.1 \text{ Hz, } 1 \text{ H}), 4.15 (t, J = 6.3 \text{ Hz, } 1 \text{ H}), 3.93 – 3.95 (m, 1 \text{ H}), 3.79 – 3.80 (m, 1 \text{ H}), 2.26 – 2.27 (m, 2 \text{ H}), 1.99 (s, 1 \text{ H}), 1.86 – 1.94 (m, 4 \text{ H}), 1.61 (s, 3 \text{ H}), 1.25 (s, 3 \text{ H}), 1.03 (s, 3 \text{ H}), 0.91 (s, 9 \text{ H}), 0.09 (a s, 6\text{ H}); \(^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \delta (ppm): 218.0, 202.2, 173.2, 169.9, 139.1, 125.4, 79.8, 74.5, 72.6, 61.9, 52.4, 47.0, 39.0, 38.2, 28.5, 26.9, 25.9, 25.6, 23.9, 22.1, 20.6, 19.9, 18.2, −4.0, −4.8; IR (film) \(\nu_{\text{max}}\) 2954, 2930, 2889, 2856, 1735, 1694, 1472, 1372, 1237, 1168, 1104, 1084, 837, 775 cm\(^{-1}\); HRMS (m/z): [M+H]\(^+\) calcd. for C\(_{27}\)H\(_{40}\)O\(_7\)Si, 505.2616; found, 505.2615. X-ray structure.

**Alcohol 3.30:**

To a stirred solution of 3.16 (major) (0.005 g, 0.010 mmol) in DCM (0.1 mL) was added BF\(_3\)•OEt\(_2\) (0.003 g, 0.020 mmol). After about 3 hours the reaction was stopped by addition of water (1 mL) and it was diluted with DCM (1 mL). The organic layer was dried with Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified on a column with EtOAc/Hexanes (first 1:4 then repeated with 1:1) to provide alcohol 3.30 in 82% yield (0.003 g). A crystal was grown for X-ray analysis from cyclohexane.

3.30: white solid; TLC (EtOAc: hexanes 1:1 v/v): \(R_F = 0.2\); \(^1\text{H NMR} (600 \text{ MHz, CDCl}_3) \delta (ppm): 6.59 (dd, J = 8.4, 7.0 \text{ Hz, } 1\text{ H}), 6.03 (dd, J = 1.6, 8.6 \text{ Hz, } 1\text{ H}), 4.42 (d, J = 12.1 \text{ Hz, } 1\text{ H}), 4.32 (dd, J = 5.3, 9.5 \text{ Hz, } 1\text{ H}), 4.24 (d, J = 12.2 \text{ Hz, } 1\text{ H}), 4.02 (dd, J = 3.6, 10.8 Hz, 1H), 3.81 – 3.93 (m, 1H), 2.16 (ddd, J = 13.6, 9.4, 2.6 Hz, 1H), 2.09 (s, 3H), 1.95 – 2.08 (m, 3H), 1.86 – 1.94 (m, 1H), 1.86 (s, 1H), 1.52 (s, 3H), 1.36 (s, 3H), 1.11 (s, 3H); \(^{13}\text{C NMR} (150 \text{ MHz, CDCl}_3) \delta (ppm): 216.20, 200.34, 173.06, 170.00, 139.90, 125.64,
Compound 3.31 (major):

To a stirred solution of 3.16 (major) (250 mg, 495 µmol) in EtOAc (25 mL) and Pd/C (49.5 g, 10% Pd, dry) was bubbled H₂ for 1 h until complete conversion was detected by TLC. N₂ was then bubbled through the solution to purge out any residual H₂. The solution was filtered through a pad of Celite and concentrated to give 3.31 (major) (686 mg, 97%) as a colorless foam.

3.31 (major): colorless foam; TLC (EtOAc: hexanes 1:1 v/v): Rₓ = 0.13; [α]D²⁰: −33.3° (c = 7.5, DCM); ¹H NMR (600 MHz, CDCl₃) δ 4.31 (d, J = 12.2 Hz, 1 H), 4.20 – 4.23 (m, 2 H), 3.86 – 3.90 (m, 1 H), 2.94 – 2.95 (m, 1 H), 2.25 – 2.29 (m, 1 H), 2.09 (s, 3 H), 1.78 – 1.85 (m, 5 H), 1.64 – 1.70 (m, 4 H), 1.60 (s, 3 H), 1.26 (s, 3 H), 1.01 (s, 3 H), 0.89 (s, 9 H), 0.09 (a s, 6 H); ¹³C NMR (150 MHz, CDCl₃) δ 217.4, 206.8, 174.4, 170.0, 82.7, 74.9, 72.6, 54.1, 52.6, 47.5, 38.8, 33.8, 27.0, 26.9, 25.9, 24.2, 23.6, 23.0, 22.0, 20.9, 18.6, 18.2, −4.0, −4.8; IR (film) νmax 2954, 2929, 2881, 2855, 1752, 1713, 1693, 1463, 1376, 1257, 1133, 1107, 1080, 888, 837, 775 cm⁻¹; HRMS (m/z): [M+H]⁺ calcd. for C₂₇H₄₂O₇Si, 505.2772; found, 507.2776.

Compound 3.31 (minor):

The preparation of 3.31 (minor) was the same procedure for 3.31 (major) with 3.16 (minor) (701 mg, 1.39 mmol) in EtOAc (70 mL), Pd/C (139 g, 10% Pd, dry) and
bubbling of \( \text{H}_2 \). After concentration \( \text{3.31 (minor)} \) (252 mg, 99\%) was obtained as a colorless foam.

\( \text{3.31 (minor)} \): colorless foam; TLC (EtOAc:hexanes 1:1 v/v): \( R_f = 0.13; \ [\alpha]_D^{20} = -34.0^\circ \) (c = 2.7, DCM); \( ^1\text{H} \) NMR (600 MHz, CDCl\(_3\) \( \delta 4.28 (d, 12.2, 1 \) H), 4.20 (d, \( J = 12.2 \) Hz, 1 H), 3.99 – 4.02 (m, 1 H), 3.89 – 3.91 (m, 1 H), 2.85 – 2.86 (m, 1 H), 2.45 – 2.49 (m, 1 H), 2.11 – 2.17 (m, 1 H), 2.06 (s, 3 H), 1.84 – 1.93 (m, 3 H), 1.68 – 1.83 (m, 5 H), 1.61 (s, 3 H), 1.23 (s, 3 H), 0.97 (s, 3 H), 0.89 (s, 9 H), 0.08 (a s, 6 H); \( ^{13}\text{C} \) NMR (150 MHz, CDCl\(_3\) \( \delta 218.8, 208.1, 174.4, 170.0, 84.30, 74.6, 72.7, 55.2, 52.6, 48.0, 38.3, 34.2, 26.8, 26.7, 26.0, 25.9, 25.1, 24.2, 23.7, 22.0, 20.5, 19.5, 18.1, –3.9, –4.8; IR (film) \( \nu_{\max} \) 2955, 2930, 2885, 2855, 1732, 1691, 1471, 1372, 1239, 1193, 1104, 888, 837, 775 cm\(^{-1}\); HRMS (\( m/z \)); [M+H]\(^+\) calcd. for C\(_{27}\)H\(_{42}\)O\(_7\)Si, 505.2772; found, 507.2768.

**Compounds 3.32 and 3.32:**

A solution of \( \text{3.31 (major)} \) (675 mg, 1.33 mmol), in MeOH (20.0 mL) and THF (20.0 mL) was degassed by bubbling argon through the solution for 15 min and with sonication. To this solution was added a solution of commercially purchased SmI\(_2\) (33.3 mL, 0.1 \( M \) in THF, 3.33 mmol) at rt until the blue color of the SmI\(_2\) solution persisted. Saturated aq. NaHCO\(_3\) solution was added to the reaction mixture with shaking. The aqueous phase was extracted with EtOAc (2 x 100mL). The combined organic phases were dried with Na\(_2\)SO\(_4\) and concentrated. Silica gel chromatography with 90:10 hexanes/EtOAc furnished \( \text{3.32/3.33} \) (131 mg, 66\%) as a mixture of diastereomers (5.6:1) as a white powder.
3.32: white powder; m.p. = 117–119 °C; TLC (Et₂O:hexanes v/v 1:1): \( R_F = 0.46 \); [α]₀^20: –38.0° (c = 3.1, DCM); \(^1\)H NMR (600 MHz, CDCl₃) δ: 4.25 (d, \( J = 12.1 \) Hz, 1 H), 4.20 (d, \( J = 12.1 \) Hz, 1 H), 4.03 – 4.05 (m, 1 H), 3.90 (dd, \( J = 4.1 \), 10.5 Hz, 1 H) 2.51 – 2.55 (m, 1 H), 2.23 – 2.26 (m, 1 H), 1.98 – 2.02 (m, 2 H), 1.76 – 1.88 (m, 4 H), 1.61 – 1.72 (m, 4 H), 1.24 (s, 3 H), 1.13 (d, \( J = 7.2 \), 3 H), 0.96 (s, 3 H), 0.90 (s, 9 H), 0.09 (a s, 6 H); \(^1^3\)C NMR (150 MHz, CDCl₃) δ: 219.4, 215.5, 175.3, 74.8, 72.7, 55.4, 52.6, 48.7, 47.9, 39.1, 33.1, 28.6, 26.9, 25.9, 25.6, 23.7, 20.2, 18.2, 13.8, –3.9, –4.7; IR (film) \( \nu_{max} \) 2955, 2929, 2881, 1752, 1693, 1463, 1367, 1257, 1179, 1133, 1107, 1080, 888, 837, 775 cm\(^{-1}\); HRMS (m/z): [M+H]^+ calcd. for C\(_{25}\)H\(_{40}\)O\(_5\)Si, 449.2718; found, 449.2721.

3.33: white powder; m.p. = 123 – 125 °C; TLC (Et₂O: hexanes v/v 1:1): \( R_F = 0.36 \); [α]₀^20: –46.2° (c = 9.3, DCM); \(^1\)H NMR (600 MHz, CDCl₃) δ: 4.22 (m, \( J = 12.3 \), 14.7 Hz, 2 H), 4.07 – 4.10 (m, 1 H), 3.89 (dd, \( J = 2.8 \), 10.4 Hz, 1 H), 2.27 – 2.31 (m, 1 H), 2.23 – 2.25 (m, 1 H), 1.95 – 1.96 (m, 1 H), 1.77 – 1.81 (m, 4 H), 1.73 – 1.75 (m 2 H), 1.55 – 1.65 (m, 3 H), 1.26 (s, 3 H), 1.14 (d, \( J = 7.5 \), 3 H), 0.97 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); \(^1^3\)C NMR (150 MHz, CDCl₃) δ 218.8, 214.6, 174.8, 74.8, 73.1, 55.3, 52.7, 47.2, 46.4, 38.9, 31.9, 27.3, 27.0, 25.9, 25.4, 24.0, 23.9, 21.8, 20.7, 18.2, 14.1, –4.0, –4.8; \( \nu_{max} \) 2953, 2930, 2879, 2856, 1752, 1713, 1691, 1471, 1375, 1255, 1133, 1107, 1074, 888, 836, 774 cm\(^{-1}\); HRMS (m/z): [M+H]^+ calcd. for C\(_{25}\)H\(_{40}\)O\(_5\)Si, 449.2718; found, 449.2710. X-ray structure.
Compounds 3.32 and 3.33:

The preparation of 3.32/3.33 was following the procedure for 3.32/3.33 using 3.31 (minor) (224 mg, 442 µmol) MeOH (6.63 mL), THF (6.63 mL) and SmI₂ (11.1 mL, 0.1 M in THF, 1.11 mmol). After chromatography 3.32/3.33 (456 mg, 76%) was obtained as a mixture of diastereomers (5.3:1) as a white powder.

Alcohol 3.35:

I. To a stirred solution of 3.32 (0.040 g, 0.089 mmol) in DCM (0.5 mL) at 0 ºC, was added triethylamine (0.081 g, 0.802 mmol) and TBSOTf (0.141 g, 0.5349 mmol). After the addition was complete the cooling bath was removed and the flask was allowed to warm to room temperature. Once the reaction was judged to be complete, it was quenched by the addition of saturated aqueous sodium bicarbonate (2 mL) and diluted with DCM (2 mL). The aqueous fraction was extracted further with DCM (3 X 2 mL) and the combined organic fractions were dried with MgSO₄ and concentrated in vacuo. The crude material was used immediately in the next step with no further purification.

II. Silyl enol ether 3.34 (0.050 g, 0.089 mmol) was dissolved in DCM (0.9 mL) and Davis’ oxaziridine (0.0211 g, 0.098 mmol) was added in one portion as a solid at room temperature. The reaction was run for about 2 hours at which point TLC indicated that no starting material remained. The stir bar was removed and the solvent was removed in vacuo. The crude residue was loaded directly onto a silica gel column using EtOAc:Hexanes (1:4) as eluent. The reaction provided 0.041 g of product for a 99% overall yield.
3.35: colorless foam; TLC (EtOAc:hexanes 1:1 v/v): \( R_f = 0.16; \) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) (ppm): 4.80 (d, \( J = 11.2 \) Hz, 1 H), 4.23 (d, \( J = 11.2 \) Hz, 1 H), 3.85 – 3.96 (m, 1 H), 2.91 (s, 1 H), 2.52 (t, \( J = 11.7 \) Hz, 1 H), 2.43 (d, \( J = 14.9 \) Hz, 1 H), 1.96 – 2.22 (m, 4 H), 1.78 (q, \( J = 12.4, 13.0 \) Hz, 4 H), 1.22 – 1.43 (m, 2 H), 1.19 (s, 3 H), 1.17 (d, \( J = 7.0 \) Hz, 3 H), 1.10 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.08 (s, 3 H); \(^{13}\)C (126 MHz, CDCl\(_3\)) \( \delta \) (ppm): 214.4, 172.2, 75.4, 73.4, 68.3, 51.8, 49.0, 48.0, 41.0, 32.1, 27.1, 25.9, 24.0, 23.7, 22.6, 21.2, 20.0, 18.2, 15.7, –3.9, –4.7, (one carbonyl resonance missing); LRMS (\( m/z \)): [M+H]\(^+\) calcd. for \( \text{C}_{25}\text{H}_{40}\text{O}_6\text{Si} \), 465; found, 465.

**Alcohol 3.38:**

Alcohol 3.38 was made using the same procedure as alcohol 3.35.

3.38: white solid; TLC (EtOAc:hexanes 1:1 v/v): \( R_f = 0.5; \) \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) (ppm): 4.89 (dd, \( J = 3.8, 12.2 \) Hz, 1 H), 4.82 (d, \( J = 11.2 \) Hz, 1 H), 4.16 (d, \( J = 11.3 \) Hz, 1 H), 3.06 (s, 3 H), 2.90 (s, 1 H), 2.53 (dd, \( J = 9.8, 13.5 \) Hz, 1 H), 2.40 (d, \( J = 15.0 \) Hz, 1 H), 2.25 – 2.31 (m, 1 H), 2.16 (s, 1 H), 1.96 – 2.12 (m, 4 H), 1.78 – 1.89 (m, 2 H), 1.48 (d, \( J = 14.5 \) Hz, 1 H), 1.31 (s, 3 H), 1.18 (s, 3 H), 1.16 (d, \( J = 7.0 \) Hz, 3 H); \(^{13}\)C (150 MHz, CDCl\(_3\)) \( \delta \) (ppm): 214.3, 214.0, 171.8, 84.9, 73.3, 68.0, 62.3, 50.5, 48.8, 47.8, 41.0, 38.5, 31.9, 25.0, 23.8, 23.3, 22.5, 21.4, 20.0, 15.7; LRMS (\( m/z \)): [M+H]\(^+\) calcd. for \( \text{C}_{20}\text{H}_{28}\text{O}_8\text{S} \), 383.1; found, 383.1; X-ray structure.

**Unsaturated lactone 3.39:**

Compound 3.39 was prepared by two different reaction sequences:

**Method A:**
I. To a stirred solution of 3.32 (0.020 g, 0.045 mmol) in DCM (0.1 mL) at 0 ºC, was added triethylamine (0.036 g, 0.357 mmol) and TBSOTf (0.071 g, 0.267 mmol). After the addition was complete the cooling bath was removed and the flask was allowed to warm to room temperature. Once the reaction was judged to be complete, it was quenched by the addition of saturated aqueous sodium bicarbonate (2 mL) and diluted with DCM (2 mL). The aqueous fraction was extracted further with DCM (3 X 2 mL) and the combined organic fractions were dried with MgSO₄ and concentrated in vacuo. The crude material was used immediately in the next step with no further purification.

II. Triethylamine (0.007 g, 0.067 mmol) was added to a solution of enol ether 3.34 (0.025 g, 0.045 mmol) in 0.5 mL of DCM and the mixture was cooled to –20 ºC. A 0.1 M stock solution of bromine (0.007 g, 0.045 mmol) in DCM was added dropwise and the solution was stirred at –20 ºC for 30 min. The reaction mixture was quenched with saturated aqueous NH₄Cl (1 mL), extracted with DCM (3 X 2 mL), dried over MgSO₄ and evaporated to dryness to give a 55% yield of 3.49 as a yellow oil (0.011 g).

Method B:

To a stirred solution of alcohol 3.35 (0.010 g, 0.022 mmol) in DCM (0.5 mL) at 0 ºC was added triethylamine (0.0087 g, 0.086 mmol) followed by methanesulfonyl chloride (0.005 g, 0.043 mmol). The reaction was stirred for 30 minutes at 0 ºC, then the cooling bath was removed and the reaction was allowed to warm to room temperature. When no starting material remained, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL) and DCM (1 mL). The reaction was extracted with DCM (3 X 1 mL) and the combined organic fractions were dried (MgSO₄) and concentrated in vacuo to give product 3.39 (0.008 g) in 85% percent yield.
**3.39:** yellow oil; TLC (EtOAc:hexanes 1:4 v/v): $R_F = 0.2$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.63 (d, $J = 6.9$ Hz, 1 H), 4.45 (d, $J = 12.0$ Hz, 1 H), 4.07 (d, $J = 12.0$ Hz, 1 H), 3.92 (dd, $J = 4.9$, 10.4 Hz, 1 H), 2.96 (dd, $J = 2.7$, 7.0 Hz, 1 H), 2.02 – 2.11 (m, 2 H), 1.98 (dd, $J = 4.1$, 12.8 Hz, 1 H), 1.82 – 1.91 (m, 2 H), 1.68 (ddd, $J = 4.6$, 9.7, 12.8 Hz, 1 H), 1.51 – 1.57 (m, 1 H), 1.36 – 1.47 (m, 2 H), 1.16 (s, 3 H), 1.13 (s, 3 H), 1.10 (d, $J = 7.2$ Hz, 3 H), 0.90 (s, 9 H), 0.09 (d, $J = 1.3$ Hz, 6 H); $^{13}$C (150 MHz, CDCl$_3$): 215.4, 213.2, 164.7, 145.9, 132.5, 76.0, 68.5, 58.1, 52.8, 47.0, 42.8, 38.5, 32.4, 27.8, 26.6, 25.1, 24.9, 24.4, 21.3, 18.9, 14.6, –3.2, –4.1; X-ray structure of TBS deprotected compound.

**Methoxy acrylate ester dieone 3.41:**

I. To a stirred solution of alcohol 3.27 (0.048 g, 0.109 mmol) and freshly made α-methoxy acrylic acid (0.022 g, 0.219 mmol) in DCM (1.1 mL) at 0 °C was added DMAP (0.04 g, 0.032 mmol) and EDCI (0.063 g, 0.327 mmol). The solution was stirred at room temperature for about 2 hours at which time the starting material had been completely consumed. The reaction mixture was diluted with DCM (5 mL) and saturated aqueous NH$_4$Cl (5 mL). The aqueous layer was washed with DCM (3 X 5 mL) and then the combined organic extracts were washed with saturated aqueous sodium bicarbonate (5 mL), water (5 mL) and brine (5 mL). The organic layer was dried with MgSO$_4$ and concentrated *in vacuo* to give the intermediate α-methoxy ester in 73% yield (0.041 g), pure enough for use in the next reaction.

**Intermediate α-methoxy ester:** colorless oil; TLC (EtOAc:hexanes 1:4 v/v): $R_F = 0.4$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.20 (d, $J = 7.4$ Hz, 1 H), 7.10 (d, $J = 6.7$ Hz, 1 H), 6.99 (t, $J = 7.6$ Hz, 1 H), 5.15 (d, $J = 2.7$ Hz, 1 H), 4.91 (d, $J = 5.6$ Hz, 1 H), 4.83 (d, $J =
5.5 Hz, 1 H), 4.51 (d, J = 2.7 Hz, 1 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.33 (d, J = 11.4 Hz, 1 H), 3.62 – 3.67 (m, 1 H), 3.56 (s, 3 H), 3.51 (s, 3 H), 2.58 (d, J = 14.6 Hz, 1 H), 2.28 (s, 3 H), 2.16 – 2.24 (m, 1 H), 1.99 – 2.09 (m, 1 H), 1.58 (dd, J = 3.9, 14.3 Hz, 1 H), 1.07 (s, 3 H), 0.86 (s, 9 H), 0.83 (s, 3 H), –0.03 (s, 6 H); 13C(126 MHz, CDCl3) δ (ppm): 210.8, 162.7, 155.2, 152.0, 132.5, 131.7, 131.5, 125.0, 123.9, 99.0, 93.3, 79.0, 70.7, 57.3, 55.7, 54.5, 52.2, 28.1, 26.3, 26.0, 26.0, 24.0, 23.0, 18.2, 17.7, –4.4, –4.9.

II. To a solution of the intermediate α-methoxy ester, from the previous step, (0.041, 0.080 mmol) in DCM (1.7 mL) at 0 ºC was added TFA (0.046 g, 0.400 mmol). After 30 min, a solution of triethylamine (0.081 g, 0.80 mmol) in CH2Cl2 (4 mL) was added quickly dropwise. The reaction mixture was filtered through a plug of silica gel, which was then washed with CH2Cl2 followed by evaporation of the organic solvent in vacuo. Silica gel chromatography with EtOAc/Hex (1:4) furnished the intermediate phenol (0.027 g, 70 %) as a colorless oil.

**intermediate phenol**: colorless oil; TLC (EtOAc:hexanes 1:4 v/v): Rf = 0.5; 1H NMR (500 MHz, CDCl3) δ (ppm): 7.08 – 7.11 (m, 1 H), 6.97 – 7.00 (m, 1 H), 6.80 (t, J = 7.5 Hz, 1 H), 5.34 (d, J = 2.8 Hz, 1 H), 4.77 (d, J = 11.5 Hz, 1 H), 4.65 (d, J = 2.8 Hz, 1 H), 4.53 (d, J = 11.4 Hz, 1 H), 3.66 (m, 4 H), 3.19 (s, 1 H), 2.23 (s, 3 H), 2.02 – 2.10 (m, 1 H), 1.62 – 1.73 (m, 1 H), 1.49 – 1.55 (m, 1 H), 1.41 (ddd, J = 4.4, 11.3, 15.6 Hz, 1 H), 1.15 (s, 3 H), 1.13 (s, 3 H), 0.91 (d, J = 0.5 Hz, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); 13C(126 MHz, CDCl3) δ (ppm): 163.0, 154.4, 152.2, 134.5, 129.9, 121.3, 120.8, 113.4, 93.8, 75.1, 67.0, 55.9, 51.1, 44.2, 30.1, 26.8, 26.0, 25.9, 22.2, 18.2, 17.8, 15.2, –4.0, –4.8.

III. To a stirred solution of intermediate phenol, from the previous step, (0.027 g, 0.056 mmol) in AcOH (2 mL) was added Pb(OAc)4 (0.037 g, 0.0834 mmol) all at once at room
temperature. After stirring for 15 min complete conversion was detected by TLC. The reaction mixture was diluted with EtOAc (5 mL) and H₂O (5 mL) and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried with Na₂SO₄ and concentrated in vacuo. Residual AcOH was removed with toluene azeotrope and was then dried under high vacuum. Silica gel chromatography with EtOAc/Hexanes (1:3) furnished 3.41 (0.016 g) as a yellow oil in 54% yield.

3.41: yellow oil; TLC (EtOAc:hexanes 1:3 v/v): Rₓ = 0.1; ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.03 (dd, J = 2.2, 5.7 Hz, 1 H), 6.27 – 6.42 (m, 2 H), 5.36 (d, J = 2.8 Hz, 1 H), 4.69 (d, J = 2.7 Hz, 1 H), 4.63 (d, J = 11.3 Hz, 1 H), 4.37 (d, J = 11.4 Hz, 1 H), 3.98 (dd, J = 2.4, 7.5 Hz, 1 H), 3.71 (s, 3 H), 2.17 – 2.26 (m, 2 H), 1.99 – 2.06 (m, 2 H), 1.81 – 1.93 (m, 1 H), 1.43 (s, 3 H), 1.23 (s, 3 H), 1.15 (s, 3 H), 0.96 (s, 6 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ¹³C(126 MHz, CDCl₃) δ (ppm): 204.9, 197.7, 169.1, 162.8, 142.1, 138.0, 137.7, 121.5, 93.9, 79.2, 68.0, 55.8, 53.4, 51.9, 26.8, 26.7, 26.0, 25.9, 24.8, 24.1, 22.1, 20.4, 18.2, –4.1, –4.7.

**Pyruvate ester diene 3.43:**

1. To a stirred solution of alcohol 3.27 (0.068 g, 0.1557 mmol) and freshly distilled pyruvic acid (0.041 g, 0.467 mmol) in DCM (1 mL) at room temperature was added DMAP (0.019 g, 0.1557 mmol) and EDCI (0.090 g, 0.156 mmol). The solution was stirred at room temperature for about 2 hours at which time the starting material had been completely consumed. The reaction mixture was diluted with DCM (5 mL) and saturated aqueous NH₄Cl (5 mL). The aqueous layer was washed with DCM (3 X 5 mL) and then
the combined organic extracts were washed with saturated aqueous sodium bicarbonate (5 mL), water (5 mL) and brine (5 mL). The organic layer was dried with MgSO$_4$ and concentrated in vacuo to give the intermediate pyruvate ester in 99% yield (0.078 g), pure enough for use in the next reaction.

**intermediate pyruvate ester:** clear oil; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.20 (dd, $J = 1.7, 7.9$ Hz, 1 H), 7.13 (d, $J = 7.8$ Hz, 1 H), 7.00 (t, $J = 7.7$ Hz, 1 H), 4.94 (d, $J = 5.6$ Hz, 1 H), 4.89 (d, $J = 5.6$ Hz, 1 H), 4.63 (d, $J = 11.3$ Hz, 1 H), 4.32 (d, $J = 11.4$ Hz, 1 H), 3.66 (t, $J = 3.6$ Hz, 1 H), 3.54 (s, 3H), 2.64 (d, $J = 14.3$ Hz, 1 H), 2.28 (s, 3 H), 2.20 – 2.27 (m, 1 H), 2.02 – 2.09 (m, 1 H), 1.07 (s, 3 H), 0.87 (s, 9 H), 0.82 (s, 3 H), −0.02 (s, 6 H); $^{13}$C(151 MHz, CDCl$_3$) $\delta$ (ppm): 210.8, 191.7, 160.3, 155.6, 131.9, 131.8, 124.8, 124.0, 99.1, 79.4, 71.8, 57.4, 54.5, 52.4, 28.3, 26.9, 26.2, 26.0, 25.9, 23.8, 23.0, 18.2, 17.8, −4.4, −4.9.

II. To a solution of intermediate pyruvate ester, from the previous step, (0.078, 0.154 mmol) in DCM (3.2 mL) at 0 ºC was added TFA (0.089 g, 0.7785 mmol). After 30 min, a solution of triethylamine (0.157 g, 1.557 mmol) in CH$_2$Cl$_2$ (4 mL) was added quickly dropwise. The reaction mixture was filtered through a plug of silica gel, which was then washed with CH$_2$Cl$_2$ followed by evaporation of the organic solvent in vacuo. Silica gel chromatography with EtOAc/Hex (1:1) furnished the intermediate phenol (0.064 g, 96 %) as a colorless oil.

**intermediate phenol:** colorless oil; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.10 (d, $J = 7.4$ Hz, 1 H), 6.98 (d, $J = 7.6$ Hz, 1 H), 6.80 (t, $J = 7.5$ Hz, 1 H), 4.69 (d, $J = 11.4$ Hz, 1 H), 4.54 (d, $J = 11.4$ Hz, 1 H), 3.60 – 3.67 (m, 1 H), 3.15 (s, 1 H), 2.45 (s, 3 H), 2.21 (s, 3 H), 1.95 – 2.11 (m, 1 H), 1.60 – 1.70 (m, 1 H), 1.48 – 1.60 (m, 2 H), 1.11 (s, 3 H), 1.07
(s, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); $^{13}$C(151 MHz, CDCl$_3$) δ (ppm): 191.5, 160.8, 154.6, 133.8, 131.6, 130.2, 121.4, 120.9, 120.6, 113.1, 75.1, 68.6, 50.8, 44.2, 26.9, 26.4, 26.0, 22.5, 18.3, 18.2, 15.2, –4.0, –4.8.

To a stirred solution of intermediate phenol, from the previous step, (0.064 g, 0.150 mmol) in AcOH (5.4 mL) was added Pb(OAc)$_4$ (0.100 g, 0.225 mmol) all at once at room temperature. After stirring for 15 min complete conversion was detected by TLC. The reaction mixture was diluted with EtOAc (10 mL) and H$_2$O (10 mL) and stirring was continued for 30 min. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried with Na$_2$SO$_4$ and concentrated in vacuo. Residual AcOH was removed with toluene azeotrope and was then dried under high vacuum. Silica gel chromatography with EtOAc/Hexanes (1:1) furnished 3.43 (0.015 g) as a yellow oil in 19% yield.

3.43: yellow oil; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.14 (dd, J = 1.3, 6.4 Hz, 1 H), 6.40 (dd, J = 6.3, 9.5 Hz, 1 H), 6.32 (dd, J = 1.6, 9.6 Hz, 1 H), 4.49 (d, J = 11.4 Hz, 1 H), 4.43 (d, J = 11.4 Hz, 1 H), 3.92 (d, J = 5.9 Hz, 1 H), 2.47 (s, 3 H), 2.42 (d, J = 12.4 Hz, 1 H), 2.11 – 2.15 (m, 2 H), 2.08 (s, 3 H), 1.72 – 1.86 (m, 1 H), 1.42 (s, 3 H), 1.15 (s, 3 H), 1.14 (s, 3 H), 0.95 (s, 9 H), 0.12 (s, 3 H), 0.12 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm): 210.0, 197.9, 191.9, 169.3, 160.4, 141.8, 137.5, 136.1, 121.8, 78.4, 69.6, 53.5, 52.3, 35.1, 27.2, 27.0, 26.3, 25.9, 24.4, 24.1, 22.6, 20.4, 18.2, –4.3, –4.8.

Lactol 3.46:

To a stirred solution of 3.31 (0.067 g, 0.132 mmol) in DCM/MeOH (4 mL, 1:1) was added NaBH$_4$ (0.015 g, 0.3937 mmol). The solution was stirred for 1 hour and was then...
quenched by the slow addition of water (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 X 10 mL), dried over Na₂SO₄ and concentrated in vacuo to give an oily residue. The compound was purified on silica gel to give lactol 3.46 (0.064 g, 95% yield) as a mixture of lactol epimers (1:5).

3.46: colorless oil; TLC (EtOAc:hexanes 1:1 v/v): R_f = 0.4; ¹H NMR (500 MHz, CDCl₃) δ (ppm): major isomer: 4.66 (t, J = 8.7 Hz, 1 H), 4.20 (d, J = 12.7 Hz, 1 H), 3.77 – 3.86 (m, 2 H), 3.44 (d, J = 12.7 Hz, 1 H), 3.33 – 3.42 (m, 2 H), 2.94 (dq, J = 2.3, 4.8 Hz, 1 H), 2.07 (s, 3 H), 1.70 – 1.78 (m, 6 H), 1.29 (s, 3 H), 1.21 (s, 3 H), 1.10 (s, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ (ppm): both isomers: 214.9, 214.8, 208.0, 207.6, 170.4, 170.3, 98.4, 94.6, 83.9, 83.6, 75.8, 75.6, 68.0, 61.4, 52.6, 52.5, 50.1, 47.3, 47.3, 37.1, 34.8, 34.3, 33.9, 32.7, 29.2, 27.43, 27.33, 27.07, 27.0, 25.9, 25.4, 24.9, 24.0, 22.4, 22.2, 22.1, 21.9, 21.7, 21.4, 19.6, 18.2, 18.1, 17.6, −3.9, −4.8.

Alcohol 3.48:

To a stirred solution of 3.32 (0.009 g, 0.020 mmol) in DCM (0.2 mL) was added BF₃•OEt₂ (0.011 g, 0.080 mmol). After about 3 hours the reaction was loaded directly onto a silica gel column packed with EtOAc/Hexanes (1:1). The residue was then purified with EtOAc/Hexanes (1:1) to provide alcohol 3.48 in 99% yield (0.008 g).

3.48: white solid; TLC (EtOAc: hexanes 1:1 v/v): R_f = 0.2; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 4.26 (d, J = 12.1 Hz, 1 H), 4.14 – 4.20 (m, 1 H), 4.02 – 4.09 (m, 1 H), 3.99 (dd, J = 3.5, 10.8 Hz, 1 H), 2.54 (dt, J = 4.1, 14.4 Hz, 1 H), 2.20 – 2.27 (m, 1 H), 1.87 – 2.03 (m, 3 H), 1.72 – 1.87 (m, 4 H), 1.58 – 1.72 (m, 4 H), 1.31 (s, 3 H), 1.13 (d, J = 7.1 Hz, 3
H), 0.99 (s, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm): 219.0, 215.5, 175.2, 74.1, 72.8, 55.6, 52.0, 48.4, 47.8, 39.0, 32.9, 28.5, 27.0, 26.3, 25.4, 23.2, 20.1, 19.5, 13.8.

**Mesylate 3.36:**

To a stirred solution of alcohol 3.48 (0.036 g, 0.108 mmol) in DCM (1.1 mL) at 0 °C was added triethylamine (0.044 g, 0.431 mmol) followed by methanesulfonyl chloride (0.025 g, 0.215 mmol). The reaction was stirred for 30 minutes at 0 °C, then the cooling bath was removed and the reaction was allowed to warm to room temperature. When no starting material remained after about 30 minutes, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL) and DCM (1 mL). The reaction was extracted with DCM (3 X 1 mL) and the combined organic fractions were dried (MgSO$_4$) and concentrated in vacuo. The residue was purified on silica gel using EtOAc/Hexanes (1:1) as eluent to give the product (0.041 g) in 92% percent yield.

3.36: colorless foam; TLC (EtOAc: hexanes 1:1 v/v): $R_f = 0.2$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 4.90 (dd, $J = 3.8$, 11.7 Hz, 1 H), 4.23 (d, $J = 12.1$ Hz, 1 H), 4.14 (dd, $J = 1.3$, 12.1 Hz, 1 H), 4.01 (dd, $J = 2.6$, 11.1 Hz, 1 H), 3.06 (s, 3 H), 2.48 – 2.58 (m, 1 H), 2.25 – 2.36 (m, 1 H), 2.20 (dt, $J = 1.7$, 7.1 Hz, 1 H), 1.83 – 2.12 (m, 4 H), 1.69 – 1.82 (m, 3 H), 1.59 – 1.71 (m, 2 H), 1.35 (s, 3 H), 1.12 (d, $J = 7.3$ Hz, 3 H), 1.03 (s, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm): 216.7, 215.2, 174.7, 72.8, 56.4, 48.4, 47.7, 38.9, 38.6, 32.7, 31.7, 28.4, 26.6, 25.2, 24.9, 23.5, 20.7, 20.0, 13.8.

**Cage structure 3.49:**

This compound could be made by two different methods:
Method A:

To a solution of mesylate 3.39 (0.013 g, 0.032 mmol) in toluene (0.4 mL) was added DBU (0.010 g, 0.063 mmol) and the solution was warmed to 90 °C for 6 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc (2 mL) and saturated aqueous NH₄Cl (2 mL). The aqueous layer was extracted with EtOAc (3 X 2 mL) and the combined organic extracts were dried (MgSO₄) and concentrated in vacuo. The resulting residue was purified on silica gel using EtOAc/Hexanes (1:1) to provide about 0.003 g of compound 3.49 (30% yield).

Method B:

A solution of mesylate 3.36 (0.009 g, 0.022 mmol) in DMSO (0.1 mL) was heated to 140 °C for 30 minutes then it was cooled to room temperature and directly subjected to chromatography on silica gel using EtOAc/Hexanes (1:1) to provide 0.003 g compound 3.49 (43% yield).

3.49: colorless oil; TLC (EtOAc: hexanes 1:1 v/v): R_{F} = 0.2; \(^1\)H NMR (600 MHz, CDCl₃) δ (ppm): 4.44 (dd, J = 0.8, 11.8 Hz, 1 H), 4.09 (dd, J = 2.2, 4.5 Hz, 1 H), 3.92 (d, J = 11.8 Hz, 1 H), 2.39 (t, J = 2.9 Hz, 1 H), 2.20 – 2.26 (m, 2 H), 2.15 – 2.20 (m, 1 H), 2.03 – 2.09 (m, 1 H), 1.99 (ddd, J = 2.2, 5.2, 13.2 Hz, 1 H), 1.86 (tt, J = 3.4, 12.9 Hz, 1 H), 1.68 – 1.73 (m, 1 H), 1.67 (s, 3 H), 1.56 – 1.66 (m, 3 H), 1.46 (ddt, J = 3.7, 8.7, 12.5 Hz, 1 H), 1.22 (s, 3 H), 1.17 (s, 3 H); \(^{13}\)C NMR (150 MHz, CDCl₃) δ (ppm): 216.1, 172.5, 146.2, 114.7, 78.5, 70.6, 50.5, 49.4, 43.8, 42.0, 36.0, 30.8, 25.6, 25.3, 25.1, 23.3, 23.1, 22.9, 13.3.
**Iodo-Enone 3.50:**

I. To a solution of ketone 3.21 (7.49 g, 29.22 mmol) in THF (97 mL) at 0 °C, was added phenyl trimethylammonium perbromide (PTAB) (12.09 g, 32.15 mmol) as a solid in one portion. When the starting material was consumed after about 30 minutes, the reaction was quenched by addition of saturated aqueous sodium thiosulfate (50 mL) and brine (50 mL). The aqueous layer was extracted with ether (3 X 100 mL) and the combined organic extracts were washed with saturated sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The combined organic extracts were dried with MgSO₄, passed through a Celite plug and concentrated in vacuo. Chromatography on silica gel with DCM/hexanes (1:4) provided the bromide (about 9.762 g) that was used immediately in the subsequent step.

II. To the bromide (9.762 g, 29.22 mmol) in DMF (95 mL) was added dry Li₂CO₃ (8.64 g, 116.88 mmol) and dry LiBr (9.52g, 109.58 mmol). The resulting suspension was heated to 120 °C for 3 hours when TLC showed consumption of the starting material. At that point the dark suspension was cooled to room temperature and diluted with water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (3 X 100 mL). The combined organic extracts were dried with MgSO₄ and concentrated in vacuo. The residue was purified on silica gel using ether/hexanes (1:7) to provide the **intermediate enone** in 78% yield (5.828 g).

**intermediate enone**: pale yellow oil; TLC (EtOAc: hexanes 2:3 v/v): Rₚ = 0.6; ¹H NMR (500 MHz, CDCl₃) δ (ppm): 6.72 (ddd, J = 3.2, 5.1, 10.1 Hz, 1 H), 5.95 (dt, J = 2.0, 10.1 Hz, 1 H), 3.82 (dd, J = 4.7, 7.7 Hz, 1 H), 2.53 (dtd, J = 1.6, 4.9, 19.0Hz, 1 H), 2.38 (ddt, J = 2.9, 7.7, 18.9 Hz, 1 H), 1.12 (s, 3 H), 1.05 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s,
13 C NMR (126 MHz, CDCl₃) δ (ppm): 204.3, 144.6, 128.7, 74.6, 48.8, 33.0, 29.9, 25.9, 21.5, 18.4, −4.1, −4.8.

III. To a room temperature stirred solution of intermediate enone, form the previous step, (5.828 g, 22.93 mmol) in DCM (100 mL), was added pyridine (18.14 g, 229.30 mmol) followed by iodine (17.46 g, 68.79 mmol). The reaction was stirred for 2 hours at room temperature at which point in was quenched with saturated aqueous sodium thiosulfate (100 mL) and diluted with EtOAc (100 mL). The aqueous layer was washed with EtOAc (3 X 100 mL) and the combined organic extracts were washed with 1 M HCl (100 mL), water (100 mL) and brine (100 mL). The combined organic extracts were dried with MgSO₄, concentrated in vacuo and purified on silica gel using EtOAc/hexanes (1:20) to provide iodo-enone 3.50 in 73 % yield (6.36 g).

3.50: pale yellow oil; TLC (EtOAc: hexanes 1:7 v/v): Rᵢ = 0.5; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.51 (dd, J = 3.6, 5.3 Hz, 1 H), 3.85 (dd, J = 4.7, 7.4 Hz, 1 H), 2.58 (dt, J = 5.0, 18.9 Hz, 1 H), 2.45 (ddd, J = 3.6, 7.4, 19.0 Hz, 1 H), 1.17 (s, 3 H), 1.09 (s, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 196.9, 153.1, 103.3, 74.1, 49.3, 36.6, 25.8, 22.3, 18.9, 18.0, −4.2, −4.8.

Boronic Ester 3.51:

MOM-protected phenol 3.23 (4.00 g, 26.28 mmol) was azeotropically dried using benzene, then dried on high vacuum and backfilled with argon. This compound was then dissolved in 130 mL of dry THF and cooled to 0 °C. To this stirred solution was added n-BuLi in hexanes (2.0 M, 15.765 mL, 31.53 mmol) dropwise. After the addition was complete the cooling bath was removed and the solution was allowed to warm to room
temperature and stirred for 1 hour at this temperature. At that point the solution was cooled to –78 °C and a THF (40 mL) solution of bis(pinacolato)diboron (7.34 g, 28.91 mmol) was added quickly dropwise. When the addition was complete the reaction was again allowed to warm to room temperature. When the reaction had reached room temperature it was allowed to stir for one hour and then quenched by slow addition of saturated aqueous NH₄Cl (50 mL). The reaction mixture was further diluted with 100 mL of water and extracted with ether (3 X 150 mL). The combined organic extracts were combined, dried over MgSO₄ and evaporated in vacuo to give a crude oil. This residue was purified on silica gel using EtOAc/hexanes (1:20) to provide 4.13 g of boronic ester 3.51 in 45% yield.

3.51: clear oil; TLC (EtOAc: hexanes 1:10 v/v): R_f = 0.4; ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.69 (dd, J = 1.9, 7.4 Hz, 1 H), 7.33 (dd, J = 1.9, 7.4 Hz, 1 H), 7.09 (t, J = 7.4 Hz, 1 H), 5.16 (s, 2 H), 3.64 (s, 3 H), 2.42 (s, 3 H), 1.40 (s, 12 H); ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 161.8, 134.6, 134.0, 130.9, 123.4, 101.2, 83.4, 57.0, 24.6, 16.8, 16.7.

**Suzuki Product 3.52:**

Iodo enone 3.50 (18.2 g, 47.9 mmol) and pinacol borate ester 3.51 (16.7 g, 60 mmol) were dissolved in 500 mL of DMF/EtOH/H₂O (10:5:3, 278 mL, 139 mL, 83 mL). Sodium carbonate (5.3 g, 50 mmol) was added and the reaction solvent was degassed by three rounds of the freeze-pump-thaw method (for smaller scale bubbling with argon with sonication for 15 minutes was sufficient for degassing to obtain comparable yields). After the solution was degassed Pd(ddpf)Cl₂•DCM (4.1 g, 5 mmol) was added and the reaction was warmed to 60 °C for 2 hours at which point TLC indicated all of the iodo
enone was consumed. The reaction was cooled and diluted with EtOAc (400 mL) and water (400 mL). The mixed solvent system was passed through a Celite plug, to remove insoluble material, and was then extracted with EtOAc (3 X 500 mL). The combined organic extracts were dried with MgSO4, concentrated in vacuo and purified on silica gel using EtOAc/hexanes (1:10) to afford 16.1 g of product (83 % yield).

3.52: off-white solid; TLC (EtOAc: hexanes 1:10 v/v): $R_f = 0.3$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.13 (d, $J = 5.7$ Hz, 1 H), 6.99 (t, $J = 7.5$ Hz, 1 H), 6.87 (dd, $J = 1.8$, 7.5 Hz, 1 H), 6.74 (dd, $J = 3.4$, 5.0 Hz, 1 H), 4.78 (q, $J = 5.9$ Hz, 2 H), 3.93 (dd, $J = 4.8$, 7.5 Hz, 1 H), 3.48 (s, 3 H), 2.70 (dt, $J = 4.9$, 19.1 Hz, 1 H), 2.54 (ddd, $J = 3.4$, 7.5, 19.0 Hz, 1 H), 2.34 (s, 3 H), 1.21 (s, 3 H), 0.92 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 201.7, 154.1, 142.8, 137.6, 131.5, 131.1, 131.0, 129.0, 124.0, 99.5, 74.8, 57.5, 48.9, 33.2, 25.9, 21.9, 18.5, 18.2, 17.2, –4.1, –4.8.

Dienone 3.53:

To a stirred solution of aryl enone 3.52 (1.72 g, 4.25 mmol) in THF (43 mL) was added a 1 M TBAF (4.67mL, 4.67 mmol) solution at room temperature. The reaction was stirred for several hours until the starting material was gone as judged by TLC analysis. The reaction solution was passed through a Celite plug and was then concentrated in vacuo to provide an oily residue that was purified on silica gel using EtOAc/hexanes (1:3) to provide 0.481 g of dienone 3.53 in 42% yield.

3.53: pale yellow oil; TLC (EtOAc: hexanes 1:3 v/v): $R_f = 0.4$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.13 – 7.18 (m, 1 H), 7.08 (dd, $J = 1.9$, 6.0 Hz, 1 H), 7.03 (t, $J = 7.4$ Hz, 1 H), 6.96 – 7.00 (m, 1 H), 6.36 (dd, $J = 1.9$, 9.5 Hz, 1 H), 6.26 (dd, $J = 6.0$, 9.4 Hz, 1 H),
4.77 (s, 2 H), 3.43 (s, 3 H), 2.34 (s, 3 H), 1.31 (s, 6 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 203.6, 154.1, 148.5, 140.6, 134.6, 131.6, 131.2, 130.2, 129.0, 124.0, 119.4, 99.3, 57.6, 48.0, 25.9, 17.1.

**Alcohol 3.54:**

Dienone 3.53 (0.096 g, 0.3536 mmol) was azeotropically dried with benzene and dried on high vacuum for a minimum of 15 minutes. The flask was backfilled with argon and charged with THF (7 mL) and cooled to $-78^\circ$C. To this stirred solution was added L-Selectride (1 M solution in THF, 0.424 mL, 0.424 mmol). The resulting bright yellow solution was stirred for 15 minutes at $-78^\circ$C, at which time a suspension of azeotropically dried paraformaldehyde (0.535 g, 17.68 mmol) in THF (5 mL) was added. The flask was slowly warmed to room temperature by removal of the cooling bath. When the flask reached room temperature the yellow color had faded to leave a milky white suspension, at which point the reaction was quenched with saturated aqueous NH$_4$Cl (5 mL) and diluted with water (5 mL). The reaction was extracted with EtOAc (3 X 50 mL), dried over MgSO$_4$ and concentrated *in vacuo*. The crude material was purified on silica gel using EtOAc/hexane as eluent to provide alcohol 3.54 in 80% yield (0.086 g).

3.54: colorless oil; TLC (EtOAc: hexanes 1:3 v/v): $R_f = 0.2$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.16 (dd, $J = 1.7$, 7.8 Hz, 1 H), 7.10 – 7.14 (m, 1 H), 7.01 (t, $J = 7.6$ Hz, 1 H), 5.74 (ddd, $J = 3.1$, 5.4, 9.7 Hz, 1 H), 5.43 (dd, $J = 2.5$, 9.7 Hz, 1 H), 4.89 (q, $J = 5.6$ Hz, 2 H), 4.23 (dd, $J = 3.9$, 11.6 Hz, 1 H), 3.56 (s, 3 H), 2.92 (dd, $J = 5.4$, 17.7 Hz, 1 H), 2.76 (dt, $J = 2.9$, 17.8 Hz, 1 H), 2.52 (d, $J = 7.8$ Hz, 1 H), 2.31 (s, 3 H), 1.17 (s, 3 H), 1.00 (s, 3 H).
H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm): 216.5, 155.8, 136.5, 132.2, 131.7, 131.1, 126.3, 124.0, 122.5, 99.2, 67.2, 57.3, 56.7, 46.4, 32.5, 27.6, 27.4, 18.2.

**Ester 3.55:**

To a stirred solution of alcohol 3.54 (0.479 g, 1.2 mmol) in DCM (15 mL) at −78 °C, was added Hünig's base (1.014 g, 7.85 mmol) and DMAP (0.010 g, 0.079 mmol) followed by acryloyl chloride (0.427 g, 4.72 mmol), under a nitrogen atmosphere. The cooling bath was removed and the flask was allowed to warm to room temperature. Once the starting material was determined to be consumed by TLC (EtOAc/Hexanes 1:3), the reaction was quenched with saturated aqueous NH$_4$Cl (10 mL) and extracted with EtOAc (3 × 25 mL). The mixture was chromatographed quickly on silica gel using EtOAc/Hexanes (1:5) to provide 47% of ester 3.55 (0.263 g) as a clear oil.

3.55: clear oil; TLC (EtOAc:hexanes 1:3 v/v): $R_f = 0.5$; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.10 (dd, $J = 1.6$, 7.4 Hz, 1 H), 7.06 (dd, $J = 1.8$, 8.0 Hz, 1 H), 6.95 (t, $J = 7.7$ Hz, 1 H), 6.25 (dd, $J = 1.5$, 17.3 Hz, 1 H), 5.99 (dd, $J = 10.4$, 17.4 Hz, 1 H), 5.66 – 5.79 (m, 2 H), 5.47 (dd, $J = 2.4$, 9.8 Hz, 1 H), 4.92 (d, $J = 1.3$ Hz, 2 H), 4.76 (d, $J = 11.6$ Hz, 1 H), 4.59 (d, $J = 11.7$ Hz, 1 H), 3.56 (s, 3 H), 3.16 (dd, $J = 5.3$, 17.6 Hz, 1 H), 2.45 (dt, $J = 2.9$, 17.6 Hz, 1 H), 2.30 (s, 3 H), 1.15 (s, 3 H), 0.98 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm): 212.4, 165.8, 155.7, 136.9, 131.7, 131.5, 130.9, 128.3, 126.6, 123.5, 121.9, 99.0, 67.4, 57.2, 54.4, 46.1, 33.4, 27.6, 27.2, 25.9, 18.1.
Phenol 3.56:

To a stirred solution of ester 3.55 (0.647 g, 0.663 mmol) in DCM (36 mL) at room temperature, was added Amberlyst 15 (0.544 g) and the solution was stirred for 2 hours, when TLC (DCM/hexanes/AcOH, 2 mL :1 mL : 0.01 mL) detected no starting material remained. The Amberlyst 15 was filtered off and the solution was concentrated in vacuo. The crude organic material was purified on silica gel using ether/hexanes (1:4) as eluent to provide phenol 3.56 in 91% yield (0.514 g).

3.56: clear oil; TLC (EtOAc:hexanes 1:3 v/v): $R_f = 0.5$; $^1$H NMR (600 MHz, CDCl$_3$) δ (ppm): 6.94 (dd, $J = 7.6$, 10.6 Hz, 2 H), 6.78 (t, $J = 7.5$ Hz, 1 H), 6.34 (d, $J = 17.2$ Hz, 1 H), 6.08 (dd, $J = 10.5$, 17.4 Hz, 1 H), 5.82 (d, $J = 10.4$ Hz, 1 H), 5.65 (dd, $J = 2.8$, 9.8 Hz, 1 H), 5.57 – 5.62 (m, 1 H), 4.70 (d, $J = 11.5$ Hz, 1 H), 4.42 (d, $J = 11.5$ Hz, 1 H), 3.21 (s, 1 H), 2.65 – 2.77 (m, 1 H), 2.36 (dd, $J = 6.8$, 16.3 Hz, 1 H), 2.18 (s, 3 H), 1.36 (s, 3 H), 1.22 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ (ppm): 165.9, 156.0, 138.4, 131.5, 131.4, 130.2, 128.2, 123.9, 121.0, 120.8, 119.4, 114.5, 67.7, 52.6, 41.1, 34.5, 23.8, 22.3, 15.3.

Dieone 3.57:

To a room temperature stirred solution of phenol 3.56 (0.514 g, 1.635 mmol) in acetic acid (16 mL) was added lead(IV)acetate (0.870 g, 1.96 mmol). The solution was stirred for about 30 minutes and TLC (EtOAc/hexanes 1:4) showed complete conversion to the dienone. The reaction was quenched with water (10 mL) and EtOAc (10 mL). The organic layer was separated, dried (MgSO$_4$), and evaporated in vacuo to give a residue (0.332 g, 55% yield) that was used without purification for the next step as a mixture of two diastereomers (1:1).
3.57 (diastereomer 1): yellow oil; TLC (EtOAc:hexanes 1:3 v/v): $R_f = 0.2$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 6.88 (dd, $J = 3.3$, 4.5 Hz, 1 H), 6.38 (dd, $J = 1.4$, 17.3 Hz, 1 H), 5.84 (dd, $J = 1.4$, 10.4 Hz, 1 H), 5.62 – 5.70 (m, 1 H), 5.61 (dd, $J = 2.4$, 10.1 Hz, 1 H), 4.53 (d, $J = 11.9$ Hz, 1 H), 4.47 (d, $J = 11.9$ Hz, 1 H), 2.91 (dt, $J = 2.5$, 17.8 Hz, 1 H), 2.24 (dd, $J = 5.4$, 17.7 Hz, 1 H), 2.07 (s, 3 H), 1.43 (s, 3 H), 1.29 (s, 3 H), 1.15 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 213.0, 197.4, 169.8, 165.7, 141.6, 138.7, 136.7, 135.5, 131.8, 128.0, 121.3, 121.3, 80.2, 64.4, 53.2, 44.5, 33.1, 28.1, 27.8, 23.6, 20.7.

3.57 (diastereomer 2): yellow oil; TLC (EtOAc:hexanes 1:3 v/v): $R_f = 0.1$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 6.82 (dd, $J = 3.5$, 4.4 Hz, 1 H), 6.37 (dd, $J = 1.5$, 17.4 Hz, 1 H), 6.22 – 6.28 (m, 2 H), 6.08 (dd, $J = 10.5$, 17.3 Hz, 1 H), 5.81 (dd, $J = 1.5$, 10.4 Hz, 1 H), 5.87 – 5.75 (m, 1 H), 5.58 – 5.65 (m, 1 H), 4.60 (d, $J = 11.3$ Hz, 1 H), 4.50 (d, $J = 11.2$ Hz, 1 H), 2.75 – 2.87 (m, 1 H), 2.41 (dd, $J = 1.5$, 4.5, 17.4 Hz, 1 H), 2.06 (s, 3 H), 1.36 (s, 3 H), 1.23 (s, 3 H), 1.16 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 211.5, 197.4, 169.2, 165.8, 142.1, 138.3, 137.0, 136.3, 131.3, 128.3, 121.9, 121.4, 79.4, 65.5, 53.5, 45.4, 31.3, 27.6, 27.0, 24.0, 20.5.

Bicycle 3.58:

A microwave vial reaction vessel was first treated with hexamethyldisilazane (1 mL) sealed and heated to reflux for 2 min. The vial was cooled, rinsed with acetone and dried under high vacuum. In the sealed pretreated vial, equipped with a magnetic stir bar, was added dienone 3.57 (diastereomer 1) (0.021 g, 0.056 mmol) and BHT (0.012 mg, 0.056 mmol). The vial was capped and evacuated on high vacuum followed by backfilling with
argon. To the vial was then added o-DCB (2 mL) and it was heated to 165 °C for 2 hours. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 1:4 EtOAc/hexanes. Furnishing bicycle 3.58 (0.015 g, 70%) as a white foam. The reaction could also be conducted on a mixture of the acetate epimers.

3.58: white foam; TLC (EtOAc: hexanes 1:3 v/v): \( R_f = 0.2 \); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) (ppm): 6.62 (dd, \( J = 6.5, 8.4 \text{ Hz, 1 H} \)), 6.02 (dd, \( J = 1.7, 8.4 \text{ Hz, 1 H} \)), 5.65 – 5.77 (m, 2 H), 4.60 (d, \( J = 12.7 \text{ Hz, 1 H} \)), 4.31 (dd, \( J = 6.4, 9.9 \text{ Hz, 1 H} \)), 4.21 (d, \( J = 12.6 \text{ Hz, 1 H} \)), 3.83 (dt, \( J = 1.7, 4.9 \text{ Hz, 1 H} \)), 2.96 – 3.02 (m, 1 H), 2.39 (ddd, \( J = 3.3, 10.0, 13.7 \text{ Hz, 1 H} \)), 2.26 – 2.35 (m, 1 H), 2.04 (s, 1 H), 1.97 (s, 3 H), 1.67 (s, 3 H), 1.32 (s, 3 H), 1.25 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) (ppm): 214.0, 201.1, 172.5, 169.9, 140.1, 136.1, 124.0, 120.4, 79.6, 71.4, 56.6, 46.1, 45.6, 38.6, 37.6, 30.2, 28.0, 28.0, 27.1, 22.1, 20.4.

**Bicycle 3.59:**

Bicycle 3.58 (mixture of acetate epimers, 0.095 g, 0.255 mmol) was dissolved in THF (1 mL) and methanol (1 mL). The solvent was degassed with sonication and bubbling with argon for 15 minutes. A commercial 0.1 \( M \) solution of samarium(II) iodide (7.6 mL, 0.76 mmol) was added to the stirred solution at room temperature. The blue color of the samarium solution dissipated immediately upon mixing with the reaction solution for the majority of the addition, however at the end of the addition the color persisted. The reaction was quenched with saturated aqueous NH\(_4\)Cl (2 mL) and EtOAc (2 mL). The aqueous layer was extracted with EtOAc (3 X 10 mL). The combined organic extracts
were dried with MgSO$_4$ and concentrated in vacuo. The residue was purified on silica gel using EtOAc/hexanes (1:3) to provide the bicycle 3.59 in 82% yield (0.066 g).

**3.59**: colorless oil; TLC (EtOAc: hexanes 1:3 v/v): $R_f = 0.3$; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm): 6.78 (dd, $J = 6.6$, 8.4 Hz, 1 H), 5.97 (dd, $J = 1.7$, 8.4 Hz, 1 H), 5.64 – 5.75 (m, 2 H), 4.58 (d, $J = 12.5$ Hz, 1 H), 4.37 (dd, $J = 6.4$, 10.1 Hz, 1 H), 4.17 (d, $J = 12.5$ Hz, 1 H), 2.87 – 2.97 (m, 1 H), 2.81 (d, $J = 1.7$ Hz, 1 H), 2.43 (ddd, $J = 3.2$, 10.1, 13.4 Hz, 1 H), 2.18 – 2.28 (m, 1 H), 2.06 – 2.15 (m, 1 H), 1.90 (s, 1 H), 1.33 (s, 3 H), 1.24 (s, 3 H), 1.18 (d, $J = 7.5$ Hz, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm): 213.6, 208.3, 173.0, 142.8, 136.1, 124.2, 120.4, 71.2, 56.9, 45.6, 45.2, 41.1, 38.5, 36.8, 30.0, 28.2, 28.1, 25.1, 15.4.

**Bicycle 3.60:**

To a stirred solution of bicycle 3.59 (0.020 g, 0.054 mmol) in EtOAc (2 mL) was added 10% palladium on carbon (0.010 g). Three balloons full of hydrogen were bubbled through the stirred suspension at which point TLC (using EtOAc/hexanes 1:3) indicated that the starting material had been consumed. The palladium was filtered off through a Celite plug and concentrated in vacuo to provide the bicycle 3.60 in 80% yield (0.016 g).

**3.60**: colorless oil; TLC (EtOAc: hexanes 1:3 v/v): $R_f = 0.5$; $^1$H NMR (500 MHz, CDCl$_3$) δ (ppm): 4.29 (d, $J = 12.1$ Hz, 1 H), 4.15 (dd, $J = 1.4$, 11.9 Hz, 1 H), 4.05 (ddd, $J = 2.4$, 4.3, 10.9 Hz, 1 H), 2.49 – 2.58 (m, 1 H), 2.22 – 2.28 (m, 1 H), 1.91 (ddd, $J = 4.0$, 8.9, 14.8 Hz, 2 H), 1.76 – 1.81 (m, 1 H), 1.70 – 1.76 (m, 4 H), 1.66 (d, $J = 2.8$ Hz, 2 H), 1.55 (s, 3 H), 1.22 (s, 3 H), 1.14 (d, $J = 7.2$ Hz, 3 H), 1.03 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ (ppm): 215.4, 210.8, 175.4, 73.0, 55.4, 49.5, 47.9, 45.7, 39.3, 37.7, 33.0, 31.8, 28.6, 27.5, 27.1, 25.4, 20.2, 18.0, 13.8.
Hydroxy bicycle 3.62:

I. To a stirred solution of the bicycle 3.60 (0.009 g, 0.024 mmol) in DCM (0.25 mL) at room temperature, was added triethylamine (0.019 g, 0.191 mmol) and TBSOTf (0.038 g, 0.144 mmol). Once the reaction was judged to be complete, it was quenched by the addition of saturated aqueous sodium bicarbonate (2 mL) and diluted with DCM (2 mL). The aqueous fraction was extracted further with DCM (3 X 2 mL) and the combined organic fractions were dried with MgSO₄ and concentrated in vacuo. The crude material (3.61) was used immediately in the next step with no further purification.

II. Crude silyl enol ether 3.61 was dissolved in DMF (0.5 mL) and 80% MMPP (0.030 g, 0.048 mmol) was added in one portion as a solid at room temperature. The reaction was run for about 2 hours at which point TLC indicated that no starting material remained. The reaction was diluted with water (2 mL) and EtOAc (2 mL). The aqueous layers were further extracted with EtOAc (3 X 5 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified on a silica gel column using EtOAc:Hexanes (1:1) as eluent, to provide 0.006 g of 3.62 for a 75% overall yield.

3.62: colorless oil; TLC (EtOAc: hexanes 1:1 v/v): Rᵣ = 0.1; ¹H NMR (600 MHz, CDCl₃) δ (ppm): 4.80 (d, J = 11.2 Hz, 1 H), 4.27 (d, J = 11.3 Hz, 1 H), 2.40 – 2.57 (m, 2 H), 2.32 (s, 1 H), 2.15 (d, J = 5.5 Hz, 1 H), 2.10 (q, J = 7.6 Hz, 1 H), 1.90 – 2.05 (m, 3 H), 1.80 – 1.89 (m, 2 H), 1.66 – 1.77 (m, 3 H), 1.48 – 1.55 (d, J = 13.5, 1 H), 1.25 (s, 3 H), 1.19 (d, J = 1.7 Hz, 3 H), 1.17 (s, 3 H). ¹³C NMR (151 MHz, CDCl₃) δ (ppm): 214.2, 171.7, 73.8, 68.4, 48.9, 48.8, 44.9, 41.4, 38.2, 32.1, 29.9, 28.9, 28.0, 27.7, 22.5, 20.1, 18.2, 15.7, (one carbonyl resonance missing).
Alcohol 3.63:
To a stirred solution of alcohol 3.54 (0.067 g, 0.220 mmol) in THF (2.2 mL) at 0 °C, was added a 1 M solution of LAH (0.440 mL, 0.440 mmol). After 10 minutes the reaction was cautiously quenched by the addition of saturated aqueous NH₄Cl (0.5 mL). The reaction was diluted with water (10 mL) and EtOAc (10 mL). The aqueous portion was washed with EtOAc (3 X 10 mL), dried over Na₂SO₄ and concentrated to dryness in vacuo. The compound was purified on silica gel using EtOAc/hexanes as eluent (1:1), to provide product alcohol in 77% yield (0.052 g). A crystal was grown for X-ray analysis.

3.63: white solid; TLC (EtOAc: hexanes 1:1 v/v): Rf = 0.2; ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.21 – 7.25 (m, 1 H), 7.20 (d, J = 7.5 Hz, 1 H), 7.08 (t, J = 7.7 Hz, 1 H), 5.69 – 5.78 (m, 1 H), 5.40 (dd, J = 2.7, 9.8 Hz, 1 H), 5.25 (d, J = 5.2 Hz, 1 H), 5.16 (d, J = 5.2 Hz, 1 H), 4.73 (d, J = 8.4 Hz, 1 H), 4.35 (dd, J = 6.4, 11.1 Hz, 1 H), 4.12 (dd, J = 6.0, 11.1 Hz, 1 H), 4.02 (d, J = 8.4 Hz, 1 H), 3.75 (s, 3 H), 2.88 (dd, J = 5.2, 17.8 Hz, 1 H), 2.63 (dt, J = 2.7, 17.7 Hz, 1 H), 2.42 (s, 3 H), 1.66 (s, 3 H), 1.12 (s, 3 H), 0.34 (s, 3 H); ¹³C NMR (126 MHz, CDCl₃) δ (ppm): 137.7, 137.6, 132.7, 131.4, 131.2, 130.4, 124.7, 121.6, 100.1, 79.9, 68.6, 58.3, 49.8, 38.5, 35.9, 30.0, 20.0, 18.6; X-ray structure.

Ester 3.64:
To a stirred solution of alcohol 3.63 (0.044 g, 0.144 mmol) in DCM (1.5 mL) at −78 °C, was added Hünig’s base (0.056 g, 0.432 mmol) and DMAP (0.001 g, 0.007 mmol) followed by acryloyl chloride (0.065 g, 0.72 mmol), under a nitrogen atmosphere. The starting material was determined to be consumed by TLC (EtOAc/Hexanes 1:3) instantly so the reaction was quenched with methanol (0.5 mL) then water (10 mL) and extracted
with EtOAc (3 X 25 mL) and dried with Na$_2$SO$_4$. The mixture was passed through a silica gel pad using EtOAc and evaporated to provide 53% of ester 3.64 (0.027 g) as a clear oil.

3.64: clear oil; TLC (EtOAc: hexanes 1:1 v/v): $R_f = 0.4$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 7.11 (dd, $J = 3.8$, 7.0 Hz, 2 H), 6.98 (d, $J = 7.7$ Hz, 1 H), 6.22 (d, $J = 17.2$ Hz, 1 H), 6.00 (dd, $J = 10.2$, 17.2 Hz, 1 H), 5.67 – 5.77 (m, 1 H), 5.63 (d, $J = 9.3$ Hz, 1 H), 5.28 – 5.42 (m, 1 H), 5.09 (q, $J = 5.4$ Hz, 2 H), 4.91 (d, $J = 11.3$ Hz, 1 H), 4.68 (dd, $J = 9.8$, 16.2 Hz, 2 H), 3.97 (d, $J = 8.3$ Hz, 1 H), 3.67 (s, 3 H), 2.75 – 2.91 (m, 1 H), 2.48 (s, 1 H), 2.33 (s, 3 H), 1.05 (s, 3 H), 0.25 (s, 3 H).

**Phenol 3.65:**

To a stirred solution of ester 3.64 (0.0.20 g, 0.056 mmol) in DCM (1.2 mL) at room temperature, was added Amberlyst 15 (0.020 g) and the solution was stirred for about 2 hours, when TLC (DCM/hexanes/AcOH, 2 mL :1 mL : 0.01 mL) detected no starting material remained. The Amberlyst 15 was filtered off and the solution was concentrated in vacuo to provide phenol 3.65 in 91% yield (0.514 g), pure enough for further use.

3.65: pale yellow oil; TLC (DCM/hexanes/AcOH 2:1: 0.01): $R_f = 0.2$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 10.74 (s, 1 H), 7.08 – 7.14 (m, 1 H), 7.02 (d, $J = 7.9$ Hz, 1 H), 6.79 (t, $J = 7.6$ Hz, 1 H), 6.59 (dd, $J = 1.3$, 17.2 Hz, 1 H), 6.27 (dd, $J = 10.4$, 17.3 Hz, 1 H), 6.03 (dd, $J = 1.2$, 10.4 Hz, 1 H), 5.69 – 5.78 (m, 1 H), 5.58 (d, $J = 11.8$ Hz, 1 H), 5.40 (dd, $J = 2.7$, 9.8 Hz, 1 H), 5.31 (d, $J = 5.1$ Hz, 1 H), 3.90 (d, $J = 4.8$ Hz, 1 H), 3.78 (d, $J = 11.9$ Hz, 1 H), 2.55 – 2.84 (m, 2 H), 2.31 (s, 3 H), 1.15 (s, 3 H), 0.59 (s, 3 H); $^{13}$C NMR
(126 MHz, CDCl$_3$) $\delta$ (ppm): 168.2, 155.1, 137.6, 132.7, 130.2, 128.0, 127.8, 127.5, 124.6, 120.9, 119.4, 79.0, 67.3, 48.3, 38.6, 33.6, 30.3, 19.0, 17.2.

**Bicycle 3.66:**

I. To a room temperature stirred solution of phenol 3.65 (0.023 g, 0.071 mmol) in acetic acid (0.70 mL) was added lead(IV)acetate (0.044 g, 0.100 mmol). The solution was stirred for about 30 minutes and TLC (EtOAc/hexanes 1:2) showed complete conversion to the dienone. The reaction was quenched with water (2 mL) and EtOAc (2 mL). The organic layer was separated, dried (MgSO$_4$), and evaporated *in vacuo* to give the crude dienone that was quickly purified on silica gel using EtOAc/hexanes (1:2) as eluent to provide the intermediate dienone.

**Intermediate dienone:** yellow oil; TLC (EtOAc:hexanes 1:2 v/v): $R_F = 0.3$.

II. A microwave vial reaction vessel was first treated with hexamethyldisilazane (1 mL) sealed and heated to reflux for 2 min. The vial was cooled, rinsed with acetone and dried under high vacuum. In the sealed pretreated vial, equipped with a magnetic stir bar, was added the intermediate dienone and BHT (0.001 mg, 0.005 mmol). The vial was capped and evacuated on high vacuum followed by backfilling with argon. To the vial was then added o-DCB (0.4 mL) and it was heated to 150 °C for 4 hours. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 1:2 EtOAc/hexanes, furnishing 3.66 (0.002 g, 5% two steps) as a white foam. A crystal was grown for X-ray crystallographic analysis.
3.66: white foam; TLC (EtOAc/hexanes 1:2): $R_F = 0.2$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 6.43 (dd, $J = 6.1$, 8.5 Hz, 1 H), 6.13 (d, $J = 8.5$ Hz, 1 H), 5.88 (dt, $J = 4.5$, 9.2 Hz, 1 H), 5.75 (d, $J = 9.8$ Hz, 1 H), 4.32 – 4.34 (m, 2 H), 4.22 (d, $J = 12.3$ Hz, 1 H), 3.53 (s, 1 H), 2.86 – 2.94 (m, 1 H), 2.76 – 2.83 (m, 2 H), 2.62 (dt, $J = 3.1$, 6.4 Hz, 1 H), 2.13 (ddd, $J = 2.0$, 4.0, 16.8 Hz, 1 H), 2.05 (ddd, $J = 3.0$, 8.8, 12.6 Hz, 1 H), 1.89 (ddd, $J = 2.7$, 6.0, 13.4 Hz, 1 H), 1.39 (s, 3 H), 1.18 (s, 3 H), 1.06 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): 174.4, 137.4, 135.9, 127.9, 125.6, 107.5, 95.1, 78.5, 74.3, 58.8, 45.2, 44.5, 37.1, 36.2, 30.7, 28.7, 26.5, 26.3, 23.7; X-ray structure.

Bis-ketal 3.67:

In a microwave vial, bicycle 3.60 (0.032 g, 0.086 mmol) was dissolved in chlorobenzene (1 mL) under argon, benzeneseleninic anhydride (0.124 g, 0.344 mmol) was added and the vial was sealed with a microwave cap. The resulting solution was heated to 110 ºC overnight (about 12 hours). The starting material was consumed after this amount of time. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the chlorobenzene was eluted (as evidenced by TLC), and the eluent was switched EtOAc/hexanes (1:4 to 2:3 to 1:1), furnishing 3.61 (0.011 g, 39%) as a white solid. A crystal was grown for X-ray crystallographic analysis.

3.67: white solid; TLC (EtOAc/hexanes 1:1): $R_F = 0.5$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 4.93 (d, $J = 12.8$ Hz, 1 H), 4.19 (d, $J = 12.8$ Hz, 1 H), 3.58 (s, 1 H), 3.18 (ddd, $J = 0.9$, 3.4, 15.6 Hz, 1 H), 2.77 (td, $J = 4.5$, 14.1 Hz, 1 H), 2.61 (t, $J = 2.9$ Hz, 1 H), 2.24 (ddd, $J = 3.8$, 11.4, 13.3 Hz, 1 H), 2.12 (dt, $J = 2.6$, 15.6 Hz, 1 H), 2.04 (dd, $J = 2.3$, 4.7 Hz, 1 H), 1.90 – 1.97 (m, 1 H), 1.65 – 1.73 (m, 1 H), 1.59 (ddd, $J = 4.8$, 11.0, 13.3 Hz, 2
H), 1.47 – 1.55 (m, 1 H), 1.41 – 1.46 (m, 1 H), 1.32 – 1.38 (m, 1 H), 1.15 (s, 3 H), 1.09 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): 208.7, 169.3, 118.4, 95.2, 78.7, 70.9, 54.8, 48.8, 42.4, 36.8, 35.5, 30.8, 26.6, 25.8, 22.0, 21.8, 18.8, 13.4; X-ray structure.

**Cycloadduct 3.81:**

To a stirred solution of 4,4-dimethylcyclohex-2-enone (3.82) (5.3 g, 42.73 mmol) and sodium bicarbonate (14.36 g, 170.92 mmol) in refluxing toluene (86 mL), was added dropwise, a solution of dibromoformoxime (26.0 g, 128.19 mmol) in toluene (86 mL) over one hour. The reaction was allowed to stir for 6 additional hours when TLC showed no remaining starting material. The reaction cooled to room temperature and filtered through a Celite pad that was washed with EtOAc (2 X 100 mL) and concentrated to give a crude residue. This residue was purified on silica gel using ether/hexane (1:4) as eluent to provide 7.02 g of cycloadduct 3.81 in 67% yield.

**3.81:** yellow oil; TLC (ether/hexanes 1:4): $R_F = 0.1$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 4.59 (dd, $J = 2.2$, 10.1 Hz, 1 H), 3.86 (d, $J = 10.2$ Hz, 1 H), 2.41 – 2.48 (m, 2 H), 2.07 – 2.16 (m, 1 H), 1.52 – 1.61 (m, 1 H), 1.13 (s, 3 H), 1.03 (s, 3 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm): 202.9, 135.9, 90.6, 61.9, 35.0, 32.6, 29.8, 25.5, 24.6; IR (film) $\nu_{\text{max}}$: 2962, 2875, 1716, 1474, 1234, 1088, 842 cm$^{-1}$; HRMS ($m/z$): [M+H]$^+$ calcd. for C$_9$H$_{12}$BrNO$_2$, 246.0124; found, 246.0125.

**Isoxazole 3.83:**

Isoxazole 3.83 was formed from compound 3.81 upon standing at ambient temperature under an air atmosphere.
3.83: yellow oil; TLC (EtOAc/hexanes 1:4): $R_f = 0.1$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 2.60 (dd, $J = 6.1$, 7.0 Hz, 2 H), 2.04 (dd, $J = 6.1$, 7.1 Hz, 2 H), 1.44 (s, 6 H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ (ppm): 190.7, 187.8, 138.1, 112.9, 37.4, 36.0, 33.9, 25.6.

**Arylated cycloadduct 3.84:**

Cycloadduct 3.81 (3.05 g, 12.40 mmol) was azeotropically dried with benzene then dried on high vacuum for a minimum of 15 minutes and backfilled with argon. Dry THF (62 mL) was then added and the flask was cooled to $-78^\circ$C and 1 M NaHMDS (14.88 mL, 14.88 mmol) was added, resulting in a dark colored solution. The solution was stirred for 15 minutes at $-78^\circ$C when triaryl(bismuth) dichloride 3.19 (10.0 g, 13.63 mmol) was added in 136 mL of dry THF. The cooling bath was then removed and the reaction flask was allowed to slowly warm to room temperature causing a color change to maroon and then to pale yellow. After the reaction had reached room temperature it was stirred for 1 hour then quenched by dilution with EtOAc (100 mL). The solution was filtered through a Celite pad and concentrated in vacuo to provide a crude residue. This residue purified using silica gel chromatography using EtOAc/hexanes (1:9) as eluent to obtain arylated product 3.84 in 39% yield (1.91 g).

3.84: yellow oil; TLC (ether/hexanes 1:4): $R_f = 0.5$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.16 – 7.22 (m, 1 H), 7.05 (t, $J = 7.7$ Hz, 1 H), 6.92 – 9.97 (m, 1 H), 4.83 (dd, $J = 0.8$, 5.7 Hz, 1 H), 4.72 (dd, $J = 0.8$, 5.6 Hz, 1 H), 4.66 (d, $J = 1.3$ Hz, 1 H), 3.55 (s, 3 H), 2.88 (ddd, $J = 5.7$, 9.7, 16.7 Hz, 1 H), 2.47 – 2.55 (m, 1 H), 2.37 (s, 3 H), 1.97 (ddd, $J = 5.0$, 9.6, 14.4 Hz, 1 H), 1.76 – 1.88 (m, 1 H), 1.11 (s, 3 H), 0.99 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 205.1, 152.9, 143.8, 132.9, 132.0, 131.5, 126.8, 124.6, 99.3, 70.1,
57.6, 53.6, 37.0, 33.4, 33.0, 26.5, 24.7, 18.0; IR (film) \( \nu_{\text{max}} \) 2961, 1713, 1462, 1163, 1076, 1038, 931 cm\(^{-1}\); HRMS \((m/z)\): \([\text{M+H}]^+\) calcd. for C\(_{18}\)H\(_{22}\)BrNO\(_4\), 396.0805; found, 396.0818.

**Hemiketal 3.80:**

To a very rapidly stirred solution of arylated cycloadduct 3.84 (0.935 g, 2.37 mmol) in THF (12 mL) at room temperature was added 12 mL of 1 \(M\) aqueous HCl. The reaction was stirred until all of the starting material had been converted to product. Water (50 mL) and EtOAc (50 mL) were added to the flask and the aqueous layer was extracted with EtOAc (3 X 50 mL), the combined organic extracts were dried with MgSO\(_4\) and concentrated in vacuo. The crude material was chromatographed using EtOAc/hexanes (1:4) to give 0.429 g of hemiketal 3.80 in 52% yield.

3.80: colorless oil; TLC (EtOAc/hexanes 1:4): \( R_F = 0.4 \); \(^1\)H NMR (500 MHz, CDCl\(_3\) ) \( \delta \) (ppm): 7.11 (dd, \( J = 1.3, 7.4 \) Hz, 1 H), 6.95 (dd, \( J = 1.4, 7.6 \) Hz, 1 H), 6.90 (t, \( J = 7.5 \) Hz, 1 H), 4.47 (s, 1 H), 3.52 (s, 1 H), 2.23 (s, 3 H), 2.04 – 2.09 (m, 1 H), 1.82 – 2.00 (m, 2 H), 1.26 – 1.34 (m, 1 H), 1.19 (s, 3 H), 0.77 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\) ) \( \delta \) (ppm): 155.9, 144.3, 132.1, 124.4, 121.7, 121.2, 121.1, 110.0, 90.5, 66.7, 33.0, 31.8, 29.9, 27.0, 25.4, 15.3; IR (film) \( \nu_{\text{max}} \); 3435, 2960, 2928, 2870, 1712, 1599, 1456, 1138, 1082, 908, 892, 728 cm\(^{-1}\); HRMS \((m/z)\): \([\text{M+H}]^+\) calcd. for C\(_{16}\)H\(_{18}\)BrNO\(_3\), 352.0543; found, 352.0541.
Primary amine 3.79:

Hemiketal 3.80 (0.429 g, 1.22 mmol) was dissolved in THF (22 mL). Water (2.4 mL) and boric acid (0.756 g, 12.22 mmol) were added. Prewashed (5 times with distilled water) Raney nickel (about 2 g) was added and a hydrogen balloon was placed on the flask. This suspension was stirred overnight at room temperature, at which point TLC indicated that starting material had been consumed. The reaction was diluted with EtOAc (20 mL) and filtered through a Celite pad, prepared with EtOAc, to remove the nickel. The filter pad was washed with EtOAc (3 x 20 mL) and methanol (3 x 10 mL). The resulting filtrate was diluted with water (150 mL). This biphasic mixture was shaken vigorously in a separatory funnel and the layers were separated. Next, the pH of the aqueous layer was confirmed to be acidic (pH ~ 4). The EtOAc was set aside and the pH of the aqueous layer was adjusted to pH ~ 9 by addition of saturated aqueous NaHCO₃. The aqueous layer was then extracted with DCM (3 x 100 mL). The DCM layer was dried with Na₂SO₄ and concentrated in vacuo to give 64% of amine 3.79 (0.216 g, 0.780 mmol) as a crude yellow oil that was pure enough to be used in the next step. The EtOAc was also dried with Na₂SO₄ and concentrated in vacuo to provide nitrile 3.86 (0.078 g, 0.275 mmol), which could be resubmitted to these conditions to afford amine 3.79.

3.79: pale yellow oil; TLC (methanol/DCM 1:9): Rₛ = 0.1; ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.02 (d, J = 7.0 Hz, 2 H), 6.81 (t, J = 7.4 Hz, 1 H), 3.77 (d, J = 12.6 Hz, 1 H), 3.23 (d, J = 12.8 Hz, 1 H), 3.08 (s, 1 H), 2.25 (s, 3 H), 2.18 – 2.24 (m, 1 H), 2.10 (d, J = 13.3 Hz, 1 H), 1.53 (s, 1 H), 1.41 – 1.51 (m, 1 H), 0.99 (s, 3 H), 0.88 (s, 3 H); ¹³C NMR (151 MHz, CDCl₃) δ (ppm): 156.2, 131.7, 130.2, 121.8, 120.4, 120.4, 113.6, 82.1, 54.7, 38.9, 34.6, 34.0, 30.5, 29.9, 20.5, 15.5; IR (film) νₘₐₓ 3358, 3313, 2950, 2868, 2244, 1595,
3.86: pale yellow oil; TLC (EtOAc/hexanes 1:4): $R_F = 0.3$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.35 (d, $J = 7.3$ Hz, 1 H), 7.12 (d, $J = 7.6$ Hz, 1 H), 6.95 (t, $J = 7.5$ Hz, 1 H), 2.97 (s, 1 H), 2.28 – 2.33 (m, 1 H), 2.24 (s, 3 H), 2.21 (dd, $J = 4.9$, 14.1 Hz, 1 H), 1.57 – 1.64 (m, 1 H), 1.48 – 1.56 (m, 1 H), 1.21 (s, 3 H), 0.99 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): 154.1, 131.8, 128.8, 122.5, 122.2, 122.1, 117.4, 109.1, 82.2, 55.6, 34.8, 34.0, 29.8, 29.0, 28.7, 17.4; LRMS ($m/z$): [M+H]$^+$ calcd. for C$_{16}$H$_{23}$NO$_3$, 274.2; found, 274.2.

**Diol 3.88:**

I. To a stirred solution of amine 3.79 (0.005 g, 0.0180 mmol) in acetic acid (0.36 mL) at room temperature, was added sodium nitrite (0.012 g, 0.180 mmol) as a solid. After 30 minutes TLC indicated that the starting material had been completely consumed. The reaction was diluted with EtOAc (2 mL) and washed with water (3 X 1 mL). The EtOAc was dried with Na$_2$SO$_4$ and concentrated in vacuo to remove the solvent and residual acetic acid.

II. The residue was then dissolved in methanol (0.36 mL) at room temperature and potassium carbonate (0.005 g, 0.036 mmol) was added. After 30 minutes TLC indicated that the starting material had been completely consumed. The reaction was diluted with water (2 mL) and EtOAc (2 mL) and the aqueous layer was extracted with EtOAc (3 X 2 mL). The combined organic extracts were dried with Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified using preparatory-TLC and EtOAc/hexanes (1:3) as eluent. Yield not determined.
3.88: colorless oil; TLC (EtOAc/hexanes 1:3): $R_f$ = 0.1; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.06 (d, $J$ = 7.4 Hz, 1 H), 7.03 (d, $J$ = 7.6 Hz, 1 H), 6.84 (t, $J$ = 7.4 Hz, 1 H), 5.54 (s, 1 H), 4.27 (dd, $J$ = 4.2, 12.6 Hz, 1 H), 4.07 – 4.20 (m, 1 H), 3.45 (d, $J$ = 3.3 Hz, 1 H), 3.01 (d, $J$ = 7.1 Hz, 1 H), 2.24 (s, 3 H), 2.03 – 2.15 (m, 2 H), 1.61 – 1.72 (m, 1 H), 1.37 – 1.45 (m, 1 H), 1.02 (s, 3 H), 0.85 (s, 3 H).

Acrylate ester 3.78:

Amine 3.79 (0.031 g, 0.136 mmol) was dissolved in acetonitrile (1.36 mL) and cooled to 0 ºC. To this solution was added acrylic acid (0.098 g, 1.36 mmol) followed by sodium nitrite (0.038 g, 0.544 mmol). The cooling bath was then removed and the solution was warmed to room temperature. When it had reached room temperature, the amine starting material was determined to be consumed by TLC using EtOAc/hexanes (1:3) as eluent. The reaction was diluted with water (2 mL) and EtOAc (2 mL) and the aqueous was extracted with EtOAc (3 X 2 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude material was purified with a silica gel column using EtOAc/hexanes (1:4) as eluent to provide ester 3.78 in 27 % yield (0.012 g).

3.78: colorless oil; TLC (EtOAc/hexanes 1:3): $R_f$ = 0.2; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.03 (d, $J$ = 7.4 Hz, 2 H), 6.82 (t, $J$ = 7.5 Hz, 1 H), 6.24 (d, $J$ = 17.4 Hz, 1 H), 5.98 (dd, $J$ = 10.5, 17.3 Hz, 1 H), 5.76 (d, $J$ = 10.5 Hz, 1 H), 5.06 (d, $J$ = 11.9 Hz, 1 H), 4.61 (d, $J$ = 12.0 Hz, 1 H), 4.00 (s, 1 H), 3.14 (d, $J$ = 5.2 Hz, 1 H), 2.25 (s, 3 H), 2.16 – 2.25 (m, 2 H), 2.01 – 2.10 (m, 1 H), 1.96 (d, $J$ = 5.8 Hz, 1 H), 1.41 – 1.54 (m, 1 H), 1.00 (s, 3 H), 0.91 (s, 3 H).
**α-methoxy acrylate ester 3.90:**

Amine 3.79 (0.017 g, 0.075 mmol) was dissolved in acetonitrile (0.75 mL) and cooled to 0 ºC. To this solution was added α-methoxy acrylic acid (0.107 g, 1.048 mmol) followed by sodium nitrite (0.041 g, 0.60 mmol). The cooling bath was then removed and the solution was warmed to room temperature. When it had reached room temperature, the amine starting material was determined to be consumed by TLC using EtOAc/hexanes (1:4) as eluent. The reaction was diluted with water (2 mL) and EtOAc (2 mL) and the aqueous layer was extracted with EtOAc (3 X 2 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified with a silica gel column using EtOAc/hexanes (1:4) as eluent to provide ester 3.90 in 15 % yield (0.004 g).

**3.90:** colorless oil; TLC (EtOAc/hexanes 1:4): R<sub>f</sub> = 0.2; 'H NMR (600 MHz, CDCl₃) δ (ppm): 7.06 (d, J = 7.5 Hz, 1 H), 7.03 (d, J = 7.6 Hz, 1 H), 6.83 (t, J = 7.5 Hz, 1 H), 5.10 (d, J = 12.1 Hz, 1 H), 5.08 (d, J = 2.9 Hz, 1 H), 4.65 (d, J = 11.9 Hz, 1 H), 4.51 (d, J = 2.8 Hz, 1 H), 4.00 (s, 1 H), 3.56 (s, 3 H), 3.14 (d, J = 5.1 Hz, 1 H), 2.25 (s, 3 H), 2.17 – 2.24 (m, 2 H), 2.07 (dd, J = 6.9, 11.5 Hz, 2 H), 1.01 (s, 3 H), 0.92 (s, 3 H).

**Diethylphosphono acetate ester 3.91:**

Amine 3.79 (0.110 g, 0.397 mmol) was dissolved in acetonitrile (4.0 mL) and cooled to 0 ºC. To this solution was added diethylphosphono acetic acid (0.234 g, 1.19 mmol) followed by sodium nitrite (0.055 g, 0.794 mmol). The cooling bath was then removed and the solution was warmed to room temperature. When it had reached room temperature, the amine starting material was determined to be consumed by TLC using EtOAc/hexanes (1:1) as eluent. The reaction was diluted with water (5 mL) and EtOAc
(5 mL) and the aqueous layer was extracted with EtOAc (3 X 5 mL), dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude material was purified with a silica gel column using EtOAc/hexanes (1:1 to 100% EtOAc) as eluent to provide ester 3.91 in 31% yield (0.055 g).

**3.91**: colorless oil; TLC (100% EtOAc): $R_f$ = 0.5; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm):

\[
\begin{align*}
7.05 & (d, J = 7.4 \text{ Hz}, 1 \text{ H}),
7.00 & (d, J = 7.5 \text{ Hz}, 1 \text{ H}),
6.81 & (t, J = 7.5 \text{ Hz}, 1 \text{ H}),
4.98 & (d, J = 11.6 \text{ Hz}, 1 \text{ H}),
4.61 & (d, J = 11.5 \text{ Hz}, 1 \text{ H}),
3.93 - 4.08 & (m, 1 \text{ H}),
3.81 - 3.93 & (m, 3 \text{ H}),
3.10 & (s, 1 \text{ H}),
2.73 - 2.92 & (m, 2 \text{ H}),
2.24 & (s, 3 \text{ H}),
2.20 & (d, J = 14.7 \text{ Hz}, 1 \text{ H}),
2.05 & (d, J = 18.7 \text{ Hz}, 1 \text{ H}),
1.51 & (tt, J = 6.5, 12.0 \text{ Hz}, 2 \text{ H}),
1.21 & (q, J = 7.5 \text{ Hz}, 6 \text{ H}),
0.99 & (s, 3 \text{ H}),
0.89 & (s, 3 \text{ H});
\end{align*}
\]

$^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): (phosphonate rotamers present) 165.2, 165.2, 154.9, 131.9, 130.0, 122.0, 121.3, 120.8, 111.1, 82.3, 63.0, 62.9, 62.9, 62.8, 62.4, 56.7, 35.0, 34.5, 34.1, 33.6, 29.7, 29.2, 20.0, 16.4, 16.3, 15.4; IR (film) $\nu_{\text{max}}$ 3377, 2926, 2860, 1739, 1464, 1394, 1261, 1025, 974 cm$^{-1}$; HRMS ($m/z$): [M+Na]$^+$ calcd. for C$_{22}$H$_{33}$O$_8$P, 479.1805; found, 479.1805.

**Diazooester 3.95:**

To a stirred solution of diethylphosphono acetate ester 3.91 (0.033 g, 0.75 mmol) in acetonitrile (0.8 mL) at 0 °C, was added $p$-ABSA (0.020 g, 0.082 mmol) followed by DBU (0.013 g, 0.082 mmol). The solution was monitored by TLC using EtOAc/hexanes (1:1) and it was determined that after 1 hour the starting material was consumed. The reaction was quenched by the addition of saturated aqueous NH$_4$Cl (2 mL) and was diluted with EtOAc (5 mL). The aqueous layer was extracted further with EtOAc (3 X 3 mL) and the combined organic extracts were dried over Na$_2$SO$_4$ and concentrated *in vacuo*. 

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The crude material was purified on a silica gel column using EtOAc/hexanes (1:1) as eluent to provide 0.015 g of diazo ester 3.95 in 41% yield.

3.95: pale yellow oil; TLC (EtOAc/hexanes 1:1): $R_F = 0.3$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 7.03 (dd, $J = 1.3$, 7.4 Hz, 1 H), 6.98 – 7.01 (m, 1 H), 6.80 (t, $J = 7.5$ Hz, 1 H), 5.34 (d, $J = 11.6$ Hz, 1 H), 5.15 (s, 1 H), 4.51 (d, $J = 11.6$ Hz, 1 H), 3.85 – 3.99 (m, 1 H), 3.69 – 3.76 (m, 2 H), 3.62 – 3.69 (m, 1 H), 3.05 (d, $J = 5.4$ Hz, 1 H), 2.24 (s, 3 H), 1.91 (d, $J = 5.4$ Hz, 1 H), 1.46 – 1.56 (m, 2 H), 1.18 (dt, $J = 7.1$, 14.2 Hz, 6 H), 0.98 (s, 3 H), 0.91 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): (phosphonate rotamers present) 164.0, 163.9, 155.0, 131.4, 130.0, 129.9, 126.6, 121.6, 121.5, 120.8, 111.3, 82.8, 63.5, 63.5, 61.9, 57.4, 34.5, 33.7, 29.7, 28.7, 19.6, 16.2, 16.2, 16.2, 16.1, 15.4.

**Insertion product 3.96:**

Diazoo ester 3.95 (0.008 g, 0.017 mmol) was dissolved in dry degassed benzene (1.7 mL) in a microwave vial under an argon atmosphere. To this solution was added rhodium(II) acetate (0.0003 g, 0.00086 mmol), the vial was sealed and it was placed in a preheated oil bath at 80 ºC. After about 2 hours the starting material was consumed. The reaction vessel was cooled the cap was removed and the rhodium solids were removed by filtration through Celite using EtOAc as eluent. The solvent was evaporated in vacuo and the crude residue was purified on a preparatory-TLC plate using EtOAc/hexanes (2:1) as eluent to provide insertion product 3.96 (0.007 g) as a mixture of two epimers in 94% yield.

3.96: TLC (EtOAc/hexanes 2:1): $R_F = 0.2$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): major isomer: 7.05 – 7.09 (m, 1 H), 7.01 (d, $J = 9.3$ Hz, 1 H), 6.80 (t, $J = 7.5$ Hz, 1 H), 5.23 (d,
$J = 11.3 \text{ Hz, } 1 \text{ H}$, $5.10 (s, 1 \text{ H})$, $4.62 (d, J = 11.4 \text{ Hz, } 1 \text{ H})$, $4.49 (dd, J = 6.1, 16.4 \text{ Hz, } 1 \text{ H})$, $4.05 – 4.12 (m, 1 \text{ H})$, $3.82 – 3.95 (m, 3 \text{ H})$, $3.19 (d, J = 5.4 \text{ Hz, } 1 \text{ H})$, $2.24 (s, 3 \text{ H})$, $2.17 – 2.22 (m, 1 \text{ H})$, $2.09 – 2.16 (m, 1 \text{ H})$, $1.53 – 1.58 (m, 1 \text{ H})$, $1.48 – 1.53 (m, 1 \text{ H})$, $1.21 – 1.24 (m, 6 \text{ H})$, $1.01 (s, 3 \text{ H})$, $0.87 (s, 3 \text{ H})$; $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ (ppm): both isomers: $169.1, 169.1, 155.0, 154.9, 132.3, 131.2, 130.2, 130.1, 122.1, 121.6, 121.5, 121.1, 120.9, 120.8, 111.0, 110.9, 82.7, 81.7, 69.3, 69.2, 68.2, 68.1, 64.3, 64.3, 64.3, 64.1, 64.1, 64.0, 64.0, 63.7, 63.7, 63.0, 57.0, 56.3, 34.6, 34.4, 33.8, 33.2, 30.1, 29.8, 29.8, 29.6, 28.6, 20.6, 19.6, 16.5, 16.5, 16.4, 16.4, 16.4, 16.3, 15.4, 15.4; HRMS ($m/z$): $[M+H]^+$ calcd. for C$_{22}$H$_{31}$O$_8$P, 455.1829; found, 455.1837.

Vinyl Ether 3.98:

Insertion product 3.96 (0.010 g, 0.022 mmol) was placed in a flame dried microwave vial, dissolved in dry THF (0.044 mL) and cooled to 0 °C. To this stirred solution was added 0.023 mL of 3.0 M MeMgBr in THF. After the addition was complete a suspension of azeotropically dried paraformaldehyde (0.066 g, 0.22 mmol) in THF (0.44 mL) was added. The sealed vial was then heated to 60 °C in an oil bath until the starting material was consumed as determined by TLC. When the reaction was complete the reaction was cooled passed through a Celite plug and concentrated. The crude residue was purified using preparatory-TLC to provide approximately 0.0005 g of vinyl ether 3.98.

3.98: $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): $7.10 (d, J = 7.4 \text{ Hz, } 1 \text{ H})$, $7.02 (d, J = 7.5 \text{ Hz, } 1 \text{ H})$, $6.88 (t, J = 7.5 \text{ Hz, } 1 \text{ H})$, $5.55 (s, 1 \text{ H})$, $5.19 (s, 1 \text{ H})$, $5.05 (d, J = 12.2 \text{ Hz, } 1 \text{ H})$, $4.85 (d, J = 12.2 \text{ Hz, } 1 \text{ H})$, $3.19 (d, J = 5.0 \text{ Hz, } 1 \text{ H})$, $2.28 – 2.42 (m, 2 \text{ H})$, $2.17 (s, 3 \text{ H})$, $\ldots$
2.00 (d, $J = 5.5$ Hz, 1 H), 1.59 – 1.67 (m, 1 H), 1.41 – 1.51 (m, 1 H), 0.97 (s, 3 H), 0.93 (s, 3 H).

**Benzofuran 3.99:**

To a stirred solution of phosphonate ester 3.91 (0.002 g, 0.0045 mmol) in trimethylorthoformate (0.3 mL) was added catalytic (~ 5 mol %, single small crystal) of toluenesulfonic acid at room temperature. After 30 minutes TLC using DCM/ether (1:1) indicated that the starting material had been consumed. The reaction was quenched with saturated aqueous sodium bicarbonate (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 X 1 mL) and the combined organic fractions were dried using Na$_2$SO$_4$ and evaporated in vacuo. The crude residue was subjected to a preparatory-TLC to provide approximately 0.001 g of benzofuran 3.99.

3.99: TLC (DCM/ether 1:1): $R_f = 0.4$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 7.38 (d, $J = 7.7$ Hz, 1 H), 7.11 (t, $J = 7.6$ Hz, 1 H), 7.03 (d, $J = 7.2$ Hz, 1 H), 5.26 (s, 2 H), 4.08 (p, $J = 7.2$ Hz, 4 H), 3.90 (s, 1 H), 3.53 (d, $J = 0.9$ Hz, 6 H), 2.96 (d, $J = 21.5$ Hz, 2 H), 2.76 – 2.88 (m, 2 H), 2.49 (s, 3 H), 1.67 – 1.77 (m, 2 H), 1.19 – 1.32 (m, 6 H), 0.98 (s, 6 H).

**Bis-silylated compound 3.101:**

Diethylphosphono acetate ester 3.91 (0.0065 g, 0.0148 mmol) was dissolved in DCM (0.2 mL) at 0 °C. Triethylamine (0.0045 g, 0.044 mmol) was added, followed by TMSOTf (0.0045 g, 0.0148 mmol). After 30 minutes the reaction was quenched by the addition of saturated aqueous NH$_4$Cl (1 mL) and DCM (1 mL). The layers were separated and the organic layer was dried over MgSO$_4$, concentrated in vacuo and
purified using preparatory-TLC to provide approximately 0.002 g of bis-silylated compound 3.101.

**3.101:** $^1$H NMR (600 MHz, CDCl$_3$) δ (ppm): 6.96 (t, $J = 7.8$ Hz, 2 H), 6.75 (t, $J = 7.4$ Hz, 1 H), 4.60 – 4.67 (m, 2 H), 4.09 – 4.21 (m, 4 H), 3.12 (s, 1 H), 2.84 (d, $J = 21.4$ Hz, 2 H), 2.22 (s, 3 H), 2.06 – 2.13 (m, 1 H), 2.00 (dd, $J = 6.0$, 11.5 Hz, 1 H), 1.37 – 1.46 (m, 2 H), 1.33 (td, $J = 2.3$, 7.2 Hz, 6 H), 0.93 (s, 3 H), 0.82 (s, 3 H), −0.03 (s, 9 H), −0.04 (s, 9 H).

**Bis-acetylated compound 3.102:**

Diethylphosphono acetate ester 3.91 (0.0044 g, 0.010 mmol) was dissolved in pyridine (0.1 mL) at room temperature. Catalytic DMAP (small crystal) was added followed by acetic anhydride (0.1 mL). The reaction was stirred overnight (about 12 hours) and was then quenched by the addition of saturated aqueous NH$_4$Cl (1 mL) and EtOAc (1 mL). The layers were separated and the organic layer was dried over MgSO$_4$, concentrated *in vacuo* and purified using preparatory-TLC to provide approximately 0.002 g of bis-acetylated compound 3.102.

**3.102:** $^1$H NMR (600 MHz, CDCl$_3$) δ (ppm): 7.01 (d, $J = 7.4$ Hz, 1 H), 6.91 (d, $J = 7.4$ Hz, 1 H), 6.81 (t, $J = 7.4$ Hz, 1 H), 4.81 (s, 1 H), 4.79 (d, $J = 11.7$ Hz, 1 H), 4.55 (d, $J = 11.6$ Hz, 1 H), 4.01 – 4.23 (m, 4 H), 3.10 (dt, $J = 4.2$, 15.1 Hz, 1 H), 2.90 (d, $J = 21.4$ Hz, 2 H), 2.35 (t, $J = 7.5$ Hz, 1 H), 2.24 (s, 3 H), 2.13 (s, 3 H), 1.96 (s, 3 H), 1.42 (d, $J = 5.5$ Hz, 1 H), 1.26 – 1.31 (m, 6 H), 0.99 (s, 3 H), 0.76 (s, 3 H).
Methoxy ketal 3.103:

To a stirred solution of arylated compound 3.80 (0.032 g, 0.081 mmol) in methanol (0.2 mL) and trimethylorthoformate (0.2 mL), was added toluenesulfonic acid (0.003 g, 0.0162 mmol). The vial was sealed and heated to 60 °C overnight (about 12 hours). After that time 0.015 g (1 equiv.) of additional toluenesulfonic acid was added and the vial was heated to 70 °C for 2 hours. At this time the starting material had been consumed so the reaction vessel was cooled to room temperature and quenched by the addition of 1 M NaOH (0.5 mL) and dilution with ether (1 mL). The aqueous layer was extracted with ether (3 X 1 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified on a silica gel column using ether/hexanes (1:9) as eluent to provide 0.007 g of methoxy ketal 3.103 in 25% yield.

3.103: colorless oil; TLC (EtOAc/hexanes 1:4): \( R_F = 0.8 \); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) (ppm): 7.11 (dt, \( J = 0.8, 7.3 \) Hz, 1 H), 6.94 (dd, \( J = 1.1, 7.0 \) Hz, 1 H), 6.89 (t, \( J = 7.5 \) Hz, 1H ), 4.41 (d, \( J = 1.4 \) Hz, 1 H), 3.53 (s, 3 H), 2.32 (ddd, \( J = 1.8, 5.2, 14.4 \) Hz, 1 H), 2.24 (s, 3 H), 1.56 – 1.81 (m, 2 H), 1.21 – 1.28 (m, 1 H), 1.18 (s, 3 H), 0.79 (s, 3 H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) (ppm): 156.4, 145.5, 131.9, 124.8, 121.5, 121.2, 121.2, 112.6, 90.4, 67.7, 51.1, 31.9, 29.6, 26.9, 25.8, 25.4, 15.2; IR (film) \( \nu_{max} \) 2959, 2924, 2868, 1598, 1464, 1259, 1205, 1147, 1094, 928, 891, 742 cm\(^{-1}\); HRMS (m/z): [M+H]\(^+\) calcd. for C\(_{17}\)H\(_{20}\)BrNO\(_3\), 366.0699; found, 366.0696.

Dienone 3.107:

To a room temperature stirred solution of ester 3.78 (0.0048 g, 0.014 mmol) in acetic acid (0.5 mL) was added lead(IV)acetate (0.010 g, 0.022 mmol). The solution was stirred for
about 30 minutes and TLC (EtOAc/hexanes 1:1) showed complete conversion to the dienone. The reaction was quenched with water (2 mL) and EtOAc (2 mL). The organic layer was separated, dried (MgSO₄), and evaporated in vacuo to give a residue (about 0.005 g, 88% yield) that was pure enough for use in the next step.

3.107: yellow oil; TLC (EtOAc:hexanes 1:1 v/v): Rᵢ = 0.2; ¹H NMR (500 MHz, CDCl₃) δ (ppm): 6.76 (dd, J = 1.9, 6.7 Hz, 1 H), 6.39 (dd, J = 1.4, 17.3 Hz, 1 H), 6.23 – 6.31 (m, 2 H), 6.06 (dd, J = 10.4, 17.3 Hz, 1 H), 5.84 (dd, J = 1.4, 10.4 Hz, 1 H), 4.89 (d, J = 11.9 Hz, 1 H), 4.33 (d, J = 11.9 Hz, 1 H), 4.15 (d, J = 3.9 Hz, 1 H), 3.30 (d, J = 5.2 Hz, 1 H), 2.53 (ddd, J = 6.0, 10.4, 14.8 Hz, 1 H), 2.39 (ddd, J = 5.2, 6.0, 14.8 Hz, 1 H), 2.07 (s, 3 H), 1.92 – 2.20 (m, 1 H), 1.40 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H).

**Bicycle 3.108:**

A microwave vial reaction vessel was first treated with hexamethyldisilazane (1 mL) sealed and heated to reflux for 2 min. The vial was cooled, rinsed with acetone and dried under high vacuum. In the sealed pretreated vial, equipped with a magnetic stir bar, was added 3.107 (0.0023 g, 0.006 mmol) and BHT (small crystal). The vial was capped and evacuated on high vacuum followed by backfilling with argon. To the vial was then added toluene (0.2 mL) and it was heated to 110 ºC for 2 hours. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 1:1 EtOAc/hexanes furnishing 3.108.

3.108: colorless oil; ¹H NMR (600 MHz, CDCl₃) δ (ppm): = 9.43 (d, J = 1.1 Hz, 1 H), 6.95 – 6.99 (m, 1 H), 6.27 (d, J = 3.2 Hz, 1 H), 6.00 (s, 1 H), 5.84 (s, 1 H), 3.34 (s, 1 H),
Bicycle 3.110 or 3.111:
I. Dienone 3.107 (0.0036 g, 0.011 mmol) was dissolved in pyridine (0.1 mL) at room temperature. Catalytic DMAP (small crystal) was added followed by acetic anhydride (0.1 mL). The reaction was stirred overnight (about 12 hours) and was then quenched by the addition of saturated aqueous NH$_4$Cl (1 mL) and EtOAc (1 mL). The layers were separated and the organic layer was dried over MgSO$_4$, concentrated in vacuo and purified using preparatory-TLC to provide approximately 0.003 g of the corresponding acetylated compound 3.109. This compound was used directly in the next step without isolation or purification.

II. A microwave vial reaction vessel was first treated with hexamethyldisilazane (1 mL) sealed and heated to reflux for 2 min. The vial was cooled, rinsed with acetone and dried under high vacuum. In the sealed pretreated vial, equipped with a magnetic stir bar, was added 3.109 (0.003 g, 0.007 mmol) and BHT (small crystal). The vial was capped and evacuated on high vacuum followed by backfilling with argon. To the vial was then added toluene (0.2 mL) and it was heated to 140 ºC for 2 hours. The reaction mixture was directly loaded on a silica gel column. The column was eluted with hexanes until the BHT was eluted (as evidenced by TLC), and the eluent was switched to 1:1 EtOAc/hexanes furnishing bicycle 3.110 or 3.111 (unclear from NMR which isomer).

3.110 or 3.111: colorless oil; TLC (EtOAc/hexanes 1:1): $R_f = 0.6$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 6.48 (t, $J = 7.8$ Hz, 1 H), 5.93 (d, $J = 8.7$ Hz, 1 H), 5.15 (d, $J = 1.8$ Hz, 1
H), 4.77 (dd, $J = 1.6, 12.1$ Hz, 1 H), 4.47 (d, $J = 11.9$ Hz, 1 H), 4.12 (d, $J = 8.8$ Hz, 1 H), 3.63 – 3.72 (m, 1 H), 2.82 (dd, $J = 6.3, 19.7$ Hz, 1 H), 2.42 (ddd, $J = 7.4, 12.1, 19.6$ Hz, 1 H), 2.35 (dt, $J = 3.7, 13.1$ Hz, 1 H), 2.17 (s, 3 H), 2.07 (s, 3 H), 2.01 (d, $J = 9.4$ Hz, 1 H), 1.67 (d, $J = 14.9$ Hz, 2 H), 1.54 (s, 3 H), 1.02 (s, 3 H), 0.97 (s, 3 H).

**Bicycle 3.112:**

To a stirred solution of bicycle 3.110 (0.002 g, 0.005) in EtOAc (2 mL) and Pd/C (spatula tip) was bubbled H$_2$ for 1 hour and then stirred under a hydrogen atmosphere for 16 h until complete conversion was detected by TLC. N$_2$ was then bubbled through the solution to purge out any residual H$_2$. The solution was filtered through a pad of Celite and concentrated to give bicycle 3.112 (0.002 g) as a colorless foam.

**3.112:** TLC (EtOAc/hexanes 1:1): $R_F = 0.6$; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ (ppm): 5.10 (s, 1 H), 4.75 (d, $J = 12.1$ Hz, 1 H), 4.41 (d, $J = 12.0$ Hz, 1 H), 4.19 (d, $J = 10.7$ Hz, 1 H), 2.82 (dd, $J = 6.4, 19.7$ Hz, 1 H), 2.66 (s, 1 H), 2.52 (d, $J = 14.0$ Hz, 1 H), 2.35 (ddd, $J = 7.5, 12.5, 19.9$ Hz, 1 H), 2.13 – 2.26 (m, 2 H), 2.12 (s, 3 H), 2.05 (s, 3 H), 1.89 (t, $J = 12.6$ Hz, 1 H), 1.66 – 1.79 (m, 4 H), 1.25 (s, 3 H), 0.98 (s, 3 H), 0.90 (s, 3 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ (ppm): 214.3, 208.5, 174.8, 170.0, 169.9, 81.9, 77.0, 71.5, 59.0, 54.6, 38.8, 37.1, 36.6, 34.0, 31.9, 29.8, 29.2, 23.9, 22.3, 21.6, 20.8, 19.6.
Appendix to

Chapter 3: Spectra
OMOMMeCl₂Bi₃
Me

OAc

Me

OTBS

Me

O

Me

OAc

Me

OTBS

H

H

H

H

H

f (ppm)

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

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

0.0  0.5  1.0  1.5  2.0  2.5  3.0  3.5  4.0  4.5  5.0  5.5  6.0  6.5  7.0  7.5
\[
\text{Me} - \text{Me} - \text{MeOH} - \text{Me}
\]
TBSO
Me
Me
I

TBSO

Me

Me
(diastereomer 1)
Me

OAc

(diastereomer 1)
(diastereomer 2)
Me

HO

CN

Me

Me

Me

OH

HO

CNMeOMeMeOHHO
Me\text{OAc} \quad \text{(tentative diastereomer)}
(tentative diastereomer)
(tentative diastereomer)
Curriculum Vitae

Paul Krawczuk
pkrawczuk@gmail.com
Cellular: 302-561-4317
Work: 858-784-7372
10550 North Torrey Pines Road, BCC169
La Jolla, CA 92037

Professional Experience

July 2005-
La Jolla, CA
Present
The Scripps Research Institute: Laboratory of Prof. Phil S. Baran.
Ph.D. Candidate, Advisor-Phil S. Baran, Ph.D.
Conducted research on the total synthesis of maoecrystal V, a complex
diterpenoid natural product. Utilized all standard organic chemistry methods, in
addition to literature searching and instrumentation use (e.g. NMR, MS, IR).
Additionally served as webmaster and graphics design artist for the group.
Expected graduation in summer 2011.

May 2003-
NYU Chemistry: Laboratory of Prof. David I. Schuster, New
York, NY
May 2005
Undergraduate Researcher, Advisor-David I. Schuster, Ph.D.
Conducted research in organic and physical organic chemistry with a main
concentration on fullerene-porphyrin hybrid dyads. Designed target systems,
synthesized and tested these systems with analysis of the data. Gained
experience with synthetic methods, chromatography and purification,
instrumentation (e.g. NMR, UV VIS, MS, IR), and training new members.

Teaching Experience

April 2006-
La Jolla, CA
April 2009
The Scripps Research Institute: Heterocyclic Chemistry. La Jolla,
Teaching Assistant, Supervisor- Phil S. Baran, Ph.D.
Served as a teaching assistant and webmaster for a graduate course in
heterocyclic chemistry.

September 2004-
May 2005
NYU Chemistry: Organic Chemistry. New York, NY
Teaching Assistant, Supervisor- Morris Fishman, Ph.D.
Taught a recitation in the organic chemistry course. Lectured on basic topics of
organic chemistry such as naming, reactions, mechanisms, and synthesis.

Education

July 2005-
Present
Ph.D. Degree
The Scripps Research Institute
10550 North Torrey Pines Road. La Jolla, CA 92037
Advisor: Phil S. Baran Ph.D., July 2005-present

September 2001-
May 2005
B.S. Degree
New York University, College of Arts and Sciences
September 1998- High School
June 2001 Salesianum School, September 1997-June 2001
1801 North Broom Street, Wilmington, DE 19802

Publications


Awards/Honors

Daniel Koshland Fellowship, The Scripps Research Institute. October 2005
This Fellowship, is awarded to one first year student by the Scripps Research Institute who has demonstrated exceptional scientific ability.

Graduated Magna Cum Laude, NYU. May 2005

Harold Seidenstein Award, NYU. May 2005
Named after Dr. Harold Seidenstein, NYU class of 1934, awarded annually to a student who shows special ability in chemistry.

Phi Lamda Upsilon National Chemistry Honor Society, NYU. 2005

NYU Summer Undergraduate Research Fellowship, NYU. Summer 2003

Dean’s List, NYU. 2001-2005

College of Arts and Science Scholarship, NYU. 2001-2005

National Honor Society

Abstracts and Presentations

“Completely Conjugated Porphyrin-Fullerene Molecular Wires” Paul Krawczuk, Sean Vail, and David Schuster, 207th Electrochemical Society Meeting, Abstract #989, May 15-May 20, 2005, Quebec City, Canada

A Synthesis of the Carbon Skeleton of Maoecystal V

Paul J. Krawczuk, Niklas Schöne, and Phil S. Baran*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037
pbaran@scripps.edu

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ABSTRACT

An enantioselective synthesis of the maoecystal V (1) carbon skeleton is described. The key transformations include arylation of a 1,3-dicarbonyl compound with a triarylboron(V) dichloride species, oxidative dearomatization of a phenol, and a subsequent intramolecular Diels–Alder reaction.

Maoecystal V (1, Figure 1) was isolated and characterized in 2004 by Sun and co-workers from the Chinese medicinal herb Isodon eriocarpus. It possesses an unusual architecture rendering it the most modified naturally occurring eriocarpinoid isolated to date. The structure was confirmed by X-ray crystallographic analysis to contain five highly congested rings and seven stereocenters, two of which are adjacent all carbon quaternary centers located in its interior. One of these all carbon quaternary centers is also the bridgehead carbon of the [2.2.2]-bicyclooctanone motif. This paper reports an early approach to 1 pursued in our laboratory from November 2007 to May 2008.2

Our initial retrosynthesis, shown in Scheme 1A, began by disconnecting the tetrahydropyran ring and simplifying the enone of the A ring to an olefin leading to 2. Next, an intramolecular Diels–Alder4 disconnection of the bicyclic ring system would generate a cyclohexadiene acrylate conjugate 3. It was initially envisioned that styyl enol ether 3 could be used as the diene component in the Diels–Alder reaction. In order to construct this substrate via the corresponding enone 4, an oxidative coupling of enolates or related substrates was proposed (i.e., 5 + 6).5

(3) During this period, one of the corresponding authors of the preceding paper was employed as a postdoctoral associate (C.-C. Li) in this laboratory: Gong, J.; Liu, G.; Li, C.-C.; Yang, Z. Org. Lett. 2009, DOI: 10.1021/ol9014392. This work was reported in an NIH proposal (received 8/11/ 2008 and reviewed on 10/9/2008 by the BCMB-B study section) and a final report to the DFG (submitted 7/12/2009).
Initial studies (Scheme 1B) with a model system using β-keto aldehyde \( \beta \) and enol ether \( \alpha \) led to the generation of the C-10 quaternary center by treatment with cerium ammonium nitrate.\(^6\) Following reduction of the formyl group and esterification, silylation of the ketone under a variety of conditions led only to the undesired regiosymmetric dienol ether \( \delta \) (presumably due to the sterically hindered α-proton at C-9). To circumvent this problem, the diene was further dehydrogenated (Pd/C, \( \text{O}_2 \)) and the resulting aromatic moiety was oxidized using a Wessely oxidation? (Pd(OAc)\(_2\)) to furnish cyclohexadienone \( \tau \) in 59% yield. A Diels–Alder reaction delivered polycycle 11 in ca. 60% yield (3 mg scale) upon heating to 165 °C.\(^8\) X-ray crystallography confirmed the structure as that corresponding to the undesired regiosymmetric outcome (based on the position of the geminal dimethyl group relative to the bicyclic portion of the molecule). Encouraged by the outcome of the intramolecular


Diels–Alder, a revised route was devised to access the correct carbon framework found in I (Scheme 1C).

The sequence begins with β-keto aldehyde 12, derived in three steps from a readily available symmetrical 1,3-diketone.2 Barton arylation3 of 12 with 13 led to 14 in 67% yield as a 7:3 readily separable mixture of diastereomers. In a fashion similar to that of the model study, reduction (to afford 15) and acylation led to 16. Removal of the MOM group with TFA and Wessely oxidation of the intermediate hemiketal 17 yielded an inconsequential mixture of diastereomeric acetates 18/19 in 53% yield over two steps.

Dienes 18 and 19 were heated in a microwave reactor in o-DCB to 165 °C for 1.5 h in the presence of BHT to give the expected endo-cycloadducts in 79% and 69% yields. The stereochemistry of the cycloadducts was verified by X-ray crystallographic analysis.11 Once the structures had been determined, both adducts were elaborated further toward 1 by hydrogenation of the bicyclic olefin (H2, Pd/C). Next, the acetate group was excised using SmI2 to give an intermediate samarium enolate that was protonated by methanol to give the α-methyl ketone as a mixture of diastereomers in 76% yield (dr = 17:3 with 25 as major).12 An X-ray crystal structure of 26 (C-16-epi-25) was obtained from the minor diastereomer as shown in Scheme 1C, establishing that the major isomer possesses the proper orientation of the C-16 methyl group in 1.

Certain elements of the sequential Barton arylation/Wessely oxidation/Diels–Alder strategy (i.e., 12→15, 17→18/19, 18/19→25) reported herein may well find use in an eventual synthesis of I.13

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Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) See the Supporting Information for details.
(11) For adduct 21, a crystal was grown directly, whereas adduct 20 was crystallized after removal of the TBS group as alcohol 22.