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PART A: STUDIES DIRECTED TOWARD
THE SYNTHESSES OF THE CORES OF KEDARCIDIN,
MADUROPEPTIN AND C-1027

PART B: STUDIES DIRECTED TOWARD THE TOTAL
SYNTHESIS OF ELEUTHEROBIN

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SYNTHESIS OF ELEUTHEROBIN

by

RICH GARRETT CARTER, B.S.

DISSERTATION
Presented to the Faculty of the Graduate School of
The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas at Austin
May, 1997
Dedication

To my wife, Linda,
and the rest of my supportive family.
Acknowledgements

First, I would like to thank Professor Philip Magnus for his support and guidance during my tenure at the University of Texas. I have learned a great deal and I will always be grateful for my time here. I would also like to thank all former and current members of the Magnus group for their advice and assistance. I am especially grateful to my proofreaders: Drs. Ian Churker, Ian Mitchell, Stephen Wren, Nick Westwood, Lewis Gazzard, Jonathan Morris and John Booth. Furthermore, the efforts of my fellow "son-of-taxol" team members (Drs. Kevin Hodgetts, Stephen Wren, Ian Mitchell and Jeff McKenna) helped to make this thesis possible. I would like to thank Andrea Magnus and a fellow Texan, Cathy Smith, for their help with all the little things of the years as well as their friendship. Finally, none of this work would ever have been possible if it wasn't for the support of my wife, Linda, as well as my family and friends.
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Publication No.

Rich Garrett Carter, Ph.D.
The University of Texas at Austin, 1997

Supervisor: Philip D. Magnus

Part One of this dissertation provides a brief introduction to the enediynes as well as a more detailed look at the biology, chemistry and synthetic approaches toward kedarcidin, maduropeptin and C-1027.

Next, Part Two discusses the strategy and results toward the synthesis of the core of kedarcidin, maduropeptin and C-1027 are discussed. The strategy for the construction of the core enediyne ring system involves the use of \( \eta^2\)-Co\(_2\)(CO)\(_6\)-complexed acetylenes which facilitates formation of the strained [7.3.0] bicyclic ring system while preventing Bergman cyclization. The results
discussed include the use of a Castro-Stephens coupling to form the enediyne function and a boron-mediated aldol reaction to construct the [7.3.0] bicyclic enediyne core. Also, an array of transformations are investigated for the completion of the synthesis.

Then, Part Three details the relevant experiments performed and physical data collected during core of this research are provided.

Part Four discusses the background of eleutherobin including the biology, chemistry and synthetic approaches toward related compounds.

Next, Part Five discusses the research conducted toward the total synthesis of eleutherobin is detailed. A strategy is discussed for the construction for two fragments: the western portion utilizing a Mukaiyama aldol reaction and a hydroboration and the eastern fragment using Sharpless methodology. Next, connection of the two fragments using a Julia coupling is detailed and a variety of cyclization strategies are investigated. Finally, modification of the approach for the construction of eleutherobin is discussed involving a Suzuki coupling, an unusual epoxidation / rearrangement, and a sulfone / lactone cyclization strategy.

Finally, Part Six details the relevant experiments performed and physical data collected during core of this research are provided.
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# List of Abbreviations

The following abbreviations have been used in this dissertation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
</tr>
<tr>
<td>approx</td>
<td>approximate</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DAMP</td>
<td>dimethyl (diazomethyl)-phosphonate</td>
</tr>
<tr>
<td>DBU</td>
<td>diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>d.e.</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>decomp</td>
<td>decomposition</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>d.s.</td>
<td>diastereomeric selectivity</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)-pyridine</td>
</tr>
<tr>
<td>DMS</td>
<td>methyl sulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
</tbody>
</table>
DMF  \( N,N\)-dimethyl formamide

DMPU  1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

\( E \)  \textit{entgenen}

e.e.  enantiomeric excess

equiv  equivalent

Et  ethyl

FT  Fourier transform

im  imidazole

IR  infra red

h  hours

hfc  hexafluoropropyl hydroxy-methylene

HMPA  hexamethylphosphoramide

HRMS  high resolution mass spectroscopy

\( i \)  iso

KHMDS  potassium \textit{bis-} (trimethylsilyl)amide

K-Selectride\textsuperscript{®}  potassium \textit{tri-sec-} butylborohydride

LA  lewis acid

LDBB  lithium \textit{di-tert-}butyl biphenyl

LDA  lithium diisopropylamide
LHMDS

L-Selectride®

m

M

MCPBA

Me

min

m.p.

MPLC

chromatography

Ms

n

NaHMDS

NMO

NMR

Nu

P

PCC

Ph

PhH

PhMe

lithium bis-(trimethylsilyl)-amide

lithium tri-sec-butylborohydride

multiple

molar

3-chloroperbenzoic acid

methyl

minutes

melting point

medium pressure liquid

methane sulfonyl

normal

sodium bis-(trimethylsilyl)-amide

$N$-methyl morpholine $N$-oxide

nuclear magnetic resonance

nucleophile

protecting group

pyridium chlorochromate

phenyl

benzene

toluene

xiv
Piv  pivaloyl
PLC  preparative layer chromatography
PNB  4-nitrobenzoyl
ppm  parts per million
PPTS  pyridinium 4-toluenesulfonate
Pr  propyl
PTSA  4-toluenesulfonic acid monohydrate
py  pyridine
R  alkyl group
q  quartet
Rf  retentation factor
r.t.l.  room temperature
s  singlet
SM  starting material
Super Hydride®  lithium triethylborohydride
t  triplet
\( t \)  tert
TBAF  tetrabutylammonium fluoride
TBHP  \( tert \)-butyl hydroperoxide
TBS  \( tert \)-butyldimethylsilyl
TDPS  \( tert \)-butyldiphenylsilyl
TES  triethylsilyl
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetraisopropylammonium-peruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>4-toluenesulfonyl</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen</td>
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</table>

xvi
Section 1:

The Chemistry and Biology of Kedarcidin, C-1027 and Maduropeptin
1 Background of Neocarzinostatin, Kedarcidin, C-1027 and Maduropeptin

1.1 Introduction

In 1985, Edo and co-workers elucidated the structure of neocarzinostatin chromophore A (1a)\(^1\) which was the first member of a the enediyne-based natural products. Since then, several other members of this family have been isolated, as shown in Figures 1 and 2, including calicheamicin \(\gamma_1\) (2),\(^2\) esperimicin A\(_1\) (3),\(^3\) dynemicin A (4),\(^4\) kedarcidin (5),\(^5\) C-1027 (6),\(^6\) and maduropeptin (7).\(^7\) Compound 1a and its aglycon 1b as well as compounds 5, 6 and 7 contain the common [7.3.0] bicyclic core ring system,\(^8\) while enediynes 2, 3 and 4 possess the related [7.3.1] bicyclic core ring system. Since all members of the enediyne family of natural products have been shown to exhibit potent cytotoxic activity against a wide array of cancerous cells, significant synthetic and biological interest has been generated, and this area has been extensively reviewed.\(^9\)
Figure 1: Enediynes Neocarzinostatin Chromophore A (1a), Neocarzinostatin Aglycon (1b), Calicheamicin $\gamma_1$ (2), Esperimicin A$_1$ (3) and Dynemicin A (4)
Figure 2: Enediynes Kedarcidin (5), C-1027 (6) and Maduropeptin (7)

A mode of action has been proposed for all enediynes (with the notable exception of neocarzinostatin 1a and 1b)\textsuperscript{10} which is illustrated in Scheme 1. This mode of action involves the formation of a 1,4-diradical species 9 \textit{via} a Bergman cyclization\textsuperscript{11} of enediyne 8 (or 10). It is this diradical intermediate which is believed to be the active species responsible for the death of the cell by DNA cleavage.\textsuperscript{12} From this point forward, this dissertation will focus on compounds 5, 6 and 7.
Scheme 1: Proposed Mechanism for Bergman Cyclization

1.2 Isolation and Biological Activity of Kedarcidin, C-1027 and Maduropeptin

Kedarcidin (5) was isolated from the fermentation broth of a novel actinomycete strain (L585-6, ATCC 53650) and has shown excellent in vitro and in vivo cytotoxic activity. The proposed mode of action, shown below with the enediyne core structure 12 (Scheme 2), was deduced by a combination of methods including sodium borohydride and sodium borodeuteride experiments. Also, the addition of nucleophiles, such as β-mercaptoethanol or dithiothreitol, has been shown to accelerate the cycloaromatization process.

Interestingly, Leet and co-workers have calculated that the end to end enediyne distance (C-2 to C-7) does not change significantly upon opening of the C-8,9 epoxide (2.849 Å in 12 versus 2.824 Å in 13). They went on to propose that the opening of the epoxide reduces the strain energy in the transition state.
leading to cycloaromatization,\textsuperscript{14} which is in agreement with the proposal put forth for all enediyne cycloaromatization processes by Magnus and co-workers.\textsuperscript{16}

Scheme 2: Proposed Mode of Action for 5

C-1027 (6) was isolated from the filtration broth of \textit{Streptomyces globisporus} C-1027\textsuperscript{17} and has shown excellent \textit{in vitro} and \textit{in vivo} cytotoxic activity.\textsuperscript{18} Once separated from the protein, C-1027 (6) was found to slowly cycloaromatize at room temperature, and it is believed that the protein stabilizes the enediyne preventing cycloaromatization (Scheme 3). Unlike 5, enediyne 6 requires no trigger for Bergman cyclization to occur, such as the addition of a nucleophile to the C-12 position as seen in compound 5. This reactivity hindered initial efforts to elucidate the structure of 6.\textsuperscript{19}
Scheme 3: Proposed Mode of Action for 6

Maduropeptin (7) was isolated from the filtration broth of Actinomeda madurae and has shown excellent in vitro and in vivo cytotoxic activity. The proposed mode of action involves an initial ring contraction of the amide 19 to form the aziridine intermediate 20 which undergoes Bergman cyclization to give the diradical 21 (Scheme 4).

Scheme 4: Proposed Mode of Action for 7
1.3 Previous Synthetic Approaches Toward Kedarcidin, C-1027 and Maduropeptin

Since most synthetic efforts concerning the [7.3.0] bicyclic members of the enediyne family have focused on the neocarzinostatin aglycon (1b)\textsuperscript{20} and has resulted in a total synthesis by Myers and co-workers;\textsuperscript{21} relatively little work has been published concerning the other three enediynes (5, 6, and 7) that possess the same [7.3.0] bicyclic ring system. One exception is Hirama and co-workers' efforts to construct of the [7.3.0] core enediyne ring system. Their strategy involved the formation of the key 9-membered ring at the C-7,8 position via an acetylide addition to an aldehyde shown below (Scheme 5).\textsuperscript{22} This strategy was also used by Myers and co-workers in their synthesis of the aglycon 1b.\textsuperscript{23}
Scheme 5: Synthesis of the Cyclic Enediynes 28a and 28b
Hirama and co-workers were able to construct the advanced C-1027 precursor 30 as a fleeting intermediate by elimination of water from 29, which underwent rapid conversion to the cycloaromatized adduct 31 (Scheme 6). Enediyne 30 possesses the C-8,9 diol functionality and C-1,12 olefin present in C-1027 (6).

\[
\begin{align*}
&\begin{array}{c}
\text{TBSO} \quad \text{OTBS} \\
\text{29}
\end{array} \\
&\begin{array}{c}
\text{TBSO} \quad \text{OTBS} \\
\text{30}
\end{array} \\
&\begin{array}{c}
\text{TBSO} \quad \text{OTBS} \\
\text{31}
\end{array}
\end{align*}
\]

i) MSCl, Et$_3$N, CH$_2$Cl$_2$; ii) DBU, CH$_2$Cl$_2$, 25°C; iii) 1,4-cyclohexadiene, CH$_2$Cl$_2$, 87% (over three steps).

Scheme 6: Synthesis of C-1027 Model Compound 30

Construction of an advanced kedarcidin intermediate 33 was possible from 28a (Scheme 7). After conversion of 28a into the epoxide 32, subsequent elimination of water gave the enediyne 33, which proved to be moderately stable to chromatography. Subsequent Bergman cyclization of enediyne 33 gave the aromatized adduct 34. Notably, enediyne 33 possesses both the crucial C-8,9 epoxide and the C-1,12 olefin present in kedarcidin (7).
Scheme 7: Synthesis of Advanced Kedarcidin Precursor 33

1.4 Conclusion

Although Hirama and co-workers have been able to construct advanced intermediates toward the synthesis of the core ring systems 12, 16, and 19, they were unable to prevent any C-1027 core structure from undergoing cycloaromatization during isolation. Additionally, Hirama and co-workers did not investigate Leet and co-workers' hypothesis concerning the end to end enediyne distances (C-2,7) of kedarcidin (5). Finally, to date no synthetic effort towards maduropeptin (7) have been explored. For these reasons, further investigation into the synthesis was warranted and will be discussed in Part 2.


8 The numbering system shown with compounds 1a and 1b will be used throughout this dissertation for all synthetic efforts towards compounds 5, 6 and 7.


10 Neocarzinostatin is proposed to involve a 1,5-diradical intermediate. Myers, A. G. Tetrahedron Lett. 1987, 28, 39.


24 No synthesis of the alcohol 29 has been directly reported to date. It is believed that 29 is accessible from the use of an alternative protecting group for the C-4 tertiary hydroxyl functionality in the cyclization.

Section 2:
Discussion of Results
1 $\eta^2$-Co$_2$(CO)$_6$-Complexed Acetylene Approach to the Core Ring Systems of Kedarcidin, C-1027 and Maduropeptin

1.1 Previous Work Utilizing $\eta^2$-Co$_2$(CO)$_6$-Complexed Acetylene Methodology

Prior to the discovery of enediynes 5, 6, and 7, studies toward the construction of 1a and 1b were initiated in this laboratory due to their potent anti-tumor activity and unusual structural features. It was felt that $\eta^2$-Co$_2$(CO)$_6$-complexed acetylenes might prove useful in the synthesis of the core [7.3.0] bicyclic enediyne ring system. Although enediynes 5, 6 and 7 were unknown at the time, this work would become the foundation for a strategy for construction of their core ring systems.

Cobalt-complexed alkynes have several noteworthy properties. First, $\eta^2$-Co$_2$(CO)$_6$-complexed acetylenes are known to stabilize a cation $\alpha$ to the cobalt complexed alkyne; this attribute was first explored by Nicolas and co-workers in the reaction that bears his name. Secondly, $\eta^2$-Co$_2$(CO)$_6$-complexation of an acetylene have been shown to bend the alkyne from 180° to approximately 150° and these complexes have been shown to allow for the formation of the ring sizes that are otherwise unattainable. Also, this laboratory has reported that $\eta^2$-Co$_2$(CO)$_6$-complexed enediynes are unable to undergo Bergman cyclization until the cobalt moiety has been removed from the enediyne. Since the use of $\eta^2$-Co$_2$(CO)$_6$-complexed acetylenes prevents cycloaromatization of the resulting product while facilitating formation of the 9-membered enediyne ring by bending the acetylene, a strategy was developed that involved their use. $\eta^2$-Co$_2$(CO)$_6$-
complexed acetylenes have also been used in this laboratory to construct the core ring systems of enediynes 2 and 4.5

The known aldehyde acetal 356 was allowed to react with phosphorane 367 to give the desired (Z)-iodoester 37 along with a small amount of its geometrical isomer (90% yield, Z:E = 17:1)8 (Scheme 1). Subsequent DIBAL-H reduction and protection of the primary hydroxyl functionality provided the silyl ether 39.

\[
\begin{align*}
\text{EtO} & \quad \text{EtO} \quad \text{EtO} \quad \text{EtO} \\
\text{\textbf{96}} & \quad \rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{\textbf{EtO}} \\
\rightarrow \quad \text{35} \\
\rightarrow \quad \text{36} \\
\rightarrow \quad \text{39 (R = TBS)} \\
\rightarrow \quad \text{38 (R = H)} \\
\rightarrow \quad \text{R} \\
\rightarrow \quad \text{CO}_2\text{Et}
\end{align*}
\]

i) ZnI₂, (EtO)₃CH, Δ, 81%; ii) HCO₂H, CH₂Cl₂, reflux, 93% iii) 36, CH₂Cl₂, -78°C to 25°C, 90% (Z:E = 17:1); iv) DIBAL-H, THF, -78° to 25°C, 92%; v) TBSOTf, CH₂Cl₂, Et₃N, 99%.

Scheme 1: Synthesis of Vinyl Iodide 39

First, selective 1,2-addition to known enone 419 was accomplished using the lithium acetylide (Scheme 2). Next, desilylation provided the terminal acetylene 42 which was coupled with the iodide 39 under standard Castro-Stephens conditions10 to give the desired enediyne 43. Subsequent silylation of the tertiary hydroxyl functionality of 43, followed by complexation of the less hindered acetylene with Co₂(CO)₈, and acidic deprotection provided the aldol precursor 46. Finally, treatment of the aldehyde 46 with n-Bu₂BOTf and Et₃N¹¹.

19
gave the desired aldol adduct 47 as a single diastereomer.\textsuperscript{12} Unfortunately, after acidic removal of the borate moiety at C-13, the attempted introduction the C-4,5 epoxide of the neocarzinostatin core under Sharpless conditions\textsuperscript{13} was unsuccessful. This problem was subsequently overcome by introduction of the epoxide prior to cyclization.\textsuperscript{14} Also, decomplexation of these acetylenes is normally accomplished under oxidative conditions as depicted with 47 which yielded the expected Bergman cyclized compound 50.
Scheme 2: Synthesis of Macrocycle 47

1.2 Retrosynthetic Analysis of the Core Ring Systems Present in Kedarcidin, C-1027 and Maduropeptin

Using the knowledge gained from previous work in this laboratory, a unified strategy was developed to construct compounds 12, 16, and 19 from the common intermediate 54 (Scheme 3). Unlike previous work in this laboratory,
this approach was designed to test the compatibility of $\eta^2$-Co$_2$(CO)$_6$-complexed enediynes with modern synthetic organic procedures, in particular oxidations and reductions, which have not been extensively explored. The devised strategy required the presence of the $\eta^2$-Co$_2$(CO)$_6$-complexed acetylene functionality in a multistep synthesis in order to install the proper functionality required for the construction of compounds 12, 16, and 19. It was necessary that the $\eta^2$-Co$_2$(CO)$_6$-complexed acetylene functionality be present on the [7.3.0] bicycloenediyne ring systems to prevent Bergman cyclization, but it was not known at this stage what chemistry would be possible on these systems. It previously has been shown in this laboratory that the enediyne functionality may be maintained during the removal of the cobalt functionality if the enediyne structure contains sufficient strain energy to prevent Bergman cyclization.$^{14}$
Scheme 3: Summary of Retrosynthetic Analysis of Core Ring Systems (12), (16) and (19)

Enediyne 12 should be accessible via selective epoxidation of the allylic alcohol 52 followed by removal of the cobalt moiety in 51 (Scheme 4). Alkene 52 could be generated by the directed reduction of the C-10 carbonyl function in the enone 53 which, in turn, should be accessible by an α-hydroxylation at C-11 of the common intermediate 54. It was believed that the hydroxylation would occur from the less hindered α face.
Scheme 4: Retrosynthetic Analysis of Enediyne 12

Diene 16 should come from opening of the epoxide 55 (Scheme 5). Since the relative, and hence absolute stereochemistry of C-1027 (6) has not been determined, it is unknown whether the trans C-8,9 stereochemistry shown in enediyne 16 is correct for 6. Next, the epoxide 56 should be available from the allylic epoxidation of allylic alcohol 57 followed by removal of the $\eta^2$-Co$_2$(CO)$_6$-functionality in 55. Finally, reduction of the common intermediate 54 would provide the epoxidation precursor 57.
Scheme 5: Retrosynthetic Analysis of Enediyne 16

The synthesis of the compound 19 should be accessible from the common intermediate 54 (Scheme 6). The O-methyl ether 59 could come from hydroxylation of the nitrile 59. The prerequisite nitrile 59 should be accessible from the epoxide 60 via the opening of the C-8,9 epoxide function and the use of Mitsunobu chemistry of the C-13 alcohol functionality. Since the epoxide 60 is nearly identical to the epoxide 56, 60 should available from the common intermediate 54 in a similar fashion to that previously described for the epoxide 56.
Scheme 6: Retrosynthetic Analysis of Compound 19

Although the route into the aldol adduct 47 (see Section 2.1.1) had been previously established, one modification had to be made to apply this strategy towards the construction of the key intermediate enone 54. The choice of protecting group for the C-13 hydroxyl functionality needed to be changed; unlike the strategy for the construction of the neocarzinostatin core, a free C-13 hydroxyl group is not necessary for further functional group manipulation to construct enediyynes 12 and 16. For this reason, a change from the acid-labile silicon protecting group to a pivalate protecting group, which should be stable to the acidic conditions necessary to remove the ketal and the acetal, was warranted.

Enone 54 could be accessible via selective conjugate reduction of the less hindered C-11,12 olefin in triene 61, which could in turn come from the elimination of the elements of water from the adduct 62 (Scheme 7). The relative
stereochemistry of C-1, C-8 and C-9 positions of the alcohol 62 is based on previously discussed work (see Section 2.1.1) and the synthesis of 62 should be available utilizing a similar the palladium-catalyzed coupling of the vinyl iodide 65 and the acetylene 42, as well as the $n$-Bu$_2$BOTf / Et$_3$N-mediated aldol reaction of aldehyde 63.

Scheme 7: Retrosynthetic Analysis of the Common Intermediate 54
1.3 Construction of Enediyne Core Ring System

Conversion of the enone 41 and the iodide 38 into the respective coupling precursors was possible in two steps and one step respectively. Although the acetylene 42 has been previously reported\(^\text{12}\) via a one step protocol using lithium acetylide in 39% yield (see Section 2.1.1, Scheme 2), the two step sequence that was developed proved to be significantly more efficient (85% over 2 steps). Hence, treatment of the enone 41 with lithium trimethylsilylacetylide in the presence of CeCl\(_3\) followed by desilylation with TBAF provided the free acetylene 42 (Scheme 8). Its coupling partner was prepared by protection of the iodo alcohol 38 as its pivalate ester 65 using PivCl and catalytic DMAP.

\[
\begin{align*}
41 & \xrightarrow{i} \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
& \xrightarrow{\text{ii}} \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
& \xrightarrow{\text{iii}} \begin{array}{c}
\text{EtO} \\
\text{EtO} \\
\text{EtO} \\
\text{EtO}
\end{array}
\end{align*}
\]

\[
\begin{align*}
38 & \xrightarrow{i} \begin{array}{c}
\text{OH} \\
\text{I}
\end{array} \\
& \xrightarrow{\text{ii}} \begin{array}{c}
\text{EtO} \\
\text{EtO}
\end{array} \\
& \xrightarrow{\text{iii}} \begin{array}{c}
\text{EtO} \\
\text{EtO}
\end{array}
\end{align*}
\]

\(i\) Trimethylsilyl acetylene, \(n\)-BuLi, CeCl\(_3\), THF, \(-78^\circ\text{C}\) to \(25^\circ\text{C}\), 92%; \(ii\) TBAF, THF, 92%; \(iii\) PivCl, DMAP, Et\(_3\)N, CH\(_2\)Cl\(_2\), 97%.

Scheme 8: Synthesis of Compounds 42 and 65

Elaboration of the vinyl iodide 65 and the terminal acetylene 42 into the macrocycle 62 was possible in five steps (Scheme 9). Thus, Castro-Stephens coupling\(^\text{10}\) of the terminal acetylene 42 and the iodide 65 yielded the enediyne 67.
in 50% yield, and subsequent silylation of the tertiary hydroxyl functionality with TBSOTf gave the silyl ether 64. Interestingly, it was imperative that this reaction be performed in a one to one mixture of Et$_3$N and CH$_2$Cl$_2$; decreasing the ratio of base relative to solvent led to extensive decomposition. Complexation of the less hindered acetylene functionality with Co$_2$(CO)$_8$ yielded the η$^2$-Co$_2$(CO)$_6$-complexed acetylene 68. Subsequent aqueous deprotection with PTSA then revealed the aldol precursor 63. Finally, slow addition of the aldehyde 63 via syringe pump over 5.5 h to a solution of n-Bu$_2$BOTf and Et$_3$N$^{11}$ under high dilution conditions yielded the aldol adduct 62 as a single diastereomer in 74% yield. The relative stereochemistry of the alcohol 62 was assigned by comparison of the H-8,9 coupling constants in the $^1$H NMR of the previously prepared enediyne 47 (6.7 Hz and 5.9 Hz for enediynes 62 and 47 respectively). Unfortunately, this reaction was limited in scale to approximately 200 mg of the aldehyde 63; any attempt using a larger amount of 63 in the cyclization led to a significant decrease in yield.
Scheme 9: Synthesis of Macrocycle 62

1.4 Conversion of Aldol Adduct into Common Intermediate

Conversion of the aldol adduct 62 into the common intermediate 54 was accomplished in two steps. Elimination of water from the alcohol 62 was accomplished using MsCl (11 equiv) and DMAP (4 equiv) in the presence of Et₃N (51 equiv) (Scheme 10). Decrease of these amounts led to incomplete reaction which was further complicated by both the inability to separate the product 61 from the starting material 62 by chromatography and the inherent instability of the product 61. Freshly prepared triene 61 decomposed significantly within 24 h at -20°C under an argon atmosphere.
Selective reduction of the C-11,12 olefin in triene 64 proved to be somewhat problematic. Numerous attempts to accomplish this transformation are shown below (Scheme 11, Table 1). It was discovered that under certain conditions, most notably with Stryker’s reagent $\{((\text{Ph}_3\text{P})\text{CuH})_6\}$, the C-2,3 acetylenic functionality was preferentially reduced, presumably so as to relieve the ring strain present in the triene 61. Reduction of an acetylene to its Z-alkene with $\{((\text{Ph}_3\text{P})\text{CuH})_6$ had been previously observed, but the reaction was reported to be rather slow. In this case, the reduced acetylene 69 was the major product, with only a trace of the desired compound 54 (Entry 6). Other reductive conditions examined included LiAlH$_4$ / CuI, DIBAL-H / MeCu catalyst / HMPA, Ph$_3$SnH$^{20}$ and K-Selectride$^{21}$. Treatment of the enone 54 with ZnCl$_2$ / NaBH$_3$CN in Et$_2$O$^{22}$ provided the desired 1,4-reduced product, albeit in low yield, with only a trace of the reduced acetylene 69 being observed. Ultimately, optimal conditions were developed with the addition of TMSCl to the reaction mixture and the subsequent use of the Davis oxaziridine 70$^{23}$ in an oxidative workup; the additive of TMSCl in such reductions and the novel use of the oxaziridine has not previously reported. Interestingly, the aldol adduct 62 did not

Scheme 10: Dehydration of Alcohol 62
react under the optimized conjugate reduction conditions (Entry 10), even upon extended reaction times. It is believed that the increased reactivity of the triene 61 relative to the alcohol 62 is due to the increased strain energy caused by the C-8,9 olefin which further activates the C-11,12 olefin to reduction.

![Chemical Structures](image)

Scheme 11: Selective Reduction of the C-11,12 Olefin of 61

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiAlH₄, CuI, THF, -10°C to 25°C</td>
<td>decomp*</td>
</tr>
<tr>
<td>2</td>
<td>K-Selectride®, THF, -78°C to 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>3</td>
<td>DIBAL-H, MeCu catalyst, HMPA, THF, -78°C to 25°C</td>
<td>SM and decomp</td>
</tr>
<tr>
<td>4</td>
<td>(Ph₃P)₃RhCl, Et₃SiH, CH₂Cl₂, 25°C to reflux</td>
<td>complex mixture**</td>
</tr>
<tr>
<td>5</td>
<td>Ph₃SnH, PhH, 55°C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6</td>
<td>[(Ph₃P)CuH]₆, PhH, 10°C</td>
<td>69 (25%) + 54 (&lt; 5%)</td>
</tr>
</tbody>
</table>

* decomp denotes no recognizable product could be observed.
** complex mixture denotes numerous compounds could be observed, but attempted purification was unsuccessful.

Table 1: Selective Reduction of the C-11,12 Olefin of 64
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>ZnCl₂, NaBH₃CN, THF, 25°C</td>
<td>63 (trace)</td>
</tr>
<tr>
<td>8</td>
<td>ZnCl₂, NaBH₃CN, Et₂O, 25°C</td>
<td>54 (22%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 61 (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ 69 (&lt; 5%)</td>
</tr>
<tr>
<td>9</td>
<td>ZnCl₂, NaBH₃CN, TMSCl, Et₂O, 0°C to 25°C</td>
<td>54 (25%)</td>
</tr>
<tr>
<td>10</td>
<td>ZnCl₂, NaBH₃CN, TMSCl, Et₂O, 0°C to 25°C; oxidative work-up with [image]</td>
<td>54 (36%)</td>
</tr>
</tbody>
</table>

Table 1 (continued): Selective Reduction of the C-11,12 Olefin of 64

1.5 Attempted α-Hydroxylation of Common Intermediate

Since an oxidation was necessary at C-11 in the enone 54 in order to construct the enediyne 12, a variety of oxidative conditions were investigated with little success (Scheme 12). These experiments included the use of t-BuOK / t-BuOH / O₂,²⁴ LDA or KHMDMS then the Davis oxaziridine,²⁵ LHMDS / O₂,²⁶ (PhSeO)₂O / NaH²⁷ and PhI(OAc)₂ / KOH / MeOH.²⁸ α-Bromination²⁹ of the ketone 54 was possible using LHMDS (1.7 equiv) and Br₂; however, attempted conversion of the α-bromide into the α-hydroxyl functionality via treatment of the bromide 71 with NaOH in DMF³⁰ led to rapid decomposition.
Scheme 12: \( \alpha \)-Oxidation of the Enone 54

1.6 Attempted Introduction of the C-8,9 Epoxide Present in Kedarcidin

As discussed in the introduction (see Section 1.1.2), the kedarcidin (5) possesses an epoxide in the C-8,9 position, which is believed to be important in its biological mode of action. The introduction of such an epoxide functionality would not only allow access to the enediyne 12, but also to the compounds 16 and 19 via opening of the epoxide. Furthermore, this transformation would be a major test of the compatibility of organocobalt complexes with modern methods in organic synthesis. It was unknown, however, whether the \( \eta^2 \)-Co\(_2\)(CO)\(_6\) functionality would be compatible with the oxidative conditions necessary to introduce the epoxide since classical epoxidations using such reagents as MCPBA on an allylic alcohol or H\(_2\)O\(_2\) / NaOH on an enone are known to be completely incompatible with the \( \eta^2 \)-Co\(_2\)(CO)\(_6\) functionality.\(^{31}\) It was hoped that a milder oxidant, such as TBHP, would be more suitable.

A potential substrate for the selective epoxidation of the C-8,9 olefin functionality was the allylic alcohol 73, which should be accessible by the reduction of the enone 54 (Scheme 13). Attempted reduction of 54 under Luche
conditions (CeCl₃, NaBH₄, MeOH)³² gave a complex mixture of compounds; however, reduction with DIBAL-H in toluene led to a stereoselective reduction of the C-10 carbonyl functionality with concomitant deprotection of the C-13 hydroxyl function to give the diol 72. Reduction of the C-10 carbonyl is proposed to occur from the α-face due to the steric encumbrance of the β-tertiary silyl ether functionality. Subsequent selective reprotection of the C-13 hydroxyl group as its naphthoate ester yielded the allylic alcohol 73 in good yield. Unfortunately, treatment of 73 with Ti(Oi-Pr)₄ and TBHP gave substantial decomposition and decomplexation, as shown by the loss of the characteristic red color associated with η²-Co₂(CO)₆-complexed acetylenes. The only isolable η²-Co₂(CO)₆-complexed product appeared to have resulted from oxidation of the allylic alcohol function to the ketone 75 as shown by the disappearance of a signal in the ¹H NMR of the crude reaction at 4.2 ppm for the C-10 H₆ present in the starting material 73. In addition, the ¹H NMR of the ketone 75 was nearly identical to the enone 54 and treatment of the product 75 with DIBAL-H yielded the allylic alcohol 72 as shown by ¹H NMR of the crude reaction mixture.
i) DIBAL-H, PhMe, -78°C, 57%; ii) 1-naphthoyl chloride, Et₃N, CH₂Cl₂, -5°C, 77%; iii) Ti(Oi-Pr)₄, TBHP, 4 Å molecular sieves, -5°C; iv) DIBAL-H, PhMe, -78°C.

Scheme 13: Attempted Epoxidation of Allylic Alcohol 73

One possible explanation for the failure of the epoxidation may be due to the steric bulk of the η²-Co₂(CO)₆ complex and the C-12 silyl ether. Alternatively, the η²-Co₂(CO)₆ complex could be simply incompatible with the oxidative conditions necessary for this transformation.

In order to further examine the compatibility of the η²-Co₂(CO)₆ complex under the epoxidation conditions, another substrate, 76, was prepared (Scheme 14). In this epoxidation, the possibility of allylic epoxidation was not limited to just the C-8,9 olefin; allylic epoxidation at the C-11,12 position was also a
potential product. The bisallylic alcohol 76 was accessible from the enone 61 via a Luche reduction.\textsuperscript{32} Although a single diastereomer of unknown stereochemistry was isolated from this reaction, the \textsuperscript{1}H NMR of the crude reaction was complex and no other product could be identified. It is well known that Luche reductions usually give the thermodynamically most stable product.\textsuperscript{33} Unfortunately, treatment of alcohol 76 with Ti(Oi-Pr)\textsubscript{4} / TBHP led to extensive decomposition.

![Diagram of chemical reactions]

\textsuperscript{i) NaBH\textsubscript{4}, CeCl\textsubscript{3}, MeOH, 40%; ii) Ti(Oi-Pr)\textsubscript{4}, TBHP, 4 Å molecular sieves, -20°C to 25°C.}

Scheme 14: Attempted Epoxidation of Bisallylic Alcohol 76

As mentioned earlier (see Section 2.1.1), previous work in this laboratory directed towards the introduction of the C-4,5 epoxide on a cyclized, \(\eta^2\)-Co\(_2\)(CO)\(_6\)-complexed compound, necessary for the synthesis of compounds 1a and 1b, was unsuccessful. For example, treatment of the allylic alcohol 79 with (-)-DET / Ti(Oi-Pr)\textsubscript{4} / TBHP\textsuperscript{34} led to multiple compounds and no isolable epoxide (Scheme 15). \textsuperscript{1}H NMR of the crude reaction appeared to indicate aldehyde
signals suggesting a possible oxidation of the allylic alcohol or retro-aldol reaction at the C-8,9 position.

\[ \text{Scheme 15: Attempted Epoxidation of Allylic Alcohol 79} \]

Due to these negative results, it was concluded that epoxidation of the C-8,9 olefin was unlikely to be successful on a cyclized, \( \eta^2 \)-Co\(_2\)(CO)\(_6\)-complexed compound. Thus, the focus of the project thus switched from the introduction of the C-8,9 oxygenation to the formation of the C-1,12 olefin found in the bicyclic core systems of compounds 5, 6, and 7 (see Section 1.1.1, Figure 2).

**1.7 Attempted Introduction of the C-1,12 Olefin Present in Kedaricd, C-1027 and Maduropeptin**

Due to the low yielding conjugate reduction of the triene 61 (see Section 2.1.4), an alternative reductive elimination strategy was investigated. This strategy would circumvent the ZnCl\(_2\) / NaBH\(_3\)CN / TMSCl reaction and introduce the required C-1,12 olefin found in all known [7.3.0] enediyne natural products. One possible method for executing the reductive elimination strategy could involve the introduction of a thiophenyl ether at C-12 followed by reductive elimination.\(^{35}\) If successful, this strategy has the additional benefit that the product 83 would be achiral (Scheme 14), allowing for the introduction of asymmetry at a very advanced stage.
Incorporation of the thiophenyl ether at the C-12 position was accomplished using PhSAlMe₂+THF³⁶ and TBSOTf³⁷ (Scheme 16); the addition of TBSOTf was necessary in order to obtain a reasonable yield. The minor amount of the ketone 82 is believed to result from incomplete silylation of the C-10,11 enolate.

![Chemical Structures](image)

i) PhSAlMe₂+THF, TBSOTf, CH₂Cl₂, -78°C to 25°C, 81 (31%) and 82 (13%).

Scheme 16: Synthesis of Thiophenyl Adducts 81 and 82

Attempted reductive elimination of the thioether 81 under a variety of conditions, however, was uniformly unsuccessful (Scheme 17). Treatment with sodium naphthalenide / THF / -78°C,³⁸ LDBB / THF / -78°C to 25°C,³⁹ or Na / NH₃ / 78°C,⁴⁰ led to decomposition of the enol ether 81. Likewise, reduction of the keto-sulfide 82 using Raney Ni²/ acetone / ethanol / reflux⁴¹ also led to decomposition. These results may be due to the fact that η²-Co₂(CO)₆-complexed acetylenes can be removed reductively as well as oxidatively. All attempted reductive eliminations ultimately led to a loss of the red color associated with a η²-Co₂(CO)₆-complexed acetylene suggesting the decomplexation of the organocobalt moiety.
Scheme 17: Attempted Reductive Eliminations of Sulfide 81

Another method for the introduction of the C-1,12 olefin involved the direct reduction of the enone 61 under reductive ionization conditions to yield the planar fulvene 85 (Scheme 18). Unfortunately, treatment of the triene 61 under a variety of conditions, including Zn / TMSCl / THF / sealed tube / 100°C42 and several different TFA / Et3SiH conditions,43 proved fruitless.

Scheme 18: Attempted Reductive Ionization of Triene 61


5 *For a review see:* Magnus, P. *Tetrahedron* 1994, 50, 1397.


8 The ratio of 37 to 37a was determined by $^1$H NMR of the crude reaction mixture. Since separation of the iodoesters 37 and 37a proved difficult, the two isomers were separated after reduction of the ester to the alcohol (38 and 38a).


31 Magnus, P.; Press, N.; Minkis, G. unpublished results.


37 Although TBSOTf has not previously been used as an additive with
    Me₂AlSPH•THF, there are examples of TMSOTf catalyzed additions of


40 Truce, W. E.; Tate, D. P.; Burdge, D. N. *J. Am. Chem Soc.* 1960, 82, 2872.


42 This method is typically used to reduce ketones to alkenes; however, it was
    hoped that the pathway shown in Scheme 18 would be dominant since no
    α-hydrogens were present. Motherwell, W. B. *J. Chem. Soc., Chem.
    Trans. 1* 1975, 809.
2 Future Work and Conclusion

2.1 Future Work

One of the major goals of this project was to explore the potential compatibility of \( \eta^2\text{-Co}_2\text{(CO)}_6 \)-complexed enediynes with multi-step organic synthesis. Although some transformations were possible, such as the elimination of the alcohol 62, most reactions tended to lead to extensive decomposition and low yields with oxidations and reductions proving particularly difficult. In light of these results, any further attempts to construct compounds 12, 16, and 19 must involve more incorporation of the required functionality prior to \( \eta^2\text{-Co}_2\text{(CO)}_6 \)-complexation. Since formation of the C-8,9 epoxide under oxidative conditions appears to be improbable, introduction of the epoxide functionality should be performed using non-oxidative methods. One possible strategy for the construction of the enediyne 12 is shown in Scheme 20, whereby a sulfonium ylide is used in order to construct both the C-8,9 epoxide and the 9-membered enediyne ring. Based on precedent, the \( \eta^2\text{-Co}_2\text{(CO)}_6 \)-complexed acetylene would be necessary to facilitate the closure of the 9-membered ring and to prevent cycloaromatization of the intermediate sulfonium alkoxide 92.
Scheme 20: Alternative Strategy for Preparation of Enediyne 12
A similar route for the construction of compounds 16 and 19 would involve the 2-cyclopentenone (86) leading to the epoxide 93 (Scheme 21). Opening of the epoxide 93 to give the diol 94 could then provide a route to the compound 19. Alternatively, elimination of water from the C-10,11 position of 94 and decomplexation could give the enediyne 16.

Scheme 21: Alternative Strategy for Targets 16 and 19

2.2 Summary and Conclusion

Several important accomplishments were made during the course of this work which are summarized in Scheme 22. Construction of the common
intermediate 54 was accomplished in 14 steps from commercially available 3,3-diethoxy-1-propyne (96). Oxidation at C-11, necessary for the enediyne 12, was accomplished by an α-bromination to yield the bromide 71 in 45% yield. Reduction at C-10 to give the diol 72 as a single diastereomer was possible in 57% yield. The unusual reactivity of the triene 61 was explored and led to the development of a new conjugate reduction system: ZnCl2, NaBH3CN, TMSCl in Et2O.

Scheme 22: Highlights of Project

Unfortunately, the η2-Co2(CO)6-complexed enediynes are not sufficiently compatible with the rigors of modern organic synthesis. Although the common intermediate 54 could allow access, in principle, to compounds 12, 16, and 19, obtaining substantial amounts of the enone 54 proved difficult due to the scale-limiting intramolecular aldol reaction, the instability of the triene 61, and its subsequent low yielding conjugate reduction. Any strategy involving η2-Co2(CO)6-complexed enediynes must avoid oxidations and reductions.
Unfortunately, construction of the core structure of kedarcidin, maduropeptin and C-1027 was not possible due to this incompatibility. Substantial modification of the initial strategy would be necessary in order to complete the synthesis of these compounds such as shown (see Section 2.2.1).
Section 3:
Experimental
General

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer neat unless otherwise indicated. $^1$H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. $^{13}$C NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter using a sodium lamp at 589 nm in CHCl$_3$ with 1% ethanol.

Routine monitoring of reactions was performed using Merck 60 F$_{254}$ silica gel, aluminum-backed TLC plates. PLC was performed using Merck 60 F$_{254}$ silica gel, glass supported plates. Flash column chromatography was performed with the indicated eluents on Merck 60H F$_{254}$ silica gel.

Air and / or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by a Bunsen flame, then cooled under argon. Solvents and commercial reagents were purified in accord with Perrin and Armarego$^1$ or used without further purification.
4-Cyclopentene-1,3-dione mono ethylene ketal (41).

\[
\begin{align*}
\text{HOCH}_2\text{CH}_2\text{OH}, \\
\text{PhH, PTSA}, \\
\text{reflux}
\end{align*}
\]

To a stirred solution of 40 (10.15 g, 0.106 mol) in PhH (400 mL) was added ethylene glycol (6.57 g, 5.9 mL, 0.106 mol) followed by PTSA (4.0 g, 0.021 mol). The solution was heated at reflux with the azeotropic removal of H\textsubscript{2}O for 2.75 h. After the mixture was cooled to ambient temperature, the dark solution was carefully quenched with saturated aqueous NaHCO\textsubscript{3} (300 mL) and extracted with Et\textsubscript{2}O (4 x 250 mL). The dried (MgSO\textsubscript{4}) extract was concentrated \textit{in vacuo} to give a yellow liquid which was purified by chromatography over silica gel, eluting with 80% Et\textsubscript{2}O / petroleum ether, to give 41 (6.00 g, 0.043 mol, 41% yield) as a yellow oil.

IR 2982, 2894, 1728 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}) \( \delta \) 7.25 (1H, d, \( J = 5.8 \) Hz), 6.22 (H, d, \( J = 5.8 \) Hz), 4.0 - 4.1 (4H, m), 2.61 (2H, s).

HRMS (CI) calcd. for C\textsubscript{7}H\textsubscript{9}O\textsubscript{3} 141.0552. Found 141.0552.
4-(2-Trimethylsilylethynyl)-4-hydroxycyclopent-2-en-1-one ethylene ketal (66).

To a stirred solution of trimethylsilylacetylene (6.46 g, 9.3 mL, 0.066 mol) in THF (150 mL) was added n-BuLi (27.8 mL, 0.69 mol, 2.5 M in hexanes) at -78°C. After 30 min at -78°C, CeCl₃²⁻ (17.00 g, 0.069 mol) was added and stirring continued for an additional 30 min. To the milky suspension, a pre-cooled solution of 41 (4.27 g, 0.031 mol) in THF (50 mL) was added via cannula over 40 min. The orange solution was stirred at -78°C for 20 min then allowed to warm to 25°C and stirred for a total of 1.33 h. The reaction mixture was diluted with Et₂O (200 mL) and quenched with saturated aqueous NH₄Cl (300 mL). The solution was filtered through Celite® and extracted with Et₂O (3 x 300 mL). The dried (MgSO₄) extract was concentrated in vacuo and the yellow liquid was purified by chromatography over silica gel, eluting with 80% Et₂O / petroleum ether, to give 66 (6.67 g, 92% yield) as a clear oil.

IR 3416, 2957, 2895, 2165, 1584 cm⁻¹.
$^1$H NMR (CDCl$_3$) δ 6.03 (1H, d, J = 5.4 Hz), 5.82 (1H, d, J = 5.4 Hz), 3.9 - 4.0 (4H, m), 2.60 (1H, d, J = 14.4 Hz), 2.5 (1H, br s), 2.28 (1H, d, J = 14.4 Hz), 0.13 (9H, s).

HRMS (Cl) calcd for C$_{12}$H$_{19}$O$_3$Si 239.1104. Found 239.1092.

4-Ethynyl-4-hydroxycyclopent-2-en-1-one ethylene ketal (42).

To a stirred solution of 66 (3.39 g, 0.014 mol) in THF (50 mL) was added TBAF (15 mL, 0.015 mol, 1 M in THF). After 25 min, the red mixture was diluted with Et$_2$O (50 mL), quenched with saturated aqueous NH$_4$Cl (100 mL) and extracted with Et$_2$O (3 x 100 mL). The dried (MgSO$_4$) extract was concentrated in vacuo, and the yellow oil was purified by chromatography over silica gel, eluting with 80% Et$_2$O / petroleum ether, to give 42 (2.23 g, 94% yield) as an off-white solid.

IR 3286, 2957, 2891, 2108 cm$^{-1}$.  

56
$^1$H NMR (CDCl$_3$) $\delta$ 6.06 (1H, d, 5.4 Hz), 5.87 (1H, d, $J = 5.4$ Hz), 3.96 (4H, s), 2.65 (1H, d, $J = 14.1$ Hz), 2.59 (1H, s), 2.36 (1H, d, $J = 14.1$ Hz), 2.26 (1H, s).

HRMS (Cl) calcd for C$_9$H$_{11}$O$_3$ 167.0708. Found 167.0714.

1,1,4,4-Tetraethoxy-2-butyne (97)$^3$

![Chemical diagram]

To a stirred solution of 96 (26.33 g, 0.203 mol) in CH(OEt)$_3$ (33.86 g, 38 mL, 0.229 mol) was added ZnI$_2$ (1.45 g, 0.005 mol). A Vigreux distillation apparatus was attached and the solution was heated to 200$^\circ$C distilling off excess ethanol. After 4 h, the dark solution was allowed to cool to ambient temperature, quenched with Na$_2$S$_2$O$_3$ (100 mL, 10% in H$_2$O) and extracted with pentane (3 x 250 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by Kugelrohr distillation (oven temperature 80$^\circ$C, 4 mm Hg) to give 97 (38.30 g, 0.164 mol, 81% yield) as a pale yellow liquid.

$^1$H NMR (CDCl$_3$) 5.31 (2H, s), 3.5 - 3.8 (8H, m) 1.22 (12H, t, $J = 7.2$ Hz).
4,4-Diethoxy-2-butyn-1-al (35).³

\[ \text{EtO} \quad \text{HCO}_2\text{H}, \text{CH}_2\text{Cl}_2, \quad \text{reflux} \quad \text{EtO} \]

To a stirred solution of 97 (26.43 g, 0.115 mol) in CH₂Cl₂ (50 mL) was added HCO₂H (25 mL, 90% in H₂O), and the solution was heated to reflux. After 1 h, the solution was allowed to cool and poured into H₂O (100 mL). The organic layer was extracted with H₂O (2 x 100 mL), followed by extraction with saturated aqueous NaHCO₃ (100 mL). The aqueous layers were extracted with CH₂Cl₂ (3 x 50 mL). The combined dried (MgSO₄) extract was concentrated in vacuo and purified by Kügelrohr distillation (oven temperature 100°C, 2 mm Hg) to give 35 (16.68 g, 0.107 mol, 93% yield) as a colorless liquid.

IR 2979, 2933, 2248, 1722 cm⁻¹.

¹H NMR (CDCl₃) 9.28 ppm (1H, s), 5.43 (1H, s), 3.6 - 3.8 (4H, m), 1.26 (6H, t, J = 6.9 Hz).

Z-Ethyl 6,6-diethoxy-2-iodo-hex-2-en-4-ynoate (37).

[Diagram: Reaction scheme showing the conversion of 35 to 37 and 37a.]

4,4-Diethoxy-2-butynal (35) (2.00 g, 12 mmol) was dissolved in CH₂Cl₂ (10 mL) and added to a solution of 36 (5.70 g) in CH₂Cl₂ (30 mL) at -78°C. The mixture was stirred at -78°C for 15 min, and allowed to warm to ambient temperature over 45 min. The solvent was evaporated and the residue purified by chromatography over silica gel, eluting with 10% ether/pentane, to give 37 (3.81 g, 90%) and the E-isomer 37a (17 : 1) as a yellow oil.

IR (CCl₄) 2981, 2932, 2898, 2888, 1715, 1581 cm⁻¹.

¹H NMR (CDCl₃) δ 7.43 (1H, d, J = 1.3 Hz), 5.36 (1H, d, J = 1.3 Hz), 3.6 - 4.0 (4H, m), 3.3 - 3.6 (2H, m), 1.1 - 1.4 (9H, m).

HRMS (Cl) calcd. for C₁₂H₁₈I₂O₄ 353.0250. Found 353.0223.
Z-6,6-Diethoxy-2-iodo-hex-2-en-4-yn-1-ol (38) and E-6,6-Diethoxy-2-iodo-hex-2-en-4-yn-1-ol (38a).

![Chemical structure](image)

To a stirred solution of 37 and 37a (13.90 g, 0.0394 mol) in THF (300 mL) was added DIBAL-H (135 mL, 0.135 mol, 1.0 M in hexanes) at -78°C over 1.25 h. Next, the mixture was warmed to 0°C for 30 min, recooled to -78°C and MeOH (22 mL) added dropwise. The cooling bath was removed and 10% aqueous sodium tartrate (300 mL) was added, and stirred for 45 min. The mixture was filtered through Celite® and extracted with CH₂Cl₂ (4 x 300 mL). The dried (MgSO₄) extract was concentrated in vacuo to give a yellow liquid which was purified by chromatography over silica gel, eluting with 40% Et₂O / petroleum ether, to give 38 (11.16 g, 0.036 mol, 92%) as a yellow oil and a trace amount of 38a.

**Alcohol 38.**

IR (CCl₄) 3460, 2979, 2930, 2898, 2222 cm⁻¹.

¹H NMR (CDCl₃) δ 6.53 (1H, m), 5.40 (1H, d, J = 1.3 Hz), 4.29 (2H, dd, J = 1.3, 6.5 Hz), 3.7 - 3.9 (2H, m), 3.5 - 3.7 (2H, m), 2.90 (OH, t, J = 6.5 Hz), 1.26 (6H, t, J = 7.2 Hz).

HRMS (Cl) calcd. for C₁₀H₁₅IO₃ 310.0066. Found 310.0042.
Alcohol 38a.

$^1$H NMR (C$_6$D$_6$) $\delta$ 6.06 (1H, s), 5.25 (1H, s), 4.05 (1H, d, $J = 6.3$ Hz), 3.62 (2H, q, $J = 7.2$ Hz), 3.44 (2H, q, $J = 7.2$ Hz), 1.07 (6H, t, $J = 7.2$ Hz), 0.46 (OH, br s).

Z-6,6-Diethoxy-2-iodo-hex-2-en-4-yn-1-pivaloate (65).

![Chemical Structure](image)

To a stirred solution of 38 (142 mg, 0.458 mmol) in CH$_2$Cl$_2$ (4 mL) was added Et$_3$N (181 mg, 250 $\mu$L, 0.0179 mmol) followed by DMAP (10 mg, 0.082 mmol) and PivCl (100 $\mu$L, 97.9 mg, 0.812 mmol). After 5 min, the orange solution was diluted with CH$_2$Cl$_2$ (50 mL), quenched with saturated aqueous NaHCO$_3$ (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The dried (MgSO$_4$) extract was concentrated $in$ vacuo and was purified by chromatography over silica gel, eluting with 10% Et$_2$O / petroleum ether, to give 65 (175 mg, 0.444 mmol, 97%) as a colorless oil.

IR 2976, 2932, 2883, 2222, 1738 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$ 6.42 (1H, m), 5.41 (1H, d, $J = 1.4$ Hz), 4.76 (2H, d, $J = 1.4$ Hz), 3.5 - 3.9 (4H, m), 1.1 - 1.3 (15H, m).
$^{13}$C NMR (CDCl$_3$) $\delta$ 176.9, 118.6, 111.3, 91.5, 90.6, 84.0, 70.3, 61.0, 38.7, 27.0, 15.0.

HRMS (Cl) calcd for C$_{15}$H$_{23}$O$_4$I 395.0719. Found 395.0705.

Z-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-hydroxycyclopent-2-en-1-one ethylene ketal (67).

To a stirred solution of CuI (1.64 g, 0.86 mmol) in degassed PhH (150 mL) was added $n$-BuNH$_2$ (5.84 g, 7.9 mL, 0.080 mol), followed by a solution of 65 (4.50 g, 11.4 mmol) in degassed PhH (50 mL). Additional degassed PhH (200 mL) was added followed by freshly prepared Pd(PPh$_3$)$_4$S (5.80 g, 5.0 mmol) and 42 (2.37 g, 14.3 mmol). Within 1 h, the solution had turned dark red. After 9.75 h, the dark reaction mixture was diluted with Et$_2$O (300 mL), poured into saturated aqueous NH$_4$Cl (400 mL) and extracted with Et$_2$O (3 x 400 mL). The dried (MgSO$_4$) extract was concentrated in vacuo to give a crude slurry which was purified by chromatography over silica gel, eluting with 50% Et$_2$O / petroleum ether, to give 67 (2.46 g, 5.7 mmol, 50%) as a yellow oil.
IR 3435, 2976, 1732, 1480 cm⁻¹.

¹H NMR (CDCl₃) δ 6.05 (1H, d, J = 5.7 Hz), 5.85 - 5.95 (1H, m), 5.85 (1H, d, J = 5.7 Hz), 5.42 (1H, d, J = 1.4 Hz), 4.78 (2H, d, J = 1.4 Hz), 3.94 (4H, s), 3.5 - 3.9 (4H, m), 2.80 (1H, s), 2.63 (1H, d, J = 14.1 Hz), 2.39 (1H, d, J = 14.1 Hz), 1.1 - 1.3 (15H, m).

¹³C NMR (CDCl₃) δ 177.4, 139.0, 132.8, 130.9, 117.2, 115.1, 99.3, 91.5, 82.1, 80.3, 74.0, 65.7, 64.9, 64.8, 64.3, 60.9, 51.7, 27.0, 14.9.

HRMS (Cl) calcd for C_{24}H_{32}O_{7} 432.2148. Found 432.2145.

Z-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-3-en]-4-[tert-butyldimethylsilyl(oxy)] cyclopent-2-en-1-one ethylene acetal (64).

![Chemical Structure](image)

To a stirred solution of 67 (45.0 mg, 0.104 mmol) in CH₂Cl₂ (1 mL) and Et₃N (1 mL) was added TBSOTf (57.5 mg, 50 μL, 0.218 mmol). An additional amount of TBSOTf (57.5 mg, 50 μL, 0.218 mmol) was added during the course of the reaction. After 3 h, the reaction mixture was diluted with CH₂Cl₂ (20 mL), quenched with saturated aqueous NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3
x 20 mL). The dried (MgSO₄) extract was concentrated in vacuo to give a crude slurry which was purified by chromatography over silica gel, eluting with 30% Et₂O / petroleum ether, to give 64 (57.0 mg, 0.104 mmol, 99%) as a pale yellow oil.

IR 2974, 2930, 2285, 1734 cm⁻¹.

¹H NMR (CDCl₃) δ 7.00 (1H, d, J = 5.6 Hz), 5.9 - 5.95 (1H, m), 5.76 (1H, d, J = 5.6 Hz), 5.41 (1H, d, J = 1.1 Hz), 4.56 (2H, d, J = 1.1 Hz), 3.85 - 3.95 (4H, m), 3.5 - 3.8 (4H, m), 2.68 (1H, d, J = 13.8 Hz), 2.34 (1H, d, J = 13.8 Hz), 1.2 (15H, m), 0.84 (9H, s), 0.18 (3H, s), 0.17 (3H, s).

¹³C NMR (CDCl₃) δ 177.4, 140.0, 131.4, 130.1, 118.9, 117.1, 115.0, 99.9, 91.7, 91.5, 81.9, 80.7, 75.4, 64.9, 64.8, 62.4, 61.0, 60.8, 53.7, 38.8, 27.1, 25.5, 17.8, 15.2, 15.0, -3.0.

HRMS (EI) calcd for C₃₀H₄₇O₇Si 547.3091. Found 547.3082.
Z-4-[3-Pivaloyl(oxy)methyl-7,7-diethoxy-hept-1,5-diyn-5,5-η²-dicobalthexacarbonyl-3-en]-4-[tert-butyldimethylsilyl(oxy)]cyclopent-2-en-1-one ethylene acetal (68).

To a stirred solution of 64 (224 mg, 0.410 mmol) in pentane (25 mL) was added Co₂(CO)₈ (140 mg, 0.410 mmol). After 1.5 h, the solution was concentrated in vacuo to give a crude oil which was purified by chromatography over silica gel, eluting with 30% Et₂O/petroleum ether, to give 68 (333 mg, 0.40 mmol, 98%) as a red oil.

IR 2930, 2055, 2027, 1732 cm⁻¹.
¹H NMR (CDCl₃) δ 6.09 (1H, d, J = 5.6 Hz), 5.71 (1H, d, J = 5.6 Hz), 5.68 (1H, s), 4.58 (2H, s), 3.5 - 3.9 (4H, m), 3.35 - 3.45 (4H, m), 2.98 (1H, d, J = 14.1 Hz), 2.68 (1H, d, J = 14.1 Hz), 1.15 - 1.25 (15H, m), 0.99 (9H, s), 0.28 (6H, s).
HRMS (CI) calcd for C₃₆H₄₆Co₂O₁₃Si 833.1450. Found 833.1455.
Z-4-[3-Pivaloyl(oxy)methyl-7-oxa-hept-1,5-diyn-5,6-\(\eta^2\)-dicobalthexacarbonyl-3-en]-4-[\(\text{tert}\)-butyl dimethylsilyl(oxy)]cyclopent-2-en-1-one (63).

To a stirred solution of 68 (105 mg, 0.126 mmol) in THF (10 mL) and H\(_2\)O (5 mL) was added PTSA (5.0 g, 0.026 mol). After 20 min, the reaction mixture was diluted with Et\(_2\)O (25 mL), quenched with saturated aqueous NaHCO\(_3\) (50 mL) and extracted with Et\(_2\)O (3 x 50 mL). The dried (MgSO\(_4\)) extract was concentrated \(\text{in vacuo}\) to give a red oil which was purified by chromatography over silica gel, eluting with 30% Et\(_2\)O/petroleum ether, to give 63 (86 mg, 0.12 mmol, 96%) as a red oil.

IR 2959, 2932, 2859, 2102, 2067, 2037, 1728, 1663 cm\(^{-1}\).

\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 10.31 (1H, s), 6.65 (1H, s), 5.88 (1H, d, J = 5.4 Hz), 4.21 (2H, apparent d), 2.99 (1H, d, J = 18.3 Hz), 2.68 (1H, d, J = 18.3 Hz), 1.14 (9H, s), 0.88 (9H, s), 0.12 (3H, s), 0.12 (3H, s).

\(^{13}\)C NMR (C\(_6\)D\(_6\)) \(\delta\) 202.9, 189.0, 177.0, 161.0, 134.4, 133.2, 129.8, 120.9, 102.1, 83.4, 82.5, 73.5, 65.4, 52.3, 38.8, 27.1, 25.9, 18.0, -2.81, -2.81.

HRMS (Cl) calcd for C\(_{30}\)H\(_{33}\)Co\(_2\)O\(_{11}\)Si 715.0518. Found 715.0456.
1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methyl-8α-hydroxy-9α-H-bicyclo[7.3.0]dodeca-2,6-diyn-6,7-η2-dicobalthexacarbonyl-4,11-dien-10-one (62).

![Chemical structure diagram]

To a stirred solution of CH₂Cl₂ (125 mL) and Et₃N (2.47 g, 3.4 mL, 0.0244 mol) at ambient temperature was added n-Bu₂BOTf (2.35 g, 2.1 mL, 8.58 mmol) followed by a solution of 63 (204 mg, 0.286 mmol) in CH₂Cl₂ (50 mL) via syringe pump over 5.5 h. After an additional 1 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (500 mL) and extracted with CH₂Cl₂ (4 x 500 mL). The dried (MgSO₄) extract was concentrated in vacuo to give a red oil which was purified by PLC, eluting with 30% Et₂O/petroleum ether, to give 62 (150 mg, 0.210 mmol, 74%) as a red oil.

IR 3482, 2957, 2930, 2858, 2093, 2055, 2029, 1734, 1718 cm⁻¹.

¹H NMR (CD₆D₆) δ 6.81 (1H, d, J = 5.7 Hz), 6.78 (1H, s), 5.71 (1H, d, J = 5.7 Hz), 5.53 (1H, apparent t), 4.37 (1H, d, J = 12.9 Hz), 4.22 (1H, d, J = 12.9 Hz), 3.22 (1H, d, J = 6.7 Hz), 3.10 (1H, bd, J = 5.1 Hz), 1.16 (9H, s), 0.89 (9H, s), 0.22 (3H, s), 0.15 (3H, s).

67
HRMS (FAB) calcd for C_{30}H_{31}Co_{2}O_{11}Si 713.0299. Found 713.0298.

1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η2-dicobalthexacarbonyl-4,8,11-trien-10-one (61).

To a stirred solution of 62 (56.2 mg, 0.0787 mmol) in CH₂Cl₂ (6 mL) was added Et₃N (406 mg, 560 μL, 4.02 mmol), followed by DMAP (39 mg, 0.32 mmol) and MsCl (103.6 mg, 70 μL, 0.904 mmol) at ambient temperature. After 1.5 h, the reaction mixture was diluted with Et₂O (20 mL), extracted with 10% aqueous sodium tartrate (20 mL), saturated aqueous NaHCO₃ (20 mL), CuSO₄ (20 mL, 1 M in H₂O) and saturated aqueous NaCl (20 mL). The dried (MgSO₄) extract was concentrated in vacuo to give 61 (53.0 mg, 0.0761 mmol, 97%) as a red oil.

IR 2958, 2930, 2858, 2060, 2029, 1730, 1707 cm⁻¹.

¹H NMR (C₆D₆) δ 7.82 (1H, s), 6.80 (1H, d, J = 6.0 Hz), 6.69 (1H, s), 5.92 (1H, d, J = 6.0 Hz), 4.32 (2H, s), 1.17 (9H, s), 0.87 (9H, s), 0.08 (3H, s), 0.06 (3H, s).
$^{13}$C NMR ($C_6D_6$) δ 198.4, 192.1, 177.1, 155.2, 141.6, 140.5, 135.1, 133.2, 120.4, 103.1, 93.1, 85.0, 82.4, 70.0, 63.2, 38.8, 27.2, 25.9, 18.4, -2.27, -2.33.

HRMS (Cl) calcd for C$_{30}$H$_{31}$Co$_2$O$_{10}$Si 697.0351. Found 697.0360.

$\alpha$-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-6-yne-6,7-η$^2$-dicobalthexacarbonyl-2,4,8,11-tetraen-10-one (69).

![Chemical Reaction Diagram]

To a stirred solution of 61 (11.4 mg, 0.0164 mmol) in PhH (1.5 mL) at 10°C was added [(Ph$_3$P)CuH]$_6$ (6.0 mg, 0.00306 mmol, 0.184 equiv). After 3 h, the mixture was quenched with saturated aqueous NaCl (15 mL) and extracted with Et$_2$O (3 x 15 mL). After drying (MgSO$_4$), the solvent was evaporated in vacuo and the residue was purified by PLC, eluting with 20% Et$_2$O / petroleum ether, to give 69 (2.9 mg, 0.0042 mmol, 26%) as a red oil.

IR 2929, 2055, 2025, 1733, 1703, 1608 cm$^{-1}$.

$^1$H NMR ($C_6D_6$) δ 7.56 (1H, s), 6.75 (1H, d, 5.8 Hz), 6.63 (1H, s), 5.99 (1H, d, J = 5.8 Hz), 5.49 (1H, d, J = 12.6 Hz), 5.19 (1H, d, J = 12.6 Hz), 4.59 (1H, d, J =
14.7 Hz), 4.47 (1H, d, J = 14.7 Hz), 1.20 (9H, s), 0.81 (9H, s), -0.02 (3H, s), -0.03 (3H, s).

HRMS (Cl) calcd for C\textsubscript{30}H\textsubscript{33}Co\textsubscript{2}O\textsubscript{10}Si 699.0507. Found 699.0524.

1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyne-6,7-η\textsubscript{2}-dicobalthexacarbonyl-4,8-dien-10-one (54).

To a stirred (10 min) solution of ZnCl\textsubscript{2} (6.1 mg, 0.045 mmol) in Et\textsubscript{2}O (4 mL) was added NaBH\textsubscript{3}CN (4.7 mg, 0.075 mmol) at ambient temperature. After 11 min, the heterogenous solution was cooled to 0°C and a solution of 61 (36.5 mg, 0.052 mmol) in Et\textsubscript{2}O (2 mL) was added followed by TMSCl (8 μL, 6.8 mg, 0.063 mmol) via syringe. After 1 h at 0°C and 2 h at 25°C, the mixture was recooled to 0°C and 3-phenyl-2-phenylsulfonyle oxaziridine\textsuperscript{7} (70) (65 mg, 0.249 mmol) added over a 15 min period. After an additional 5 min at 0°C, the solution was warmed to 25°C and diluted with saturated aqueous NaHCO\textsubscript{3} (10 mL). The phases were separated and the aqueous phase was extracted with Et\textsubscript{2}O (3 x 10 mL). The dried (MgSO\textsubscript{4}) extract was evaporated \textit{in vacuo} and the residue was
purified by PLC, eluting with 30% Et₂O / petroleum ether, to give 54 (13.0 mg, 0.019 mmol, 36%) as a red oil.

IR 2931, 2060, 2029, 1724, 1640, 1577 cm⁻¹.

¹H NMR (CD₆D) δ 7.55 (1H, s), 6.67 (1H, s), 4.36 (2H, s), 2.4 - 2.6 (1H, m), 1.9 - 2.1 (2H, m), 1.6 - 1.8 (1H, m), 1.18 (9H, s), 0.87 (9H, s), 0.25 (3H, s), 0.22 (3H, s).

¹³C NMR (CD₆D) δ 202.2, 197.8, 177.1, 140.3, 139.7, 130.0, 120.3, 103.5, 89.3, 83.8, 81.0, 73.1, 63.4, 38.9, 35.6, 34.6, 27.2, 25.7, 18.2, -2.9.

HRMS (FAB) calcd for C₃₀H₃₃Co₂O₁₀Si 699.0510. Found 699.0500.

1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diy-6,7-η²-dicobalthexacarbonyl-11-bromo-4,8-dien-10-one (71).

![Chemical Structure](image)

To a stirred solution of 54 (16.6 mg, 0.0238 mmol) in THF (2 mL) at -78°C was added LHMDS (40 μL, 0.04 mmol, 1 M in THF). After 25 min, a precooled solution of Br₂ (4.7 mg, 1.5 μL, 0.029 mmol) in THF (0.3 mL) was added via cannula. After 17 min, the reaction mixture was quenched with
saturated aqueous NH₄Cl (1 mL) and allowed to warm to ambient temperature. The mixture was further diluted with saturated aqueous NH₄Cl (15 mL) and extracted with CH₂Cl₂ (3 x 15 mL). After drying (MgSO₄), the solvent was evaporated in vacuo and the residue was purified by PLC, eluting with 20% Et₂O / petroleum ether, to give 71 (8.2 mg, 0.0106 mmol, 44%) as a red oil.

IR 2929, 2095, 2064, 2051, 1732, 1641 cm⁻¹.

¹H NMR (C₆D₆) δ 7.66 (1H, s), 6.64 (1H, d, 1.2 Hz), 4.77 (1H, dd, J = 8.1, 11.1 Hz), 4.3 - 4.35 (2H, m), 2.75 (1H, dd, J = 8.1, 13.2 Hz), 2.23 (1H, dd, J = 11.1, 13.2 Hz), 1.17 (9H, s), 0.78 (9H, s), 0.17 (3H, s), 0.15 (3H, s).

HRMS (CI) calcd for C₃₀H₃₂BrCo₂O₁₀Si 776.9612. Found 776.9627.
1α-tert-Butyldimethylsilyl(oxy)-4-hydroxymethylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η2-dicobalt hexacarbonyl-4,8-dien-10α-ol (72).

To a stirred solution of 54 (12 mg, 0.017 mmol) in PhMe (3 mL) was added dropwise a solution of DIBAL-H (60 μL, 0.060 mmol, 1.0 M in CH₂Cl₂) at -78°C. After 35 min, MeOH (50 μL) was added followed by saturated aqueous NH₄Cl (2 mL). The solution was allowed to warm to 25°C. The phases were separated and the aqueous phase extracted with Et₂O (4 x 5 mL). The dried (MgSO₄) extract was evaporated in vacuo and the residue was purified by PLC, eluting with 30% Et₂O / petroleum ether, to give 72 (6.0 mg, 0.0097 mmol, 57%) as a red oil.

IR 3417, 2929, 2857, 2089, 2054, 2023 cm⁻¹.

¹H NMR (C₆D₆) δ 6.76 (1H, s), 6.71 (1H, s), 4.2 - 4.3 (1H, m), 3.6 - 3.7 (2H, m), 2.64 (OH, d, J = 10.0 Hz), 1.2 - 2.1 (4H, m), 0.90 (9H, s), 0.71 (OH, t, J = 6.1 Hz), 0.29 (3H, s), 0.27 (3H, s).

HRMS (Cl) calcd for C₂₅H₂₆Co₂O₅Si 616.0010. Found 615.9985.
1α-tert-Butyldimethylsilyl(oxy)-4-[1-naphthoyl(oxy)]methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η2-dicobalthexacarbonyl-4,8-dien-10α-ol (73).

To a stirred solution of 72 (5.7 mg, 0.0093 mmol) in CH₂Cl₂ (1 mL) was added Et₃N (22 mg, 30 µL, 0.22 mmol) followed by 1-naphthoyl chloride (1.8 mg, 1.4 µL, 0.0093 mmol) at -5°C. After 1.5 h, saturated aqueous NH₄Cl (2 mL) was added and diluted with Et₂O (4 mL). The mixture was allowed to warm to 25°C and the phases were separated. The aqueous phase was extracted with Et₂O (4 x 5 mL). The dried (MgSO₄) extract was evaporated in vacuo and the residue was purified by PLC, eluting with 30% Et₂O / petroleum ether, to give 73 (5.5 mg, 0.0071 mmol, 77%) as a red oil.

IR 3550, 2930, 2361, 2055, 2023, 1720 cm⁻¹.

¹H NMR (CD₆D₆) δ 9.41 (1H, dd, J = 1.2, 8.4 Hz), 8.32 (1H, dd, J = 1.2, 7.5 Hz), 7.59 (1H, d, J = 8.0 Hz), 7.52 (1H, dd, J = 8.0, 0.6 Hz), 7.42 (1H, ddd, J = 1.5, 1.8, 8.0 Hz), 7.0 - 7.3 (2H, m), 6.76 (1H, s), 6.70 (1H, s), 4.5 - 4.7 (2H, m), 4.1 -
4.3 - 4.35 (1H, m), 2.62 (OH, d, J = 10.2 Hz), 1.4 - 2.1 (4H, m), 0.82 (9H, s), 0.22 (3H, s), 0.16 (3H, s).

HRMS (Cl) calcd for C\textsubscript{36}H\textsubscript{32}Co\textsubscript{2}O\textsubscript{10}Si 770.0429. Found 770.0357.

1\textalpha-\textit{tert}-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-\eta\textsuperscript{2}-dicobalthexacarbonyl-4,8,11-trien-10-ol (76).

To a stirred solution of 61 (5.1 mg, 7.3 \textmu mol) in MeOH (0.5 mL) was added CeCl\textsubscript{3} (43 mg, 0.174 mmol), followed by NaBH\textsubscript{4} (0.3 mg, 7 \textmu mol). After 5 min, the reaction mixture was concentrated and purified by PLC, eluting with 30% Et\textsubscript{2}O/petroleum ether, to give 76 (2.0 mg, 2.9 \textmu mol, 40% yield) as a red oil.

IR: 3451, 2926, 2856, 2089, 2054, 2023, 1737 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (C\textsubscript{6}D\textsubscript{6}) \delta 6.81 (1H, d, J = 1.2 Hz), 6.71 (1H, s), 5.83 (1H, dd, J = 1.8, 6.0 Hz), 5.60 (1H, dd, J = 1.2, 6.0 Hz), 4.95 - 5.0 (1H, m), 4.38 (2H, s), 1.18 (9H, s), 0.93 (9H, s), 0.22 (3H, s), 0.14 (3H, s).

HRMS (Cl) calcd. for C\textsubscript{30}H\textsubscript{33}Co\textsubscript{2}O\textsubscript{10}Si 699.0507. Found 699.0529.
1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,8,10-trien-10-tert-butyldimethylsilyl(oxy)-12-S-phenyl (81) and 1α-tert-Butyldimethylsilyl(oxy)-4-pivaloyl(oxy)methylbicyclo[7.3.0]dodeca-2,6-diyn-6,7-η²-dicobalthexacarbonyl-4,8-dien-10-one-12-thiophenyl ether (82).

\[
\begin{align*}
\text{To a stirred solution of AlMe}_3 \ (100 \ \mu\text{L}, 0.20 \ \text{mmol}, 2 \ \text{M in CH}_2\text{Cl}_2) \text{ in CH}_2\text{Cl}_2 \ (10 \ \text{mL}) \text{ at } 0^\circ\text{C was added PhSH} \ (22 \ \text{mg}, 20.5 \ \mu\text{L}, 0.20 \ \text{mmol}). \text{ After 20 min, the resulting solution (PhSAIme}_2) \text{ was cooled to } -78^\circ\text{C and THF} \ (15.1 \ \text{mg}, 17 \ \mu\text{L}, 0.21 \ \text{mmol}) \text{ was added dropwise. After 10 min, TBSOTf} \ (63.3 \ \text{mg}, 55 \ \mu\text{L}, 0.239 \ \text{mmol}) \text{ and a solution of } 61 \ (115 \ \text{mg}, 0.165 \ \text{mmol}) \text{ in CH}_2\text{Cl}_2 \ (10 \ \text{mL}) \text{ were simultaneously added to the PhSAIme}_2^\ast\text{THF solution. After 50 min, the reaction mixture was warmed to } 0^\circ\text{C for 20 min and r.t. for 5 min. The reaction mixture was diluted with CH}_2\text{Cl}_2 \ (40 \ \text{mL}), \text{ quenched with saturated aqueous NaHCO}_3 \ (60}\end{align*}
\]
mL) and extracted with CH₂Cl₂ (3 x 50 mL). After drying (MgSO₄), the solvent was evaporated in vacuo and the residue was purified by PLC, eluting with 20% Et₂O / petroleum ether, to give 81 (47 mg, 0.051 mmol, 31%) as a red oil and 82 (17 mg, 0.021 mmol, 13%) as a red oil.

**Enol ether 81.**

IR 2957, 2058, 2054, 2024, 1732 cm⁻¹.

¹H NMR (C₆D₆) δ 7.62 (2H, d, J = 7.2 Hz), 6.8 - 7.2 (3H, m), 6.91 (1H, s), 6.70 (1H, s), 5.26 (1H, d, J = 2.7 Hz), 4.3 - 4.4 (2H, m), 4.20 (1H, d, J = 3.3 Hz), 1.18 (9H, s), 0.94 (9H, s), 0.93 (9H, s), 0.27 (3H, s), 0.23 (3H, s), 0.11 (3H, s), 0.08 (3H, s).

HRMS (CI) calcd for C₄₂H₅₀Co₂O₁₀SSi₂ 930.1327. Found 930.1414.

**Ketone 82.**

IR 2956, 2857, 2094, 2061, 2030, 1727, 1634 cm⁻¹.

¹H NMR (C₆D₆) δ 7.77 (1H, s), 6.8 - 7.4 (5H, m), 6.68 (1H, s), 4.25 - 4.35 (2H, m), 3.96 (1H, d, J = 6.5 Hz), 3.02 (1H, dd, J = 6.5, 18.6 Hz), 2.48 (1H, d, J = 18.6 Hz), 1.17 (9H, s), 0.85 (9H, s), 0.30 (3H, s), 0.23 (3H, s).

HRMS (CI) calcd for C₃₆H₃₇Co₂O₁₀SSi 807.0541. Found 807.0546.


Section 4:
The Chemistry and Biology of Eleutherobin and Related Compounds
1 Background of Eleutherobin and Related Compounds

1.1 Introduction

The eunicellans are a class of marine diterpenes possessing the core carbon skeleton shown in the diterpene 1 (Figure 1).\textsuperscript{1} Although there are over thirty known members of this family of diterpenes,\textsuperscript{2} relatively little interest has been focused on their synthesis or biological activity [with the notable exception of Overman and co-workers' synthetic efforts toward eunicellin (2)].\textsuperscript{3} Also, two members of the eunicellans have shown interesting \textit{in vitro} cytotoxic activity: sclerophytin A (3)\textsuperscript{4} and eleutherobin (4).\textsuperscript{5}
Figure 1: Members of the Eunicellan Class of Diterpenes

Eleuthoside A (5) and B (6), two compounds that are closely related to Eleutherobin (4), possess a similar structure to sarcodictyin A - F (7 - 12 respectively), as well as valdivone A (13), 4-O-methyl valdivone A (14), valdivone B (15), 4-O-methyl valdivone B (16), and dihydrovaldivone (17), as shown in Figure 2. The focus of this dissertation will be directed towards eleutherobin (4).
Figure 2: The Eleutherobin, Sarcodictyin and Valdivone Diterpenes
1.2 Isolation and Biological Activity of Eleutherobin5

Eleutherobin (4) was isolated from the fermentation broth of the soft, red-colored coral *Eleutherobia cf. albiflora*, found in the Indian Ocean. The structure was elucidated by a variety of NMR techniques and mass spectroscopy. Although the absolute stereochemistry is unknown at this time, it is believed to be as shown by analogy to the previously mentioned natural products (see Section 4.1.1).

Eleutherobin (4) has been shown to possess cytotoxic activity with a IC50 of 10.7 nM against the HCT116 human colon carcinoma cell line and a IC50 of 13.7 nM against the A2780 human ovarian carcinoma cell line (Table 1). Also, compound 4 was tested against a multidrug resistant subline, HCT116 / VM46, which overexpresses P-glycoprotein and is greater than 100-fold resistant to another diterpene: taxol (18)9 (Figure 3). Eleutherobin (4) was found to be 52-fold cross resistant in the HCT116 / VM46 subline.5 Unfortunately, substantial amounts of 4 are unavailable which makes further testing, including *in vivo* testing, impossible.
Figure 3: Cytotoxic Compounds 4 and 18

<table>
<thead>
<tr>
<th>Cell line</th>
<th>HCT116</th>
<th>HCT116 / VM46</th>
<th>A2780</th>
</tr>
</thead>
<tbody>
<tr>
<td>taxol (18)</td>
<td>4.6</td>
<td>5.37 (117)**</td>
<td>6.7</td>
</tr>
<tr>
<td>eleutherobin (4)</td>
<td>10.7</td>
<td>554 (52)</td>
<td>13.7</td>
</tr>
</tbody>
</table>

* Cytotoxicity was determined by XTT assay after 3 days.
** Value in parenthesis is fold resistance as compared to the corresponding parent cell line.

Table 1: In vitro Cytotoxicity Activity of Taxol (18) and Eleutherobin (4)

1.3 Fragmentation Patterns of the Sarcodictyins

Although very little is known about the stability or inherent chemistry of eleutherobin (4), Pietra and co-workers were able to study the sarcodictyin diterpenes. They found that treatment of the diterpene 7 with basic methanol for three hours gave the alcohol 19 in 48% yield (Scheme 1). Furthermore, prolonged reaction time (four days) under similar conditions led to cleavage of the
C-3,4 bond and a possible mechanism is illustrated below. Following removal of the C-8 ester moiety, the C-8 hydroxyl functionality adds to the enone at the C-2 position. Subsequent proton transfer from the C-4 hydroxyl and retro-Claisen reaction yields the butenolide 22 and its methanol adduct 23.\(^\text{11}\)

\[\text{7} \xrightarrow{\text{i}} \text{19} \xrightarrow{\text{ii}} \text{20} \]

\[\text{22} \rightleftharpoons \text{21} \]

i) MeOH, \text{NaOMe}, 25\text{oC}, 3 h, 19 (48%); ii) MeOH, KOH, 25\text{oC}, 4 days, 22 (50%), 23 (33%).

Scheme 1: Fragmentation of \text{7}

Interestingly, treatment of the alcohol 9 with basic methanol does lead to the similar type of the retro-Claisen pathway shown in Scheme 1 to yield compounds 24 and 25, but another cleavage pattern is also observed (Scheme 2).
In contrast to the C-13 deoxy compound 7, cleavage of the C-7,8 bond in the butenolide 27 occurs to give the aldehyde 28 and, it is presumed, the butenolide 29. For the sacrodictyins, this second cleavage pathway was found to require the C-13 hydroxyl functionality.

\[
\text{MeOH, KOH, 25^\circ C, 4 days, 24 (35\%), 25 (35\%), 28 (12\%).}
\]

Scheme 2: Fragmentation of 9

Treatment of diterpene 9 with CD$_3$OD / KOD led to butenolide 30 and its O-methyl adduct 31 with deuterium incorporation at as shown below (Scheme 3). It is worth noting that compounds, such as the appropriately deuterated version of the aldehyde 28, were reported in trace amounts in this experiment.$^{11}$

86
Scheme 3: Possible Mechanism for Deuterium Incorporation in Diterpene 9

The surprising stereospecific incorporation of the C-9 deuterium appears to occur prior to cleavage of the C-3,4 bond; treatment of the butenolide 25 with CD3OD / KOD for one week yields no significant incorporation of deuterium at the C-9 position. Although no mechanism has been put forward by Pietra and co-workers to explain this unusual C-9 deuteration, a possible explanation is shown below involving stereospecific enolization and deuteration of the aldehyde 35 under the reaction conditions (Scheme 4). Based on these results, it was believed that the cleavage pathway of C-7,8 bond, observed in sarcodictyin C (9), should not occur in eleutherobin (4) due to the lack of the C-13 hydroxyl functionality.7
Scheme 4: Deuterium Incorporation in Diterpene 9

1.4 Synthetic Efforts Towards Eunicellin

Although there have been no synthetic efforts to date towards cletherobin (4), Overman and co-workers have recently reported their approach toward eunicellin (2) which resulted in the synthesis of (-)-7-deacetoxyalcyonin acetate (48). Their strategy involves a Prins-Pinacol reaction of the diol 39 and the aldehyde 40 to set the C-1,10 cis-ring fusion and subsequent Nozaki coupling of the aldehyde 46 to form the core ring system 47 shown below (Scheme 5).
Scheme 5: Synthesis of Diterpene 48

i) t-BuLi, -78°C then 38; ii) PPTS, MeOH, 64%; iii) 40, BF$_3$-Et$_2$O, CH$_2$Cl$_2$, -55°C to -20°C, 79%; iv) AcOH, H$_2$O; v) hv, 72%; vi) (+)-DET, Ti(Oi-Pr)$_4$, TBHP, 4 Å molecular sieves, -20°C; vii) Red-Al$^\text{®}$, THF, -15°C, then H$_2$O, 79%; viii) PivCl, py; ix) TBSOTf, 2,6-lutidine, 84%; x) B-I-9-BBN, AcOH; xi) Dibal-H; xii) TPAP, NMO, 93%; xiii) Ph$_3$P=CHMe, THF, -30°C; xiv) TiOH, i-PrOH, CH$_2$Cl$_2$, 77%; xv) NiCl$_2$, CrCl$_2$, DMSO, 65%; xvi) Ac$_2$O, py; xvii) TBAF, 88%.
1.5 Conclusion

Although Overman's synthesis of (-)-7-deacetoxyalcyonin acetate (48) is concise and elegant, it is not readily apparent that this strategy could be applied to the synthesis of eleutherobin (4) or the eleuthosides and the sarcodictyins. Also, since significant amounts of 4 are not available from natural sources, a synthetic route is necessary in order to further study its cytotoxicity. In addition, relatively little is known about the eunicellan family of diterpenes. For these reasons, a novel strategy had to be developed in order to construct these compounds. The strategy should be enantioselective and primarily focus on eleutherobin (4) due to its promising cytotoxic activity.
1 The numbering system shown will the core skeleton 1 will be used through this dissertation. Roussis, V.; Fenical, W.; Vagias, C.; Kornprobst, J.-M.; Miralles, J. Tetrahedron 1996, 52, 2735.


Section 5: Discussion of Results
1 Initial Aldol Approach to Eleutherobin

1.1 Retrosynthetic Strategy

Due to the challenging structural features and interesting biological activity of eleutherobin (4), a strategy was devised for its asymmetric construction (Scheme 1). The C-8 ester side chain and the carbohydrate moiety at C-15 should be accessible from commercially available urocanic acid (49) and D-arabinose (51) respectively. The two major synthetic challenges to the synthesis of the aglycon 50 are the control of its multiple stereogenic centers and the formation of the oxygenated B ring. Although the aglycon 50 contains 6 stereogenic centers, only control of the absolute stereochemistry at C-14 and C-7 should be necessary to establish all stereocenters in the diterpene 50. The isopropyl functionality at C-14 could be used to govern the stereochemistry at C-1 and C-10 and the tertiary hydroxyl function at C-7 should allow for the establishment of the C-4 and C-8 stereocenters.

Synthesis of the key B ring could be envisaged by formation of the C-2,3 olefin via a Mukaiyama-type\(^1\) condensation of the ester 52 which should, in turn, be accessible from the aldehyde 53 utilizing Wittig methodology\(^2\) (Scheme 1). Since formation of medium-sized rings are notoriously difficult, the strategy was devised to be flexible in order to circumvent any potential problems discovered during the course of the research. The key intermediate 53 should not only allow access to compounds such as ester 52, but also a wide range of substrates for formation of the crucial B-ring.
Scheme 1: Initial Retrosynthetic Analysis of Eleutherobin (4) to Key Intermediate 53

The aldehyde 53 may be prepared by a Julia coupling\(^3\) between the sulfone 55 and the aldehyde 56 (Scheme 2). The aldehyde 56 should be available from 2-methyl-2-propene-1-ol (58) using Sharpless methodology\(^4\) to establish the key C-7 stereocenter while the sulfone 55 could come from commercially available \((S)\)-\((+)-carvone (59) by way of hydroboration\(^5\) of the diene 57.
Scheme 2: Initial Retrosynthetic Analysis of Key Intermediate 53

1.2 Construction of Eastern Fragment Aldehyde

The requisite aldehyde 56 was synthesized in 6 steps in an overall 45% yield as shown in Scheme 3. Sharpless asymmetric epoxidation of 2-methyl-2-propene-1-ol (58) followed by in situ protection gave the known epoxide 60 in 90% e.e.\(^4\) The e.e. could be improved to >98% by recrystallization in diisopropyl ether, as determined using the chiral NMR shift reagent\(^6\) Eu(hfc)\(_3\) in benzene-\(d_6\). The epoxide 60 was converted into the diol 61\(^7\) and protected as its cyclohexyl ketal 62. After oxidation to the sulfoxide,\(^8\) Pummerer rearrangement\(^9\) gave 64 as a 1:1.6 mixture of inseparable diastereomers which could be converted into the desired aldehyde 56 via hydrolysis with basic methanol.\(^10\)
Scheme 3: Synthesis of Aldehyde 56

1.3 Construction of the Western Fragment Sulfone

As shown in Scheme 4, Takazawa and co-workers\textsuperscript{11} reported that treatment of the enol ether 65 with BF\textsubscript{3} \textbullet Et\textsubscript{2}O in the presence of triethylorthoformate led to acetals 66\textsubscript{a} and 66\textsubscript{b} in a 6.7:1 ratio of diastereomers (66\textsubscript{a}:66\textsubscript{b}). Although this exact transformation was not useful for the synthesis of eleutherobin (4), the Mukaiyama aldol\textsuperscript{1} concept was applicable.
Scheme 4: Synthesis of Acetal 66

After hydrogenation of (1S)-(−)-carvone (59), the crude enol ether 68 was allowed to react with trimethylorthoformate in the presence of BF$_3$·Et$_2$O to provide the acetal 69 as a single diastereomer in 48% yield over two steps from 67 (Scheme 5). This overall transformation could be improved by utilizing Evans' titanium enolate chemistry to yield the acetal 69 in 61% yield, again as a single diastereomer, together with 37% of the recovered starting material 67. The C-1 epimer was not observed in either the BF$_3$·Et$_2$O or the TiCl$_4$-mediated reactions.

Scheme 5: Synthesis of Acetal 69
Conversion of the enone 69 into the diene 57 was envisioned using ylide chemistry (Scheme 6, Table 1). Among the procedures that were examined were triphenylphosphonium methyliide,\textsuperscript{15} Lombardo's reagent (Zn / CH\textsubscript{2}Br\textsubscript{2} / TiCl\textsubscript{4}),\textsuperscript{16} Zn / Cp\textsubscript{2}ZrCl\textsubscript{2} / CH\textsubscript{2}Br\textsubscript{2},\textsuperscript{17} as well as TMSCH\textsubscript{2}MgBr and TMSCH\textsubscript{2}Li\textsuperscript{18} (Table 1). Isolation of the enol ether 70 (Entry 6) indicated that enolization at C-1 may be the cause for the decomposition of 69 observed under several conditions. Petasis and co-workers have reported that Cp\textsubscript{2}TiMe\textsubscript{2} has been successful with a diverse array of substrates, including easily enolizable systems\textsuperscript{19} and, indeed, treatment of the enone 69 with Cp\textsubscript{2}TiMe\textsubscript{2} in THF yielded the desired diene 57 in good yield (Entry 8).
Scheme 6: Synthesis of the Diene 57

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃P=CH₂, THF, reflux</td>
<td>decomp*</td>
</tr>
<tr>
<td>2</td>
<td>PhSO₂CH₂Li, THF, -78°C to 0°C</td>
<td>decomp</td>
</tr>
<tr>
<td>3</td>
<td>DMSO, NaH then Ph₃P+MeBr⁻, 55°C</td>
<td>decomp</td>
</tr>
<tr>
<td>4</td>
<td>Zn, Cp₂ZrCl₂, CH₂Br₂, THF, 25°C to 40°C</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>TMSCH₂MgBr, THF, -78°C to 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>6</td>
<td>TMSCH₂Li, THF, -78°C to 25°C</td>
<td>57 (35%) + 70 (44%)</td>
</tr>
<tr>
<td>7</td>
<td>Zn, CH₂Br₂, TiCl₄, CH₂Cl₂, 0°C to 25°C</td>
<td>57 (25%)</td>
</tr>
<tr>
<td>8</td>
<td>Cp₂TiMe₂, THF, reflux</td>
<td>57 (71%)</td>
</tr>
</tbody>
</table>

* decomp denotes no recognizable product could be observed.

Table 1: Attempted Methylenation of Enone 57

Hydroboration of the diene 57 was accomplished with 9-BBN²⁰ in THF (0.5 M, 1.1 equiv) to give, after oxidative workup, the desired alcohol 72 as a single diastereomer along with the diol 73²¹ (Scheme 7). The stereochemistry of
the alcohol 72 was proven by X-ray analysis of the corresponding PNB ester 74 (Figure 1).

\[
\begin{align*}
57 & \xrightarrow{i} 71 \xrightarrow{ii} 72, 73, 74 \\
\text{i) } & 9-	ext{BBN (1.1 equiv), THF, 50°C - 60°C, 72 (61%), 57 (22%), 73 (approx 15%)}; \text{ ii) PNBCl, im, DMAP, CH}_2\text{Cl}_2, 9\%.
\end{align*}
\]

Scheme 7: Hydroboration of Diene 57
Although 9-BBN is proposed to approach the C-9,10 olefin from the less hindered \( \beta \)-face (opposite the C-2 dimethyl acetal functionality); it is not believed that steric effects are not solely governing the high selectively of the hydroboration.\(^{22}\) One possible explanation is that the hydroboration of the C-9,10 olefin is reversible\(^{23}\) and driven to the desired C-10 stereochemistry by chelation of the 9-BBN adduct 71 by the C-2 dimethyl acetal function (Scheme 7).

It was found to be critical that the C-2 position was functionalized as a dimethyl acetal; attempted hydroboration of the ethylene glycol-derived acetal 75 gave inferior results (40 - 50% yield of 76) with significantly more dihydroboration to give the diol 77 (approximately 35% yield)\(^{10}\) (Scheme 8). Interestingly, no hydroboration was observed on either the dibenzyl acetal 78\(^{24}\) or the silyl ether 81\(^{25}\) which may be due destabilization of corresponding borane adducts 79 and 82 by increased steric bulk at C-2. It is well known that \textit{tert-}
butyldimethylsilyl ethers do not normally participate in chelation;\textsuperscript{26} however, it has recently been reported that this effect may due to steric effect instead of electronic effects.\textsuperscript{27} These results provided further evidence that the dimethyl acetal functionality preferentially stabilizes the 9-BBN adduct 71 via coordination to the boron atom.

\begin{equation}
\text{75} \xrightarrow{\text{i}} \text{76} + \text{77}
\end{equation}

\begin{equation}
\text{78} \xrightarrow{\text{ii}} \text{79} \rightarrow \text{80}
\end{equation}

\begin{equation}
\text{81} \xrightarrow{\text{ii or iii}} \text{82} \rightarrow \text{83}
\end{equation}

i) 9-BBN (1.1 equiv), THF, 50°C - 60°C, 76 (40 - 50%), 77 (approximately 35%); ii) 9-BBN (1.1 eq), THF, 50°C - 60°C; iii) 9-BBN (4 equiv), THF, 50°C - 60°C.

Scheme 8: Attempted Hydroboration of Dienes 75, 78 and 81

Numerous attempts were made to improve the yield of the hydroboration of the diene 57 without success. Varying the number of equivalents of 9-BBN led
to inferior yields. Other methods tried included (Ph$_3$P)$_3$RhCl / catecholborane,$^{28}$ Schwartz’s reagent (Cp$_2$ZrHCl)$^{29}$ and a variety of borane reagents,$^{30}$ but without success (Scheme 9, Table 2). Some conditions led to deprotection of the dimethyl acetal (Entries 6, 9 and 11) and, in one case, reduction of the acetal 57 to the O-methyl ether 85 (Entry 7). It is believed that these observations are due to the Lewis acidic nature of the borane species. Also, formation of O-methyl ether 85 in Entry 7 is presumably due to reduction of the corresponding oxonium ion.
Scheme 9: Attempted Hydroboration and Hydrometallation of Diene 57

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions*</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9-BBN (1.1 equiv), 50°C - 60°C, THF (0.5 M)</td>
<td>72 (61%) + 57 (22%) + 73 (approx 15%)</td>
</tr>
<tr>
<td>2</td>
<td>Cp$_2$ZrHCl, THF or PhH, sealed tube, 100°C</td>
<td>complex mixture**</td>
</tr>
<tr>
<td>3</td>
<td>BH$_3$•THF, THF, -10°C to 0°C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>BH$_3$•DMS, PhMe, 0°C to 25°C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>BH$_3$•NMe$_3$, PhMe, reflux</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

* All conditions involved a NaOH (4 M in H$_2$O) / H$_2$O$_2$ (30% in H$_2$O) quench (0°C to 25°C) of the borane adducts.

** complex mixture denotes numerous compounds could be observed, but attempted purification was unsuccessful.

Table 2: Attempted Hydroboration or Hydrometalation of Diene 57
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>BH$_3$·t-BuNH$_2$, THF, 25°C</td>
<td>![Chemical Structure 84]</td>
</tr>
<tr>
<td>7</td>
<td>(Ph$_3$P)$_3$RhCl, catecholborane, THF, 0°C to 25°C</td>
<td>![Chemical Structure 85]</td>
</tr>
<tr>
<td>8</td>
<td>Et$_2$BH, Et$_2$O, 0°C to 25°C</td>
<td>68:69 (1:1)</td>
</tr>
<tr>
<td>9</td>
<td>![Chemical Structure 86], THF, 0°C, to 25°C,</td>
<td>![Chemical Structure 84]</td>
</tr>
<tr>
<td>10</td>
<td>(H$_2$BH)$_2$, THF, reflux</td>
<td>complex mixture</td>
</tr>
<tr>
<td>11</td>
<td>![Chemical Structure 88], THF, reflux</td>
<td>![Chemical Structure 84]</td>
</tr>
</tbody>
</table>

Table 2 (Continued): Attempted Hydroboration or Hydrometalation of 57
It was hoped that conversion of the alcohol 72 into the sulfide 89 could be accomplished in the presence of the dimethyl acetal functionality as shown in Scheme 10. Unfortunately, attempted construction of the sulfide 89 using \(N\)-thiophenylsuccinimide and tributylphosphine\(^{31}\) led to the formation of the lactol \(92\).\(^{32}\) In addition, treatment of 72 with triphenylphosphine and carbon tetrabromide\(^{33}\) also yielded the lactol \(92\).\(^{25}\) It is believed that thiophenolate and bromide ion are the respective dealkylating agents in these reactions.

![Scheme 10: Attempted Conversion of 72 into Sulfide 89](image)

The above mentioned problem was solved by the construction of the sulfone \(98\) in 6 steps in overall 48% yield from the alcohol 72 (Scheme 11). Classical Jones oxidation\(^{34}\) of 72 gave cleanly the lactone \(93\). Since formation of the lactol \(92\) was instantaneous upon the addition of the acidic Jones' reagent (as followed by TLC), no oxidation of the C-9 hydroxyl function was observed. Subsequent \(O\)-alkyl cleavage of the lactone \(93\) with lithium phenyllithiate in DMF, followed by esterification and reduction provided the alcohol \(96\).\(^{35}\) Several oxidants were screened for the sulfide to sulfone oxidation and sodium tungstate
dihydrate was found to be the most efficient. Finally, silylation of the primary hydroxyl functionality yielded the desired sulfone 98 in excellent overall yield.

Scheme 11: Synthesis of Sulfone 98

1.4 Julia Coupling of Sulfone and Aldehyde

With a viable route to both the sulfone 98 and the aldehyde 56 in hand, attention was turned towards the Julia coupling between the two components. Treatment of the sulfone 98 with n-BuLi (1.03 equiv) followed by the addition of the aldehyde 56 yielded the coupled products 99a and 99b as a 50:1 mixture at the C-8 stereocenter in 66% yield (Scheme 12). The major component 99a possessed the incorrect stereochemistry at C-8 for eleutherobin (4) as shown by X-ray
crystal analysis (Figure 2).\textsuperscript{37} The same transformation could also be accomplished using EtMgBr\textsuperscript{38} (1.13 equiv) in PhH to give the sulfones 99\textsubscript{a} and 99\textsubscript{b} as a 10:1 mixture (99\textsubscript{a}:99\textsubscript{b}) at C-8 in 64\% yield. The latter organomagnesium method was preferred because it was found to be more reliable and more straightforward experimentally.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics{molecule}};
\node at (4,0) {\includegraphics{molecule}};
\node at (8,0) {\includegraphics{molecule}};
\node at (12,0) {\includegraphics{molecule}};
\node at (16,0) {\includegraphics{molecule}};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tabular}{lll}
\textbf{n-BuLi:} & d.s. 50:1 (99\textsubscript{a}:99\textsubscript{b}) \\
\textbf{EtMgBr:} & d.s. 10:1 (99\textsubscript{a}:99\textsubscript{b})
\end{tabular}
\end{center}

\textsuperscript{i}) n-BuLi (1.03 equiv), THF, -78\textdegree C to 0\textdegree C, then 56, -78\textdegree C to 25\textdegree C, 66\%; \textsuperscript{ii}) EtMgBr (1.13 equiv), PhH, reflux, then 56, 25\textdegree C, 64\%.

Scheme 12: Julia Coupling of Sulfone 98 and Aldehyde 56
1.5 Establishment of the Correct C-8 Stereochemistry

The stereochemistry of sulfone 99b was established by a series of correlation experiments. Separate dissolving metal reduction of the sulfones 99a and 99b gave the alcohols 100a and 100b respectively which conclusively established the C-8 stereochemistry in the sulfone 100b (Scheme 13).\textsuperscript{39} It is believed that the C-9 stereochemistry of the sulfone 99b was as drawn because oxidation\textsuperscript{40} of the mixture of sulfones 99a and 99b gave a single ketosulfone 101.
It is, however, possible that epimerization of the C-9 position in 101 could occur during the oxidation.

\[ \text{99a} \xrightarrow{i} \text{100a} \]
\[ \text{99b} \xrightarrow{ii} \text{100b} \]

\[ \text{99} \xrightarrow{iii} \text{102} \]

i) Na, NH\textsubscript{3}, THF, -78°C, 20%; ii) Na, NH\textsubscript{3}, THF, -78°C, 55%; iii) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}, 94%; iv) Na, NH\textsubscript{3}, THF, -78°C, 92%.

Scheme 13: Reduction of Sulfones 99a, 99b and 101

Subsequent reduction of the sulfone 101 under dissolving metal conditions\textsuperscript{41} gave the ketone 102 in good yield (Scheme 13). Several reagents were tried in order to reduce the C-8 ketone 102 diastereoselectively, including the catalytic chiral oxazaborolidine system\textsuperscript{42} (Scheme 14, Table 3). It is believed that substantial hydroboration of the C-11,12 olefin by BH\textsubscript{3}•DMS occurred in this
reaction (Entry 3) as shown analysis of the $^1$H NMR of the crude reaction mixture. It was found that DIBAL-H reduced the ketone 102 to preferentially give the alcohol 100a (Entry 4) possessing the incorrect stereochemistry at C-8 while the Selectride® reagents favored the desired C-8 stereochemistry with K-Selectride® yielding the best results (15:1, 100b:100a, 82% overall yield). Since this the structure of sulfone 99a was known from an X-ray structure, the stereochemistry from the reduction was assigned via the previously mentioned correlation experiments.
Scheme 14: Reduction of Ketone 102

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, MeOH</td>
<td>1:1 (100b:100a)</td>
</tr>
<tr>
<td>2</td>
<td>NaBH₄, CeCl₃, MeOH</td>
<td>1:1 (100b:100a)</td>
</tr>
<tr>
<td>3</td>
<td>103 BH₃·DMS, CH₂Cl₂, -20°C</td>
<td>1:1 (100b:100a)</td>
</tr>
<tr>
<td>4</td>
<td>DIBAL-H, CH₂Cl₂, -78°C</td>
<td>1:4 (100b:100a)</td>
</tr>
<tr>
<td>5</td>
<td>L-Selectride®, THF, -78°C to 0°C</td>
<td>4:1 (100b:100a)</td>
</tr>
<tr>
<td>6</td>
<td>K-Selectride®, THF, 0°C to 25°C</td>
<td>100b (77%) + 100a (5%) (15:1)</td>
</tr>
</tbody>
</table>

*The product ratios for entries 1 - 5 were determined by ¹H NMR of the crude reaction mixture and the product ratio for Entry 6 was determined by MPLC.

Table 3: Reduction of Ketone 102
1.6 Conversion to Internal Acetal

Protection of the C-8 hydroxyl function was briefly explored, but proved to be futile because the acidic conditions, necessary to remove the cyclohexylidene ketal, also removed the protecting group (silyl ether 104 and benzyl ether 105), presumably due to neighboring group participation (Scheme 15). Since the only isolated product from these reactions was the acetal 110, protection the C-8 hydroxyl functionality was effectively accomplished by the formation of the internal acetal shown in compound 110.

Scheme 15: Neighboring Group Participation Involved in Deprotection of Ethers 104 and 105
The C-2 stereochemistry of the acetal 110 can be readily deduced by the absence of any coupling for H-2 which is consistent with a 90° H-1,2 dihedral angle as shown in Figure 3. The stereochemistry of 110 was confirmed by an X-ray structure of a similar compound (see Section 5.1.8, Figure 4). In addition, inspection of models reveals that only one stereochemistry at C-2 is feasible. In order to maintain consistency throughout this dissertation, the style shown in drawing 2 will be used to represent this type of structure.

![Chemical structures](image)

Figure 3: Methods for Drawing Acetal 110

Synthesis of the acetal 110 could be more directly accomplished (without C-8 silylation or benzylolation) in 4 steps. Deprotection of the silyl ether 100b followed by oxidation using TPAP\(^4\) gave the lactone 112 (Scheme 16). Subsequent reduction of 112 with DIBAL-H provided the lactol 113 as a single diastereomer. The reducing agent is proposed to approach from the outside (or β-face) and the H-1,2 coupling constant of 8.6 Hz is consistent with this hypothesis. Treatment of the crude lactol 113 with PTSA in methanol yielded the acetal 110 in 67% yield together with the methoxy acetal 114 in 23% yield. The methoxy acetal 114 appeared to possess the α-stereochemistry at C-2 (H-1,2 coupling
constant of 8.7 Hz) presumably due to the anomeric effect. The diol 114 could be separated and re-equilibrated to provide a further quantity of the acetal 110.

\[
\begin{align*}
\text{i)} & \text{ TBAF, THF, 25°C, 99%; ii) TPAP, NMO, 4 Å molecular sieves, CH}_2\text{Cl}_2, 25°C, 87%; iii) DIBAL-H, CH}_2\text{Cl}_2, -78°C; iv) PTSA, MeOH, 25°C, 110 (67% over 2 steps) + 114 (23% over 2 steps); v) PTSA, MeOH, 25°C, 110 (70%) + 114 (21%).}
\end{align*}
\]

Scheme 16: Conversion to Ketal 110

1.7 Attempted Mukaiyama-Type Cyclization of β-Keto Ester

Conversion of the acetal 110 into the potential cyclization precursor 117 was readily accomplished in 2 steps (Scheme 17). Oxidation of the alcohol 110 gave the crystalline aldehyde 115 which is the synthetic equivalent of the previously discussed intermediate 53 (see Section 5.1.1). Next, treatment of the aldehyde 115 with the ylide derived from phosphonium salt 116 gave the desired β-keto ester 117 (Z:E, 14:1).45 Although the yields using the literature
conditions were low and irreproducible, this problem was overcome by the use of DMPU as a co-solvent.

\[ \text{110} \xrightarrow{\text{i}} \text{115} \]

\[ \text{117a} + \]

\[ \text{117} \]

\[ \text{116} \]

i) Dess-Martin periodinane, CH\(_2\)Cl\(_2\), 25\(^\circ\)C, 89%; ii) NaH, DMPU, 116, 25\(^\circ\)C to 40\(^\circ\)C, 117 (84%) + 117a (6%).

Scheme 17: Conversion to \(\beta\)-Keto Ester 117

In an attempt to form the B-ring from ester 117, a variety of conditions were examined that yielded several important observations, but no C-2,3 bond formation (Scheme 18, Table 4). One result was the isolation of four different lactols with the gross structure of 120 (Entries 4, 5, and 7), however no attempt was made in order to further distinguish their stereochemical differences. The most important observation was that cleavage of the C-7,8 bond was found to be a major pathway under several of the Lewis acidic conditions as shown by the isolation of the furan 121 (Entries 5, 6 and 7). It is believed that the lactols 120a-
d are intermediates (as their alkoxide 125) in the pathway toward the formation of the furan 121.
Scheme 18: Attempted Cyclizations of Ester 117

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (R = H)</td>
<td>TiCl₄, i-Pr₂NEt, CH₂Cl₂, -78°C to 25°C</td>
<td>SM + decomp</td>
</tr>
<tr>
<td>2 (R = H)</td>
<td>CSA, CH₂Cl₂, 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>3 (R = H)</td>
<td>ZnCl₂, Et₂O, sealed tube, 80°C</td>
<td>decomp</td>
</tr>
<tr>
<td>4 (R = H)</td>
<td>BF₃·Et₂O (0.38 equiv), CH₂Cl₂, -78°C</td>
<td>120a (56%), 120b (16%) + 117 (28%)</td>
</tr>
<tr>
<td>5 (R = H)</td>
<td>BF₃·Et₂O (0.20 equiv), CH₂Cl₂, -35°C to -10°C</td>
<td>120a (14%) + 120b (14%) + 120c (12%) + 121 (trace)</td>
</tr>
<tr>
<td>6 (R = H)</td>
<td>BF₃·Et₂O (4.5 equiv), CH₂Cl₂, -78°C to -5°C</td>
<td>121 (18%)</td>
</tr>
<tr>
<td>7 (R = TMS)</td>
<td>TiCl₄ (1.05 equiv), CH₂Cl₂, -78°C to -10°C</td>
<td>120d (39%) + 121 (29%)</td>
</tr>
</tbody>
</table>

Table 4: Attempted Cyclizations of Ester 117
A possible mechanism is shown below (Scheme 19) for the cleavage of the C-7,8 bond leading to the isolated furan 121 and the proposed dialdehyde 125 (although not isolated, aldehyde signals were observed in the $^1$H NMR of the crude reaction mixture). The dialdehyde 125 could also exist as a hydrate or a bridged hydrate. As discussed earlier (see Section 4.1.3), a similar cleavage pattern was observed in the sarcodictyin isolation studies; however, the cleavage required the presence of a C-13 hydroxyl functionality and a basic medium. Since the transformation shown below was found to be the major pathway in preference to the desired reactivity, an alternative approach was investigated.
Scheme 19: Proposed Mechanism for Fragmentation of Ester 117

1.8 Attempted Mukaiyama-Type Cyclization Using Ethyl Ketone

A similar strategy for the formation of the C-2,3 bond involved using the ethyl ketone 130 (Scheme 20) in place of the β-keto ester functionality. It was hoped that the proposed fragmentation pattern, shown in Scheme 19, would be suppressed in the ketone 130 because the ester moiety at C-15 would no longer be
present to act as an electron acceptor. Also, using Pearson's hard / soft, acid / base nomenclature, it is possible that the $\beta$-keto ester and the acetal functionalities were mismatched.\textsuperscript{48}

Synthesis of the ethyl ketone 130 was accomplished in 3 steps from the aldehyde 115 (Scheme 20). Formation of the acetylene 127 was best accomplished using the DAMP reagent (MeO)$_2$PO(CHN$_2$).\textsuperscript{49} The use of the Corey-Fuchs\textsuperscript{50} methodology gave lower yields of 127 (50 - 80%) possibly due to the Lewis acidic nature of the triphenylphosphine / carbon tetrabromide conditions. Next, the acetylene 127 was allowed to react with $n$-BuLi followed by addition of the Weinreb amide 128\textsuperscript{51} to give the ethyl ketone 129. The reaction of propionyl chloride with the acetylide anion gave inferior results (36 - 45% yield). Finally, reduction with the Lindlar catalyst\textsuperscript{52} gave the Z-olefin 130 whose structure was proven by X-ray crystal analysis (Figure 4). Quinoline was necessary to prevent over-reduction of the C-5,6 olefin.
Scheme 20: Synthesis of Ethyl Ketone 130

i) (MeO)₂PO(CHN₂), KOt-Bu, THF, -78°C to 25°C, 93%; ii) n-BuLi, THF, -78°C, then 128, -78°C to 25°C, 129 (75%) + 127 (13%); iii) Lindlar catalyst, quinoline, MeOH, H₂, 78%.

Figure 4: Chem 3D Representation of Ethyl Ketone 130 Using X-Ray Coordinates
After conversion of the ketone 130 into its silyl enol ether 131, several attempted Mukiyama aldol reactions\(^1\) were unsuccessful in the formation of the C-2,3 bond, including TiCl\(_4\) and BF\(_3\)•Et\(_2\)O (Scheme 21, Table 5). Although no new compounds could be isolated from these reactions, \(^1\)H NMR analysis of the crude reaction mixture showed signals with a triplet multiplicites between 9 and 10 ppm which indicated possible cleavage of the C-7,8 bond as seen previously (see Section 5.1.7).\(^{24}\)

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

130, i) TMSOTf, i-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), 99%.

Scheme 21: Attempted Cyclization of Acetal 131

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClTi(Oi-Pr)(_3), CH(_2)Cl(_2), -78°C to reflux</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>BF(_3)•Et(_2)O, CH(_2)Cl(_2), -78°C to 25°C</td>
<td>decomp and SM</td>
</tr>
<tr>
<td>3</td>
<td>BF(_3)•Et(_2)O, MeNO(_2), -15°C</td>
<td>decomp and SM</td>
</tr>
<tr>
<td>4</td>
<td>TiCl(_4), CH(_2)Cl(_2), -78°C</td>
<td>decomp</td>
</tr>
</tbody>
</table>

Table 5: Attempted Cyclizations of Acetal 131

One potential reason for the inability to form the C-2,3 bond with the β-keto ester 117 and the enol ether 131 may have been an inaccessibility of the
required trajectory. Since the oxonium ion is cyclic and rigid, the intramolecular nucleophile may be unable to approach the electrophile at the appropriate trajectory\textsuperscript{53} due to strain energy in the transition state. Two potential solutions for this problem are to lower the strain energy by making the nucleophile more flexible or to unlock the electrophile by using the free aldehyde at C-2. Both of these strategies were investigated.

1.9 Attempted Nicholas-type Closure Using $\eta^2$-Co$_2$(CO)$_6$-Complexed Acetylene

A strategy that could potentially improve the geometric flexibility of the nucleophile involved the Nicholas reaction\textsuperscript{54} in order to form the C-2,3 bond. It is well known that $\eta^2$-Co$_2$(CO)$_6$-complexed acetylenes can facilitate ring closures that are otherwise impossible.\textsuperscript{55} The possible cyclization precursor 134 was synthesized from acetylene 127 by a Castro-Stevens coupling\textsuperscript{56} with E-1-bromo-1-propene followed by cobalt complexation gave the $\eta^2$-Co$_2$(CO)$_6$-complexed enyne 134 (Scheme 22). Unfortunately, treatment with TiCl$_4$ or BF$_3$·Et$_2$O gave no evidence of the formation of the C-2,3 bond and instead led to rapid decomposition.
Scheme 22: Attempted Cyclization of Olefin 134

1.10 Migration of Cyclohexylidene Ketal

An alternative approach to those based on the internal ketal 110 involved the use of a free aldehyde function at C-2 (Scheme 23). The alcohol 136, readily accessible from the diol 111, was allowed to react with PTSA in MeOH to give the migrated ketal 137 together with only a small amount of the expected triol 138. This migration has been previously observed and requires the internal trans 1,2-functionality to be present in the ketal 137 at the C-7,8 positions. Dess-Martin oxidation of the alcohol 139 followed by treatment under the optimized conditions used for the synthesis of the β-keto ester 117 (see Section 5.1.7) yielded the desired compound 140 in moderate yield. Unfortunately, all attempts
to remove the pivaloate protecting group at C-2 were unsuccessful\(^{10}\) necessitating the development of an alternative approach to allow access to the C-2 aldehyde moiety.

\[
\begin{align*}
\text{111} & \xrightarrow{\text{i}} \text{136} & \xrightarrow{\text{ii}} & \text{137} + \text{138} \\
\text{140} & \xrightarrow{\text{iii}} & \text{116} & \xrightarrow{\text{iv}} \text{139}
\end{align*}
\]

i) PivCl, py, DMAP, CH\(_2\)Cl\(_2\), 94%; ii) MeOH, PTSA, 137 (58%) + 138 (13%); iii) Dess-Martin periodinane, CH\(_2\)Cl\(_2\), 85%; iv) NaH, 116, DMPU, THF, 25°C to 50°C, 32%.

Scheme 23: Attempted Synthesis of β-Keto Ester 141

1.11 Attempted Aldol Closure of Aldehyde

Construction of the aldehyde 150, however, was more successful (Scheme 24). First, transformation of the aldehyde 139 into the dibromide 142 followed by

127
removal of the pivaloate protecting group at C-2 and reprotection gave its silyl ether 144. Next, the dibromide 144 was eliminated to give the acetylene 145 using EtMgBr to which was preferred over more classical methods (LHMDS / n-BuLi or n-BuLi) due to a superior yield and a straightforward experimental protocol. Subsequent treatment of the terminal acetylene 145 with n-BuLi followed by the addition of the previously mentioned Weinreb amide 128 (see Section 5.1.8) yielded the ethyl ketone 146 in excellent yield. Removal of the silicon protecting group followed by reduction of the acetylene 147 using the Lindlar catalyst gave the Z-olefin 149. Quinoline was again necessary to prevent over reduction of the C-5,6 olefin. Use of the Pd on BaSO₄ / py / MeOH / H₂ system resulted in complete over-reduction of the C-5,6 olefin. Finally, oxidation of the C-2 hydroxyl functional gave the potential cyclization precursor 150.
Scheme 24: Synthesis of Ethyl Ketone 150

With the ethyl ketone 150 in hand, the aldol reaction under several conditions\(^1\) was attempted in order to form the C-2,3 bond (Scheme 25, Table 6). Although none of the conditions tried led to formation of the C-2,3 bond in an intramolecular fashion, several important observations were made. Isolation of the enol ether 153 (Entry 3) in high yield as well as the observation of the product 154 resulting from epimerization at C-1 (Entry 5) suggested that intramolecular

\(^{1}\) Reaction conditions: i) \(\text{Ph}_3\text{P}, \text{CBr}_4, \text{CH}_2\text{Cl}_2, 0^\circ\text{C}\); ii) DIBAL-H, \(\text{CH}_2\text{Cl}_2\), -78\(^\circ\text{C}\) to 25\(^\circ\text{C}\), 89\% over two steps; iii) TBSCI, imidazole, \(\text{CH}_2\text{Cl}_2\), 95\%; iv) \(\text{EtMgBr}, \text{THF}, 25^\circ\text{C}\), 92\%; v) \(\text{n-BuLi}, \text{THF}, -78^\circ\text{C}\), then 128, -78\(^\circ\text{C}\) to 25\(^\circ\text{C}\), 96\%; vi) \(\text{AcOH}, \text{dioxane}, \text{H}_2\text{O}, 70^\circ\text{C}\), 147 (78\%) + 148 (7\%); vii) Lindlar catalyst, quinoline, petroleum ether, \(\text{H}_2\), 92\%; viii) Dess-Martin periodinane, \(\text{CH}_2\text{Cl}_2\), 89\%.
proton transfer occurred in preference to formation of the C-2,3 bond. The counterion of the enolate (lithium versus potassium) appeared to control this epimerization at C-1.

Interestingly, treatment of the ketone 150 with i-PrOTiCl\textsubscript{3} / i-Pr\textsubscript{2}NEt (Entry 7) yielded the dimeric product 152 in 11% yield along with the isomerized olefin 155 (44%). The dimeric product 152, isolated as one major undetermined diastereomer containing the E-olefin in the C-5,6 position (J = 15.8 Hz), showed that the inability to form the C-2,3 bond intramolecularly in the aldehyde 150 may be due to a poor trajectory of attack. Also, isomerization of the C-5,6 alkene function to the thermodynamically favored E-olefin may have occurred via addition / elimination of chloride ion to the enone system. Finally, it is believed that the C-5,6 olefin isomerizes before the dimerization reaction takes place because no Z-olefin was observed in the dimeric product.
Scheme 25: Attempted Cyclization of Ketone 150

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$n$-Bu$_2$BOTf, i-Pr$_2$NEt, CH$_2$Cl$_2$, -78°C to reflux</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>LDA, THF, -78°C to 0°C</td>
<td>decomp</td>
</tr>
<tr>
<td>3</td>
<td>LHMDS, THF, -78°C to 25°C, then TMSCl</td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Attempted Cyclizations of Ketone 150
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>LHMDS, THF, -78°C to reflux, then Ac₂O</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>KHMDS, THF, -78°C to 25°C</td>
<td><img src="image1.png" alt="Image" /> 154 42%</td>
</tr>
<tr>
<td>6</td>
<td>LHMDS, -78°C to 25°C, then CITi(Oi-Pr)₃, -78°C to reflux, then Ac₂O</td>
<td>complex mixture</td>
</tr>
<tr>
<td>7</td>
<td>i-PrOTiCl₃, i-Pr₂NEt, CH₂Cl₂, -78°C to 0°C</td>
<td><img src="image2.png" alt="Image" /> 152 (11%) + 155 (44%)</td>
</tr>
</tbody>
</table>

Table 6 (Continued): Attempted Cyclizations of Ketone 150

Using the enol ether 153 (Table 6, Entry 3), several Mukaiyama-type cyclizations were also tried without success (Scheme 26, Table 7). Based on results from all the attempted cyclizations to form the C-2,3 bond on a wide
variety of substrates, it is improbable that cyclization at the C-2,3 position would prove successful. The isolation of the dimer 152 (Table 6, Entry 7) suggested that lack of intramolecular reaction at the C-2 position was due to poor trajectory and not Pearson's mis-matched hard / soft system. For these reasons, an alternate strategy to eleutherobin had to be developed.

Scheme 26: Attempted Cyclization of Enol Ether 153

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl₂, Et₂O, 80°C, sealed tube</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Me₂AlCl, CH₂Cl₂, -78°C to reflux</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(i-PrO)TiCl₃, CH₂Cl₂, -78°C to 25°C</td>
<td>21% (155)</td>
</tr>
</tbody>
</table>

Table 7: Attempted Cyclizations of Enol Ether 153


10 Magnus, P. D.; McKenna, J. unpublished results.


14 One possible explanation for the recovery of the starting material 67 is the TiCl$_4$ carbonyl complex is in a reversible equilibrium (approximately 2:1 complex:uncomplexed) until the addition of the t-Pr$_2$NEt.


21 The structure of the diol 73 was proven by acetylation of the crude reaction mixture and characterization of the the diacetate; otherwise, isolation of 73 was difficult.

22 The corresponding C-10 epimer was not observed.

24 Magnus, P. D.; Wren, S. unpublished results.


32 The same result was also observed with the ethylene glycol derived acetal 71. Magnus, P. D.; McKenna, J. unpublished results.


35 Reduction of the acid 94 using DIBAL-H or LiAH₄ proved to be lower yielding (<80%) than this two step procedure.


37 The stereochemistry of minor component 99b was deduced by a series of correlation experiments (see Section 5.1.5).


39 The yields of this transformations were unoptimized. Magnus, P. D.; McKenna, J. unpublished results.


45 H-5,6 coupling constants for 117 and 117a are 12.5 and 15.5 Hz respectively.


J. C. personal communication.


Caple, R.; Veretnov, A. L.; Shashkov, A. S.; Vorontsova, L. G.; Kurella, 
M. G.; Chertkov, V. S.; Carapetyan, A. A.; Kosnikov, A. Y.; Alexanyan, 
M. S.; Lindeman, S. V.; Panov, V. N.; Maleev, A. V.; Struchkov, Y. T.; 
Veretnov, A. L.; Smit, W. A.; Vorontsova, L. G.; Kurella, M. G.; Caple, 


60 Treatment of the silyl ether 146 and the corresponding cis-olefin with TBAF led to decomposition. Magnus, P. D.; McKenna, J. unpublished results.

2 Approaches Utilizing the Intermolecular Opening of the C-2 Acetal

2.1 Intermolecular Opening of Acetal

Due to unsuccessful results involving intramolecular reaction at C-2, an intermolecular strategy was adopted (Scheme 27) which should allow access to a variety of compounds. Treatment of the silylated compound 156 with a diverse group of nucleophiles\(^1\) gave successful reaction only with trimethylsilylcyanide and allyltrimethylsilane (165) (Scheme 27, Table 8). The reactivity of the acetal 156 appeared to not only be dependent on steric effects, but also dependent on electronic effects. For example, although trimethylsilyl acetylene (164) and ethyl vinyl ether (162) are nearly isosteric with TMSCN and the allyl silane 165 respectively, no product is observed with either nucleophile. The reaction with the allyl silane 165 gave the more useful product 158 and was chosen as the preferred substrate for further transformations.
Scheme 27: Opening of C-2 Acetal 156

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSO(\text{O})(\text{OEt})(,) TiCl(_4), CH(_2)Cl(_2), -78(^\circ)C to reflux</td>
<td>156 and decomp</td>
</tr>
<tr>
<td>2</td>
<td>OTBS(\text{O})(\text{Or-Bu})(,) TiCl(_4), CH(_2)Cl(_2), -78(^\circ)C to reflux</td>
<td>156 and decomp</td>
</tr>
<tr>
<td>3</td>
<td>OTMS(\text{O})(\text{OEt})(,) CH(_2)Cl(_2), -78(^\circ)C to 25(^\circ)C</td>
<td>156 and decomp</td>
</tr>
<tr>
<td>4</td>
<td>(\text{O})(\text{OEt})(,) ZnCl(_2), Et(_2)O, reflux</td>
<td>156 and decomp</td>
</tr>
<tr>
<td>5</td>
<td>(\text{EtO}==\text{TMS})(,) TiCl(_4), CH(_2)Cl(_2), -78(^\circ)C to 25(^\circ)C</td>
<td>156 and decomp</td>
</tr>
</tbody>
</table>

Table 8: Opening of the C-2 Position of Acetal 156
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>$\equiv$-TMS, $\text{164}$, TiCl$_4$, CH$_2$Cl$_2$, -78°C to 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>7</td>
<td>TMSCN, PhH, ZnI$_2$, reflux</td>
<td>157 (67%)</td>
</tr>
<tr>
<td>8</td>
<td>$\equiv$-TMS, $\text{165}$, TiCl$_4$, CH$_2$Cl$_2$, -78°C</td>
<td>158 (99%)</td>
</tr>
</tbody>
</table>

Table 8 (Continued): Opening of C-2 Acetal 156

The C-2 stereochemistry for compounds 157 and 158 is proposed to be as drawn, based on inspection of models and coupling constants. It is believed that the C-1,10 *cis*-ring fusion is the governing factor that leads to the approach of the nucleophile from the β-face (Scheme 28). Also, the H-1,2 coupling constant of 10.2 Hz in nitrile 157 is in agreement with a *trans* H-1,2 relationship.
Scheme 28: Explanation for C-2 Stereochemistry in Opening of Acetal 156

2.2 Wadsworth-Emmons and Nozaki Strategies for B-Ring Formation

All previous approaches required the closure of the desired 8 or 10-membered ring at the C-2,3 position. As mentioned earlier (see Section 5.1.1), the key intermediate 53 was chosen because it allowed for a wide range of flexibility in the methods for formation of the B-ring. Using the successful opening of the acetal 156 with allyltrimethylsilane (165), construction of the desired 8-membered ring was now envisioned to be possible at either the C-5,6 position using a Wadsworth-Emmons reaction or at the C-4,5 position using a Nozaki-type coupling (Scheme 29). Both of these reactions have been previously used to form medium and large rings. The initial strategy chosen was the Wadsworth-Emmons closure of the C-5,6 bond using the substrate 167.
Scheme 29: Revised Retrosynthetic Analysis of Core Structure 50

2.3 Functionalization of the C-4,5 Olefin

After silyl protection of the tertiary alcohol functionality of 158, two options for functionalization of the C-4,5 position of the alkene 169 were considered: Wacker oxidation to give the ketone 170 or dihydroxylation to yield the diol 171 (Scheme 30). Wacker oxidation of the alkene 169, using several literature conditions\(^5\) involving PdCl\(_2\), CuCl\(_2\) and O\(_2\), provided the desired ketone
170 in only a low yield. Dihydroxylation of the olefin 169 under standard conditions (OsO₄ / NMO / t-BuOH / H₂O) yielded a complex mixture with substantial over-oxidation as shown by the disappearance of the signal corresponding to the C-11,12 olefin in the ¹H NMR of the crude reaction mixture.⁶ This was not surprising as it has been previously observed that the C-11,12 olefin is relatively electron-rich and reactive under a variety of conditions.⁷

It was hoped that Sharpless' asymmetric dihydroxylation⁸ technology would be uniquely useful in this situation (Table 9). Thus, it was found that AD mix β*⁹ reacted preferentially with the C-4,5 olefin to give the diol 171 as an approximately 3:1 diastereomeric mixture at C-4 as shown by ¹H NMR of the crude reaction mixture. Treatment of the alkene 169 with AD mix α*⁹ appeared to provide the C-11,12 dihydroxylated adduct 172 as the preferred product, but no yield could be determined due to an inseparable impurity. Since none of the C-11,12 dihydroxylated adduct 172 was observed in the AD mix β* experiment (Entry 3), it is believed that the osmate ester intermediate from dihydroxylation at the C-4,5 position is the active dihydroxylating intermediate of the C-11,12 olefin. Unfortunately, the addition of MeSO₂NH₂, as recommended by Sharpless and coworkers to increase the rate of hydrolysis of the osmate ester,⁸ did not appear to slow hydroxylation of the C-11,12 olefin.
i) TESOTf, i-Pr₂NEt, CH₂Cl₂, 25°C, 99%.

Scheme 30: Functionalization of Alkene 169

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OsO₄, NMO, t-BuOH, H₂O, 25°C</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>AD mix α*, t-BuOH, H₂O, 25°C</td>
<td>172:171 (3:1)</td>
</tr>
<tr>
<td>3</td>
<td>AD mix β*, t-BuOH, H₂O, 25°C</td>
<td>171 (55%) + 173 (21%) + 169 (17%)</td>
</tr>
</tbody>
</table>

Table 9: Dihydroxylation of Alkene 169
Using Sharpless' models,\textsuperscript{10} it was proposed that AD mix $\alpha^\ast$ would approach the C-11,12 olefin of 169 from the relatively unhindered top face and AD mix $\beta^\ast$ should approach the C-11,12 olefin from the lower or bottom face (Figure 5). Since the bottom face of the C-11,12 alkene is sterically encumbered due to the C-1,10 cis-ring fusion, dihydroxylation with AD mix $\beta^\ast$ occurs preferentially at the less electron-rich, but less hindered C-4,5 position. Thus, the unwanted dihydroxylation of the C-11,12 double bond could be suppressed by the use of the mis-matched reagent AD mix $\beta^\ast$.

![Diagram](image)

Figure 5: Explanation for Selectivity in the Dihydroxylation of Alkene 169

2.4 Attempted Watsworth-Emmons Cyclization of $\beta$-Keto Phosphonate

Now that a method had been developed for the functionalization of the C-4,5 olefin, synthesis of the $\beta$-keto phosphonate 180 was possible in 6 steps (Scheme 31). Cleavage\textsuperscript{11} of the diol 171 to the aldehyde 174 followed by oxidation and esterification gave the ester 176 in 83% yield over three steps.
Addition the ester 176 to a solution of the anion of diethyl methylphosphonate\textsuperscript{12} (3.2 equiv) gave the β-keto phosphonate 177 along with a small amount of the ether-bridge opened compound 178 presumably via the dianion of 177. Interestingly, addition of the anion of diethyl methylphosphonate to the ester 176 gave incomplete reaction with large amounts of recovered starting material (>75\%) possibly due to enolization of the C-4 ester moiety in preference to nucleophilic attack of the ester function. Removal of the two silicon protecting groups of 177 with TBAF in the presence of 4 Å molecular sieves followed by immediate oxidation\textsuperscript{13} gave the hydroxy-aldehyde 180. It was imperative that the deprotection be performed in the presence of molecular sieves in order to ensure a reasonable yield, but even with this precaution the yield was still found to be variable due to possible hydrolysis of phosphonate functionality.
Scheme 31: Synthesis of α-Hydroxy-Aldehyde 180

Treatment of the hydroxy-aldehyde 180 with TESOTf yielded the potential cyclization precursor 167 via a somewhat capricious reaction (Scheme 32). It is believed that the cause of the unreliable nature of this reaction is the
phosphonate functionality which appeared to decompose under the reaction conditions. Silylation of the tertiary alcohol in substrates not containing the phosphonate functionality, such as the ester 176, worked reproducably well. Finally, attempted cyclization of the phosphonate 167 by slow addition to a solution of LiCl and DBU\textsuperscript{14} caused extensive decomposition. The only product that could be observed was trace amounts of the deprotected aldehyde 180. Also, slow addition of the aldehyde 167 to a solution of LHMDS had a similar outcome. It is not known why the desilylation of the tertiary hydroxyl functionality occurred during the attempted cyclizations; however, one possible cause may be the presence of small amounts of LiOH. Due to the difficulty in obtaining the cyclization precursor 167 as well as its disappointing reactivity, an alternative route based on the Nozaki coupling was pursued (see Section 5.2.2).

\[ \begin{align*}
&\text{Me}_2\text{OH} \quad \text{CHO} \\
&\text{Me}_2\text{O} \quad \text{CHO} \\
&\text{O} \quad \text{CHO} \\
&\text{O} \quad \text{CHO} \\
&\text{DBU, LiCl} \quad \text{MeCN} \\
&\text{or} \quad \text{LHMDS} \quad \text{THF}
\end{align*} \]

\[ \begin{align*}
\text{i} & \quad \text{180} \quad \text{P = H} \\
\text{180} \quad \text{P = TES} \\
\text{167} \quad \text{P = TES}
\end{align*} \]

i) TESOTf, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, 10 - 87%.

Scheme 32: Attempted Cyclization of Phosphonate 167

2.5 Attempted Nozaki Cyclization of Iodide

The potential cyclization precursor 190 was prepared from the aldehyde 174 in 8 steps with an overall 40% yield (Scheme 33). Thus, reduction of
aldehyde 174 followed by pivaloylation provided 183. Next, the silyl ether 183 was treated with TBAF to give the diol 184 which was subsequently oxidized and protected as its methoxymethyl ether to yield the aldehyde 186. It was found that protection of the tertiary alcohol as its silyl ether gave poor results in subsequent steps due to desilylation as seen previously with β-keto phosphonate 167 (see Section 5.2.4). The aldehyde 186 was allowed to react with the ylide of iodomethyltriphenylphosphonium iodide (187),\textsuperscript{15} following a procedure introduced by Stork and co-workers,\textsuperscript{16} which provided the Z-vinyl iodide (H-5,6 coupling constant of 8.9 Hz) as a single isomer in 81% yield. If this reaction was conducted using DMPU instead of HMPA or in the absence of a co-solvent, the yields were significantly lower (50 - 60%). Removal of the pivaloate protecting group of 188 with Super-Hydride® and oxidation with TPAP gave the cyclization precursor 190. Removal of the pivalolate using DIBAL-H gave inferior results (50 - 70% yield).
Scheme 33: Synthesis of Cyclization Precursor 190

With a viable route to the aldehyde 190 in hand, a variety of conditions were examined in order to form the C-4,5 bond, but without success (Scheme 34). Treatment under the conditions utilized by Overman and co-workers in their work toward eunicellin (2)\(^\text{17}\) (see Section 4.1.4) led to extensive decomposition. Other conditions\(^\text{18}\) tried are listed in Table 10. It is believed that reduction of the aldehyde function occurred in preference to cyclization. Oxidation of the crude reaction (Entry 3) appeared to lead to an increase in the amount of olefin 192 by \(^1\)H NMR analysis after oxidation.
Scheme 34: Attempted Cyclization of Aldehyde 180

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrCl₂, NiCl₂, DMSO, 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>CrCl₂, NiCl₂, DMSO, slow addition, 25°C</td>
<td>complex mixture + 192</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(trace)</td>
</tr>
<tr>
<td>3</td>
<td>CrCl₂, NiCl₂, DMSO, THF, slow addition, 25°C followed by Dess-Martin</td>
<td>complex mixture + 192</td>
</tr>
<tr>
<td></td>
<td>periodinane, CH₂Cl₂, 25°C</td>
<td>(trace)</td>
</tr>
<tr>
<td>4</td>
<td>CrCl₂, NiCl₂, DMSO, DMS, 25°C</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>CrCl₂, NiCl₂, DMF, 25°C to 100°C</td>
<td>decomp</td>
</tr>
<tr>
<td>6</td>
<td>CrCl₂, Ni(acac)₂, DMF, 25°C to 100°C</td>
<td>complex mixture + 192</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(trace) + 190 (trace)</td>
</tr>
</tbody>
</table>

Table 10: Attempted Cyclization of Aldehyde 190

Although a working route existed for the construction of advanced cyclization precursors such as the phosphonate 167 and the iodide 190, it was felt that the sequence had become too lengthy. Synthesis of the cyclization precursors
167 and 190 required 30 and 32 steps respectively. For this reason, methods for shortening the general route were investigated.


6 Magnus, P. D.; Wren, S. unpublished results.

7 Magnus, P. D.; Hodge, K. unpublished results.


9 1 mol % Os content and 2.5 mol % ligand content. Commerically available AD mixes were unreactive in this system.


   Overman, L. C. personal communication.

3 An Alternative Approach Utilizing a Suzuki Coupling

3.1 Retrosynthetic Strategy

In order to shorten the synthesis of eleutherobin (4), a different approach involving a Suzuki coupling was investigated. Suzuki and co-workers first reported the coupling of alkyl 9-BBN adducts with vinyl or aryl halides using palladium catalysis in 1986 (Scheme 35).\textsuperscript{1}

\[
\text{Palladium} \quad \text{Alkyl-9-BBN} + \text{RX} \xrightarrow{\text{catalysis}} \text{Alkyl-R}
\]

\[ R = \text{alkenyl, aryl} \]

Scheme 35: Generalized Suzuki Coupling Reaction Using Alkyl-9-BBN Species

As previously mentioned (see Section 5.1.3), hydroboration of the diene 57 with 9-BBN gave the alkyl-9-BBN adduct 71. A Suzuki coupling between the borane 71 and a vinyl halide could prove useful. Thus, the known vinyl bromide 196 was constructed in 3 steps;\textsuperscript{2} however, one major modification to the literature procedure was necessary involving the use of DBU instead of NaOMe in the elimination of the dibromide 194 (Scheme 36). It was found that the literature conditions gave substantial amounts of the O-methyl enol ether via addition / elimination of NaOMe into the enone system.
Treatment of the 9-BBN adduct 71 with the vinyl bromide 196 under classical Suzuki conditions [PdCl$_2$(dppf)$_2$, K$_2$CO$_3$, DMF, THF] gave no coupling; however, the use of one of Suzuki's alternative conditions$^3$ [Pd(PPh$_3$)$_4$ (3 mol %) / NaOH (3 M in H$_2$O) / THF / 65°C, 6 h] yielded the coupled adduct 197 in 44% yield over the two steps (hydroboration and coupling, Scheme 37). It is worth noting that the maximum possible yield of this two step procedure is approximately 65%, the yield of the hydroboration step (see Section 5.1.3). Also, the amount of diene 57 recovered (33%) was greater than the amount isolated using a oxidative workup of the hydroboration (22%), possibly due to the borane adduct 71 competitively eliminating to the diene 57 under the Suzuki reaction conditions.
Scheme 37: Suzuki Coupling of Borane 71 and Bromide 196

It was hoped that a directed oxygenation of the C-7,8 olefin could lead to a substantially shorter route to the acetal 110 than the previously utilized Julia route shown below (Scheme 38).
Scheme 38: Comparison of Julia and Suzuki / Sharpless Routes
3.2 Attempted Dihydroxylation of the C-7,8 Olefin of Alkene

The most direct method for construction of the triol 198 is an asymmetric dihydroxylation of the allylic alcohol 197. Although the C-11,12 olefin is the more electron-rich olefin, it was hoped that the less hindered C-7,8 olefin would be more reactive on steric grounds. Using Sharpless' models,⁴ AD mix α would be expected to give the correct stereochemistry at C-7 and C-8; however, considering the observations made during the dihydroxylation of the alkene 169 (see Section 5.2.3), it would not be surprising if AD mix α preferentially dihydroxylated the C-11,12 olefin. Treatment of allylic alcohol 197 with AD mix α*⁵ gave slow reaction, but ¹H NMR of the crude reaction mixture appeared to indicate preferential dihydroxylation to be occurring at the internal C-11,12 olefin as shown in by the disappearance of the H-12 signal (Scheme 39). Classical dihydroxylation conditions⁶ (OsO₄ / NMO / acetone / H₂O) gave a complex mixture.

Since Corey and co-workers have shown that the use of an aromatic protecting group α to the olefin often improves the enantioselectivity of the dihydroxylation via aryl-aryl or π-stacking interactions in the binding pocket of the catalyst,⁷ it was hoped that this interaction may also be used to improve the regioselectivity of the dihydroxylation. Unfortunately, after protection of the primary hydroxyl functionality as its 4-methoxybenzoyl ester, treatment with AD mix α*⁵ gave a complex mixture with substantial over-hydroxylation as well as preferential dihydroxylation of the internal C-11,12 olefin as judged by ¹H NMR.
analysis of the crude reaction mixture. Due to these somewhat expected results, the focus was changed to the epoxidation of the C-7,8 olefin.

\[
\begin{align*}
\text{AD mix } \alpha^*, & \quad \text{t-BuOH, H}_2\text{O, MeSO}_2\text{NH}_2, 12 \\
\text{or } & \quad \text{OsO}_4 \text{ (catalytic), NMO, Acetone}
\end{align*}
\]

\begin{align*}
201 \ P = H & \quad 197 \ P = H \\
202 \ P = 4\text{-methoxybenzoyl} & \quad 199 \ P = 4\text{-methoxybenzoyl} \\
\text{or } & \quad 200 \ P = 4\text{-methoxybenzoyl}
\end{align*}

i) 4-methoxybenzoyl chloride, DMAP, Et\text{3}N, CH\text{2}Cl\text{2}, 70%.

Scheme 39: Attempted Dihydroxylation of Alkenes 197 and 199

3.3 Epoxidation of the C-7,8 Position of Alkene

An alternative method for oxygenation of the allylic alcohol 197 was the use of Sharpless' asymmetric allylic epoxidation chemistry. Using Sharpless' models, epoxidation of the C-7,8 olefin using the (+)-DIPT / Ti(Oi-Pr)_4 / TBHP system would be expected to yield the epoxide 203 with the correct absolute stereochemistry at C-7 and C-8. Unfortunately, in order to convert the epoxide 203 into the acetal 110, the epoxide functionality must be opened in an S\text{N}_2 process, causing an inversion of the C-8 stereochemistry (Scheme 40). An alternative approach would involve the use of the Z-olefin geometry at the C-7,8 position which, upon opening of the epoxide at C-8 with an oxygen nucleophile, would yield the correct C-7 and C-8 stereochemistry. This strategy was also investigated and will be discussed later (see Section 5.3.4).
Opening of the epoxide 203 with PhSH followed by formation of the internal acetal and the use of Pummerer chemistry\textsuperscript{10} would allow for the construction the ketone 205. Stereoselective reduction of ketone 205, analogous to the ketone 102 (see Section 5.1.5), followed by acidic equilibration with the methanol / PTSA system would yield the previously synthesized acetal 110.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{reaction_diagram}
\caption{Scheme 40: Epoxidation Strategy to Construct Acetal 110}
\end{figure}

Treatment of allylic alcohol 197 with (+)-DIPT / Ti(Oi-Pr)\textsubscript{4} / TBHP at -25°C yielded an unknown compound A as a inseparable mixture of diastereoisomers in a 4:1 ratio as shown by \textsuperscript{1}H NMR. It was suspected that unknown compound A was not the desired epoxide 203 due to the chemical shift of H-8 in the \textsuperscript{1}H NMR at 3.2 ppm. In order to gain further insight into the reaction, the allylic alcohol 197 was allowed to react with (-)-DIPT / Ti(Oi-Pr)\textsubscript{4} / TBHP and gave an unknown compound B (d.s. > 20 to 1) (Scheme 41).
Protection of the primary hydroxyl function as its PNB ester yielded the crystalline compound C. X-ray crystal analysis revealed that the unknown compound was not the epoxide 209 but rather the rearranged methyl ether 210. It is worth noting that although the C-8 stereochemistry is correct for the synthesis of eleutherobin (4), the crucial C-7 stereochemistry is incorrect. Furthermore, this observed stereochemistry in 210 is in agreement with Sharpless' models for asymmetric epoxidation of allylic alcohol 197 using the (-)-DIPT / Ti(O\textit{i}-Pr)\textsubscript{4} / TBHP system.\textsuperscript{9}

\[
\begin{align*}
\text{197} & \xrightarrow{i} \text{Unknown Compound B} \xrightarrow{\text{ii}} \text{Unknown Compound C} \\
\end{align*}
\]

\[
\begin{align*}
\text{207} & \quad P = H \\
\text{209} & \quad P = 4\text{-nitrobenzoyl} \\
\text{208} & \quad P = H \\
\text{210} & \quad P = 4\text{-nitrobenzoyl} \\
\end{align*}
\]

i) Ti(O\textit{i}-Pr)\textsubscript{4}, (-)-DIPT, TBHP, 3 Å molecular sieves, CH\textsubscript{2}Cl\textsubscript{2}, -25°C, 71%; ii) PNBCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 89%.

Scheme 41: (-)-DIPT Epoxidation of Allylic Alcohol 197
A potential mechanism for this transformation is shown below (Scheme 42). It is believed that the epoxide 211 is initially formed, but it is rapidly opened in an intramolecular manner to give the intermediate 212 which rearranges to give the O-methyl ether 208. This intramolecular rearrangement appears to be previously unreported; however, Sharpless did report the opening of some epoxides during the epoxidation reaction in the presence of stoichiometric amounts of reagents.\textsuperscript{11} The proposed epoxide 207 can be isolated (36\% yield, d.s. > 20:1) along with the O-methyl ether 208 (64\% yield, d.s. > 20:1) if the reaction time is shortened from 24 h to 1.75 h.
Scheme 42: Possible Mechanism for Formation of O-Methyl Ether 208

The selectivity of the desired (+)-DIPT / Ti(Oi-Pr)₄ / TBHP epoxidation of 197 could be improved by performing the reaction at -40°C (Scheme 43). At this temperature, the O-methyl ether 214 was isolated as a single diastereomer in 84% yield together with a small amount (10%) of the previously isolated epoxide 207. Compound 214 contains the correct stereochemistry at C-7 and incorrect stereochemistry at C-8. It is believed that the (+)-DIPT / Ti(Oi-Pr)₄ / TBHP system catalyzes the rearrangement of only one of two diastereomeric epoxides at -40°C because of a mismatched / matched system. Sharpless and co-workers have been able to resolve racemic secondary allylic alcohols by taking advantage of similar energetic differences between the diastereomeric transition states.⁹
i) (+)-DIPT, Ti(Oi-Pr)_4, TBHP, 3 Å molecular sieves, CH_2Cl_2, -40°C, 214 (84%) + 207 (10%).

Scheme 43: (+)-DIPT Epoxidation / Rearrangement of Allylic Alcohol 197

In order to make this rearrangement useful, two tasks must be accomplished. First, the C-8 O-methyl ether must be cleaved to provide the free alcohol. Second, the stereochemistry at C-8 in the O-methyl ether 214 is wrong and must be corrected. In order to test the possibility of the demethylation of the C-8 O-methyl ether 214, the alternative O-methyl ether 208 was allowed to react in acetonitrile with TMSI, generated in situ from TMSCl and NaI, and yielded two major demethylated products, unknown compounds D and E, which are believed to be the acetics 215 and 217 (Scheme 44). The ^1H NMR of the crude reaction mixture contained no signals in the region of 3 - 4 ppm associated with an O-methyl ether functionality.
Scheme 44: Demethylation of O-Methyl Ether 208

The HRMS of compounds D and E is in agreement with the molecular formula C_{16}H_{26}O_{3}, therefore indicating the loss of CH_{3}O and CH_{3} from O-methyl ether 208. Both compounds were contaminated with inseparable impurities; however, the $^1$H NMR for compounds D and E contains singlets at 5.44 and 5.17 ppm respectively assigned as H-2 acetal protons. A possible explanation for the formation of acetals 215 and 217 is shown below (Scheme 45). The choice of acetals 215 and 217 over the acetal 216 is based on comparison to previously prepared compounds.\textsuperscript{13} Since the stereochemistry is incorrect at C-7 and C-8 in the methyl ethers 208 and 214 respectively, this reaction was not explored further.
Scheme 45: Possible Mechanism for Demethylation of O-Methyl Ether 208

3.4 Modified Suzuki / Sharpless Route

As mentioned previously (see Section 5.3.3), the most direct method to obtain the correct C-7 and C-8 stereochemistry for eleutherobin (4) was to use the opposite Z-olefin geometry. Construction of the appropriate Z-vinyl halide 223 was possible using a known one step procedure (Scheme 46). In contrast to the reported conditions, it was found that pre-mixing the copper iodide and the methyl
magnesium bromide prior to addition of propargyl alcohol (221) greatly improved the yield and reproducibility of the reaction.$^{15}$

\[ \text{\begin{align*}
\text{221} & \xrightarrow{i} \text{222} \\
\text{i) MeMgBr, Et}_{2}\text{O, CuI (catalytic), 0°C to 25°C, then, I}_2, 0°C \text{ to 25°C, 52%.}
\end{align*}} \]

Scheme 46: Synthesis of Iodide 222

Suzuki coupling between the borane 71 and iodide 222 under the modified Suzuki conditions used previously [Pd(PPh$_3$)$_4$ (3 mol %) / NaOH (3 M in H$_2$O) / THF / 65°C, 6 h] gave trace amounts of the desired coupled product 223. The yield of this transformation could be improved to 35% yield over two steps (hydroboration and coupling, Scheme 47) as a result of optimizing three variables: i) the amount of Pd(PPh$_3$)$_4$ was changed from 3 mol % to 15 mol %; ii) amount of iodide was increased from 1 equiv to 2.7 equiv; iii) the reaction time was extended from 6 hours to 48 hours (Scheme 47). As seen in the previous Suzuki coupling between the borane adduct 71 and the bromide 196 (see Section 5.3.1), a substantial amount of the starting diene 57 was observed by $^1$H NMR of the crude reaction mixture. Unfortunately, purification and recycling of the recovered diene 57 has been unsuccessful to date. One potential method for reducing the elimination of the 9-BBN adduct 71 and, therefore, facilitating Suzuki coupling was to perform the reaction under pressure. Unfortunately, when the reaction was conducted under 60 psi, the yield decreased to 24%.
Scheme 47: Synthesis of Alcohol 223

It is well known that Sharpless epoxidation of a Z-olefin is often slow and unselective.\(^9\) Treatment of the allylic alcohol 223 under catalytic Sharpless conditions \[\text{[(+)-DIPT (50 mol %) / Ti(Oi-Pr)\(_4\) (40 mol %) / TBHP / -10\degree C)]\] gave largely the starting alcohol 223 and a small amount of what appeared to be the epoxide 224; however, this product was quite labile and attempted purification was unsuccessful. Treatment of the allylic alcohol 223 under modified Sharpless conditions \[\text{[(+)-DIPT (3 equiv) / Ti(Oi-Pr)\(_4\) (2.5 equiv) / TBHP / -10\degree C)]\] gave the expected the O-methyl ether 225 as a single diastereomer in 50% yield. Also, as expected, the corresponding epoxide 224 was not observed under these conditions. Furthermore, the use of (+)-DET instead of (+)-DIPT and the presence of equimolar reagents \[\text{[(+)-DET (1.3 equiv) / Ti(Oi-Pr)\(_4\) (1.0 equiv) / TBHP / -8\degree C)]\] gave the optimum results with a yield of 63% and was shown to be a single diastereomer by \(^1\text{H}\) and \(^13\text{C}\) NMR analysis (Scheme 48).
Scheme 48: Epoxidation / Rearrangement of Allyl Alcohol 223

In order to prove the C-7 and C-8 stereochemistry, conversion of O-methyl ether 225 into the previously prepared acetal 110 was necessary. Reaction of the alcohol 225 with TMSI, generated in situ from TMSCl and NaI, in propene-saturated acetonitrile\textsuperscript{16} yielded the acetal 110 as the major demethylated product, but in a poor yield (Scheme 49). Analysis of the $^1$H NMR of this product was completely identical to that of the previously prepared acetal 110. Several other methods were tried in order to improve the deprotection of the O-methyl ether 225, including TMSSMe / ZnI\textsubscript{2} / Bu\textsubscript{4}NI\textsuperscript{17} EtSH / BF\textsubscript{3}•Et\textsubscript{2}O,\textsuperscript{18} and BBr\textsubscript{3},\textsuperscript{19} but all attempts led to extensive decomposition.

Interestingly, demethylation of the O-methyl ether 225 under the in situ TMSI conditions was a minor pathway, unlike the case with the previously discussed compound 208 (see Section 5.3.3). The major product appeared to be the acetal 227, but attempted purification was unsuccessful. The stereochemistry at C-7 appeared to affect the rate of demethylation, possibly by preventing the conversion of 227 into 110. This C-7 stereochemical difference of acetics 219 and 227 results in a relative stereochemistry of syn and anti respectively concerning the the C-7 methyl and the C-8 O-methyl ether.
Scheme 49: Demethylation of O-Methyl Ether 225

If the hypothesis shown is correct, one solution to this problem may be to remove the ability of the C-6 hydroxyl functionality to participate, therefore preventing Path A. It is unlikely, however, that any protecting group on the C-6 hydroxyl function would survive the harsh reaction conditions necessary for demethylation.


5 1 mol % Os content and 2.5 mol % ligand content. Commerically available AD mixes were unreactive in this system.


8 Magnus, P. D.; Hodgetts, K. unpublished results.


13 The acetals 215 and 217 were compared to acetals 110 and 219 respectively. Magnus, P. D.; Hodgetts, K. unpublished results.


4 Approach Utilizing a Sulfone / Lactone Ring Closure

4.1 New Retrosynthetic Strategy

With the more direct method for construction of the C-7 and C-8 stereocenters utilizing a Suzuki coupling and an unusual Sharpless epoxidation / rearrangement (see Section 5.3.4), a new strategy had to be developed that addressed both the problem of deprotection of the O-methyl ether function at C-8 and the formation of the B-ring of eleutherobin (4). The sulfone / lactone approach, as shown in Scheme 50, could solve both problems. The sulfone 229 should be a ideal intermediate for two reasons. First, the sulfone 229 should be robust enough to survive the harsh deprotection conditions necessary for C-8.¹ Second, the C-6 hydroxyl functionality found in the alcohol 225, which was believed to competitively attack the C-2 oxonium ion (see Section 5.3.4), is no longer present, thus preventing this unwanted reactivity. Opening of the acetal 230 followed by conversion to the acid 232 should be possible using previously developed methodology (see Sections 5.2.3 and 5.2.4). Formation of the lactone 233 would then provide a suitable substrate for formation of the core of eleutherobin. Unlike all previous routes to the core of eleutherobin which necessitated the formation of a medium-sized ring (8 or 10), this approach requires the formation of a 5-membered ring to yield the core compound 234. This closure should reduce the unfavorable entropy loss associated with the previous ring closure strategies.
Scheme 50: Sulfone / Lactone Approach to Eleutherobin (4)

4.2 Demethylation of O-Methyl Ether

Construction of the demethylation substrate 229 was possible in 3 steps with an overall 50% yield (Scheme 51). Oxidation of the alcohol 225 followed by treatment with the Wadsworth-Emmons reagent 236 generated in situ gave exclusively the E-α,β-unsaturated sulfone 237 (H-5,6 coupling constant of 15.1 Hz). Reduction of the olefin 237 was possible using either Strkyer's reagent, [(Ph₃P)CuH]₆,² or NaBH₄³ in 80% or 61% yield respectively.
Scheme 51: Synthesis of Sulfone 229

With the sulfone 229 in hand, attention was turned toward the removal of the C-8 O-methyl ether. Treatment of O-methyl ether 229 with TMSI, generated in situ from TMSCl and NaI, in the presence of 1-pentene yielded the unstable tertiary iodide 238 as the major product (Scheme 52). The C-11 stereochemistry is assumed to be as drawn due to approach by the electrophile from the less hindered β-face.

i) Dess-Martin periodinane, CH₂Cl₂; ii) 236, THF, -78°C to 25°C, 63% over 2 steps; iii) [(Ph₃P)CuH]₆, PhH, reflux, 80% or NaBH₄, MeCN, reflux, 61%.
It was now believed that it was HI that had demethylated the C-8 O-methyl ether and not TMSI. In order to supply further evidence in support of this hypothesis a more electron rich olefin, 2-methyl-2-butene, was used as an HI scavenger. Since both the C-11,12 olefin 229 and 2-methyl-2-butene are trisubstituted olefins, it was hoped that HI would preferentially react with 2-methyl-2-butene if it was used in excess. Treatment of O-methyl ether 229 with TMSI, generated in situ from TMSCl and NaI, in the presence of a large excess of 2-methyl-2-butene followed by the addition of DBU to eliminate the presumed 2-iodo-2-methyl-butane intermediate\textsuperscript{4} yielded only the epimerized acetal 239\textsuperscript{5} in 64% yield (Scheme 53) (no H-1,2 coupling was observed in the $^1$H NMR of the acetal 239 versus an observed H-1,2 coupling constant of 4.5 Hz in the acetal 229). Since any HI appeared to be efficiently removed by the large excess of 2-methyl-2-butene, the only possible demethylating reagent in the reaction should be TMSI. Unlike the previous experiment using 1-pentene as an HI scavenger where demethylation was observed as a major pathway, no demethylation appears to occur with 2-methyl-2-butene as a HI scavenger. This result is in direct
contradiction to Jung and co-workers' hypothesis\textsuperscript{6} that TMSI and not HI is the demethylating agent.

\textbf{Scheme 53: Synthesis of Acetal 239}

The use of classic HI demethylation conditions (PTSA / NaI / MeCN)\textsuperscript{7} with 229 followed by the addition of DBU to eliminate the iodide intermediate 238 gave the desired acetal 230 in 48\% yield along with two compounds which are believed to be the enol ether 240 and the lactol 241 (Scheme 54). The iodide intermediate 238 can be isolated prior to treatment with DBU, however, the overall yield is lower (20\%) presumably due to the instability of the iodide 238 as previously mentioned.
i) PTSA, NaI, MeCN then 229, 0°C followed by DBU, 0°C to 25°C, 230 (48%) + 240 (22%) + 241 (16%).

Scheme 54: Synthesis of Acetal 229

4.2 Conversion to Advanced Intermediate

Conversion of the acetal 230 into the acid 232 was possible in 3 steps. Addition of allyltrimethylsilane (165) to the acetal 230 under the conditions used previously with acetal 156 (see Section 5.2.1) yielded the desired olefin 231 which could be efficiently dihydroxylated using AD mix β*8 to give the desired triol 242 as an approximate 3 to 1 mixture at C-4 as shown by 1H NMR of the crude reaction mixture (Scheme 55). Interestingly, only a trace amount of over reaction at the C-11,12 olefin was observed compared to approximately 20% with the previous substrate 169. Two variables are different between the olefins 231 and 169: i) the tertiary hydroxyl functionality at C-7 is unprotected in compound 231 versus the silyl ether 169; ii) a sulfone is present at the C-5 position in 231 as compared to the C-6 silyl ether present in 169. One possible explanation for the
increased efficiency of this reaction may be that the tertiary hydroxyl facilitates hydrolysis of the osmate ester intermediate. As discussed earlier (see Section 5.2.3), it is believed that this intermediate is the active reagent for dihydroxylation of the C-11,12 alkene.

Scheme 55: Synthesis of Triol 242

Periodate cleavage of the triol 242 yielded the unstable aldehyde 243, which upon isolation and oxidation gave the acid 232 in moderate yield (32% over 2 steps) (Scheme 56). The yield of this transformation could be improved by direct oxidation of the aldehyde without isolation. When both oxidations are conducted in a single operation, the yield improved to 60%. Work in this area is currently ongoing in this laboratory.
Scheme 56: Synthesis of Acid 232


4 No change by TLC is observed upon addition of the DBU. Since the iodo adduct 238 has been previously prepared and has a different Rf to the observed compound 239, it is believed that the DBU is present only to eliminate the 2-iodo-2-methyl butane to 2-methyl-2-butene. Attempted isolation of the product 239 without the addition of DBU yields substantial decomposition upon concentration.

5 As mentioned earlier (see Section 5.1.6), it is believed that epimerization of the C-2 acetal 229 to give the more sterically encumbered structure 239 occurs due an anomeric efffect.


8 1 mol % Os content and 2.5 mol % ligand content.
5 Future Work and Conclusion

5.1 Future Work

With a viable 12 step route to the acid 232, only conversion to the lactone 233 is necessary before cyclization of 233 can be investigated. Since this strategy involves the closure of a 5-membered ring as opposed to previous unsuccessful 8 or 10-membered ring closures, it is hoped that this route will prove more fruitful (Scheme 57). There are several examples of sulfone / ester ring closures reported in the literature. In addition to the lactone 233, cyclization of the methyl ester 244 might also be possible. Interesting, treatment of the ester 244 under basic conditions might form the lactone 233 in situ as an intermediate toward the cyclized product 234.

![Scheme 57: Proposed Cyclization of Core Ring System 234](image)

If the cyclization of the sulfone 233 proves to be successful, conversion to eleutherobin (4) should be possible. After conversion of the lactol 234 into its methoxy ketal 245, treatment of 245 with \((\text{CH}_2\text{O})_n\) and excess base should yield the hydroxymethylene adduct 250 as shown below (Scheme 58). Upon inspection
of models, it is believed that reaction with formaldehyde will occur at the less hindered C-3 position. It is hoped that the elimination of the C-2,8 ether bridge will also occur under these reaction conditions. Furthermore, elimination of the C-4 O-methyl ether is thought to be improbable as it would yield a C-4,5 anti-Bredt double bond.²

Scheme 58: Proposed Synthesis of Diterpene 250

Conversion of the diterpene 250 into eleutherobin should then be possible as described (Scheme 59). After selective protection of the primary hydroxyl functional at C-15, the C-8 side chain can be attached. The necessary acid chloride 252 should be directly accessible from the known acid 45.³ Elimination of the sulfone 253 to the alkene 254 followed by deprotection should yield the eleutherobin core structure 255.
As previously mentioned (see Section 5.1.1), the sugar side chain that is necessary for the total synthesis of eleutherobin (4) should be available from commercially available D-arabinose (51). The coupling of the alcohol 256 and the suitably protected, activated sugar 257 should be possible under a variety of conditions. Since it has been observed that C-2" acetates often participate during the coupling protocols, the acetate function must be installed after coupling to the aglycon 256. The necessary deprotection and acetylation would then yield the target (4).
Scheme 59: Proposed Final Stages of Synthesis of Eleutherobin (4)
A further area of future work may involve the optimization of two of the less efficient steps in the working route: i) the Suzuki coupling of the iodide 222 and the borane 71; ii) the demethylation of O-methyl ether 225. One potential modification for the Suzuki coupling would be the use of TIOH\textsuperscript{7} or other additives which might suppress the elimination of the 9-BBN adduct 71. Also, modification of the concentration, temperature, solvent, and equivalents of reagents might also improve the yield of this transformation. Some possible modifications for the demethylation of O-methyl ether 225 are the use of an alternative base for the elimination, such as i-Pr\textsubscript{2}NET, and the use of alternative demethylation conditions, such as dichloromethyl ether / NaI.\textsuperscript{8}

5.2 Summary and Conclusion

These studies have led to the development of a concise method for the 5 step synthesis of the alcohol 225, which contains all the important stereocenters present in eleutherobin (4). The unique epoxidation / rearrangement of the allylic alcohol 223 to yield the O-methyl ether 225 was also discovered during the course of this research (Scheme 60).

Scheme 60: Synthesis of O-Methyl Ether 225

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Construction of the advanced intermediates 117, 130, 134, 150, 167, and 190 led to the investigation of an array of strategies for the formation of the core ring system of eleutherobin (Figure 7). These attempted cyclizations have shown that the formation of a medium-sized ring is unlikely in this system. This conclusion led to the development of the sulfone / lactone strategy (see Section 5.4) which should hopefully circumvent this problem.

![Chemical structures](image)

Figure 7: Cyclization Precursors Prepared During These Studies

The novel fragmentation of the C-7,8 bond of the ester 117 under Lewis acid conditions during attempted cyclization was also investigated (Scheme 61). A mechanism was proposed to explain this fragmentation. It can be concluded from this fragmentation that attempted closure of the C-2,3 bond is not likely under the Mukaiyama conditions.
Scheme 61: Fragmentation of 117

The unusual use of Sharpless' AD methodology was developed in order to selectively functionalize the alkenes 169 and 231 (Figure 8). Also, an explanation for this result was proposed.

Figure 8: Selective Functionization of Olefins 169 and 231 Using AD mix β∗
Finally, the advanced intermediate 232 (Figure 9) was constructed with the hope that it may subsequently provide a viable route the core ring system 234 (Scheme 57).

![Diagram of compound 232]

**Figure 9:** Advanced intermediate 232


4 Wright, K. personal communication.


Section 6: Experimental
General

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer neat unless otherwise indicated. $^1$H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz in the indicated solvent and are reported in ppm relative to tetramethyldisilane and referenced internally to the residually protonated solvent. $^{13}$C NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated and are reported in ppm relative to tetramethyldisilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter using a sodium lamp at 589 nm in CHCl$_3$ with 1% ethanol.

Routine monitoring of reactions was performed using Merck 60 F$_{254}$ silica gel, aluminum-backed TLC plates. PLC was performed using Merck 60 F$_{254}$ silica gel, glass supported plates. Flash column chromatography was performed with the indicated eluents on Merck 60H F$_{254}$ silica gel.

Air and / or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by a Bunsen flame, then cooled under argon. Solvents and commercial reagents were purified in accord with Perrin and Armarago$^1$ or used without further purification.
(2R)-Methyl, 3-[4'-nitrobenzoyl(oxy)]-1,2-epoxy-propane (60).²

\[ \begin{align*}
\text{CH}_2\text{Cl}_2 & \quad \text{3 Å molecular sieves} \\
\text{58} & \quad \text{CH}_2\text{Cl}_2 \\
\text{60} & \quad \text{P(OMe)}_3 \\
\text{Et}_3\text{N} & \quad \text{PNBCl}
\end{align*} \]

To a solution of powdered 3 Å molecular sieves (approximately 3.5 g) in CH₂Cl₂ (150 mL) at -20°C was added (+)-DIPT (1.40 g, 6.0 mmol) in CH₂Cl₂ (10 mL) via cannula followed sequentially by Ti(Oi-Pr)₄ (1.42 g, 1.5 mL, 5.0 mmol) and cumene hydroperoxide (1.31 g, 36 mL, 0.200 mol). After 1 h, a solution of 2-methallyl alcohol (58) (7.20 g, 8.40 mL, 0.100 mol) in CH₂Cl₂ (15 mL) was added dropwise via cannula.

After 16 h, the reaction was treated dropwise with P(OMe)₃ (18.62 g, 17.70 mL, 150 mmol), taking care that the temperature did not rise above -20°C. On warming to 0°C, Et₃N (17.0 mL, 0.122 mmol) was added followed by a suspension of PNBCl (18.60 g, 0.100 mmol) in CH₂Cl₂ (100 mL) via cannula. After 1 h, the reaction mixture was filtered through a pad of Celite®, the filtrate was washed with sequentially with a tartaric acid solution (100 mL, 10% in H₂O), saturated aqueous NaHCO₃ (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na₂SO₄) extract was filtered through a small pad of silica gel and concentrated under in vacuo (60°C, 0.2 mmHg) to remove any volatiles. The oil which solidified on standing, was recrystallized (twice from Et₂O, then i-Pr₂O) to
give 60 (12.25 g, 0.053 mol, 52%, >98% e.e.) as an off-white solid. Enantiomeric excess was determined by chiral shift analysis of the methyl signal at 1.2 ppm using Eu(hfc)₃ (7 mg of 60, 4.5 mg of Eu(hfc)₃, 0.5 mL of C₆D₆).

[α]D²³ -6° (c 2.98).

m.p. 85 - 86°C

¹H NMR (CDCl₃) δ 8.2 - 8.4 (4H, m), 4.60 (1H, d, J = 11.0 Hz), 4.25 (1H, d, J = 11.0 Hz), 2.89 (1H, d, J = 4.0 Hz), 2.78 (1H, d, J = 4.0 Hz), 1.49 (3H, s).

1-Thiophenyl-(2S),3-propanediol (61).

To a solution of 60 (9.46 g, 39.90 mmol) in dioxane (37 mL) was added PhSH (4.30 mL, 41.85 mmol) and then NaOH (21.0 mL, 42.0 mmol, 2 M in H₂O) dropwise. After 2 h at ambient temperature, solid NaHCO₃ (20 mL) was added and the aqueous phase was extracted with CH₂Cl₂ (4 x 100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 70% EtOAc / petroleum ether, to give 61 (7.56 g, 38.2 mmol, 96%) as a colorless oil.
IR 3406, 2929 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.35 - 7.45 (2H, m), 7.2 - 7.3 (2H, m), 7.1 - 7.2 (1H, m), 3.55 (1H, dd, \(J = 5.7, 11.2\) Hz), 3.46 (1H, dd, \(J = 5.0, 11.2\) Hz), 3.05 - 3.25 (4H, m), 1.22 (3H, s).

\(^13\)C NMR (CDCl\(_3\)) \(\delta\) 136.6, 129.3, 128.9, 126.1, 73.1, 68.4, 42.9, 23.3.

HRMS (CI) calcd. for C\(_{10}H_{14}O_2S\) 198.0715. Found 198.0707.
1-Thiophenyl-(2S),3-propanediol cyclohexyl ketal (62).

**Procedure 1:** To a stirred solution of 61 (7.56 g, 38.20 mmol) and 3 Å molecular sieves (1.00 g) in cyclohexanone (65 mL) was added PTSA (0.073 g, 0.38 mmol). After heating for 9 h at reflux, the mixture was filtered and concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 60% EtOAc / petroleum ether, to give 62 (9.53 g, 34.3 mmol, 90%).

**Procedure 2:** To a stirred solution of 61 (7.84 g, 39.60 mmol) in DMF (10 mL) was added 1-methoxycyclohexene (259)^3 (6.00 g, 53.6 mmol) followed by PTSA (0.300 g, 1.50 mmol). After 40 h at ambient temperature, the reaction was diluted with saturated aqueous brine (250 mL), extracted with EtOAc (3 x 300 mL). The dried (Na$_2$SO$_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% EtOAc / petroleum ether, to give 62 (10.68 g, 38.4 mmol, 97%) as a colorless oil.

IR 2932 cm$^{-1}$. 

201
$^1$H NMR (CDCl$_3$) δ 7.35 - 7.4 (2H, m), 7.25 - 7.35 (2H, m), 7.1 - 7.2 (1H, m), 3.99 (1H, d, J = 8.6 Hz), 3.71 (1H, d, J = 8.6 Hz), 3.15 (2H, s), 1.50 - 1.65 (8H, m), 1.39 (3H, s), 1.3 - 1.5 (2H, m).

$^{13}$C NMR (CDCl$_3$) δ 137.0, 129.2, 128.8, 126.0, 110.4, 80.7, 72.6, 43.5, 36.7, 36.3, 25.0, 24.7, 23.9, 23.80.

HRMS (Cl) calcd. for C$_{16}$H$_{22}$O$_2$S 278.1341. Found 278.1335.

1-Phenylsulfoxyl-(2S),3-propandiol cyclohexyl ketal (63).

![Chemical Structure](image)

To a stirred solution of 62 (10.54 g, 37.90 mmol) in CH$_2$Cl$_2$ (200 mL) at -20°C was added a solution of MCPBA (7.90 g, 41.20 mmol, approximately 90%) in CH$_2$Cl$_2$ (100 mL) via cannula. After 30 min, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ (50 mL) and extracted with Et$_2$O (4 x 100 mL) followed by washing of the combined organic phase with saturated aqueous NaHCO$_3$ (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo to give 63 (11.14 g, 37.90 mmol, 99%) as a colorless oil.
IR 2935, 1042 cm\(^{-1}\). 

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.4 - 7.65 (5H, m), 4.37 (1H, d, \(J = 8.9\) Hz), 4.06 (1H, d, \(J = 8.9\) Hz), 3.77 (2H, m), 2.8 - 3.0 (2H, m), 1.3 - 1.8 (10H, m).

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 144.8, 144.6, 130.8, 129.2, 123.8, 123.7, 110.8, 110.2, 78.5, 73.7, 71.8, 68.3, 68.0, 36.8, 36.4, 36.1, 35.9, 26.7, 24.94, 24.90, 24.4, 23.8, 23.6.

HRMS (Cl) calcd. for C\(_{16}\)H\(_{22}\)O\(_3\)S 295.1368. Found 295.1363.

1-Thiophenyl-1-acetoxy-(2S),3-propanediol cyclohexyl ketal (64).

To a stirred solution of 63 (10.87 g, 37.0 mmol) in Ac\(_2\)O (100 mL) was added NaOAc (20.0 g, 244 mmol) and the mixture heated at reflux. After 16 h, the reaction was allowed to cool to ambient temperature, NaOH (100 mL, 1 M in H\(_2\)O) was added and the mixture stirred for 1 h at ambient temperature, followed by extraction with CH\(_2\)Cl\(_2\) (3 x 200 mL). The combined organic layers were washed with saturated aqueous NaCl (300 mL). The dried (Na\(_2\)SO\(_4\)) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting
with 20% EtOAc / petroleum ether, to give the diastereoisomeric acetates 64 (1.7:1)\(^4\) (11.69 g, 34.8 mmol, 94%) as a colorless oil.

IR 2933, 1749 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.45 - 7.55 (6H, m), 7.25 - 7.35 (4H, m), 6.26 (1H, s, major), 6.19 (1H, s, minor), 4.23 (1H, d, \(J = 9.3\) Hz, major), 4.02 (1H, d, \(J = 8.8\) Hz, minor), 3.79 (1H, d, \(J = 9.3\) Hz, major), 3.72 (1H, d, \(J = 8.8\) Hz, minor), 2.05 (3H, s, major), 2.01 (3H, s, minor), 1.25 - 1.75 (20H, m), 1.45 (3H, s), 1.44 (3H, s).

\(^13\)C NMR (CDCl\(_3\)) \(\delta\) 169.5, 169.2, 133.6, 132.6, 132.5, 132.3, 129.0, 128.9, 128.2, 128.0, 111.4, 111.1, 85.2, 84.8, 82.0, 81.9, 71.9, 71.0, 36.5, 36.1, 36.0, 35.8, 25.0, 23.8, 22.7, 20.9.

HRMS (CI) calcd. for C\(_{18}\)H\(_{24}\)O\(_4\)S 336.1395. Found 336.1388.
1-Propanal-(2S),3-diol cyclohexyl ketal (56).

To a stirred solution of 64 (3.50 g, 10.42 mmol) in MeOH (20 mL) was added solid K$_2$CO$_3$ (0.950 g, 6.88 mmol) and the mixture heated at reflux. After 5 h, the reaction mixture was allowed to cool to ambient temperature, concentrated in vacuo and Et$_2$O (100 mL) was added precipitating a white solid. After filtration through Celite® (Et$_2$O rinse), the organic phase was concentrated in vacuo followed by purification by Kügelrohr distillation (oven temperature 100°C, 1 mm Hg) to give 56 (1.91 g, 10.3 mmol, 99%) as a colorless oil.

IR 2939, 2863, 1737 cm$^{-1}$.
$^1$H NMR (CDCl$_3$) $\delta$ 9.66 (1H, s), 4.23 (1H, d, $J = 8.9$ Hz), 3.73 (1H, d, $J = 8.9$ Hz), 1.35 - 1.7 (10H, m), 1.35 (3H, s).
$^{13}$C NMR (CDCl$_3$) $\delta$ 202.3, 111.8, 84.1, 70.4, 36.3, 35.9, 24.9, 23.8, 19.4.

HRMS (Cl) calcd. for C$_{10}$H$_{17}$O$_3$ 185.1178. Found 185.1171.
1-Methyl-(4S)-isopropyl-1-cyclohexene-6-one (67).^5

To a stirred solution of (Ph₃P)₃RhCl (1.60 g, 1.73 mmol) in PhH (500 mL) under an atmosphere of H₂ was added (1S)-(+) -carvone (59) (24.1 g, 25.0 mL, 160 mmol) at ambient temperature. After 20 h, the reaction was concentrated in vacuo, filtered through a plug of silica gel (Et₂O rinse), concentrated in vacuo and purified by distillation (115 - 117°C, 18 mm Hg) to yield 67 (22.53 g, 148 mmol, 93% yield) as a colorless liquid.

¹H NMR (CDCl₃) δ 6.7 - 6.8 (1H, m) 2.5 - 2.6 (1H, m), 2.3 - 2.45 (1H, m), 2.0 - 2.2 (2H, m), 1.8 - 1.9 (1H, m), 1.77 (3H, s), 1.5 - 1.6 (1H, m), 0.91 (6H, d, J = 6.7 Hz).
1-Methyl-(4S)-isopropyl-6-trimethylsiloxy-1,5-cyclohexadiene (67).

\[
\text{\begin{align*}
\text{67} & \xrightarrow{1) \text{LDA, THF, } -78^\circ\text{C}} \text{68} \\
& \xrightarrow{2) \text{TMSCl}}
\end{align*}}
\]

*LDA Preparation:* To a stirred solution of i-Pr$_2$NH (1.2 g, 1.6 mL, 1.2 mmol) in THF (6 mL) was added n-BuLi (5 mL, 12.5 mmol, 2.5 M in hexanes) at -78°C. The LDA solution was warmed to 0°C and stirred for 25 min.

To a stirred solution of 67 (1.33 g, 8.75 mmol) in THF (50 mL) was added the LDA solution via cannula. After 20 min at -78°C, TMSCl (1.1 g, 10 mmol, 1.3 mL) was added to the reaction over 1 min. After stirring at -78°C for 5 min, the reaction was allowed to warm to ambient temperature, quenched with saturated aqueous NaCl (100 mL), extracted with Et$_2$O (4 x 200 mL), concentrated *in vacuo*, diluted with NaCl (50 mL) and extracted with Et$_2$O (4 x 100 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* to give crude 68 (1.83 g, 8.17 mmol) as a pale yellow liquid. This material was used without further purification.

$^1$H NMR (CDCl$_3$) δ 5.74 (1H, br s), 5.37 (1H, br s), 1.8 - 2.2 (2H, m), 1.4 - 1.7 (5H, m), 0.8 - 0.9 (6H, m), 0.18 (9H, s).

HRMS (Cl) calcd. for C$_{13}$H$_{25}$OSi 225.1675. Found 225.1672.

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1-Methyl-(4S)-isopropyl-(5R)-dimethyl acetal-1-cyclohexen-6-one (69).

\[ \text{CH(OME)}_3, \text{BF}_3\cdot\text{Et}_2\text{O} \]

\[ \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \]

To a stirred solution of crude 68 (1.83 g, 8.17 mmol) in CH$_2$Cl$_2$ (8 mL) with CH(OME)$_3$ (1.07 g, 1.10 mL, 10.1 mmol) was added a solution of BF$_3$•Et$_2$O (1.15 g, 1.0 mL, 8.1 mmol) in CH$_2$Cl$_2$ (2.5 mL) via cannula at -78°C. An additional portion of CH$_2$Cl$_2$ (2.5 mL) was added to rinse the BF$_3$•Et$_2$O flask. After 1.5 h, the reaction was quenched by the sequential addition of MeOH (2 mL) followed by saturated aqueous NaHCO$_3$ (30 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL), dried (Na$_2$SO$_4$), concentrated in vacuo and purified by chromatography over silica gel, eluting with 10 - 20% Et$_2$O / petroleum ether, to give 69 (0.96 g, 4.2 mmol, 48%) as a pale yellow liquid. Acetal 69 was identical to previously prepared material.

$[\alpha]_D^{23} + 19^\circ$ (c 2.50).

IR 2958, 2833, 1678 cm$^{-1}$.
$^1$H NMR (CDCl$_3$) $\delta$ 6.55 - 6.65 (1H, m), 4.64 (1H, d, J = 7.2 Hz), 3.32 (3H, s), 3.30 (3H, s), 2.80 (1H, dd, J = 3.0, 7.2 Hz), 2.2 - 2.3 (1H, m), 1.90 - 2.05 (1H, m), 1.75 (3H, d, J = 1.5 Hz), 1.6 - 1.8 (2H, m), 0.87 (3H, d, J = 5.4 Hz), 0.85 (3H, d, J = 5.4 Hz).

$^{13}$C NMR (CDCl$_3$) $\delta$ 198.8, 143.1, 135.2, 103.6, 53.9, 53.1, 52.3, 40.8, 29.4, 25.9, 20.5, 15.9.

HRMS (Cl) calcd. for C$_{13}$H$_{23}$O$_3$ 227.1672. Found 227.1643.

**1-Methyl-(4S)-isopropyl-(5R)-dimethyl acetal-1-cyclohexen-6-one (69).**

\[
\begin{align*}
&\text{67} \\
&\text{1) TiCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \\
&\text{2) i-Pr}_2\text{NEt, -78}^\circ\text{C} \\
&\text{3) CH(OMe)}_3, -78^\circ\text{C to } 0^\circ\text{C} \\
\end{align*}
\]

To a stirred solution of 67 (86.7 g, 0.57 mol) in CH$_2$Cl$_2$ (1.6 L) was added TiCl$_4$ (110.7 g, 64.0 mL, 0.58 mol) at -78°C over a 5 min period. After an additional 15 min, i-Pr$_2$NEt (74.2 g, 100.0 mL, 0.57 mol) was added to the orange solution over 5 min. The dark red solution was stirred an additional 1.5 h at -78°C. Then, CH(OMe)$_3$ (121.2 g, 125.0 mL, 1.1 mol) was added over 7 min. After 4 h at -78°C, the reaction mixture was warmed to 0°C over 25 min. The dark solution was poured into saturated aqueous NH$_4$Cl (1.5 L) and extracted with
CH$_2$Cl$_2$ (3 x 800 mL). The dried (MgSO$_4$) extract was concentrated in vacuo to give a yellow liquid. This reaction was repeated on 87.3 g scale of the enone under identical conditions. The combined crude liquids were passed quickly through a short plug of silica gel, eluting with 20% Et$_2$O / petroleum ether. The filtrate was concentrated in vacuo and purified in 50 mL batches of the crude liquid by chromatography over silica gel, eluting with 12 - 15% Et$_2$O / petroleum ether, to give starting enone 67 (38.2 g, 0.25 mol, 37%) followed by the acetal 69 (158.6 g, 0.70 mol, 61% yield) as a pale yellow liquid.

1-Methyl-(4R)-isopropyl-(5S)-dimethyl acetal-6-yl-1-cyclohexene (57).

\[
\begin{align*}
\text{69} & \quad \text{dimethyl titanocene,}
\quad \text{THF, reflux}
\end{align*}
\]

\[
\begin{align*}
\text{57}
\end{align*}
\]

Dimethyl Titanocene Preparation: To a stirred solution of titanocene dichloride (136 g, 0.55 mol) in Et$_2$O (1.8 L) was added MeLi (800 mL, 1.12 mol, 1.4 M in Et$_2$O) via cannula over 1.25 h at 0°C in the dark. The orangeish, brown solution was allowed to warm to ambient temperature. After 2 h, cold H$_2$O (750 mL) was added slowly and extracted Et$_2$O (3 x 700 mL). The dried (MgSO$_4$) extract was
concentrated in vacuo in the dark and the orange solid was immediately dissolved in THF (100 mL).

The dimethyl titanocene solution was added to a stirred solution of 69 (45.0 g, 0.20 mol) in THF (200 mL) via cannula in the dark. An additional amount of THF (2 x 25 mL) was used to rinse the dimethyl titanocene flask. After 20 h of heating the dark red solution at reflux in the dark, the reaction mixture was concentrated in vacuo. The crude slurry was dissolved in Et2O (500 mL) and silica gel (500 mL) was added slowly. The solid was filtered and rinsed with Et2O (1.5 L). The filtrate was concentrated in vacuo and this silica gel cycle repeated twice. The dark liquid was distilled (2.5 mm Hg, 112 - 115°C) to give 57 (31.5 g, 0.14 mol, 71% yield) as a colorless liquid.6

[α]D23 -117° (c 1.27).

IR 2942, 1608 cm⁻¹.

1H NMR (CDCl₃) δ 5.47 (1H, br s), 5.05 (1H, s), 4.88 (1H, s), 4.23 (1H, d, J = 8.4 Hz), 3.30 (3H, s), 3.28 (3H, s), 2.66 (1H, dd, J = 2.1, 8.4 Hz), 2.0 - 2.3 (2H, m), 1.78 (3H, d, 1.2 Hz), 1.45 - 1.55 (1H, m), 1.30 - 1.45 (1H, m), 0.86 (3H, d, J = 3.3 Hz), 0.84 (3H, d, J = 3.3 Hz).

13C NMR (CDCl₃) δ 145.2, 135.5, 128.7, 115.9, 108.1, 58.2, 55.9, 50.3, 43.2, 31.3, 28.9, 24.9, 23.6, 22.9.

HRMS (Cl) calcd. for C₁₄H₂₄O₂ 225.1895. Found 225.1892.
1-Methyl-\((dR)\)-isopropyl-(5R)-dimethyl acetal-(6S)-hydroxymethyl-1-cyclohexene (72).

A solution of 9-BBN (515 mL, 0.26 mol, 0.5 M in THF) was added to 57 (52.32 g, 0.23 mol). After heating the stirred solution at 60 - 65°C for 18 h, the reaction was cooled to 0°C and NaOH (150 mL, 4 M in H₂O) was added followed by the dropwise addition of H₂O₂ (150 mL, 30% in H₂O). After 30 min at 0°C and 45 min at ambient temperature, the THF was removed in vacuo and the aqueous layer was extracted with Et₂O (4 x 300 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over florisil, eluting with 5 - 50% Et₂O / petroleum ether followed by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give the starting diene 57 (10.40 g, 0.05 mol, 22%) followed by the alcohol 72 (33.33 g, 0.14 mol, 61% yield) as a colorless oil.

\([\alpha]_D^{23} +66^\circ \ (c \ 0.89)\).

IR 3453, 2957 cm⁻¹.
$^1$H NMR (CDCl$_3$) δ 5.38 (1H, br s), 4.40 (1H, d, J = 5.0 Hz), 3.6 - 3.7 (3H, m), 3.47 (3H, s), 3.39 (3H, s), 2.4 - 2.45 (1H, m), 1.95 - 2.05 (2H, m), 1.7 - 1.85 (2H, m), 1.69 (3H, s), 1.15 - 1.3 (1H, m), 0.90 (3H, d, J = 6.3 Hz), 0.82 (3H, d, J = 6.3 Hz).

$^{13}$C NMR (C$_6$D$_6$) δ 133.6, 122.7, 106.5, 62.2, 55.1, 54.1, 42.0, 39.8, 36.6, 27.1, 24.7, 22.1, 21.2, 17.4.


1-Methyl-(4R)-isopropyl-(5R)-dimethyl acetate - (6S)-[4'-nitrobenzoyloxy]methyl]-1-cyclohexene (74).

To a stirred solution of crude 72 (120 mg, 0.5 mmol) in CH$_2$Cl$_2$ (5 mL) with DMAP (3 mg, 0.02 mmol) and imidazole (85 mg, 1.25 mmol) was added PNBCl (140 mg, 0.75 mmol). After 2 days at ambient temperature, the reaction was diluted with CH$_2$Cl$_2$ (10 mL) and was washed with H$_2$O (3 x 10 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by vapor diffusion
crystallization with petroleum ether, to give 74 (18 mg, 0.046 mmol, 9%) as a off-white solid. Crystals suitable for X-ray crystallography were obtained by recrystallization in petroleum ether. X-ray coordinates for 74 are found in Appendix 1.

IR (nujol) 2923, 2854, 1728 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.15 - 8.3 (4H, m), 5.46 (1H, br s), 4.67 (1H, dd, \(J = 5.1, 11.3\) Hz), 4.47 (1H, dd, \(J = 5.3, 11.3\) Hz), 4.36 (1H, d, \(J = 5.1\) Hz), 3.36 (3H, s), 3.31 (3H, s), 2.6 - 2.65 (1H, m), 1.3 - 2.1 (8H, m), 0.89 (3H, d, \(J = 6.6\) Hz), 0.82 (3H, d, \(J = 6.6\) Hz).

\(^1^3\)C NMR (CDCl\(_3\)) \(\delta\) 164.6, 150.3, 136.3, 133.0, 130.6, 130.6, 123.6, 123.5, 106.6, 66.8, 55.6, 55.1, 52.8, 40.4, 38.0, 36.2, 27.0, 24.4, 22.4, 21.2, 16.5.

HRMS (Cl) calcd. for C\(_{21}\)H\(_{30}\)NO\(_6\) 392.2073. Found 392.2069.
1-Methyl-(4S)-isopropyl-(5R)-dimethyl acetal-(6S)-acetoxyethyl-1-cyclohexene (257) and (1R)-Methyl-(2R)-acetoxyethyl-(4R)-isopropyl-(5R)-dimethyl acetal-(6S)-acetoxyethyl-cyclohexane (258).

\[
\begin{align*}
\text{(57)} & \quad \text{i) 9-BBN, THF} \\
& \quad \text{ii) 4 M NaOH} \\
& \quad \text{iii) Ac}_2\text{O, py} \\
\rightarrow & \quad \text{(258) + (259)} \\
& \quad 30\% \text{ H}_2\text{O}_2
\end{align*}
\]

A solution of 9-BBN (3.1 mL, 1.5 mmol, 0.5 M in THF) was added to the diene 57 (0.170 g, 0.76 mmol). After heating the stirred solution at 60 - 65°C for 55 h, the reaction was cooled to 0°C and NaOH (5 mL, 4 M in H₂O) was added followed by the dropwise addition of H₂O₂ (5 mL, 30% in H₂O). After 30 min at 0°C and 45 min at ambient temperature, the aqueous layer was extracted with Et₂O (4 x 30 mL). The dried (Na₂SO₄) extract was concentrated \textit{in vacuo} and dissolved in py (1 mL) and Ac₂O (1 mL) added. After 16 h, the reaction mixture was diluted with CuSO₄ (25 mL, 1 M in H₂O) extracted with Et₂O (50 mL), followed by washing with HCl (25 mL, 0.2 M in H₂O), H₂O (25 mL), and saturated aqueous NaCl (25 mL). The dried (Na₂SO₄) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 30% Et₂O / petroleum ether, to give the acetate 257 (92 mg, 0.32 mmol, 43%) as a colorless oil followed by the diacetate 258 (112 mg, 0.33 mmol, 43%) as a colorless oil.
mono acetate 257:

IR 2958, 1741 cm\(^{-1}\).

\(^{1}C\) NMR (CDCl\(_3\)) \(\delta\) 5.42 (1H, br s), 4.38 (1H, dd, \(J = 5.2, 11.0\) Hz), 4.33 (1H, d, \(J = 6.5\) Hz), 4.17 (1H, dd, \(J = 6.4, 11.0\) Hz), 3.35 (6H, s), 2.45 (1H, m), 2.03 (3H, s), 2.00 (2H, m), 1.7 - 1.9 (6H, m), 0.90 (3H, d, \(J = 6.5\) Hz), 0.82 (3H, d, \(J = 6.5\) Hz).

HRMS (Cl) calcd. for C\(_{16}\)H\(_{29}\)O\(_4\) 285.2066 Found 285.2063.

diacetate 258:

IR 2960, 1732 cm\(^{-1}\).

\(^{1}H\) NMR (CDCl\(_3\)) \(\delta\) 4.83 (1H, dt, \(J = 4.6, 11.0\) Hz), 4.34 (1H, dd, \(J = 3.4, 11.8\) Hz), 4.29 (1H, d, \(J = 3.2\) Hz), 4.22 (1H, dd, \(J = 5.2, 11.8\) Hz), 3.39 (3H, s), 3.37 (3H, s), 2.26 (1H, m), 2.05 (6H, s), 1.5 - 2.0 (6H, m), 0.96 (3H, d, \(J = 6.9\) Hz), 0.88 (3H, d, \(J = 6.9\) Hz), 0.76 (3H, d, \(J = 6.7\) Hz).

\(^{13}C\) NMR (CDCl\(_3\)) \(\delta\) 170.7, 170.5, 107.3, 74.8, 62.4, 56.0, 55.9, 44.7, 40.1, 39.4, 38.1, 32.4, 30.1, 26.5, 21.4, 21.1, 15.1, 14.8.

HRMS (Cl) calcd. for C\(_{18}\)H\(_{33}\)O\(_6\) 345.2277. Found 345.2283.
1-Methyl-(4R)-isopropyl-(5R)-keto-(6S)-yl-7,8-oxido-1-cyclohexene (93).

To a stirred solution of 74 (28.33 g, 0.12 mol) in acetone (600 mL) was added slowly Jones reagent\(^7\) (250 mL) over 25 min. After 11 h, the reaction was transferred to an Erlenmeyer flask, diluted with H\(_2\)O (200 mL), and quenched with i-PrOH (25 mL). Solid NaHCO\(_3\) was added portion wise until the effervescence ceased. The slurry was filtered through Celite® and rinsed with acetone (4 L). The acetone was removed in vacuo and the aqueous layer was extracted with Et\(_2\)O (4 x 300 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et\(_2\)O / petroleum ether, to give 93 (16.67 g, 0.086 mol, 73% yield) as a colorless oil.

IR 2961, 1771 cm\(^{-1}\).
\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.5 - 5.6 (1H, m), 4.36 (1H, dd, \(J = 7.2, 8.9\) Hz), 4.15 (1H, dd, \(J = 4.4, 8.9\) Hz), 2.85 - 2.9 (1H, m), 2.75 - 2.8 (1H, m), 1.9 - 2.15 (2H, m), 1.75 - 1.85 (2H, m), 1.65 - 1.8 (3H, m), 0.95 (3H, d, \(J = 6.4\) Hz), 0.92 (3H, d, \(J = 6.4\) Hz).
$^{13}$C NMR (CDCl$_3$) $\delta$ 178.5, 130.0, 124.1, 70.6, 43.5, 41.3, 39.1, 36.8, 27.6, 23.6, 21.0, 19.2.

HRMS (Cl) calcd. for C$_{12}$H$_{19}$O$_2$ 195.1385. Found 195.1379.

1-Methyl-(4$R$)-isopropyl-(5$R$)-(6$S$)-7-thiophenyl-8-oic-1-cyclohexene (94).

To a stirred solution of PhSH (13.1 g, 12.2 mL, 0.12 mol) in DMF (40 mL) was added LiH (945 mg, 0.12 mol) portion wise. After 45 min, a solution of 93 (16.67 g, 0.086 mol) in DMF (40 mL) was added via cannula to the lithium thiolate solution. An additional amount of DMF (3 mL) was used to rinse the lactone flask. After heating the yellow solution at 110°C for 4 h, the solution was cooled to 0°C, poured into a HCl solution (200 mL, 2 M in H$_2$O) and Et$_2$O (300 mL), and extracted with Et$_2$O (4 x 300 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5 - 50% Et$_2$O / petroleum ether, to give 94 (23.25 g, 0.076 mol, 89% yield) as a off-white solid.
m.p. 69 - 70°C.

$[\alpha]_D^{23} +47^\circ$ (c 0.90).

IR 2500 - 3500, 2960, 1703 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$ 7.35 - 7.4 (2H, m), 7.15 - 7.3 (3H, m), 5.40 (1H, br s), 3.22 (1H, dd, $J = 7.6$, 13.4 Hz), 3.04 (1H, dd, $J = 4.1$, 13.4 Hz), 2.7 - 2.8 (1H, m), 2.45 - 2.55 (1H, m), 1.9 - 2.1 (3H, m), 1.85 - 1.9 (1H, m), 1.63 (3H, br s), 0.87 (3H, d, $J = 6.5$ Hz), 0.77 (3H, d, $J = 6.5$ Hz).

$^{13}$C NMR (CDCl$_3$) $\delta$ 180.7, 136.3, 133.9, 130.6, 128.8, 126.3, 122.3, 46.1, 40.2, 35.9, 34.9, 27.6, 23.5, 21.9, 20.8, 16.3.

HRMS (Cl) calcd. for C$_{18}$H$_{24}$O$_2$S 304.1497. Found 304.1488.
1-Methyl-(4R)-isopropyl-(5R),(6S)-7-thiophenyl-8-methyl ester-1-cyclohexene (95).

\[ \text{94} \xrightarrow{\text{MeI, } K_2CO_3, \text{ Acetone}} \text{95} \]

To a stirred solution of 94 (23.25 g, 0.076 mol) in acetone (575 mL) was added solid K\textsubscript{2}CO\textsubscript{3} (53.0 g, 0.38 mol). After 10 min, MeI (104.9 g, 46 mL, 0.74 mol, filtered through a small plug of basic alumina prior to use) was added. After 1.5 h, H\textsubscript{2}O (10 mL) was added, filtered and concentrated \textit{in vacuo}. The oil was dissolved in Et\textsubscript{2}O (300 mL) and saturated aqueous NaCl (300 mL) and extracted with Et\textsubscript{2}O (4 x 300 mL). The dried (MgSO\textsubscript{4}) extract was concentrated \textit{in vacuo} to give 95 (24.16 g, 0.076 mol) as off-white solid which was used crude.

\([\alpha]_D^{23} +40^\circ (c \ 1.19)\).

IR 2958, 1730 cm\textsuperscript{-1}.

\( ^1\text{H} \text{NMR (CDCl}_3 \) \delta 7.15 - 7.4 (5H, m), 5.39 (1H, br s), 3.70 (3H, s), 3.15 (1H, dd, \( J = 7.4, 12.4 \) Hz), 2.96 (1H, dd, \( J = 3.7, 12.4 \) Hz), 2.69 (1H, dd, \( J = 4.7, 9.9 \) Hz), 2.4 - 2.45 (1H, m), 1.9 - 2.0 (3H, m), 1.75 - 1.85 (1H, m), 1.62 (3H, br s), 0.88 (3H, d, \( J = 6.5 \) Hz), 0.73 (3H, d, \( J = 6.5 \) Hz).
$^{13}$C NMR (CDCl$_3$) $\delta$ 174.3, 136.5, 134.2, 130.6, 128.8, 126.4, 122.2, 51.5, 46.1, 41.0, 35.4, 34.8, 27.5, 23.5, 22.0, 20.8, 15.9.

HRMS (Cl) calcd. for C$_{19}$H$_{26}$O$_2$S 318.1654. Found 318.1651.

1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-7-thiophenylmethyl-1-cyclohexene (96).

To a stirred solution of crude 95 (24.16 g, 0.076 mol) in CH$_2$Cl$_2$ (1 L) was added DIBAL-H (170 mL, 0.17 mol, 1.0 M in CH$_2$Cl$_2$) over 1.25 h via a dropping funnel at -78°C. After an additional 30 min, the reaction was warmed to 0°C for 20 min and recooled to -78°C. The reaction was quenched by the dropwise addition of MeOH (30 mL) followed by the addition of a sodium tartrate solution (700 mL, 10% in H$_2$O). The mixture was allowed to warm to ambient temperature and stirred for 2 h followed by extraction with CH$_2$Cl$_2$ (4 x 400 mL). The dried (MgSO$_4$) extracted was concentrated $\textit{in vacuo}$ and purified by chromatography over silica gel, eluting with 30% Et$_2$O / petroleum ether, to give 96 (19.15 g, 0.066 mol, 86% over 2 steps) as a colorless oil.
IR 3418, 2959 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.20 - 7.45 (5H, m), 5.39 (1H, br s), 3.83 (1H, dd, \(J = 4.9, 11.8\) Hz), 2.96 (1H, dd, \(J = 9.6, 11.8\) Hz), 2.9 - 3.1 (2H, m), 2.4 - 2.5 (1H, m), 1.7 - 2.0 (4H, m), 1.6 - 1.65 (2H, m), 0.88 (3H, d, \(J = 6.8\) Hz), 0.81 (3H, d, \(J = 6.8\) Hz).

\(^13\)C NMR (CDCl\(_3\)) \(\delta\) 136.1, 134.6, 130.1, 129.0, 126.6, 122.7, 61.6, 41.0, 39.3, 36.0, 34.2, 26.7, 24.2, 21.9, 21.0, 15.9.

HRMS (Cl) calcd. for C\(_{18}\)H\(_{26}\)OS 290.1704. Found 290.1704.

1-Methyl-(4\(R\))-isopropyl-(5\(R\))-hydroxymethyl-(6\(S\))-7-sulfonylphenylmethyl-1-cyclohexene (97).

\[
\begin{array}{c}
\text{96} \quad \text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O, Aliquat® 336} \\
\text{H}_2\text{O}_2, \text{CH}_2\text{Cl}_2, \text{H}_2\text{O, reflux} \quad \rightarrow \\
\text{97}
\end{array}
\]

To a stirred solution of 96 (18.34 g, 0.063 mol) in CH\(_2\)Cl\(_2\) (200 mL) and H\(_2\)O (7.5 mL) was added Na\(_2\)WO\(_4\)H\(_2\)O (1.63 g, 4.9 mmol) and Aliquat\({\text{®}}\) 336 (15 mL) followed by the dropwise addition of H\(_2\)O\(_2\) (30 mL, 30% in H\(_2\)O). The yellow solution was heated to reflux. An additional amount of H\(_2\)O\(_2\) (70 mL,
30% in H₂O) was added portion wise periodically during the course of the reaction. After 40 h, the reaction was cooled to ambient temperature, solid NaHSO₃ was added portion wise until effervescence ceased followed by extraction with CH₂Cl₂ (3 x 200 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% EtOAc / petroleum ether, to give 97 (18.00 g, 0.054 mol, 89%) as a off-white solid.

m.p. 103-104°C.
[α]D²³ +136° (c 1.23).
IR 3525, 2959 cm⁻¹.
¹H NMR (CDCl₃) δ 7.9 - 8.0 (2H, m), 7.55 - 7.7 (3H, m), 5.34 (1H, br s), 3.88 (1H, dd, J = 3.9, 12.3 Hz), 3.62 (1H, dd, J = 10.2, 12.3 Hz), 3.45 (1H, dd, J = 5.7, 15.9 Hz), 2.85 - 3.0 (2H, m), 1.75 - 2.0 (4H, m), 1.45 - 1.5 (3H, m), 1.25 - 1.4 (2H, m), 0.86 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.8 Hz).
¹³C NMR (CDCl₃) δ 139.1, 134.7, 134.0, 129.4, 128.0, 123.0, 60.9, 57.4, 42.0, 35.6, 33.6, 26.5, 24.2, 21.3, 21.0, 15.2.
HRMS (Cl) calcd. for C₁₈H₂₇O₃S 323.1681. Found 323.1673.
1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxyethyl-(6S)-7-sulfonylethylmethyl-1-cyclohexene (98).

To a stirred solution of 97 (3.00 g, 9.32 mmol) in DMF (6 mL) was added imidazole (1.50 g, 22.0 mmol) and TBSCI (1.45 g, 9.62 mmol). After 4 h, the reaction mixture was quenched with saturated aqueous NaCl (50 mL) and extracted with Et₂O (3 x 100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et₂O/petroleum ether, to give 98 (3.915 g, 9.00 mmol, 96%) as a colorless oil.

[α]D²³ +52° (c 1.09).

IR 2956, 2929, 2891, 2857 cm⁻¹.

¹H NMR (CDCl₃) δ 7.9 - 8.0 (2H, m), 7.5 - 7.65 (3H, m), 5.38 (1H, br s), 3.84 (1H, dd, J = 4.4, 14.5 Hz), 3.75 (1H, dd, J = 4.3, 10.6 Hz), 3.70 (1H, dd, J = 6.2, 10.6 Hz), 3.07 (1H, dd, J = 5.8, 14.5 Hz), 2.84 (1H, m), 1.75 - 2.0 (3H, m), 1.64 (3H, br s), 1.45 (2H, m), 0.86 (3H, d, J = 6.6 Hz), 0.85 (9H, s), 0.79 (3H, d, J = 6.6 Hz), 0.06 (3H, s), 0.04 (3H, s).
\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 140.7, 134.5, 133.3, 129.1, 127.8, 123.2, 63.2, 57.2, 40.9, 36.9, 35.8, 27.0, 25.9, 23.9, 22.1, 20.9, 18.1, 16.9, -5.4, -5.8.  
HRMS (Cl) calcd. for C\(_{24}\)H\(_{41}\)O\(_3\)Si 437.2546. Found 437.2540.

1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxyethyl-(6S)-[(7S)-phenylsulfonyl-(9S)-methyl-(8S),9,10-butanetriol 9,10-cyclohexyl ketal]-1-cyclohexene (99a) and 1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxy-(6S)-[(7S)-phenylsulfonyl-(9S)-methyl-(8R),9,10-butanetriol 9,10-cyclohexyl ketal]-methyl-1-cyclohexene (99b).

![Diagram](image)

**EtMgBr**: d.s. 10:1 (99a:99b)  
**n-BuLi**: d.s. 50:1 (99a:99b)

**Procedure I**: To a stirred solution of 98 (3.91 g, 8.97 mmol) in PhH (18 mL) was added EtMgBr (3.75 mL, 10.13 mmol, 2.7 M\(^{8}\) in Et\(_2\)O) and the mixture was then heated at reflux. After 16 h, the solution was allowed to cool to ambient...
temperature and a solution of 56 (4.95 g, 9.11 mmol) in PhH (8 mL) was added via cannula. After 2 h, the reaction mixture was quenched with saturated aqueous NH₄Cl (100 mL), extracted with EtOAc (3 x 100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10 - 30% Et₂O / petroleum ether, to give 99a and 99b⁹ (3.56 g, 5.74 mmol, 64%) as a off-white solid.

Procedure 2: To a stirred solution of 98 (1.17 g, 2.68 mmol) in THF (9 mL) at -78°C was added n-BuLi (1.20 mL, 2.76 mmol, 2.3 M in hexanes). The mixture was immediately warmed to 0°C. After 15 min, the reaction was recooled to -78°C and a solution of 56 (0.495 g, 2.69 mmol) in THF (6 mL) was added via cannula. After 1 hour, the mixture was warmed to 0°C for an additional hour, quenched with saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10 - 30% Et₂O / petroleum ether, to give 99a and 99b⁹ (1.10 g, 1.77 mmol, 66%) as an off-white solid. Crystals suitable for X-ray crystallography were obtained by recrystallization in hexanes. X-ray coordinates for 99a can be found in Appendix 2.

Major diasteromer 99a:

m.p 139 - 140°C.

[α]D²³ +75° (c 0.44).

¹H NMR (CDCl₃) δ 8.05 - 8.1 (2H, m), 7.45 - 7.6 (3H, m), 5.48 (1H, br s), 4.72 (1H, br s), 4.29 (1H, d, J = 9.4 Hz), 4.12 (1H, dd, J = 2.2, 10.9 Hz), 4.05 (1H, d, J
= 5.9 Hz), 3.91 (1H, d, J = 9.4 Hz), 3.83 (1H, dd, J = 5.9, 10.9 Hz), 3.11 (1H, d, J = 4.1 Hz), 3.05 (OH, m), 1.40 - 2.15 (16H, m), 1.35 (3H, s), 1.24 (3H, s), 0.93 (9H, s), 0.87 (3H, d, J = 6.9 Hz), 0.74 (3H, d, J = 6.9 Hz), 0.14 (3H, s), 0.11 (3H, s).

$^{13}$C NMR (CDCl$_3$) δ 141.0, 134.2, 133.2, 130.4, 129.1, 128.2, 125.6, 108.7, 84.6, 75.9, 71.2, 65.7, 63.6, 42.9, 42.8, 37.4, 35.9, 35.6, 33.3, 26.5, 26.0, 25.0, 24.9, 23.9, 23.6, 23.4, 21.0, 18.7, 14.4, -5.1, -5.6.

HRMS (Cl) calcd. for C$_{34}$H$_{57}$O$_6$SSi 621.3586. Found 621.3601.

**Minor diasteromer 99b:**

$^1$H NMR (CDCl$_3$) δ 7.85 - 7.95 (2H, m), 7.55 - 7.6 (1H, m), 7.45 - 7.5 (2H, m), 5.50 (1H, br s), 4.25 (1H, br d, J = 11.1 Hz), 4.11 (1H, d, J = 8.0 Hz), 4.06 (1H, d, J = 10.3 Hz), 3.90 (1H, dd, J = 5.5, 11.1 Hz), 3.65 - 3.8 (2H, m), 3.54 (1H, d, J = 8.0 Hz), 3.12 (OH, br s), 1.5 - 2.0 (12H, m), 1.35 - 1.5 (2H, m), 0.9 - 1.0 (12H, m), 0.80 (3H, d, J = 6.6 Hz), 0.06 (3H, s), 0.05 (3H, s).
1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxyethyl-(6S)-(7-(9S)-methyl-(8R),9,10-butanetriol 9,10-cyclohexyl ketal]-1-cyclohexene (100a).

To a solution of 99a (90 mg, 0.15 mmol) in THF (1 mL) and NH$_3$ (5 mL, distilled over Na) at -78°C was added Na (30 mg, 1.30 mmol). After 10 min, the blue solution was quenched at -78°C with solid NH$_4$Cl. After warming to ambient temperature, the mixture was diluted with CH$_2$Cl$_2$ and filtered through Celite® (CH$_2$Cl$_2$ rinse). The organic extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et$_2$O / petroleum ether, to give 100a (38 mg, 0.079 mmol, 53%) as a colorless oil.

[α]$_D^{23}$ +127° (c 1.24).

IR 3430, 2923 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) δ 5.26 (1H, br s), 4.24 (1H, d, J = 1.7 Hz), 4.14 (1H, d, J = 8.7 Hz), 3.85 (1H, dd, J = 5.0, 11.1 Hz), 3.72 (1H, d, J = 8.7 Hz), 3.6 - 3.65 (2H, m), 2.2 - 2.25 (1H, m), 1.3 - 1.9 (20H, m), 1.23 (3H, s), 0.90 (9H, s), 0.88 (3H, d, J = 6.8 Hz), 0.80 (3H, d, J = 6.8 Hz), 0.10 (3H, s), 0.09 (3H, s).
$^{13}$C NMR (CDCl$_3$) $\delta$ 138.9, 119.3, 109.7, 82.4, 76.6, 73.3, 62.8, 41.8, 37.2, 36.7, 36.5, 36.2, 32.1, 26.6, 25.9, 25.2, 24.3, 23.9, 23.9, 22.9, 21.1, 19.3, 18.3, 15.3, -5.0, -5.4.

HRMS (Cl) calcd. for C$_{28}$H$_{52}$O$_4$Si 480.3635. Found 480.3606.

1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxymethyl-(6S)-[7-(9S)-methyl-(8S),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene (100b).

![Chemical structure](image)

To a solution of 99b (38 mg, 0.06 mmol) in THF (1 mL) and NH$_3$ (2 mL, distilled over Na) at -78°C was added Na (0.020 g, 0.87 mmol). After 15 min, the blue solution was quenched at -78°C with solid NH$_4$Cl. After warming to ambient temperature, the mixture was diluted with CH$_2$Cl$_2$ and filtered through Celite® (CH$_2$Cl$_2$ rinse). The organic extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et$_2$O / petroleum ether, to give 100b (6.0 mg, 0.013 mmol, 21%) as a colorless oil.
$[^{\alpha}]D^{23} +54^\circ$ (c 0.90).

IR 3566, 2934 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$ 5.32 (1H, br s), 3.90 (1H, d, J = 8.4 Hz), 3.75 (2H, m), 3.68 (1H, d, J = 8.4 Hz), 3.52 (1H, apparent t), 2.50 (1H, m), 2.44 (1H, d, J = 3.7 Hz), 1.3 - 2.0 (20H, m), 1.26 (3H, s), 0.9 - 1.0 (12H, m), 0.83 (3H, d, J = 6.7 Hz), 0.05 (6H, s).

$^{13}$C NMR (CDCl$_3$) $\delta$ 137.1, 120.9, 110.1, 83.5, 73.7, 71.2, 62.4, 40.5, 36.6, 36.4, 34.6, 31.5, 27.0, 26.0, 25.1, 24.2, 23.9, 22.3, 20.9, 20.5, 18.2, 17.2, -5.3, -5.4.

HRMS (Cl) calcd. for C$_{28}$H$_{52}$O$_4$Si 480.3635. Found 480.3609.
1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxyethyl-(6S)-[(7S)-phenylsulfonyl-(9S)-methyl-9,10-butadiol-8-one 9,10-cyclohexyl ketal]-1-cyclohexene (101).

To a solution of 99 (1.35 g, 2.18 mmol) in CH$_2$Cl$_2$ (20 mL) was added Dess-Martin periodinane 260$^{10}$ (1.15 g, 2.71 mmol). After 2 h, the reaction was quenched by addition of saturated aqueous NaHCO$_3$ (15 mL) and NaHSO$_3$ (15 mL, 1 M in H$_2$O), diluted with Et$_2$O (15 mL) and stirred until the solution became clear. The layers were allowed to separate and the aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et$_2$O/petroleum ether, to give 101 (1.26 g, 2.04 mmol, 94%) as a colorless oil.

$\left[\alpha\right]_D^{23} -0.5^\circ$ (c 0.99).

IR 2938, 1719 cm$^{-1}$. 

231
1H NMR (CDCl₃) δ 7.5 - 8.0 (2H, m), 7.5 - 7.65 (3H, m), 5.69 (1H, d, J = 1.5 Hz), 5.32 (1H, br s), 3.75 - 3.9 (2H, m), 3.78 (1H, d, J = 9.0 Hz), 3.61 (1H, dd, J = 3.3, 10.8 Hz), 3.25 (1H, br s), 1.35 - 1.95 (21H, m), 0.93 (9H, s), 0.84 (3H, d, J = 6.7 Hz), 0.76 (3H, d, J = 6.7 Hz), 0.11 (3H, s), 0.10 (3H, s).

13C NMR (CDCl₃) δ 204.4, 140.0, 135.6, 133.7, 129.7, 128.6, 123.4, 112.3, 112.3, 86.6, 73.7, 68.3, 63.2, 43.6, 42.0, 36.4, 36.0, 35.7, 27.0, 26.03, 25.96, 24.9, 24.3, 24.0, 23.6, 23.5, 20.4, 18.6, 15.2, -5.1, -5.4.

HRMS (Cl) calcd. for C₃₄H₅₅O₆SiS 619.3489. Found 619.3478.

1-Methyl-(4R)-isopropyl-(5R)-tert-butyldimethylsiloxymethyl-(6S)-[7-(9S)-methyl-9,10-butanediol-8-one 9,10-cyclohexyl ketal]-1-cyclohexene (102).

To NH₃ (250 mL, distilled over Na) at -78°C was added Na (1.30 g, 54.20 mmol). After 30 min, a solution of 101 (3.39 g, 5.49 mmol) in THF (50 mL) was added via cannula and stirred for a further 30 min. The reaction was quenched at -78°C by the sequential addition of isoprene (4 mL) followed by solid NH₄Cl.
After warming to ambient temperature, the mixture was diluted with H₂O (100 mL) and extracted with EtOAc (4 x 100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% Et₂O / petroleum ether, to give 102 (2.42 g, 5.06 mmol, 92%) as a colorless oil.

[α]D²³ +66° (c 1.10).

IR 2956, 1716 cm⁻¹.

¹H NMR (CDCl₃) δ 5.30 (1H, br s), 4.24 (1H, d, J = 8.8 Hz), 3.76 (1H, d, J = 8.8 Hz), 3.64 (1H, dd, J = 5.8, 10.6 Hz), 3.51 (1H, dd, J = 8.0, 10.6 Hz), 2.9 - 3.0 (2H, m), 2.65 (1H, dd, J = 8.0, 10.4 Hz), 1.4 - 2.0 (16H, m), 1.39 (3H, s), 0.91 (3H, d, J = 5.9 Hz), 0.86 (9H, s), 0.81 (3H, d, J = 5.9 Hz), 0.00 (3H, s), -0.01 (3H, s).

¹³C NMR (CDCl₃) δ 212.6, 136.9, 121.2, 111.5, 86.0, 72.0, 63.0, 40.7, 37.8, 37.5, 36.1, 35.7, 33.1, 27.0, 25.9, 25.0, 24.2, 23.8, 23.7, 22.4, 21.1, 18.2, 17.0, -5.4, -5.5.

HRMS (Cl) calcd. for C₂₈H₄₇O₄Si 479.3557. Found 479.3537.
1-Methyl-(4R)-isopropyl-(5R)-tert-butylidimethylsiloxyethyl-(6S)-[7-(9S)-methyl-(8R),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene (100a) and 1-Methyl-(4R)-isopropyl-(5R)-tert-butylidimethylsiloxyethyl-(6S)-[7-(9S)-methyl-(8S),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene (100b).

![Chemical Reaction Diagram]

To a solution of 102 (221 mg, 0.462 mmol) in THF (1.5 mL) was added K-Selectride® (2.1 mL, 2.1 mmol, 1 M in THF) was added dropwise over 5 min via syringe pump at 0°C. After 1 h, the reaction was allowed to warm to ambient temperature. An additional amount of K-Selectride® (1 mL, 1.0 mmol, 1 M in THF) was added during the course of the reaction. After 7 h total reaction time, the solution was cooled to 0°C and quenched with aqueous ethanol solution (3 mL, 50% in H₂O) followed by NaOH (3 mL, 3 M in H₂O) then H₂O₂ (3 mL, 30% in H₂O). After 15 min at 0°C, the solution was diluted with H₂O (30 mL) and extracted with Et₂O (5 x 30 mL). The dried (MgSO₄) extract was concentrated in vacuo, filtered through a small plug of silica gel (30% Et₂O / petroleum ether rinse) and purified by MPLC, eluting with 7% Et₂O / petroleum ether, to give the undesired alcohol 100a (11 mg, 0.0229 mmol, 5%) as a colorless oil followed by
the desired alcohol 100b (171 mg, 0.356 mmol, 77%) as a colorless oil. Both compounds 100a and 100b were identical to previously prepared materials.

1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-[7-(9S)-methyl-(8S),9,10-butanetriol 9,10-cyclohexyl ketal]-1-cyclohexene (111).

$$\text{100b} \xrightarrow{\text{TBAF, THF}} \text{111}$$

To a stirred solution of 100b (1.84 g, 3.83 mmol) in THF (27 mL) was added TBAF (16 mL, 16 mmol, 1 M in THF) at ambient temperature. After 10 min, saturated aqueous NaHCO₃ (200 mL) was added and the THF removed in vacuo. The aqueous layer was extracted with Et₂O (4 x 200 mL), dried (MgSO₄), concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% Et₂O / petroleum ether, to give 111 (1.40 g, 3.83 mmol, 99%) as a viscous, colorless oil.

IR 3441, 2937, 1447 cm⁻¹.
\[^1\text{H} \text{NMR (CDCl}_3\text{)}\) 8 5.35 (1H, br s), 3.94 (1H, d, J = 8.6 Hz), 3.6 - 3.8 (4H, m), 2.5 - 2.55 (1H, m), 1.3 - 2.1 (20H, m), 1.28 (3H, s), 0.92 (3H, d, J = 6.7 Hz), 0.83 (3H, d, 6.7 Hz).

HRMS (Cl) calcd. for C\(_{22}\)H\(_{38}\)O\(_4\) 266.2770. Found 366.2753.

1-Methyl-(4\(R\))-isopropyl-(5\(R\))-keto-(6\(S\))-[7-(8\(S\))-(9\(S\))-methyl-9,10-butandiol 9,10-cyclohexyl ketal]-8,11-oxido-1-cyclohexene (112)

To a stirred solution of 111 (1.40 g, 3.83 mmol) in CH\(_2\)Cl\(_2\) (47 mL) with powdered 4 Å molecular sieves (approx 5 g) was added NMO (1.76 g, 15.0 mmol) and TPAP (50 mg, 0.14 mmol) at ambient temperature. An additional amount of TPAP (29 mg, 0.08 mmol) was added during the course of the reaction. After 27 h, the reaction was diluted with Et\(_2\)O (100 mL), filtered through silica gel (500 mL Et\(_2\)O rinse) and concentrated in \textit{vacuo}. The residue was purified by chromatography over silica gel, eluting with 50% Et\(_2\)O / petroleum ether, to give 112 (1.21 g, 3.34 mmol, 87%) as a colorless oil.
$[\alpha]_D^{23}$ - 40° (c 0.78).

IR 2935, 2863, 1729 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) δ 5.51 (1H, br s), 4.10 (1H, d, J = 9.0 Hz), 3.97 (1H, dd, J = 2.6, 11.7 Hz), 3.67 (1H, d, J = 9.0 Hz), 2.7 - 2.8 (1H, m), 2.5 - 2.6 (1H, br s), 2.26 (1H, dt, J = 3.6, 14.4 Hz), 1.9 - 2.1 (2H, m), 1.4 - 1.9 (19 H, m), 0.91 (6 H, d, J = 6.6 Hz).

$^{13}$C NMR (CDCl$_3$) δ 173.7, 131.8, 125.0, 110.7, 80.6, 79.2, 69.8, 43.0, 40.3, 36.2, 35.6, 31.3, 26.6, 25.7, 25.1, 24.6, 24.1, 23.84, 23.78, 21.1, 20.7, 20.3.

HRMS (Cl) calcd. for C$_{22}$H$_{34}$O$_4$ 262.2457. Found 362.2445.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-9,10-butandiol 9,10-cyclohexyl ketal)-(11S)-hydroxyl-8,11-oxido-1-cyclohexene (113).

A stirred solution of 112 (1.21 g, 3.34 mmol) in CH₂Cl₂ (43 mL) was cooled to -78°C and DIBAL-H (3.4 mL, 3.4 mmol, 1.0 M in CH₂Cl₂) was added via syringe pump over 10 min. An additional amount of DIBAL-H (0.4 mL, 0.4 mmol, 1.0 M in CH₂Cl₂) was added during the course of the reaction. After 70 min, the reaction was quenched with MeOH (0.5 mL) followed by HCl (50 mL, 2 M in H₂O), warmed to ambient temperature and stirred for 15 min. The aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL), dried (MgSO₄) and concentrated in vacuo to give 113 as a colorless oil which was >95% pure by ¹H NMR and used without further purification.

IR 3429, 2983, 2859 cm⁻¹.
¹H NMR (CDCl₃) δ 5.42 (1H, br s), 4.76 (1H, dd, J = 5.7, 8.6 Hz), 4.01 (1H, d, J = 8.7 Hz), 3.65 (1H, d, J = 8.7 Hz), 3.24 (1H, d, J = 11.2 Hz), 2.74 (OH, d, J = 5.6
Hz), 2.5 (1H, br s), 2.1 (1H, br s), 1.96 (1H, d, J = 13.7 Hz), 1.3 - 1.8 (2H, m), 0.90 (3H, d, J = 6.3 Hz), 0.87 (3H, d, J = 6.3 Hz).

HRMS (Cl) calcd. for C_{22}H_{36}O_{4} 264.2614. Found 364.2606.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-butanol]-8,9,(11R)-bis-oxido-1-cyclohexene (110) and 1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-9,10-butandiol)-(11S)-methoxy-8,11-oxido-1-cyclohexene (114).

![Chemical structures](image)

To a stirred solution of crude 113 (1.22 g, 3.34 mmol) in MeOH (173 mL) was added PTSA (2.13 g, 11.2 mmol) at ambient temperature. After 14 h, solid NaHCO₃ was added followed by saturated aqueous NaHCO₃, filtered and rinsed with H₂O and Et₂O. The filtrate was concentrated in vacuo to remove the MeOH, extracted with EtOAc (6 x 200 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by chromatography over silica gel, eluting with 50% Et₂O / petroleum ether, to give 110 (590 mg, 2.21 mmol, 67%) as a colorless oil and with EtOAc to give the diol 114 (225 mg, 0.76 mmol, 23%) as a colorless oil.
**Internal Ketal 110:**

\[ \alpha \]D\textsuperscript{23} = -11° (c 1.09).

IR 3448, 2926 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.61 (1H, s), 5.39 (1H, m), 4.05 (1H, d, \(J = 3.4\) Hz), 3.49 (1H, d, \(J = 10.5\) Hz), 3.42 (1H, d, \(J = 10.5\) Hz), 2.55 - 2.7 (1H, m), 2.0 - 2.15 (2H, m), 1.8 - 2.0 (2H, m), 1.5 - 1.8 (6H, m), 1.45 (3H, s), 0.87 (3H, d, \(J = 7.0\) Hz), 0.76 (3H, d, \(J = 7.0\) Hz).

\(^1\)\(^3\)C NMR (CDCl\(_3\)) \(\delta\) 135.5, 121.7, 102.7, 81.6, 68.8, 40.7, 36.0, 33.0, 28.3, 26.0, 24.1, 21.2, 15.9, 14.7.


**Methoxy lactol/diol 114:**

IR 3445, 2961 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.41 (1H, br s), 4.40 (1H, d, \(J = 8.7\) Hz), 3.64 (1H, dd, \(J = 3.5, 11.1\) Hz), 3.4 - 3.6 (4H, m), 3.46 (1H, dd, \(J = 1.3, 12.0\) Hz), 2.7 (OH, s), 2.4 - 2.6 (2H, m), 1.9 - 2.1 (3H, m), 1.75 - 1.85 (1H, m), 1.4 - 1.7 (8H, m), 0.90 (3H, d, \(J = 6.3\) Hz), 0.87 (3H, d, \(J = 6.3\) Hz).

HRMS (Cl) calcd. for C\(_{17}\)H\(_{30}\)O\(_4\) 298.2144. Found 298.2139.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-butanol]-8,9,(11R)-
bis-oxido-1-cyclohexene (110).

To a solution of 114 (339 mg, 1.14 mmol) in MeOH (5 mL) was added
PTSA (304 mg, 1.60 mmol) at ambient temperature. After 16 h, the reaction was
quenched with solid NaHCO₃, diluted with H₂O (25 mL) and extracted with
EtOAc (4 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo and
purified by chromatography over silica gel, eluting with 50% Et₂O / petroleum
ether, to give 110 (213 mg, 0.801 mmol, 70%) as a colorless oil and, with EtOAc,
to give starting material 114 (71 mg, 0.238 mmol, 21%). Both compounds 110
and 114 were identical to previously prepared materials.
1-Methyl-(4R)-(5R)-isopropyl(6S)-[7-(8S)-(9R)-methyl-10-butanal]--8,9,(11R)-bis-oxido-1-cyclohexene (115).

To a solution of 110 (52.0 mg, 0.195 mmol) in CH$_2$Cl$_2$ (2.5 mL) was added Dess-Martin periodinane 260$^{10}$ (120 mg, 0.283 mmol) at ambient temperature. After 2 h, the reaction was quenched by addition of saturated aqueous NaHCO$_3$ (5 mL) and NaHSO$_3$ (5 mL, 1 M in H$_2$O), diluted with Et$_2$O (5 mL) and stirred until the solution was clear. The layers were allowed to separate and the aqueous layer was extracted with Et$_2$O (3 x 20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et$_2$O / petroleum ether, to give 115 (46.0 mg, 0.174 mmol, 89%) as an off-white solid.

$[\alpha]_D^{23}$ +44° (c 0.99).

IR 2959, 1732 cm$^{-1}$.
$^1$H NMR (CDCl$_3$) $\delta$ 9.65 (1H, s), 5.80 (1H, s), 5.4 - 5.45 (1H, m), 4.42 (1H, d, $J = 5.0$ Hz), 2.5 - 2.6 (1H, m), 2.0 - 2.1 (1H, m), 1.8 - 2.0 (2H, m), 1.5 - 1.8 (7H, m), 1.40 (3H, s), 0.91 (3H, d, $J = 6.9$ Hz), 0.79 (3H, d, $J = 6.9$ Hz).
$^{13}$C NMR (CDCl$_3$) $\delta$ 204.2, 135.0, 122.0, 103.9, 85.4, 77.2, 40.5, 36.0, 32.8, 28.0, 26.0, 24.1, 21.1, 14.7, 13.6.

HRMS (Cl) calcd. for C$_{16}$H$_{25}$O$_3$ 265.1804. Found 265.1795.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-Z-octen-12-on-14-oate ethyl ester]-8,9,(15R)-bis-oxido-1-cyclohexene (117) and 1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-E-octen-12-on-14-oate ethyl ester]-8,9,(15R)-bis-oxido-1-cyclohexene (117a).

![Chemical reaction diagram]

To a solution of the phosphonium salt 116$^{11}$ (307 mg, 0.651 mmol) in THF (2 mL) and DMPU (2 mL) was added NaH (55 mg, 1.38 mmol, 60% in mineral oil) at ambient temperature. After 20 min, a solution of 115 (101 mg,
0.383 mmol) in THF (1 mL) was added via cannula. An additional amount of THF (2 x 0.5 mL) was added to rinse the aldehyde flask. After 50 min at ambient temperature, the solution was heated to 40°C. After 1.5 h, the reaction was allowed to cool to ambient temperature and quenched with saturated aqueous NH₄Cl (10 mL), extracted with Et₂O (3 x 20 mL), washed with saturated aqueous NaCl (50 mL) and extracted with Et₂O (3 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give the desired cis isomer 117 (121 mg, 0.322 mmol, 84%) as a colorless oil followed by the undesired trans isomer 117a (8.0 mg, 0.213 mmol, 6%) as a colorless oil.

cis β-keto ester 117:

IR 2958, 1741, 1695, 1649 cm⁻¹.

¹H NMR (C₆D₆) δ 6.30 (1H, d, J = 13.1 Hz, enol), 6.04 (1H, d, J = 12.5 Hz, ketone), 5.84 (1H, s, enol), 5.76 (1H, s, ketone), 5.61 (1H, d, J = 12.5 Hz, ketone), 5.3 - 5.4 (1H, m), 5.21 (1H, dd, J = 1.9, 13.1 Hz, enol), 5.01 (1H, s, enol), 4.87 (1H, d, J = 3.5 Hz, enol), 4.45 (1H, d, J = 3.4 Hz, ketone), 3.91 (2H, q, J = 7.2 Hz), 3.18 (2H, s, ketone), 2.5 - 2.7 (1H, m), 2.0 - 2.2 (1H, m), 1.7 - 2.0 (4H, m), 1.5 - 1.7 (9H, m), 0.91 (3H, t, J = 7.3 Hz), 0.82 (3H, apparent t), 0.6 - 0.7 (3H, m).

¹³C NMR (C₆D₆) δ 193.7, 173.5, 169.8, 166.8, 154.6, 153.3, 136.0, 135.8, 124.5, 121.9, 120.4, 102.5, 102.1, 94.0, 83.6, 83.3, 80.7, 79.6, 61.0, 60.3, 50.8, 41.0, 40.8, 36.4, 33.4, 30.2, 28.7, 28.6, 26.2, 24.6, 24.5, 21.4, 21.3, 19.7, 18.2, 14.9, 14.1, 14.0.
HRMS (Cl) calcd. for C_{22}H_{33}O_{5} 377.2328. Found 377.2321.

trans β-keto ester 117a:

$^1$H NMR (C$_6$D$_6$) δ 6.78 (1H, apparent t, ketone / enol), 6.52 (1H, d, J = 15.5 Hz, ketone), 6.26 (1H, d, J = 15.5 Hz, enol), 5.75 (1H, s, enol), 5.72 (1H, s, ketone), 5.37 (1H, br s), 5.17 (1H, s, enol), 3.9 - 4.0 (2H, m), 3.60 (1H, d, J = 2.7 Hz, enol), 3.56 (1H, d, J = 2.7 Hz, ketone), 3.26 (2H, s, ketone), 2.45 - 2.65 (1H, m), 2.0 - 2.1 (1H, m), 1.7 - 1.9 (2H, m), 1.1 - 1.7 (10H, m), 0.85 - 1.0 (3H, m), 0.82 (3H, d, J = 6.8 Hz), 0.6 - 0.7 (3H, m).

HRMS (Cl) calcd. for C$_{22}$H$_{33}$O$_{5}$ 377.2328. Found 377.2324.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-Z-octen-12-en-14-oate ethyl ester]-8,15-oxido-9,12-oxido-1-cyclohexene (120).

To a stirred solution of 117 (24.5 mg, 0.0652 mmol) in CH$_2$Cl$_2$ (1 mL) was added BF$_3$•Et$_2$O (3.5 mg, 3.0 µL, 0.024 mmol) at -78°C. After 1 h, the
reaction was quenched with saturated aqueous NaHCO₃ (1 mL) and extracted with CH₂Cl₂ (4 x 2 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et₂O / petroleum ether, to give 120a (14 mg, 0.037 mmol, 56%) as a colorless oil, 120b (4.0 mg, 0.011 mmol, 16%) as a colorless oil and starting material 117 (6.8 mg, 0.018 mmol, 28%).

**Major Lactol 120a:**

IR 3424, 2969, 2927, 1696, 1635 cm⁻¹.

¹H NMR (C₆D₆) δ 7.69 (1H, d, J = 5.9 Hz), 6.33 (1H, dd, J = 1.2, 5.9 Hz), 5.73 (1H, d, J = 1.2 Hz), 5.27 (1H, br s), 4.48 (1H, d, J = 8.3 Hz), 4.0 - 4.2 (2H, m), 3.30 (1H, d, J = 11.4 Hz), 2.32 (1H, br s), 2.16 (1H, br s), 1.9 - 2.1 (2H, m), 1.55 -1.75 (3H), 1.48 (3H, s), 1.2 - 1.45 (4H, m), 1.02 (3H, t, J = 7.1 Hz), 0.85 (3H, d, J = 6.6 Hz), 0.78 (3H, d, J = 6.6 Hz).

HRMS (CI) calcd. for C₂₂H₃₃O₅ 377.2328. Found 377.2319.

**Minor lactol 120b:**

IR 3435, 1733 cm⁻¹.

¹H NMR (C₆D₆) δ 6.19 (1H, d, J = 5.7 Hz), 5.55 (1H, d, J = 5.7 Hz), 5.29 (1H, br s), 5.08 (1H, s), 4.46 (1H, d, J = 8.6 Hz), 4.0 - 4.25 (2H, m), 3.44 (1H, dd, J = 1.1, 11.6 Hz), 1.85 - 2.3 (3H, m), 1.6 - 1.7 (4H, m), 1.2 - 1.45 (7H, m), 0.9 - 1.05 (3H, m), 0.84 (3H, d, J = 6.6 Hz), 0.76 (3H, d, J = 6.6 Hz).

HRMS (CI) calcd. for C₂₂H₃₃O₅ 377.2328. Found 377.2325.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-Z-octen-12-en-14-oate ethyl ester]-8,15-oxido-9,12-oxido-1-cyclohexene (120) and 5-methyl-1-furyl-ethyl acetate (121).

To a stirred solution of 117 (22 mg, 0.059 mmol) in CH₂Cl₂ (1 mL) was added BF₃•Et₂O (1.5 mg, 1.3 µL, 0.011 mmol) at -35°C. After 30 min, the reaction was allowed to warm to -20°C over 1 h followed by warming to 0°C. After 1 h, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 × 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et₂O / petroleum ether, to give sequentially 121 (trace), 120c (2.6 mg, 6.9 µmol, 12%) as a colorless oil, 120a (3.0 mg, 8.0 µmol, 14%) as a colorless oil and 120b (3.0 mg, 8.0 µmol, 14%) as a colorless oil.

Lactol 120c:
$^1$H NMR (C$_6$D$_6$) $\delta$ 7.70 (1H, d, $J = 6.0$ Hz), 6.32 (1H, dd, $J = 1.4$, 6.0 Hz), 5.71 (1H, d, $J = 1.4$ Hz), 5.48 (1H, br s), 4.88 (1H, d, $J = 8.9$ Hz), 4.0 - 4.2 (2H, m), 3.33 (1H, d, $J = 11.1$ Hz), 2.35 - 2.5 (2H, m), 2.15 - 2.3 (1H, m), 2.0 - 2.15 (2H, m), 1.9 - 2.0 (1H, m), 1.70 (1H, d, $J = 14.3$ Hz), 1.51 (3H, s), 1.1 - 1.5 (4H, m), 1.03 (3H, t, $J = 7.1$ Hz), 0.90 (3H, d, $J = 6.6$ Hz), 0.77 (3H, d, $J = 6.6$ Hz).

HRMS (CI) calcd. for C$_{22}$H$_{33}$O$_5$ 377.2328. Found 377.2325.

**Lactol 120a:**

IR 3424, 2969, 2927, 1696, 1635 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) $\delta$ 7.69 (1H, d, $J = 6.0$ Hz), 6.33 (1H, dd, $J = 1.2$, 6.0 Hz), 5.73 (1H, d, $J = 1.2$ Hz), 5.27 (1H, br s), 4.48 (1H, d, $J = 8.3$ Hz), 4.0 - 4.2 (2H, m), 3.30 (1H, d, $J = 11.4$ Hz), 2.32 (1H, br s), 2.16 (1H, br s), 1.9 - 2.1 (2H, m), 1.55 - 1.75 (3H), 1.48 (3H, s), 1.2 - 1.45 (4H, m), 1.02 (3H, t, $J = 7.1$ Hz), 0.85 (3H, d, $J = 6.6$ Hz), 0.78 (3H, d, $J = 6.6$ Hz).

HRMS (CI) calcd. for C$_{22}$H$_{33}$O$_5$ 377.2328. Found 377.2319.

**Lactol 120b:**

IR 3435, 1733 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) $\delta$ 6.19 (1H, d, $J = 5.7$ Hz), 5.55 (1H, d, $J = 5.7$ Hz), 5.29 (1H, br s), 5.08 (1H, s), 4.46 (1H, d, $J = 8.6$ Hz), 4.0 - 4.25 (2H, m), 3.44 (1H, dd, $J = 1.1$, 11.6 Hz), 1.85 - 2.3 (3H, m), 1.6 - 1.7 (4H, m), 1.2 - 1.45 (7H, m), 0.9 - 1.05 (3H, m), 0.84 (3H, d, $J = 6.6$ Hz), 0.76 (3H, d, $J = 6.6$ Hz).

HRMS (CI) calcd. for C$_{22}$H$_{33}$O$_5$ 377.2328. Found 377.2325.
5-Methyl-1-furyl-ethyl acetate (121).

\[
\begin{array}{c}
\text{Me} \quad \text{O} \quad \text{O} \\
\text{H} \quad \text{Me} \quad \text{O} \\
117 \quad \text{BF}_3\cdot\text{Et}_2\text{O} (4.5 \text{ eq}) \\
\text{CH}_2\text{Cl}_2, -78^\circ\text{C} \text{ to } -5^\circ\text{C} \\
\text{Me} \quad \text{O} \quad \text{OEt} \\
121
\end{array}
\]

To a stirred solution of 117 (18.5 mg, 0.0492 mmol) in CH$_2$Cl$_2$ (1 mL) was added BF$_3$·Et$_2$O (31.2 mg, 27.0 µL, 0.220 mmol) at -78°C. After 20 min, the reaction was warmed to -5°C. After 1.25 h, the reaction was quenched with saturated aqueous NaHCO$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (4 x 15 mL). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by PLC, eluting with 30% Et$_2$O / petroleum ether, to give 121 (1.5 mg, 0.089 mmol, 18%) as a colorless liquid.

IR 2926, 1730 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) δ 6.02 (1H, d, J = 2.9 Hz), 7.73 (1H, d, J = 2.9 Hz), 3.84 (2H, q, J = 7.4 Hz), 3.40 (2H, s), 1.96 (3H, s), 0.86 (3H, t, J = 7.4 Hz).

HRMS (Cl) calcd. for C$_9$H$_{13}$O$_3$ 169.0865. Found 169.0867.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-12-trimethylsiloxy-10-
Z-octen-12-Z-en-14-oate ethyl ester]-8,9,(15R)-bis-oxido-1-cyclohexene (118).

![Chemical structure](image)

To a stirred solution of 117 (21.5 mg, 0.0572 mmol) in CH$_2$Cl$_2$ (1 mL) with i-Pr$_2$NEt (13 mg, 17 µL, 0.098 mmol) was added TMSOTf (18 mg, 16 µL, 0.083 mmol). After 15 h at ambient temperature, the reaction was diluted with CH$_2$Cl$_2$ (5 mL), concentrated *in vacuo*, diluted with Et$_2$O (10 mL), filtered, concentrated *in vacuo*, diluted with pentane (10 mL), filtered and concentrated *in vacuo* to give crude 118 (23 mg, 0.051 mmol) as a pale yellow oil. This compound was found to be quite labile and was used immediately without any further purification.

$^1$H NMR (CD$_6$D$_6$) δ 7.42 (1H, d, J = 12.9 Hz), 6.03 (1H, dd, J = 1.2, 12.9 Hz), 5.71 (1H, d, J = 1.2 Hz), 5.42 (1H, s), 5.37 (1H, br s), 4.30 (1H, d, J = 3.5 Hz), 4.05 (2H, q, J = 7.1 Hz), 2.6 - 2.7 (1H, m), 2.0 - 2.1 (1H, m), 1.7 - 1.9 (3H, m), 1.4 - 1.6 (9H, m), 1.03 (3H, t, J = 7.1 Hz), 0.84 (3H, d, J = 7.0 Hz), 0.65 (3H, d, J = 7.0 Hz), 0.10 (9H, s).
1-Methyl(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-Z-octen-12-en-14-oate ethyl ester]-8,15-oxido-9,12-oxido-1-cyclohexene (120) and 5-methyl-1-furyl-ethyl acetate (121).

To a stirred solution of crude 118 (23 mg, 0.051 mmol) in CH₂Cl₂ (1 mL) was added TiCl₄ (10 mg, 6.0 µL, 0.055 mmol) at -78°C. After 40 min, the reaction was sequentially warmed to -45°C for 40 min and -10°C for 2.5 h. Then, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by PLC, eluting with 30% Et₂O / petroleum ether, to give 120d (7.5 mg, 0.020 mmol, 39%) as a colorless oil and 121 (2.5 mg, 0.015 mmol, 29%) as a colorless liquid.

**Lactol 120d:**

$^1$H NMR (CDCl₃) δ 7.70 (1H, d, J = 6.2 Hz), 6.25 (1H, dd, J = 1.8, 6.2 Hz), 5.72 (1H, d, J = 1.8 Hz), 5.13 (1H, s), 4.30 (1H, dd, J = 4.9, 11.5 Hz), 4.0 - 4.2 (3H, m), 1.7 - 1.8 (1H, m), 0.8 - 1.7 (17H, m), 0.75 (3H, d, J = 6.6 Hz), 0.67 (3H, d, J = 6.6 Hz).
Furan 121:
IR 2926, 1730 cm\(^{-1}\).
\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 6.02 (1H, d, \(J = 2.9\) Hz), 7.73 (1H, d, \(J = 2.9\) Hz), 3.84 (2H, q, \(J = 7.4\) Hz), 3.40 (2H, s), 1.96 (3H, s), 0.86 (3H, t, \(J = 7.4\) Hz).
HRMS (Cl) calcd. for C\(_9\)H\(_{13}\)O\(_3\) 169.0865. Found 169.0867.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-pentyne]-8,9,(12R)-bis-oxido-1-cyclohexene (127).

\[ \text{115} \xrightarrow{\text{EtO}_2\text{P} = \text{N}_2} \text{261} \xrightarrow{\text{r-BuOK, THF}} \text{127} \]

To a solution of r-BuOK (96 \(\mu\)L, 0.096 mmol, 1.0 M in THF) was added a solution of DAMP 261\(^{12}\) (14.5 mg, 0.081 mmol) in THF (0.1 mL) at -78\(^\circ\)C via cannula. An additional amount of THF (0.1 mL) was added to rinse the diazomethyl diethylphophonate flask. After 7 min, a solution of 115 (18.0 mg, 0.068 mmol) in THF (0.1 mL) via cannula. An additional amount of THF (0.1 mL) was added to rinse the aldehyde flask. After 11 min, the solution was allowed to warm to ambient temperature. After 15 h, the reaction was quenched with saturated aqueous NH\(_4\)Cl (10 mL) and extracted with Et\(_2\)O (4 x 15 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} and purified by
chromatography over silica gel, eluting with 15% Et₂O / petroleum ether, to give 127 (16.4 mg, 0.063 mmol, 93%) as a colorless oil.

m.p. 75 - 76°C.

[α]D²³ -19° (c 0.65).

IR 3310, 2959, 2926 cm⁻¹.

¹H NMR (C₆D₆) δ 5.76 (1H, d, J = 1.1 Hz), 5.35 - 5.4 (1H, m), 4.29 (1H, d, J = 3.7 Hz), 2.4 - 2.5 (1H, m), 2.40 (1H, s), 2.05 - 2.15 (1H, m), 1.92 (1H, d, J = 5.9 Hz), 1.87 (1H, d, J = 5.9 Hz), 1.6 - 1.8 (10H, m), 0.90 (3H, d, J = 6.7 Hz), 0.76 (3H, d, J = 6.7 Hz).

¹³C NMR (CDCl₃) δ 135.2, 121.9, 103.3, 87.3, 80.7, 69.9, 40.3, 36.1, 32.7, 29.7, 28.0, 25.9, 24.1, 21.1, 20.7, 14.7.

HRMS (Cl) calcd. for C₁₇H₂₅O₂ 261.1855. Found 261.1855.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-octyn-12-one)-8,9,(15R)-bis-oxido-1-cyclohexene (129).

To a stirred solution of 127 (100 mg, 0.385 mmol) in THF (2.1 mL) was added n-BuLi (310 µL, 0.775 mmol, 2.5 M in hexanes) at -78°C. After 30 min, N-methyl-N-methoxypropionamide\(^\text{13}\) (128) (135 µL, approximately 1 mmol) was added via syringe. The reaction was allowed to warm to ambient temperature, quenched with saturated aqueous NH\(_4\)Cl (25 mL) and extracted with Et\(_2\)O (4 x 40 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% Et\(_2\)O / petroleum ether, to give 129 (90.7 mg, 0.287 mmol, 75%) as a colorless oil and the starting material 127 (13 mg, 0.05 mmol, 13%).

IR 2960, 2213, 1680 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.75 (1H, s), 5.40 (1H, m), 4.33 (1H, d, \(J = 3.4\) Hz), 2.57 (2H, q, \(J = 7.3\) Hz), 2.45 (1H, m), 1.8 - 2.1 (2H, m), 1.5 - 1.8 (11H, m), 1.11 (3H, t, \(J = 7.2\) Hz), 0.91 (3H, d, \(J = 6.9\) Hz), 0.77 (3H, t, \(J = 6.9\) Hz).
HRMS (Cl) calcd. for C_{20}H_{28}O_{3} 316.2039. Found 316.2029.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-Z-octen-12-one)-8,9,(15R)-bis-oxido-1-cyclohexene (130).

A stirred solution of 129 (90.7 mg, 0.287 mmol) in MeOH (4.75 mL) with Lindlar’s catalyst (30.6 mg) and quinoline (20 mg, 18 µL, 0.15 mmol) was evacuated and an atmosphere of H₂ was introduced at ambient temperature. After 1.66 h, the reaction was filtered through Celite® (Et₂O rinse) and concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et₂O / petroleum ether, to give 130 (71.1 mg, 0.224 mmol, 78%) as an off-white solid. Crystals suitable for X-ray crystallography were obtained by recrystallization from PhH. X-ray coordinates for 130 can be found in Appendix 3.

m.p. 109 - 111°C.
IR 2954, 1691 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.40 (1H, d, \(J = 13.6\) Hz), 5.81 (1H, s), 5.56 (1H, d, \(J = 13.6\) Hz), 5.35 (1H, br s), 4.61 (1H, d, \(J = 6.0\) Hz), 2.60 - 2.65 (1H, m), 1.55 - 2.15 (12H, m), 1.57 (3H, s), 0.92 (3H, t, \(J = 7.1\) Hz), 0.82 (3H, d, \(J = 6.5\) Hz), 0.67 (3H, d, \(J = 6.5\) Hz).

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 201.3, 154.0, 135.9, 129.3, 124.9, 121.9, 102.5, 83.5, 79.7, 40.9, 37.6, 36.4, 33.5, 28.7, 26.2, 24.6, 21.2, 18.3, 14.8, 7.8.

HRMS (Cl) calcd. for C\(_{20}\)H\(_{31}\)O\(_3\) 319.2273. Found 319.2268.

\(1\)-Methyl-(4\(R\))-isopropyl-(5\(R\))-[(7)-(8\(S\))-(9\(S\))-methyl-12-trimethylsiloxy-10-Z-12-Z-octdiene]-8,9,(15\(R\))-bis-oxido-1-cyclohexene (130).

To a stirred solution of 130 (12.2 mg, 0.0354 mmol) in CH\(_2\)Cl\(_2\) (0.66 mL) was added i-Pr\(_2\)NEt (8.5 mg, 11.4 \(\mu\)L, 0.065 mmol) followed by TMSOTf (12.2 mg, 10.6 \(\mu\)L, 0.055 mmol) at ambient temperature. After 4.5 h, the reaction was diluted with Et\(_2\)O (5 mL), filtered through Celite\(^\text{®}\) (Et\(_2\)O rinse) and concentrated.
in vacuo. This filtration cycle was repeated once with Et₂O and once with pentane to yield crude 131 (approx. 70% conversion) which was used immediately.

1H NMR δ 5.85- 5.95 (2H, m), 5.74 (1H, d, J = 12.9 Hz), 5.4 - 5.5 (1H, m), 5.37 (1H, q, J = 7.1 Hz), 4.35 (1H, br d, J = 5.0 Hz), 2.65 - 2.8 (1H, m), 1.5 - 2.2 (16H, m), 0.94 (3H, d, J = 6.8 Hz), 0.77 (3H, d, J = 6.8 Hz), 0.32 (9H, s).

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10-octyn-12-E-ene)-8,9,(15R)-bis-oxido-1-cyclohexene (133).

To a solution of CuI (16.5 mg, 0.0866 mmol) in degassed PhH (0.5 mL) was added n-BuNH₂ (48 µL) followed sequentially by E-1-bromo-1-propene (9.2 mg, 6.5 µL, 0.0756 mmol), Pd(PPh₃)₄ (7.0 mg, 6.06 µmol), and a solution of 127 (16.4 mg, 0.0631 mmol) in THF (0.4 mL). An additional amount of THF (0.4 mL) was added to rinse the acetylene flask. After 30 min in the dark at ambient temperature, the reaction was quenched with saturated aqueous NH₄Cl (10 mL)
and extracted with Et$_2$O (4 x 15 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5 - 15% Et$_2$O / petroleum ether, to give 133 (16.0 mg, 0.0533 mmol, 85%) as a colorless oil.

IR 2960 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) $\delta$ 6.08 (1H, dq, $J = 6.8, 15.7$ Hz), 5.86 (1H, s), 5.42 (1H, m), 5.34 (1H, m), 4.18 (1H, d, $J = 3.6$ Hz), 2.45 - 2.55 (1H, m), 1.7 - 1.9 (2H, m), 1.62 (3H, s), 1.4 - 1.65 (8H, m), 1.34 (3H, dd, $J = 1.7, 6.7$ Hz), 0.81 (3H, d, $J = 6.9$ Hz), 0.56 (3H, d, $J = 6.9$ Hz).

HRMS (Cl) calcd. for C$_{20}$H$_{29}$O$_2$ 301.2168. Found 301.2168.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-10,11-$\eta^2$-dicobalt hexacarbonyl-12-E-octene]-8,9,(15R)-bis-oxido-1-cyclohexene (134).

To a solution of 133 (14 mg, 0.0467 mmol) in pentane (1.5 mL) was added Co$_2$(CO)$_8$ (18 mg, 0.053 mmol) at ambient temperature. After 15 min, the
reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% Et$_2$O / petroleum ether, to give 134 (24 mg, 0.041 mmol, 88%) as a red oil.

IR  2961, 2019, 2018 cm$^{-1}$.

$^1$H NMR (CD$_3$D) $\delta$ 6.70 (1H, m), 6.20 (1H, dq, $J = 6.9$, 14.6 Hz), 5.91 (1H, d, $J = 0.9$ Hz), 5.3 - 5.4 (1H, m), 4.15 (1H, d, $J = 3.6$ Hz), 2.55 - 2.65 (1H, m), 2.1 - 2.2 (1H, m), 1.7 - 2.0 (2H, m), 1.5 - 1.7 (10H, m), 1.48 (3H, dd, $J = 1.3$, 6.9 Hz), 0.79 (3H, d, $J = 6.9$ Hz), 0.64 (3H, d, $J = 6.9$ Hz).

HRMS (Cl) calcd. for C$_{26}$H$_{29}$Co$_2$O$_8$ 587.0526. Found 587.0524.

1-Methyl-(4R)-isopropyl-(SR)-pivaloyl(oxy)methyl-(6S)-(7-(9S)-methyl-(8S),9,10-butantriol 9,10-cyclohexyl ketal]-1-cyclohexene (136).

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{H} & \quad \text{O} \\
\text{OH} & \quad \text{O} \\
\text{Piv} & \quad \text{Me} \\
\text{111} & \quad \text{136}
\end{align*}
\]

To a solution of 111 (1.56 g, 4.27 mmol) in CH$_2$Cl$_2$ (15 mL), py (15 mL) was added PivCl (12.0 mL, 97.0 mmol) and DMAP (0.200 g). After 12 h at
ambient temperature, the reaction mixture was quenched with CuSO₄ (50 mL, 1 M in H₂O) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with HCl (100 mL, 0.2 M in H₂O), H₂O (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15% Et₂O / petroleum ether, to give 1.36 (1.80 g, 4.00 mmol, 94%) as a colorless oil.

IR 3526, 2934, 1726 cm⁻¹.

¹H NMR (CDCl₃) δ 5.32 (1H, br s), 4.20 (1H, dd, J = 7.4, 10.3 Hz), 3.90 (1H, m), 3.88 (1H, d, J = 8.6 Hz), 3.69 (1H, d, J = 8.6 Hz), 3.60 (1H, dd, J = 1.9, 10.3 Hz), 2.45 (1H, m), 2.12 (1H, ddd, J = 4.7, 8.1, 15.7 Hz), 1.8 - 2.0 (2H, m), 1.35 - 1.75 (18H, m), 1.24 (3H, s), 1.19 (9H, s), 0.90 (3H, d, J = 6.8 Hz), 0.87 (3H, d, J = 6.8 Hz);

¹³C NMR (CDCl₃) δ 176.5, 136.3, 121.0, 110.2, 83.4, 73.6, 71.5, 63.5, 38.8, 36.9, 36.8, 36.6, 34.3, 31.4, 27.3, 27.2, 26.5, 25.1, 24.1, 23.9, 23.8, 22.1, 20.8, 20.2, 17.8.

1-Methyl-(4R)-isopropyl-(5R)-pivaloyl(oxy)methyl-(6S)-[7-(9S)-methyl-(8S),9,10-butantriol 8,9-cyclohexyl ketal]-1-cyclohexene (137) and 1-Methyl-(4R)-isopropyl-(5R)-pivaloyl(oxy)methyl-(6S)-[7-(9S)-methyl-(8S),9,10-butantriol]-1-cyclohexene (138).

![Chemical structure diagram]

To a solution of 136 (1.79 g, 3.98 mmol) in MeOH (20 mL) was added PTSA (0.20 g, 1.1 mmol). After 80 h at ambient temperature, the reaction was quenched with solid NaHCO₃. The reaction mixture was diluted with EtOAc (150 mL), filtered through Celite® (EtOAc rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 20 - 50% Et₂O / petroleum ether, to give the desired compound 137 (1.040 g, 2.31 mmol, 58%) as a colorless oil and, followed by with EtOAc, to give the triol 138 (0.190 g, 0.514 mmol, 13%) as a colorless oil.

**Ketal 137:**

IR  3503, 2934, 1728 cm⁻¹.
$^1$H NMR (CDCl$_3$) $\delta$ 5.36 (1H, br s), 4.20 (1H, dd, J = 6.9, 11.1 Hz), 4.07 (2H, m), 3.54 (1H, d, J = 11.6 Hz), 3.40 (1H, d, J = 11.6 Hz), 2.37 (1H, m), 1.4 - 2.15 (20H, m), 1.20 (9H, s), 1.05 (3H, s), 0.89 (3H, d, J = 6.4 Hz), 0.87 (3H, d, J = 6.4 Hz).

$^{13}$C NMR (CDCl$_3$) $\delta$ 178.8, 135.8, 121.4, 107.6, 82.0, 75.8, 66.1, 63.5, 38.9, 38.7, 37.3, 36.5, 36.0, 35.9, 29.0, 27.2, 25.1, 24.2, 24.0, 23.8, 22.2, 20.7, 19.1, 17.4.

HRMS (Cl) calcd. for C$_{27}$H$_{47}$O$_5$ 451.3424. Found 451.3407.

Triol 138:

[α]$_D^{23}$ - 4° (c 0.98).

IR 3444, 2963, 1720 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$ 5.32 (1H, br s), 4.20 (1H, dd, J = 6.6, 11.2 Hz), 3.90 (1H, apparent t), 3.77 (1H, d, J = 11.2 Hz), 3.69 (1H, d, J = 11.2 Hz), 3.4 - 3.5 (1H, m), 3.09 (OH, br s), 2.95 (OH, br s), 2.62 (OH, br s), 2.45 - 2.55 (1H, m), 1.8 - 2.2 (4H, m), 1.3 - 1.7 (6H, m), 1.18 (9H, s), 1.06 (3H, s), 0.87 (6H, d, J = 6.5 Hz).

$^{13}$C NMR (CDCl$_3$) $\delta$ 179.3, 135.4, 121.3, 74.4, 72.0, 68.3, 63.3, 38.9, 37.7, 35.7, 33.2, 30.2, 27.4, 27.2, 24.1, 22.0, 20.7, 19.5, 18.5.

HRMS (Cl) calcd. for C$_{21}$H$_{39}$O$_5$ 371.2800. Found 371.2779.
1-Methyl-(4R)-isopropyl-(5R)-pivaloyl(oxy)methyl-(6S)-(7-(9R)-methyl-(8S),9-butandiol-10-al 8,9-cyclohexyl ketal]-1-cyclohexene (139).

To a solution of 137 (1.040 g, 2.31 mmol) in CH$_2$Cl$_2$ (30 mL) was added Dess-Martin periodinone 260$^{10}$ (1.18 g, 2.78 mmol). After 1 h, the reaction was quenched by addition of saturated aqueous NaHCO$_3$ (25 mL) and NaHSO$_3$ (25 mL, 1 M in H$_2$O), diluted with Et$_2$O (25 mL) and stirred until the solution was clear. The layers were allowed to separate and the aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et$_2$O / petroleum ether, to give 139 (0.884 g, 1.97 mmol, 85%) as a colorless oil.

IR 2936, 1732 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) $\delta$ 9.64 (1H, s), 5.37 (1H, br s), 4.29 (1H, dd, $J = 6.5$, 11.2 Hz), 4.18 (1H, dd, $J = 2.0$, 11.2 Hz), 3.88 (1H, dd, $J = 9.1$, 11.2 Hz), 2.36 (1H, m), 1.3 - 2.1 (20H, m), 1.19 (9H, s), 1.18 (3H, s), 0.88 (6H, apparent t, $J = 6.5$ Hz).
$^{13}$C NMR (CDCl$_3$) δ 202.5, 135.2, 121.9, 110.0, 85.6, 74.4, 63.5, 38.8, 38.2, 37.2, 36.3, 36.0, 35.6, 28.2, 27.3, 27.2, 25.0, 24.1, 23.7, 22.1, 20.8, 17.1, 16.4.

HRMS (Cl) calcd. for C$_{27}$H$_{45}$O$_5$ 449.3267. Found 449.3253.

1-Methyl-(4R)-isopropyl-(5R)-tert-butyloxymethyl-(6S)-[7-(9S)-methyl-(8S),9-octandiol-10-Z-ene-12-on-14-oate ethyl ester 8,9-cyclohexyl ketal]-1-cyclohexene (140).

To a solution of the phosphonium salt 116$^{14}$ (0.058 g, 0.12 mmol) in THF (0.35 ml) and DMPU (0.35 ml) was added NaH (0.011 g, 0.13 mmol, 60% in mineral oil). After 30 min, a solution of the aldehyde 139 (0.025 g, 0.06 mmol) in THF (0.3 ml) added via cannula. After 1 h, the mixture was heated at 50°C. After 2 h, the reaction was quenched by addition of saturated aqueous NH$_4$Cl (50 mL), extracted with Et$_2$O (3 x 50 mL). The combined organic extracts were washed with H$_2$O (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na$_2$SO$_4$)
extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et2O / petroleum ether, to give \textbf{140} (10 mg, 0.018 mmol, 32%) as a colorless oil.

IR 2934, 1729 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.94 (1H, d, \(J = 12.6\) Hz), 5.79 (1H, d, \(J = 12.6\) Hz), 5.37 (1H, br s), 4.25 - 4.35 (1H, m), 4.19 (2H, q, \(J = 7.2\) Hz), 3.9 - 4.0 (2H, m), 3.71 (2H, apparent d), 2.35 - 2.45 (1H, m), 1.35 - 2.15 (20H, m), 1.27 (3H, t, \(J = 7.2\) Hz), 1.25 (3H, s), 1.19 (9H, s), 0.88 (6H, apparent t).

HRMS (Cl) calcd. for C\(_{33}\)H\(_{52}\)O\(_7\) 560.3713. Found 560.3707.

1-Methyl-(4R)-isopropyl-(5R)-pivaloyl(oxy)methyl-(6S)-[7-(9S)-methyl-11,11-dibromo-(8S),9-pentandiol-10-ene 8,9-cyclohexyl ketal]-1-cyclohexene (142).

![Chemical Reaction Diagram]

To a solution of CBr\(_4\) (1.76 g, 5.30 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at 0\(^\circ\)C was added portionwise Ph\(_3\)P (2.78 g, 10.60 mmol). After 1 h, \textbf{139} (0.880 g, 1.96
mmol) in CH$_2$Cl$_2$ (15 mL) was added to the reaction mixture via cannula. After an additional hour at 0°C, the reaction mixture was poured into hexanes (375 mL). The resulting slurry was filtered through Celite® (hexanes rinse), the solvents removed, diluted with Et$_2$O, filtered through Celite® (Et$_2$O rinse) and concentrated in vacuo. This cycle was repeated twice further using hexanes as solvent to give the crude product 142 (1.06 g, > 94% pure by $^1$H NMR) as a colorless oil. This oil was contaminated with trace amounts of triphenylphoshine which could not be removed, hence this material was used at this level of purity.

$^1$H NMR (CDCl$_3$) δ 6.68 (1H, s), 5.38 (1H, br s), 4.29 (1H, dd, J = 7.2, 11.2 Hz), 4.17 (1H, dd, J = 2.7, 10.1 Hz), 3.97 (1H, dd, J = 8.5, 11.2 Hz), 2.35 - 2.5 (1H, m), 2.1 - 2.2 (1H, m), 1.8 - 2.1 (2H, m), 1.25 - 1.8 (19H, m), 1.21 (9H, s), 0.92 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz).
1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-[7-(9S)-methyl-11,11-dibromo-(8S),9-pentandiol-10-ene 8,9-cyclohexyl ketal]-1-cyclohexene (142).

To a solution of 142 (1.055 g, 1.75 mmol) in CH₂Cl₂ (18 mL) at -78°C was added DIBAL-H (4.75 mL, 4.75 mmol, 1.0 M in CH₂Cl₂). After 1 h, the reaction was allowed to warm to ambient temperature. The mixture was quenched by addition of MeOH (1 mL) followed by sodium tartrate (20 mL, 10% in H₂O) and Et₂O (40 mL). After stirring until the phases were clear, extraction into Et₂O (3 x 50 mL) and washing with saturated aqueous NaCl (100 mL). The dried (Na₂SO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20% Et₂O / petroleum ether, to give 143 (0.810 g, 1.56 mmol, 89%) as a colorless oil.

IR 3448, 2933 cm⁻¹.

¹H NMR (CDCl₃) δ 6.67 (1H, s), 5.41 (1H, br s), 4.21 (1H, dd, J = 3.0, 9.8 Hz), 3.74 (2H, m), 2.47 (1H, m), 1.5 - 2.05 (19H, m), 1.34 (3H, s), 0.92 (3H, d, J = 6.8 Hz), 0.84 (3H, d, J = 6.8 Hz).
$^{13}$C NMR (CDCl$_3$) δ 141.7, 135.4, 122.2, 109.2, 88.4, 82.8, 78.6, 62.7, 39.8, 38.3, 36.5, 36.2, 35.7, 28.7, 27.1, 25.0, 24.2, 24.0, 23.7, 22.1, 20.8, 20.6, 17.3.

HRMS (Cl) calcd. for C$_{23}$H$_{35}$O$_3$Br$_2$ 518.1031. Found 518.1032.

1-Methyl-(4R)-isopropyl-(5R)-tert-butylsiloxymethyl-(6S)-[7-(9S)-methyl-11,11-dibromo-(8S),9-pentandiol-10-ene 8,9-cyclohexyl ketal]-1-cyclohexene (144).

To a solution of 143 (0.770 g, 1.48 mmol) in CH$_2$Cl$_2$ (10 mL) at ambient temperature was added imidazole (0.250 g, 3.67 mmol) and TBSCl (0.265 g, 1.76 mmol). After 3 h, the reaction mixture was diluted with H$_2$O (10 mL) followed by HCl (25 mL, 0.2 M in H$_2$O) and extracted with Et$_2$O (4 × 50 mL). The organic extracts were washed with saturated aqueous NaHCO$_3$ (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% Et$_2$O / petroleum ether, to give 144 (0.890 g, 1.41 mmol, 95%) as a colorless oil.
$^1$H NMR (CDCl$_3$) δ 6.65 (1H, s), 5.34 (1H, br s), 4.18 (1H, dd, J = 4.3, 9.0 Hz),
3.70 (1H, dd, J = 6.5, 10.4 Hz), 3.56 (1H, apparent t, J = 10.4 Hz), 2.45 - 2.55
(1H, m), 1.4 - 2.05 (23H, m), 1.32 (3H, s), 1.25 - 1.35 (1H, m), 0.85 - 0.95 (6H,
m), 0.84 (3H, d, J = 6.6 Hz), 0.07 (3H, s), 0.06 (3H, s).

$^{13}$C NMR (CDCl$_3$) δ 141.8, 136.8, 121.2, 108.8, 88.1, 82.6, 79.7, 61.9, 40.3, 38.4,
36.5, 35.6, 35.5, 29.1, 27.1, 26.0, 24.2, 24.1, 23.8, 22.4, 20.8, 20.6, 18.3, 17.4,
-5.2.

HRMS (CI) calcd. for C$_{29}$H$_{48}$O$_3$Br$_2$Si 632.1896. Found 632.1882.

1-Methyl-(5R)-tert-butylsiloxymethyl-(4R)-isopropyl-(6S)-[7-(9S)-methyl-
(8S),9-pentandiol-10-yne 8,9-cyclohexyl ketal]-1-cyclohexene (145).

To a solution of 144 (116 mg, 0.18 mmol) in THF (1 mL) was added
EtMgBr (0.200 mL, 0.50 mmol, 2.5 M in Et$_2$O) at ambient temperature. After 1
h, the reaction slurry was quenched with saturated aqueous NH$_4$Cl (25 mL),

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extracted into EtOAc (4 x 30 mL). The combined organic extracts were washed with saturated aqueous NaCl. The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15% Et₂O / petroleum ether, to give 145 (80.0 g, 0.169 mmol, 92%) as a colorless oil.

IR 3311, 2933 cm⁻¹.

¹H NMR (CDCl₃) δ 5.35 (1H, br s), 4.33 (1H, dd, J = 2.8, 9.6 Hz), 3.69 (1H, dd, J = 6.6, 10.4 Hz), 3.61 (1H, apparent t, J = 10.4 Hz), 2.49 (1H, m), 2.42 (1H, s), 1.4 - 2.05 (23H, m), 1.33 (3H, s), 1.30 (1H, m), 0.90 (6H, m), 0.83 (3H, d, J = 6.5 Hz), 0.05 (3H, s), 0.04 (3H, s).

¹³C NMR (CDCl₃) δ 136.5, 121.3, 109.1, 85.5, 80.3, 74.9, 71.9, 61.6, 40.5, 38.3, 36.2, 35.6, 35.0, 28.2, 27.0, 26.0, 25.1, 24.2, 24.0, 23.8, 23.5, 22.3, 20.8, 18.3, 17.1, -5.3.

HRMS (Cl) calcd. for C₂₉H₄₉O₃Si 475.3608. Found 475.3577.
1-Methyl-(4R)-isopropyl-(5R)-tert-butyldioxymethyl-(6S)-(7-(9S)-methyl-(8S),9-octandiol-10-yn-12-one 8,9-cyclohexyl ketal)-1-cyclohexene (146).

To a solution of the acetylene 145 (490 mg, 1.04 mmol) in THF (6.7 mL) at -78°C was added n-BuLi (880 μL, 2.20 mmol, 2.5 M in hexanes). After stirring at -78°C for 1 h, N-methyl-N-methoxypropionamide (128)\textsuperscript{13} (0.022 mL, 0.19 mmol) was added. After 30 min, the reaction mixture was warmed to ambient temperature for 30 min, quenched with saturated aqueous NH\textsubscript{4}Cl (25 mL) and extracted with EtOAc (4 x 40 mL). The combined organic extracts were washed with H\textsubscript{2}O (100 mL) and saturated aqueous NaCl (100 mL). The dried (Na\textsubscript{2}SO\textsubscript{4}) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 10% Et\textsubscript{2}O / petroleum ether, to give 146 (541 mg, 1.02 mmol, 96%) as a colorless oil.

IR 2936, 2857, 2216, 1687 cm\textsuperscript{-1}.
$^1$H NMR (CDCl$_3$) $\delta$ 5.36 (1H, br s), 4.39 (1H, dd, $J = 2.2$, 10.0 Hz), 3.72 (1H, dd, $J = 6.0$, 10.1 Hz), 3.56 (1H, apparent t, $J = 10.1$ Hz), 2.57 (2H, q, $J = 7.2$ Hz), 2.45 - 2.55 (1H, m), 1.4 - 2.0 (19H, m), 1.37 (3H, s), 1.30 (1H, m), 1.12 (3H, t, $J = 7.2$ Hz), 0.85 - 0.95 (12H, m), 0.82 (3H, d, $J = 6.7$ Hz), 0.03 (6H, s).

$^{13}$C NMR (CDCl$_3$) $\delta$ 136.6, 121.4, 109.7, 92.6, 82.4, 80.3, 74.8, 61.8, 41.0, 38.8, 38.2, 36.0, 35.7, 35.0, 28.6, 27.0, 26.0, 25.0, 24.2, 24.0, 23.8, 23.0, 22.4, 20.9, 18.3, 16.7, 7.9, -5.2, -5.4.

HRMS (Cl) calcd. for C$_{32}$H$_{55}$O$_4$Si 531.3870. Found 531.3855.

1-Methyl-(4$R$)-isopropyl-(5$R$)-acetoxyethyl-(6$S$)-(7-(9$S$)-methyl-(8$S$),9-octandiol-10-yn-12-one 8,9-cyclohexyl ketal]-1-cyclohexene (148) and 1-Methyl-(4$R$)-isopropyl-(5$R$)-hydroxymethyl-(6$S$)-(7-(9$S$)-methyl-(8$S$),9-octandiol-10-yn-12-one 8,9-cyclohexyl ketal]-1-cyclohexene (147).

To a stirred solution of 146 (210 mg, 0.396 mmol) in THF (4.2 mL) and H$_2$O (4.2 mL) was added AcOH (12.6 mL) and heated to 70°C. After 3 h, the
reaction was allowed to cool to ambient temperature, poured slowly into saturated aqueous NaHCO₃ (200 mL) and extracted with Et₂O (3 x 250 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give O-acetate 148 (13 mg, 0.0284 mmol, 7%) as a colorless oil followed by the desired product 147 (129 mg, 0.309 mmol, 78%) as a colorless oil.

**Alcohol 147:**

[α]D²³ +63° (c 0.89).

IR 3449, 2936, 2216, 1680 cm⁻¹.

¹H NMR (CDCl₃) δ 5.40 (1H, br s), 4.34 (1H, dd, J = 4.0, 7.9 Hz), 3.7 - 3.8 (2H, m), 2.57 (2H, q, J = 7.2 Hz), 2.4 - 2.5 (1H, m), 1.5 - 2.0 (20H, m), 1.37 (3H, s), 1.11 (3H, t, J = 7.2 Hz), 0.89 (3H, d, J = 6.7 Hz), 0.81 (3H, d, J = 6.7 Hz).

¹³C NMR (CDCl₃) δ 188.2, 135.2, 122.3, 110.0, 92.2, 82.4, 79.8, 75.0, 62.2, 40.0, 38.7, 36.2, 34.9, 28.0, 27.0, 24.9, 24.1, 23.9, 23.8, 22.8, 22.1, 20.9, 17.0, 7.8.

HRMS (Cl) calcd. for C₁₉H₃₄O₄ 417.3005. Found 417.2998.

**O-acetate 148:**

IR 2937, 2216, 1741, 1682 cm⁻¹.

¹H NMR (CDCl₃) δ 5.38 (1H, br s), 4.2 - 4.35 (2H, m), 3.96 (1H, dd, J = 9.1, 11.1 Hz), 2.57 (2H, q, J = 7.3 Hz), 2.43 (1H, br s), 1.2 - 2.1 (23H, m), 2.04 (3H, s) 1.11 (3H, t, J = 7.3 Hz), 0.89 (3H, d, J = 6.7 Hz), 0.84 (3H, d, J = 6.7 Hz).

HRMS (Cl) calcd. for C₂₈H₄₃O₅ 459.3111. Found 459.3102.
1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-[7-(9S)-methyl-(8S),9-octandiol-10-Z-en-12-one 8,9-cyclohexyl ketal]-1-cyclohexene (149) and 1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-[7-(9S)-methyl-(8S),9-octandiol-12-one 8,9-cyclohexyl ketal]-1-cyclohexene (263).

A stirred solution of 147 (125 mg, 0.300 mmol) in petroleum ether (7.5 mL) with Lindlar catalyst (42 mg) and quinoline (41.5 mg, 38 μL, 0.322 mmol) was evacuated and an atmosphere of H₂ was introduced. After 20 min at ambient temperature, the reaction was diluted with Et₂O (30 mL), filtered through Celite® and concentrated in vacuo and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give 149 (115 mg, 0.275 mmol, 92%) as a colorless oil followed by a trace amount of the overreduced product 263.

IR 3420, 2939, 1700 cm⁻¹.

¹H NMR (CDCl₃) δ 5.89 (1H, d, J = 12.7 Hz), 5.77 (1H, d, J = 12.7 Hz), 5.36 (1H, br s), 4.03 (1H, dd, J = 2.7, 9.8 Hz), 3.69 (2H, br s), 2.6 - 2.8 (2H, m), 2.4 - 2.6.
2.6 (2H, m), 2.29 (1H, br s), 1.3 - 2.0 (19H, m), 1.25 (3H, s), 1.05 (3H, t, J = 7.2 Hz), 0.88 (3H, d, J = 6.8 Hz), 0.81 (3H, d, J = 6.8 Hz).

$^{13}$C NMR (CDCl$_3$) δ 206.0, 141.4, 135.6, 127.8, 122.0, 108.8, 82.8, 79.5, 62.5, 40.1, 38.5, 37.4, 36.4, 36.3, 35.3, 29.7, 28.7, 27.1, 25.0, 24.2, 24.0, 23.7, 21.2, 20.8, 17.2, 7.6.

HRMS (Cl) calcd. for C$_{26}$H$_{43}$O$_4$ 419.3161. Found 419.3148.

1-Methyl-(4R)-isopropyl-(5R)-hydroxymethyl-(6S)-[7-(9S)-methyl-(8S),9-octandiol-12-one 8,9-cyclohexyl ketal]-1-cyclohexene (263).

A stirred solution of 147 (5.6 mg, 0.013 mmol) in MeOH (0.5 mL) with py (2.0 mg, 2.0 µL, 0.025 mmol) and Pd on BaSO$_4$ (1.3 mg, unreduced) was evacuated and an atmosphere of H$_2$ was introduced. After 25 min, the reaction was diluted with Et$_2$O (5 mL), filtered through Celite® and concentrated in vacuo.
and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give 263 (5.1 mg, 0.012 mmol, 93%) as a colorless oil.

\(^1\)H NMR (CDCl₃) \& 5.34 (1H, br s), 3.7 - 3.85 (3H, m), 2.55 (2H, t, 7.7 Hz), 2.3 - 2.5 (3H, m), 1.4 - 2.0 (23H, m), 1.0 - 1.1 (6H, m), 0.88 (3H, d, \(J = 6.7\) Hz), 0.80 (3H, d, \(J = 6.7\) Hz).

HRMS (Cl) calcd. for C_{26}H_{44}O_{4} 420.3240. Found 420.3246.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(9S)-methyl-(8S),9-octandiol-10-Z-en-12-one 8,9-cyclohexyl ketal]-15-al-1-cyclohexene (150).

![Chemical Reaction Diagram](image)

To a stirred solution of 149 (45 mg, 0.108 mmol) in CH₂Cl₂ (3 mL) was added Dess-Martin periodinone 260\(^{10}\) (51 mg, 0.120 mmol). After 20 min, the reaction was quenched by addition of saturated aqueous NaHCO₃ (10 mL) and saturated aqueous NaHSO₃ (10 mL), and stirred until the solution was clear. The
layers were allowed to separate and the aqueous layer was extracted with Et<sub>2</sub>O (3 x 20 mL). The dried (MgSO<sub>4</sub>) extract was concentrated \textit{in vacuo} to give crude 150 (40 mg, 0.0962 mmol, 89\%) as a colorless oil.

\[ \alpha \] D<sup>23</sup> +26° (c 3.05).

IR 2934, 1712 cm<sup>-1</sup>.

$^1$H NMR (C<sub>6</sub>D<sub>6</sub>) δ 9.88 (1H, d, J = 2.9 Hz), 5.68 (1H, d, J = 12.6 Hz), 5.52 (1H, d, J = 12.6 Hz), 5.28 (1H, br s), 4.05 (1H, dd, J = 1.9, 11.3 Hz), 2.6 - 2.75 (2H, m), 2.3 - 2.45 (2H, m), 1.5 - 1.8 (16H, m), 1.2 - 1.5 (6H, m), 1.04 (3H, t, J = 7.2 Hz), 0.88 (3H, d, J = 6.7 Hz), 0.74 (3H, d, J = 6.7 Hz).

$^{13}$C NMR (C<sub>6</sub>D<sub>6</sub>) δ 205.4, 203.0, 143.6, 135.3, 122.0, 108.8, 83.3, 79.9, 51.0, 39.0, 37.9, 37.3, 35.9, 34.9, 29.9, 28.3, 25.4, 24.8, 24.5, 24.1, 21.8, 21.4, 20.5, 18.7, 7.8.

HRMS (CI) calcd. for C<sub>26</sub>H<sub>41</sub>O<sub>4</sub> 417.3005. Found 417.2988.
1-Methyl-(4R)-isopropyl-(5S)-(6S)-(7-(9S)-methyl-(8S),9-octandiol-10-Z-en-12-one 8,9-cyclohexyl ketal]-15-al-1-cyclohexene (154).

To a stirred solution of 150 (14.4 mg, 0.0346 mmol) in THF (1.5 mL) was added KHMDS (90 µL, 0.045 mmol, 0.5 M in toluene) dropwise at -78°C. After 1 h, the reaction was allowed to warm to ambient temperature over 1 h, quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by PLC, eluting with 20% Et₂O / petroluem ether, to give 154 (6.0 mg, 0.014 mmol, 42%) as a colorless oil.

IR  2981, 1698 cm⁻¹.

¹H NMR (CD₆D₆) δ 9.69 (1H, d, J = 1.7 Hz), 5.96 (1H, d, J = 12.4 Hz), 5.46 (1H, d, J = 12.4 Hz), 5.38 (1H, br s), 4.32 (1H, dd, J = 5.4, 7.9 Hz), 2.8 - 2.9 (2H, m), 1.6 - 2.2 (16H, m), 1.40 (3H, s), 1.2 - 1.4 (5H, m), 1.07 (3H, d, J = 6.5 Hz), 0.91 (3H, d, J = 6.5 Hz), 0.85 (3H, t, J = 5.1 Hz).
HRMS (Cl) calcd. for C_{26}H_{40}O_{4} 416.2927. Found 416.2920.
1-Methyl-(4R)-isopropyl-(5S)-(6S)-(7-(9S)-methyl-(8S),9-octandiol-10-E-en-12-one 8,9-cyclohexyl ketal]-15-al-1-cyclohexene (155) and Intermolecular Aldol Adduct 152.

To a stirred solution of TiCl₄ (7.6 mg, 4.4 µL, 0.040 mmol) in CH₂Cl₂ (0.2 mL) was added Ti(Oi-Pr)₄ (3.8 mg, 4.0 µL, 0.013 mmol) at 0°C for 15 min. The Cl₃Ti(Oi-Pr) solution was added via cannula to a solution of 150 (17 mg, 0.041 mmol) and i-Pr₂NEt (6.5 mg, 8.7 µL, 0.050 mmol) in CH₂Cl₂ (1.5 mL) at -78°C. An additional amount of CH₂Cl₂ (0.1 mL) was added to rinse the Cl₃Ti(Oi-Pr) flask. After 25 min, the reaction was warmed to 0°C for 15 min, quenched with NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 x 15 mL). The
dried (MgSO₄) extract was concentrated *in vacuo* and purified by PLC, eluting with 20% Et₂O / petroleum ether, to give the isomerized olefin 155 (7.5 mg, 0.018 mmol, 44%) as a colorless oil followed by the intermolecular aldol product 152 (3.9 mg, 4.7 μmol, 11%) as a colorless oil.

**Trans compound 155:**

IR  2937, 1713, 1677 cm⁻¹.

¹H NMR (C₆D₆) δ 9.64 (1H, d, J = 2.8 Hz), 6.79 (1H, d, J = 15.8 Hz), 6.49 (1H, d, J = 15.8 Hz), 5.26 (1H, br s), 3.87 (1H, dd, J = 2.0, 10.2 Hz), 2.45 - 2.6 (1H, m), 2.2 - 2.3 (1H, m), 1.45 - 1.9 (17H, m), 1.2 - 1.4 (4H, m), 1.08 (3H, s), 1.04 (3H, t, J = 7.2 Hz), 0.85 (3H, d, J = 6.5 Hz), 0.70 (3H, d, J = 6.5 Hz).

HRMS (CI) calcd. for C_{26}H_{40}O_{4} 416.2927. Found 416.2923.

**Intermolecular aldol adduct 152:**

IR  3485, 2933, 1713, 1675 cm⁻¹.

¹H NMR (C₆D₆) δ 9.67 (1H, d, J = 2.8 Hz), 7.03 (1H, d, J = 15.8 Hz), 6.89 (1H, d, J = 15.8 Hz), 6.77 (1H, d, J = 15.8 Hz), 6.51 (1H, d, J = 15.8 Hz), 5.39 (1H, br s), 5.25 (1H, br s), 4.4 - 4.5 (1H, m), 4.29 (1H, dd, J = 1.9, 8.8 Hz), 3.89 (1H, dd, J = 1.9, 8.9 Hz), 3.25 - 3.35 (1H, m), 3.1 - 3.2 (1H, m), 2.75 - 2.85 (1H, m), 2.5 - 2.65 (1H, m), 0.9 - 2.3 (63H, m), 0.72 (3H, d, J = 6.5 Hz).

HRMS (CI) calcd. for C_{52}H_{80}O_{8} 832.5853. Found 832.5848.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(9S)-methyl-12-trimethylsiloxy-(8S),9-octandiol-10-Z-12-E-diene 8,9-cyclohexyl ketal]-15-al-1-cyclohexene (153).

To a stirred solution of 150 (17 mg, 0.0409 mmol) in THF (1.7 mL) was added LHMDS (55 μL, 0.055 mmol, 1 M in THF) at -78°C. After 30 min, the reaction was allowed to warm to ambient temperature for 15 min. Then, the solution was recooled to -78°C and TMSCl (6.0 mg, 7.0 μL, 0.55 mmol) was added. After 10 min at -78°C, the reaction was allowed to warm to ambient temperature for 15 min, quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo to give crude 153 (18 mg, 0.037 mmol, >95% pure by ¹H NMR) as a colorless oil.

IR 2935, 2860, 1719, 1655 cm⁻¹.
¹H NMR (CDCl₃) δ 9.80 (1H, d, J = 2.9 Hz), 5.84 (1H, d, J = 12.9 Hz), 5.42 (1H, d, J = 12.9 Hz), 5.34 (1H, q, J = 7.1 Hz), 5.28 (1H, br s), 4.13 (1H, dd, J = 2.4,
10.7 Hz), 2.6 - 2.75 (2H, m), 1.2 - 2.0 (25H, m), 0.91 (3H, d, J = 6.7 Hz), 0.75
(3H, d, J = 6.7 Hz), 0.21 (9H, s).

HRMS (Cl) calcd. for C_{28}H_{48}O_{4}Si 488.3322. Found 488.3307.

1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(9S)-methyl-(8S),9-octandiol-10-E-en-
12-one 8,9-cyclohexyl ketal]-15-al-1-cyclohexene (155).

To a stirred solution of TiCl$_4$ (8.7 mg, 5.0 µL, 0.046 mmol) in CH$_2$Cl$_2$
(0.2 mL) was added Ti(Oi-Pr)$_4$ (4.3 mg, 4.5 µL, 0.15 mmol) at 0°C for 15 min.
The Cl$_3$Ti(Oi-Pr) solution was added to a solution of crude 153 (18 mg, 0.037
mmol) in CH$_2$Cl$_2$ (1.8 mL) at -78°C. After 10 min, the reaction was warmed to
ambient temperature, quenched with saturated aqueous NaHCO$_3$ (10 mL) and
extracted with CH$_2$Cl$_2$ (4 x 15 mL). The dried (MgSO$_4$) extract was concentrated
in vacuo and purified by PLC, eluting with 20% Et$_2$O / petroleum ether, to give
153 (3.5 mg, 0.084 mmol, 23%) as a colorless oil.
IR 2937, 1713, 1677 cm\(^{-1}\).

\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 9.64 (1H, d, J = 2.8 Hz), 6.79 (1H, d, J = 15.9 Hz), 6.49 (1H, d, J = 15.9 Hz), 5.26 (1H, br s), 3.87 (1H, dd, J = 2.0, 10.2 Hz), 2.45 - 2.6 (1H, m), 2.2 - 2.3 (1H, m), 1.45 - 1.9 (17H, m), 1.2 - 1.4 (4H, m), 1.08 (3H, s), 1.04 (3H, t, J = 7.2 Hz), 0.85 (3H, d, J = 6.5 Hz), 0.70 (3H, d, J = 6.5 Hz).

HRMS (Cl) calcd. for C\(_{26}\)H\(_{40}\)O\(_4\) 416.2927. Found 416.2923.

1-Methyl-(4\(R\))-isopropyl-(5\(R\))-\(\gamma\)-(6\(S\))-\(\gamma\)-(7\(R\))-\(\gamma\)-(8\(S\))-\(\gamma\)-(9\(R\))-methyl-10-tert-butyldiphenylsiloxybutane]-8,9,(11\(R\))-bis-oxido-1-cyclohexene (156).

![Chemical structure](image)

To a stirred solution of 110 (86 mg, 0.32 mmol) in DMF (0.4 mL) with imidazole (160 mg, 2.4 mmol) was added TBDPSCI (100 mg, 95 \(\mu\)L, 0.37 mmol) at ambient temperature. After 1 h, the reaction was quenched with saturated aqueous NH\(_4\)Cl (10 mL) and extracted with Et\(_2\)O (4 x 15 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} and purified by chromatography over
silica gel, eluting with 5% Et₂O / petroleum ether, to give 156 (129 mg, 0.28 mmol, 86%) as a colorless oil.

IR 3071, 3048, 2930 cm⁻¹.

¹H NMR (CDCl₃) δ 7.5 - 7.6 (4H, m), 7.25 - 7.35 (6H, m), 5.35 (1H, br s), 5.30 (1H, d, J = 5.4 Hz), 4.21 (1H, d, J = 3.3 Hz), 3.60 (1H, d, J = 9.3 Hz), 3.16 (1H, d, J = 9.3 Hz), 2.50 - 2.55 (1H, m), 1.9 - 1.95 (1H, m), 1.8 - 1.85 (2H, m), 1.45 - 1.65 (3H, m), 1.55 (3H, s), 1.41 (3H, s), 0.95 (9H, s), 0.81 (3H, d, J = 6.9 Hz), 0.64 (3H, d, J = 6.9 Hz).

HRMS (CI) calcd. for C₃₂H₄₅O₃Si 505.3138. Found 505.3124.


To a stirred solution of 156 (33.5 mg, 0.0665 mmol) in PhH (1.5 mL) with TMSCN (65.9 mg, 88.6 μL, 0.664 mmol) was added ZnI₂ (21.2 mg, 0.0664 mmol) at ambient temperature. After 30 min, the reaction was heated to reflux.
After 15 min, the reaction was allowed to cool to ambient temperature, quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et₂O/petroleum ether, to give 157 (23.8 mg, 0.448 mmol, 67%) as a colorless oil.

IR 3569, 2933, 2372 cm⁻¹.

¹H NMR (CDCl₃)  δ 7.6 - 7.7 (4H, m), 7.3 - 7.4 (6H, m), 5.43 (1H, br s), 4.10 (1H, d, J = 10.2 Hz), 3.69 (1H, d, J = 9.5 Hz), 3.48 (1H, d, J = 9.5 Hz), 3.37 (1H, dd, J = 1.0, 12.0 Hz), 2.50 (1H, br s), 2.28 (OH, br s), 1.4 - 2.2 (11H, m), 1.18 (3H, s), 1.04 (9H, s), 0.93 (3H, d, J = 6.2 Hz), 0.90 (3H, d, J = 6.2 Hz).

HRMS (Cl) calcd. for C₃₃H₄₆NO₃Si 532.3247. Found 532.3239.

To a stirred solution of 156 (177 mg, 0.351 mmol) in CH$_2$Cl$_2$ (7.4 mL) with allyltrimethylsilane (165) (403 mg, 0.56 mL, 3.52 mmol) was added TiCl$_4$ (657 mg, 0.38 mL, 3.47 mmol) dropwise at -78°C. After 15 min, the reaction was briefly (2 min) removed from the cooling bath then quenched with saturated aqueous NaHCO$_3$ (50 mL) and extracted with Et$_2$O (4 x 75 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% Et$_2$O / petroleum ether, to give 158 (191 mg, 0.351 mmol, 99%) as a colorless oil.

IR 3564, 3071, 2960, 2931, 2857 cm$^{-1}$.
$^1$H NMR (CDCl$_3$) $\delta$ 7.6 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 5.75 (1H, m) 5.40 (1H, br s), 4.9 - 5.0 (2H, m), 3.66 (1H, d, $J = 9.4$ Hz), 3.45 - 3.55 (2H, m), 3.35 (1H, d, $J = 12.7$ Hz), 2.59 (OH, s), 2.43 (1H, br s), 2.30 - 2.35 (1H, m), 2.1 - 2.15 (1H, m), 1.8 - 2.05 (3H, m), 1.66 (3H, s), 1.4 - 1.75 (2H, m), 1.2 - 1.3 (2H, m), 1.17 (3H, s), 1.04 (9H, s), 0.89 (3H, d, $J = 6.4$ Hz), 0.84 (3H, d, $J = 6.4$ Hz).
$^{13}$C NMR (CDCl$_3$) $\delta$ 135.6, 135.3, 133.5, 133.4, 130.0, 127.6, 122.5, 116.2, 75.9, 74.4, 73.9, 68.3, 39.0, 38.9, 37.3, 33.2, 27.3, 26.9, 24.4, 21.9, 21.4, 20.44, 20.40, 19.3.

HRMS (CI) calcd. for C$_{35}$H$_{51}$O$_3$Si 547.3607. Found 547.3600.

To a stirred solution of 158 (95 mg, 0.174 mmol) and i-Pr₂NEt (111 mg, 150 µL, 0.861 mmol) in CH₂Cl₂ (2.5 mL) was added TESOTf (70 mg, 60 µL, 0.265 mmol) at ambient temperature. After 20 min, the reaction was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with CH₂Cl₂ (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1 - 5% Et₂O / petroleum ether, to give 169 (115 mg, 0.174 mmol, 99%) as a colorless oil.

IR 3072, 2957 cm⁻¹.

¹H NMR (CDCl₃) δ 7.6 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 5.75 - 5.9 (1H, m), 5.35 (1H, br s), 4.9 - 5.0 (2H, m), 3.77 (1H, d, J = 9.6 Hz), 3.4 - 3.5 (3H, m), 3.15 (1H, d, J = 10.7 Hz), 2.25 - 2.4 (2H, m), 1.8 - 2.2 (3H, m), 1.6 - 1.75 (4H, m) 1.3 - 1.55 (2H, m), 1.1 - 1.2 (4H, m), 1.03 (9H, s), 0.8 - 0.95 (15H, m), 0.51 (6H, q, J = 5.5 Hz).

HRMS (Cl) calcd. for C₄₁H₆₅O₃Si₂ 661.4472. Found 661.4456.
(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13,14-butanediol]-(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyldiphenylsiloxybutane]-8,11-oxido-1-cyclohexene (171) and 1-Methyl-(4R)-isopropyl-(5R)-[(11S)-13,14-butanediol]-(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyldiphenylsiloxybutane]-8,11-oxido-1,2-cyclohexadiol (173).

$\textbf{169}$ \[\xrightarrow{\text{AD mix } \beta^*} \]
\[t\text{-BuOH, H}_2\text{O}\]

$\textbf{171}$

$\textbf{173}$

$AD \text{ mix } \beta^*$: $K_3\text{Fe(CN)}_6$ (6.996 g, 0.0215 mol), $K_2\text{CO}_3$ (2.936 g, 0.0212 mol), (DHQD)$_2$PHAL (152 mg, 0.195 mmol), $K_2\text{OsO}_4\cdot2\text{H}_2\text{O}$ (25.5 mg, 0.0692 mmol) were vigorously stirred until a homogeneous powder was observed.

To a stirred solution of 169 (300 mg, 0.455 mmol) in $t$-BuOH (4 mL) and H$_2$O (4 mL) was added AD mix $\beta^*$ (514 mg). After 18 h at ambient temperature,
the reaction was diluted with EtOAc (10 mL) and quenched with saturated aqueous Na_2SO_3 (1 mL). After 15 min, the reaction was diluted with saturated aqueous NaCl (10 mL) and extracted with EtOAc (4 x 15 mL). The dried (MgSO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% Et_2O/petroleum ether, to give starting material 169 (52 mg, 0.0788 mmol, 17%) followed by the desired diol 171 (175 mg, 0.252 mmol, 55%) as a colorless oil, and then EtOAc, to give 173 (72 mg, 0.0989 mmol, 22%) as a colorless oil.

**Diol 171:**

IR 3428, 2956 cm⁻¹.

_1^H NMR (CDCl₃) δ 7.55 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 5.39 (1H, br s), 3.9 - 4.0 (1H, m), 3.6 - 3.85 (2H, m), 3.2 - 3.6 (4H, m), 2.35 - 2.5 (1H, m), 1.4 - 2.0 (12H, m), 1.1 - 1.3 (3H, m), 1.04 (9H, s, minor), 1.03 (9H, s, major), 0.85 (15H, apparent q), 0.46 (6H, q, J = 7.5 Hz).

HRMS (Cl) calcd. for C_{41}H_{67}O_5Si_2 695.4527. Found 695.4513.

**Tetraol 173:**

IR 3382, 2955 cm⁻¹.

_1^H NMR (CDCl₃) δ 7.55 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 3.9 - 4.0 (1H, br s), 3.7 - 3.85 (2H, m), 3.4 - 3.65 (4H, m), 3.30 (1H, d, J = 8.9 Hz), 1.4 - 2.15 (9H, m), 1.3 - 1.5 (1H, m), 1.24 (3H, s), 1.11 (3H, s), 1.04 (9H, s), 0.93 (3H, d, J = 6.9 Hz), 0.84 (9H, t, J = 7.9 Hz), 0.74 (3H, d, J = 6.9 Hz), 0.46 (6H, q, J = 7.9 Hz).

HRMS (Cl) calcd. for C_{41}H_{69}O_7Si_2 729.4582. Found 729.4581.
(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-propanal]-[(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyl-diphenylsiloxybutane]-8,11-oxido-1-cyclohexene (174).

![Chemical structure of 171 and 174](image)

To a stirred solution of 171 (65 mg, 0.094 mmol) in THF (5 mL) and Et₂O (5 mL) was added NaIO₄ (450 mg, 2.10 mmol) followed by H₂O (1.5 mL) at ambient temperature. After 1 h, the reaction quenched with saturated aqueous NaCl (20 mL) and extracted with Et₂O (4 x 25 mL). The dried (MgSO₄) extract was concentrated in vacuo to give crude 174 (62 mg, 0.94 mmol) as a colorless oil.

IR 2928, 1734 cm⁻¹.

¹H NMR (CDCl₃) δ 9.67 (1H, t, J = 2.6 Hz), 7.8 - 7.9 (4H, m), 7.2 - 7.4 (6H, m), 5.29 (1H, br s), 4.01 (1H, d, J = 9.5 Hz), 3.85 - 3.95 (1H, m), 3.68 (1H, d, J = 9.5 Hz), 3.34 (1H, d, J = 11.1 Hz), 2.26 (1H, br s), 2.15 - 2.25 (1H, m), 2.05 - 2.15 (1H, m), 1.45 - 1.9 (5H, m), 1.3 - 1.45 (8H, m), 1.20 (9H, s), 1.03 (6H, t, J = 7.7 Hz), 0.80 (3H , d, J = 6.5 Hz), 0.6 - 0.75 (12H, m).
HRMS (Cl) calcd. for C₄₀H₆₂O₄Si₂ 662.4187. Found 662.4166.

(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-propanoic acid]-(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyl-diphenylsiloxybutane]-8,11-oxido-1-cyclohexene (175).

To a stirred solution of crude 174 (62 mg, 0.094 mmol) in t-BuOH with 2-methyl-2-butene (100 μL) was added sequentially solutions of NaClO₂ (2.1 mL, 0.65 mmol, 0.31 M in H₂O) and NaH₂PO₄ (1.5 mL, 0.555 mmol, 0.37 M in H₂O). After 30 min at ambient temperature, the reaction was diluted with saturated aqueous NaCl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo to give crude 175 (63 mg, 0.093 mmol) as a colorless oil.

IR 3500 - 2500, 2956, 1713 cm⁻¹.

¹H NMR (CDCl₃) δ 10.33 (1H, br s), 7.55 - 7.65 (4H, m), 7.3 - 7.45 (6H, m), 5.41 (1H, br s), 3.78 (1H, d, J = 9.3 Hz), 3.65 - 3.75 (1H, m), 3.44 (1H, d, J = 13.5 Hz), 3.34 (1H, d, J = 9.3 Hz), 2.4 - 2.5 (2H, m), 1.95 - 2.1 (2H, m), 1.7 - 1.9 (2H, m), 1.1 - 1.7 (10H, m), 1.03 (9H, s), 0.8 - 0.9 (15H, m), 0.47 (6H, q, J = 7.9 Hz).
HRMS (Cl) calcd. for C_{40}H_{63}O_{5}Si_{2} 679.4214. Found 679.4191.

(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-propanoate methyl ester]-(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyl-diphenylsiloxybutane]-8,11-oxido-1-cyclohexene (176).

To a stirred solution of crude 175 (63 mg, 0.093 mmol) in CH_{2}Cl_{2} (4 mL) was added a solution of CH_{2}N_{2} (800 µL, approximately 0.5 M in Et_{2}O) at ambient temperature. After 20 min, the reaction was quenched with AcOH (1 mL, 30% in H_{2}O) followed by saturated aqueous NaHCO_{3} (15 mL) and extracted with CH_{2}Cl_{2} (4 x 20 mL). The dried (MgSO_{4}) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5 - 15% Et_{2}O / petroleum ether, to give 176 (54 mg, 0.078 mmol, 83% over 3 steps) as a colorless oil.

IR 2928, 1742 cm\(^{-1}\).

\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 7.6 - 7.7 (4H, m), 7.3 - 7.4 (6H, m), 5.38 (1H, br s), 3.8 - 3.9 (1H, m), 3.65 (1H, d, \(J = 9.7\) Hz), 3.55 (3H, s), 3.53 (1H, d, \(J = 9.7\) Hz), 3.10 (1H,
d, J = 11.0 Hz), 2.53 (1H, dd, J = 3.9, 14.7 Hz), 2.2 - 2.4 (3H, m), 2.06 (1H, d, 12.3 Hz), 1.95 (1H, br s), 1.1 - 1.7 (10H, m), 1.04 (9H, s), 0.8 - 0.9 (15H, m), 0.51 (6H, q, J = 8.0 Hz).

$^{13}$C NMR (CDCl$_3$) δ 172.4, 135.8, 135.7, 133.9, 133.6, 133.5, 129.4, 127.5, 122.3, 78.4, 77.1, 74.4, 68.2, 51.3, 40.0, 39.9, 39.2, 32.5, 27.2, 26.9, 24.2, 22.7, 21.8, 21.3, 20.5, 19.3, 7.1, 6.8.

HRMS (CI) calcd. for C$_{41}$H$_{65}$O$_3$Si$_2$ 693.4371. Found 693.4370.
(1S)-Methyl-(4R)-isopropyl-(5R)-[11-14-diethylphosphonate-12-E-butene-13-one]-(6S)-[7-(9R)-methyl-9-triethoxysiloxyl-10-tert-butyl-diphenylsiloxyl-(8S)-butanol]-8,9-oxido-1-cyclohexene (178) and (1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-14-diethylphosphonate-13-butanone]-(6S)-[7-(8S)-(9R)-methyl-9-triethoxysiloxyl-10-tert-butyl-diphenylsiloxylbutane]-8,11-oxido-1-cyclohexene (177).

To a stirred solution of diethyl methylphosphonate (24 mg, 23 μL, 0.16 mmol) in THF (1.6 mL) was added n-BuLi (60 μL, 0.15 mmol, 2.5 M in hexanes) at -78°C. After 30 min, a solution of 176 (34 mg, 0.049 mmol) in THF (0.4 mL) was added via cannula. An additional amount of THF (0.2 mL) was added to rinse the ester flask. After 30 min, the reaction was allowed to warm to ambient
temperature for 10 min. The solution was quenched with saturated aqueous
NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract
was concentrated \textit{in vacuo} and purified by PLC, eluting with 50% Et₂O / petroleum ether, to give the eliminated ether bridge compound 178 (5.0 mg, 0.0062 mmol, 13%) as a pale yellow oil followed by the desired compound 177 (27 mg, 0.033 mmol, 68%) as a pale yellow oil.

\textit{Trans-olefin / β-keto phosphonate 178:}

IR 3421, 2928, 1731, 1668 cm⁻¹.

$^1$H NMR (CDCl₃) δ 7.55 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 6.96 (1H, dd, J = 10.7, 16.0 Hz), 6.19 (1H, d, J = 16.0 Hz), 5.34 (1H, br s), 4.0 - 4.2 (4H, m), 3.5 - 3.7 (2H, m), 2.9 - 3.4 (3H, m), 2.4 - 2.5 (1H, m), 2.2 - 2.3 (1H, m), 1.75 - 2.2 (3H, m), 1.0 - 1.75 (25H, m), 0.8 - 0.95 (12H, m), 0.67 (3H, d, J = 6.5 Hz), 0.51 (6H, q, J = 7.7 Hz).

HRMS (Cl) calcd. for C₄₅H₇₄O₇PSi₂ 813.4695. Found 813.4711.

β-keto phosphonate 177:

IR 2930, 1719 cm⁻¹.

$^1$H NMR (CDCl₃) δ 7.55 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 5.39 (1H, br s), 4.0 - 4.15 (4H, m), 3.8 - 3.95 (1H, m), 3.60 (1H, d, J = 9.9 Hz), 3.44 (1H, d, J = 9.9 Hz), 2.9 - 3.2 (3H, m), 2.7 - 2.8 (1H, m), 2.5 - 2.6 (1H, m), 2.3 - 2.4 (1H, m), 1.9 - 2.1 (4H, m), 1.35 - 1.7 (11H, m), 1.1 - 1.35 (12H, m), 1.03 (9H, s), 0.8 - 0.9 (15H, m), 0.50 (6H, q, J = 7.8 Hz).
HRMS (Cl) calcd. for C_45H_74O_7PSi_2 813.4665. Found 813.47108.

To a stirred solution of 177 (10.0 mg, 0.0123 mmol) with 4 Å molecular sieves (200 mg) in THF (0.2 mL) was added TBAF (0.2 mL, 0.2 mmol, 1 M in THF) at ambient temperature. After 16 h, the reaction was diluted with EtOAc (2 mL), quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with
EtOAc (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo to give crude 179 as a pale yellow oil which was used immediately.

To a stirred solution of crude 179 (0.0123 mmol) in DMSO (0.2 mL) and Et₃N (0.2 mL) was added SO₃·py (32 mg, 0.20 mmol) at ambient temperature. After 30 min, the reaction was diluted with CH₂Cl₂ (5 mL), quenched with saturated aqueous NH₄Cl (20 mL) and extracted with CH₂Cl₂ (4 x 25 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over a small plug of silica gel, eluting with 70% Et₂O / petroleum ether to EtOAc, to give 180 (4.2 mg, 0.00917 mmol, 75% over 2 steps) as a pale yellow oil.

¹H NMR (CDCl₃) δ 9.46 (1H, s), 5.26 (1H, br s), 3.9 - 4.1 (5H, m), 3.33 (1H, dd, J = 1.3, 11.5 Hz), 3.07 (1H, d, J = 5.0 Hz), 2.99 (1H, d, J = 5.0 Hz), 2.6 - 2.7 (2H, m), 2.15 - 2.3 (2H, m), 1.7 - 1.9 (2H, m), 1.6 - 1.7 (1H, m), 1.4 - 1.6 (8H, m), 1.04 (6H, dt, J = 1.2, 7.1 Hz), 1.02 (3H, s), 0.80 (3H, d, J = 6.6 Hz), 0.75 (3H, d, J = 6.6 Hz).

HRMS (CI) calcd. for C₂₃H₄₀O₇P 459.2512. Found 459.2508.

\[ \text{180} \xrightarrow{\text{TESOTf, i-Pr}_2\text{NEt}} \text{167} \]

To a stirred solution of 180 (4.9 mg, 0.011 mol) in CH$_2$Cl$_2$ (300 μL) and i-Pr$_2$NEt (22 mg, 30 μL, 0.17 mmol) was added TESOTf (5.8 mg, 5.0 μL, 0.022 mol). An additional amount of TESOTf (5.8 mg, 5.0 μL, 0.022 mol) was added during the course of the reaction. After 1 h at ambient temperature, the reaction was quenched with saturated aqueous NH$_4$Cl (15 mL) and extracted with CH$_2$Cl$_2$ (4 x 20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over a small plug of silica gel, eluting with 50 - 100% Et$_2$O / petroleum ether, to give 167 (5.5 mg, 0.0096 mmol, 87%) as a pale yellow oil.

IR 2957, 1722, 1713 cm$^{-1}$.

$^1$H NMR (CDCl$_3$) δ 9.55 (1H, s), 5.29 (1H, br s), 3.9 - 4.2 (5H, m), 3.2 - 3.4 (2H, m), 2.85 - 3.0 (1H, m), 2.7 - 2.8 (1H, m), 2.2 - 2.3 (1H, m), 1.7 - 2.1 (3H, m), 1.5 - 1.7 (4H, m), 0.6 - 1.4 (25H, m).
HRMS (CI) calcd. for C$_{29}$H$_{53}$O$_7$PSi 573.3377. Found 573.3377.
(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-propanol]-[(6S)-[7-(8S)-(9R)-methyl-9-triethylsiloxy-10-tert-butyl-diphenylsiloxybutane]-8,11-oxido-1-cyclohexene (182).

![Chemical structure](image)

To a stirred solution of crude 174 (79.4 mg, 0.119 mmol) in MeOH (5 mL) was added NaBH₄ (33 mg, 0.87 mmol) at ambient temperature. After 40 min, the reaction was quenched with saturated aqueous NH₄Cl (20 mL) and extracted with EtOAc (4 x 30 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30% Et₂O / petroleum ether, to give 182 (72 mg, 0.108 mmol, 91% over 2 steps) as a colorless oil.

IR 3456, 3071, 2958 cm⁻¹.

¹H NMR (CDCl₃) δ 7.55 - 7.7 (4H, m), 7.3 - 7.45 (6H, m), 5.39 (1H, br s), 3.5 - 3.8 (4H, m), 3.34 (1H, d, J = 9.4 Hz), 3.25 (1H, d, J = 11.0 Hz), 3.10 (OH, t, J = 4.5 Hz), 2.41 (1H, br s), 1.8 - 2.1 (4H, m), 1.4 - 1.7 (8H, m), 1.18 (3H, s), 1.04 (9H, s), 0.8 - 0.9 (15H, m), 0.47 (6H, q, J = 8.2 Hz).

303
HRMS (Cl) calcd. for $C_{40}H_{65}O_4Si_2$ 665.4421. Found 665.4407.

$\text{(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-pivaloyl(oxy)-propanol-(6S)-[7-(8S)-(9R)-methyl-9-triethyldimethylsiloxy-10-\text{-\textit{tert}}-\text{butyl-diphenylsiloxybutane]-8,11-oxido-1-cyclohexene (183)}.$

![Chemical Reaction](image)

To a stirred solution of 182 (200 mg, 0.301 mmol) in $\text{CH}_2\text{Cl}_2$ (4.2 mL) and Et$_3$N (420 µL) was added DMAP (18 mg, 0.147 mmol) and PivCl (117 mg, 120 µL, 0.974 mmol) at ambient temperature. An additional amount of PivCl (78 mg, 80 µL, 0.649 mmol) and DMAP (15 mg, 0.123 mmol) were added during the course of the reaction. After 3 h, the reaction was quenched with saturated aqueous NH$_4$Cl (20 mL) and extracted with $\text{Et}_2\text{O}$ (4 x 30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5 - 50% $\text{Et}_2\text{O} / \text{petroleum ether},$ to give 183 (200 mg, 0.268 mmol, 89%) as a colorless oil.
IR 2959, 1730 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.6 - 7.7 (4H, m), 7.3 - 7.4 (6H, m), 5.35 (1H, br s), 3.95 - 4.2 (2H, m), 3.68 (1H, d, J = 9.9 Hz), 3.4 - 3.5 (2H, m), 3.05 (1H, d, J = 11.0 Hz), 2.3 - 2.4 (1H, br s), 1.8 - 2.1 (3H, m), 1.3 - 1.7 (9H, m), 1.16 (9H, s), 1.04 (9H, s), 0.8 - 0.9 (18H, m), 0.52 (6H, q, J = 7.4 Hz).

HRMS (Cl) calcd. for C\(_{45}H_{72}O_5Si_2\) 748.4918. Found 748.4896.

\((1S)-\)Methyl-(4R)-isopropyl-(6S)-(5R)-\([((12S)-13\text{-pivaloyl(oxy)-propane}]-[7-(8S)-(9S)-methyl-9,10\text{-butandiol}]-8,11\text{-oxido-1-cyclohexene\ (184).}\]

To a stirred solution of 183 (215.0 mg, 0.287 mmol) in THF (3.6 mL) was added TBAF (3.6 mL, 3.6 mmol, 1 M in THF). After 1.75 h, the reaction was quenched with saturated aqueous NaHCO\(_3\) (25 mL) and extracted with Et\(_2\)O (4 x 50 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 50 - 70\% Et\(_2\)O / petroleum ether, to give 184 (105.2 mg, 0.266 mmol, 93\%) as a colorless oil.
IR 3478, 2953, 1728 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.36 (1H, br s), 4.42 (1H, dt, \(J = 5.1, 10.1\) Hz), 4.0 - 4.1 (1H, m), 3.4 - 3.6 (3H, m), 3.21 (1H, dd, \(J = 1.2, 11.6\) Hz), 2.70 (OH, br s), 2.43 (OH, br s), 1.9 - 2.1 (3H, m), 1.7 - 1.9 (1H, m), 1.4 - 1.7 (10H, m), 1.16 (9H, s), 1.07 (3H, s), 0.8 - 0.9 (6H, m).

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 178.7, 133.2, 122.4, 76.9, 73.5, 73.4, 68.3, 65.8, 60.6, 39.9, 32.2, 32.1, 27.2, 27.1, 24.1, 21.7, 21.3, 20.5, 19.9, 15.2.

HRMS (Cl) calcd. for C\(_{23}\)H\(_{41}\)O\(_5\) 397.2954. Found 397.2949.

(\(1S\))-Methyl-(\(4R\))-isopropyl-(\(5R\))-[(\(11S\))-13-pivaloyl(oxy)-propane]-(6S)-[7-(8S)-(9R)-methyl-9-butanol-10-al]-8,11-oxido-1-cyclohexene (184).

![Diagram of chemical structures 184 and 185]

To a stirred solution of 184 (16.4 mg, 0.0414 mmol) in DMSO (1 mL) and Et\(_3\)N (125 μL) was added SO\(_3\)*py (78 mg, 0.49 mmol) via cannula. After 20 min at ambient temperature, the reaction was quenched with saturated aqueous NH\(_4\)Cl
(10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated *in vacuo* to give crude 185 as a pale yellow oil.

IR 3499, 2926, 1729 cm⁻¹.

¹H NMR (C₆D₆) δ 9.46 (1H, s), 5.27 (1H, br s), 4.25 - 4.4 (1H, m), 4.1 - 4.2 (1H, m), 3.46 (1H, td, J = 1.8, 10.4 Hz), 3.2 - 3.4 (2H, m), 2.0 - 2.3 (2H, m), 1.6 - 1.9 (3H, m), 0.85 - 1.6 (20H, m), 0.80 (3H, d, J = 6.6 Hz), 0.72 (3H, d, J = 6.6 Hz).

HRMS (Cl) calcd. for C₂₃H₃₉O₅ 395.2798. Found 395.2804.

(1S)-Methyl-(4R)-isopropyl-(5R)-[(11S)-13-pivaloyl(oxy)-propane]-(6S)-[7-(8S)-(9R)-methyl-9-methoxymethyl-10-butanal]-8,11-oxido-1-cyclohexene (186).

![Chemical structure](image)

To a stirred solution of crude 185 (0.0414 mmol) in i-Pr₂NEt (150 µL) and CH₂Cl₂ (50 µL) was added MOMCl (53 mg, 50 µL, 0.66 mmol) at ambient temperature. After 15 h, the reaction was quenched with saturated aqueous
NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give 186 (13.1 mg, 0.0300 mmol, 73%) as a colorless oil.

IR 2963, 1729 cm⁻¹.

¹H NMR (C₆D₆) δ 9.82 (1H, s), 5.29 (1H, br s), 4.67 (1H, d, J = 7.2 Hz), 4.58 (1H, d, J = 7.2 Hz), 4.25 - 4.4 (2H, m), 3.50 (1H, dt, J = 2.4, 10.2 Hz), 3.38 (1H, dd, J = 1.2, 11.6 Hz), 3.12 (3H, s), 2.25 (1H, br s), 2.02 (1H, d, J = 4.2 Hz), 1.85 - 2.0 (1H, m), 1.75 - 1.85 (2H, m), 1.3 - 1.7 (6H, m), 1.24 (3H, s), 1.19 (9H, s), 0.80 (3H, d, J = 6.5 Hz), 0.73 (3H, d, J = 6.5 Hz).

¹³C NMR (C₆D₆) δ 203.0, 177.7, 133.2, 123.1, 92.6, 83.4, 78.8, 74.3, 61.3, 55.4, 40.3, 39.9, 38.8, 32.6, 32.3, 27.6, 27.4, 27.3, 24.4, 21.8, 21.4, 20.6, 16.1.

HRMS (CI) calcd. for C₂₅H₄₁O₄ 437.2903. Found 437.2902.
(LS)-Methyl-(4R)-isopropyl-(5R)-[(12S)-14-pivaloyl(oxy)-propane]-(6S)-[7-(8S)-(9S)-methyl-9-triethyldisiloxo-11-ido-10-Z-pentene]-8,12-oxido-1-cyclohexene (188).

![Chemical structure](image)

To a stirred solution of the phosphonium salt 18716 (22.9 mg, 0.043 mmol) in THF (190 μL) was added NaHMDS (43.5 μL, 0.0435 mmol, 1.0 M in THF) at ambient temperature. After 3 min, HMPA (23.3 mg, 22.6 μL, 0.130 mmol) was added. After 1 min, the reaction was cooled to -78°C and a solution of 186 (9.1 mg, 0.020 mmol) in THF (160 μL) was added via cannula. An additional amount of THF (2 x 50 μL) was added to rinse the aldehyde flask. The reaction was allowed to warm to ambient temperature slowly over 1.66 h. Then, the reaction was quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (4 x 10 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give 188 (9.4 mg, 0.017 mmol, 81%) as a colorless oil and a trace amount of the starting material 186.
IR 2962, 1728 cm\(^{-1}\).

\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 6.34 (1H, d, J = 8.9 Hz), 6.13 (1H, d, J = 8.9 Hz), 5.34 (1H, br s), 4.80 (1H, d, J = 7.0 Hz), 4.73 (1H, d, J = 7.0 Hz), 4.35 - 4.5 (2H, m), 3.60 (1H, dt, J = 2.1, 10.2 Hz), 3.43 (1H, d, J = 11.3 Hz), 3.27 (3H, s), 2.32 (1H, br s), 2.19 (1H, d, J = 13.7 Hz), 1.9 - 2.05 (1H, m), 1.86 (1H, br s), 1.35 - 1.7 (12H, m), 1.20 (9H, s), 0.82 (3H, d, J = 6.5 Hz), 0.75 (3H, d, J = 6.5 Hz).

HRMS (CI) calcd. for C\(_{26}\)H\(_{44}\)I\(_2\)O\(_5\) 563.2234. Found 563.2233.
(1S)-Methyl-(4R)-isopropyl-(5R)-[(12S)-14-propanol]-(6S)-(7-(8S)-(9R)-methyl-9-triethylsiloxy-11-iodo-10-Z-pentene]-8,12-oxido-1-cyclohexene (189).

To a stirred solution of 188 (8.8 mg, 0.016 mmol) in THF (300 μL) was added Super Hydride® (60 μL, 0.060 mmol, 1.0 M in THF) via syringe at -78°C. An additional portion of Super Hydride® (60 μL, 0.060 mmol, 1.0 M in THF) was added during the course of the reaction. After 30 min, the reaction was allowed to warm to 0°C for 5 min, quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (5 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give 189 (6.8 mg, 0.014 mmol, 91%) as a colorless oil.

IR 3437, 2925 cm⁻¹.

¹H NMR (CDCl₃) δ 6.15 (1H, d, J = 9.1 Hz), 6.10 (1H, d, J = 9.1 Hz), 5.34 (1H, br s), 4.80 (1H, d, J = 7.5 Hz), 4.70 (1H, d, J = 7.5 Hz), 3.6 - 3.9 (3H, m), 3.35 (3H, s), 3.0 - 3.15 (1H, m), 2.25 - 2.35 (1H, m), 1.92 (1H, d, J = 13.6 Hz), 1.5 - 1.9
(8H, m), 1.47 (3H, s), 1.3 - 1.5 (3H, m), 0.83 (3H, d, J = 6.4 Hz), 0.77 (3H, d, J = 6.4 Hz).

HRMS (Cl) calcd. for C_{21}H_{36}IO_{4} 479.1658. Found 479.1630.

(1S)-Methyl-(4R)-isopropyl-(5R)-[(12S)-14-propanal]-[6S]-[7-(8S)-(9R)-methyl-9-triethysilox-11-iodo-10-Z-pentene]-8,12-oxido-1-cyclohexene (190).

![Chemical structure of 189 and 190](image)

To a stirred solution of 189 (6.8 mg, 0.014 mmol) and 4 Å molecular sieves (approximately 500 mg) in CH$_2$Cl$_2$ (0.6 mL) was added TPAP (0.8 mg, 0.002 mmol) and NMO (3.0 mg, 0.026 mmol). After 15 min at ambient temperature, the reaction was diluted with Et$_2$O (5 mL), filtered through silica gel (Et$_2$O rinse) and concentrated in vacuo to give crude 190 (6.8 mg, 0.014 mmol, 99%) as a colorless oil.

IR 2927, 1728 cm$^{-1}$.
$^1$H NMR (C₆D₆) δ 9.64 (1H, t, J = 2.0 Hz), 6.22 (1H, d, J = 9.0 Hz), 6.09 (1H, d, J = 9.0 Hz), 5.29 (1H, br s), 4.76 (1H, d, J = 7.3 Hz), 4.69 (1H, d, J = 7.3 Hz), 3.75 - 3.9 (1H, m), 3.39 (1H, d, J = 11.1 Hz), 3.25 (3H, s), 2.2 - 2.3 (1H, m), 2.1 - 2.2 (2H, m), 1.1 - 1.85 (13H, m), 0.79 (3H, d, J = 6.4 Hz), 0.69 (3H, d, J = 6.4 Hz).
HRMS (Cl) calcd. for C₂₁H₃₄IO₄ 477.1502. Found 477.1492.

2-(±)-methyl-2,3-dibromo-propanoate methyl ester (194).

\[
\begin{align*}
\text{Me} & \quad \text{Br}_2, 0°C \\
\text{193} & & \text{Br} & \quad \text{194}
\end{align*}
\]

To a stirred solution of methyl methacrylate (193) (10.0 g, 0.1 mol) at 0°C was added dropwise Br₂ (5.6 mL, 0.11 mol). After 20 min at 0°C, the reaction was complete by $^1$H NMR. The reaction mixture was washed with saturated aqueous Na₂S₂O₃ (5 x 25 mL) and saturated aqueous NaCl (25 mL). The dried (MgSO₄) extract was concentrated in vacuo to give 194 (25 g, 0.097 mol, 97%) as a pale yellow oil.

IR 2953, 1744 cm⁻¹.
$^1$H NMR (CDCl₃) δ 4.21 (1H, d, J = 9.6 Hz), 3.82 (3H, s), 3.71 (1H, d, J = 9.6 Hz), 2.02 (3H, s).
HRMS (Cl) calcd. for C₅H₉Br₂O₂ 258.8969. Found 258.8952.
2-methyl-3-bromo-\(E\)-propenoyl methyl ester (195).

\[
\begin{align*}
\text{Br} & \quad \text{Br} \\
\text{Me} & \quad \text{CO}_2\text{Me} \\
194 & \\
\text{DBU, THF} & \quad 0^\circ \text{C} \\
\text{Br} & \quad \text{Me} \\
\text{CO}_2\text{Me} & \\
195
\end{align*}
\]

To a stirred solution of the 194 (12.9 g, 0.05 mol) in THF (60 mL) at 0°C was added DBU (8.95 mL, 0.06 mol) dropwise. After 30 min, the reaction mixture was warmed to ambient temperature. After 3 h, the reaction was quenched with saturated aqueous NH\(_4\)Cl (30 mL) was added and the mixture extracted with Et\(_2\)O (3 x 75 mL). The combined extracts were washed with H\(_2\)O (3 x 50 mL) and saturated aqueous NaCl (50 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} to give 195 (6.8 g, 0.038 mol, 76%) as a colorless oil.

IR 2952, 1722 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.50 (1H, s), 3.74 (3H, s), 1.98 (3H, s).

HRMS (Cl) calcd. for C\(_5\)H\(_8\)BrO\(_2\) 178.9708. Found 178.9694.
2-methyl-3-bromo-\(E\)-propanol (196).

\[
\begin{align*}
\text{Br} & \quad \text{Me} \\
\text{Me} & \quad \text{CO}_2\text{Me} \\
195 & \quad \overset{\text{DIBAL-H, CH}_2\text{Cl}_2}{\text{\(-78^\circ\text{C to } 0^\circ\text{C}\)}} \\
\text{Br} & \quad \text{Me} \\
\text{Me} & \quad \text{OH} \\
196
\end{align*}
\]

To a stirred solution of 195 (5.4 g, 0.03 mol) in CH\(_2\)Cl\(_2\) (125 mL) at -78°C was added dropwise DIBAL-H (66.00 mL, 0.066 mol, 1.0 M in CH\(_2\)Cl\(_2\)). After 1 h. at -78°C, the reaction mixture was warmed to 0°C over an additional hour. Then, MeOH (3 mL) and saturated aqueous sodium tartrate (300 mL) were sequentially added to the stirred reaction mixture. After 1 h, the two phases were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 125 mL). The combined extracts were washed with H\(_2\)O (3 x 150 mL) and saturated aqueous NaCl (150 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} to give 196 (4.44 g, 0.030 mol, 98%) as a colorless oil.

\[\text{IR} \quad 3320, 2919, 2865, 1635 \text{ cm}^{-1}.\]

\[\text{\(^1H\) NMR (CDCl\(_3\)) } \delta 6.22 (1H, s), 4.07 (3H, s), 1.80 (3H, s), 1.60 (OH, s).\]

\[\text{HRMS (CI) calcd. for C}_4\text{H}_8\text{BrO }150.9758. \text{ Found } 150.9765.\]

315
1-Methyl-(4R)-isopropyl-(5R)-dimethyl acetal-(6R)-[7-9-methyl-9-E-butene-10-ol]-1-cyclohexene (197).

```
57       1. 9-BBN, THF, 45°C
       2. Pd(PPh3)4, NaOH
               THF-H2O, 65°C
       Br          OH
196     197
```

A solution of 9-BBN (0.5 M in THF, 10.5 mL, 5.25 mmol) was added dropwise to 57 (1.12 g, 5.0 mmol). After 20 h at 45°C, the mixture was allowed to cooled to ambient temperature.

To a stirred solution of freshly prepared¹⁷ Pd(PPh3)4 (175 mg, 0.15 mmol) and the vinyl bromide 196 (755 mg, 5.0 mmol) in THF (3 mL) was added the borane adduct prepared above followed by NaOH (5.0 mL, 3 M in H2O) in the dark. The resulting mixture was heated at 65°C for 6 h, cooled to 0°C and treated with H2O2 (1.5 mL, 30% in H2O). After stirring at ambient temperature for 1 h, H2O (25 mL) was added and the mixture was extracted with Et2O (5 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL). The dried (MgSO4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 25% Et2O / petroleum ether, to give starting diene 57 (367 mg, 1.64 mmol, 33%) followed by the desired material 197 (651 mg, 2.20 mmol, 44%) as a yellow oil.
IR 3378, 2955 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.50 (1H, m), 5.29 (1H, br s), 4.28 (1H, d, \(J = 5.8\) Hz), 3.95 (2H, s), 3.31 (6H, s), 2.2 - 2.25 (3H, m), 1.5 - 1.9 (8H, m), 1.64 (3H, s), 0.85 (3H, d, \(J = 7.0\) Hz), 0.77 (3H, d, \(J = 7.0\) Hz).

\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 137.2, 133.7, 127.5, 121.1, 107.1, 69.3, 54.5, 54.3, 40.9, 39.2, 36.4, 28.8, 27.4, 24.5, 23.0, 21.3, 16.8, 13.8.

HRMS (Cl) calcd. for C\(_{18}\)H\(_{33}\)O\(_3\) 297.2417. Found 297.2429.

1-Methyl-(4\(R\))-isopropyl-(5\(R\))-(6\(R\))-[7-(8\(R\))-methoxy-(9\(S\))-methyl-10-butanol]-(11\(R\))-methoxy-9,11-oxido-1-cyclohexene (214) and 1-Methyl-(4\(R\))-isopropyl-(5\(R\))-dimethyl acetals-[6\(R\)]-(7-(9\(R\))-methyl-(8\(R\)),9-epoxy-10-butanol]-1-cyclohexene (207).

\[
\text{197} \xrightarrow{(+)-DIP, TBHP, Ti(Oi-Pr)\(_4\), CH}_2\text{Cl}_2, 3 \text{Å molecular sieves, } -40^\circ\text{C}\] \[\rightarrow \text{214} + \text{207}\]

To a stirred solution of (+)-DIP (56 mg, 0.24 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at -40\(^\circ\)C was added powdered 3 Å molecular sieves (60 mg) followed by Ti(Oi-Pr)\(_4\) (56 mg, 0.20 mmol) and TBHP (0.66 mL, 2.0 mmol, 3 M in isooctane). After 45 min, a solution of 197 (296 mg, 1.0 mmol) in CH\(_2\)Cl\(_2\) (1 mL) was added dropwise. After 24 h, the reaction was allowed to warm to 0\(^\circ\)C and poured into a
stirred solution of ferrous sulphate heptahydrate (1.6 g), tartaric acid (0.5 g) and H₂O (5 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). Then, the combined organic extracts were poured into a stirred, precooled solution of (0°C, 1.0 mL) prepared from NaCl (5 g) and NaOH (30 g) in H₂O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H₂O (5 mL) and the two phases separated. The aqueous layer was extracted with Et₂O (2 x 10 mL), the combined organics washed with saturated aqueous NaCl (20 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et₂O / petroleum ether, to give the acetal 214 (262 mg, 0.840 mmol, 84%) as a colorless oil followed by the epoxide 207 (31 mg, 0.0993 mmol, 10%) as a colorless oil.

**Acetal (214):**

IR 3433, 2928 cm⁻¹.

¹H NMR (CDCl₃) δ 5.42 (1H, br s), 5.05 (1H, s), 4.51 (1H, d, J = 7.9 Hz), 3.65 - 3.75 (2H, m), 3.37 (3H, s), 3.34 (3H, s), 3.19 (1H, dd, J = 8.7, 3.7 Hz), 2.44 (OH, br s), 1.8 - 1.95 (5H, m), 1.73 (3H, s), 1.45 - 1.55 (2H, m), 1.18 (3H, s), 0.86 (3H, d, J = 6.2 Hz), 0.83 (3H, d, J = 6.2 Hz).

¹³C NMR (CDCl₃) δ 133.9, 123.6, 99.7, 79.2, 67.6, 57.9, 55.1, 45.7, 39.2, 34.1, 29.5, 27.1, 24.0, 21.6, 20.8, 20.3, 17.7.

HRMS (Cl) calcd. for C₁₈H₃₃O₄ 313.2379. Found 313.2373.

**Epoxide (207):**

IR 3446, 2958 cm⁻¹.
$^1$H NMR (CDCl$_3$) $\delta$ 5.34 (1H, br s), 4.31 (1H, d, $J = 5.4$ Hz), 3.5 - 3.65 (2H, m), 3.36 (3H, s), 3.34 (3H, s), 3.24 (1H, dd, $J = 4.5$, 7.5 Hz), 2.4 - 2.5 (1H, m), 1.6 - 2.15 (6H, m), 1.68 (3H, d, $J = 1.5$ Hz), 1.45 - 1.6 (1H, m), 1.26 (3H, s), 0.87 (3H, d, $J = 6.8$ Hz), 0.78 (3H, d, $J = 6.8$ Hz).

$^{13}$C NMR (CDCl$_3$) $\delta$ 136.5, 121.9, 107.2, 66.1, 61.5, 60.3, 55.0, 54.8, 41.5, 36.6, 35.6, 29.0, 27.2, 24.2, 22.9, 21.3, 16.3, 14.5.

HRMS (Cl) calcd. for C$_{18}$H$_{33}$O$_4$ 313.2379. Found 313.2372.

1-Methyl-(4R)-isopropyl-(5R)-(6R)-(7-(8S)-methoxy-(9R)-methyl-10-butanol]-(11R)-methoxy-9,11-oxido-1-cyclohexene (208) and 1-Methyl-(4R)-isopropyl-(5R)-dimethyl acetate-(6R)-(7-(9R)-methyl-(8R),9-epoxy-10-butanol]-1-cyclohexene (207).

![Chemical Reaction Diagram]

**Procedure 1:** To a stirred solution of (-)-DIPT (28 mg, 0.12 mmol) and powdered 3 Å molecular sieves (approx. 500 mg) in CH$_2$Cl$_2$ (4 mL) was added sequentially Ti(Oi-Pr)$_4$ (28 mg, 0.10 mmol) and TBHP (0.66 mL, 2.0 mmol, 3 M in isooctane) at -25°C. After 45 min, a solution of 197 (296 mg, 1.00 mmol) in CH$_2$Cl$_2$ (1 mL)
was added via syringe. After 24 h, the reaction was allowed to warm to 0°C and poured into a stirred solution of ferrous sulphate heptahydrate (3.2 g), tartaric acid (1.0 g) and H₂O (10 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). Then, the combined organic extracts were poured into a stirred, precooled solution of (0°C, 5 mL) prepared from NaCl (5 g) and NaOH (30 g) in H₂O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H₂O (5 mL) and the two phases separated. The aqueous layer was extracted with Et₂O (2 x 10 mL), the combined organics washed with saturated aqueous NaCl (20 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et₂O / petroleum ether, to give the acetal 208 (220 mg, 0.705 mmol, 71%, d.s. > 20:1) as a colorless oil.

Procedure 1: To a stirred solution of (-)-DIPT (14 mg, 0.060 mmol) and 2 scoops of powdered 4 Å molecular sieves (approximately 1 g) in CH₂Cl₂ (2 mL) was added sequentially at Ti(Oi-Pr)₄ (12 mg, 12 μL, 0.041 mmol) and TBHP (230 μL, 1.2 mmol, 5 M in isoctane) -20°C. After 30 min, a precooled solution of 197 (100 mg, 0.338 mmol) in CH₂Cl₂ (0.5 mL) was added via cannula. An additional amount CH₂Cl₂ (0.5 mL) was added to rinse the alcohol flask. After 1.75 h at -20°C, the reaction was allowed to warm to 0°C and poured into a stirred solution of ferrous sulphate heptahydrate (1.6 g), tartaric acid (0.5 g) and H₂O (5 mL) at 0°C. After 10 min, the two phases were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). Then, the combined organic extracts were poured into a stirred, precooled solution of (0°C, 10 mL) prepared from NaCl (5
g) and NaOH (30 g) in H₂O (90 mL). The mixture was stirred at 0°C for 1 h, diluted with H₂O (5 mL) and the two phases separated. The aqueous layer was extracted with Et₂O (2 x 10 mL), the combined organics washed with saturated aqueous NaCl (20 mL). The dried (Na₂SO₄) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 40\% Et₂O / petroleum ether, to give the acetal 208 (38 mg, 0.12 mmol, 36\%, d.s. > 20:1) as a colorless oil followed by the epoxide 207 (67 mg, 0.21 mmol, 64\%, d.s. > 20:1) as a colorless oil.

**Acetal 208:**

IR 3465, 2932 cm⁻¹.

¹H NMR (C₆D₆) δ 5.35 (1H, br s), 4.45 (1H, d, J = 7.1 Hz), 3.6 - 3.8 (2H, m), 3.51 (1H, dd, J = 3.0, 11.6 Hz), 3.09 (3H, s), 3.07 (3H, s), 2.41 (OH, br s), 2.21 (1H, t, J = 7.7 Hz), 2.0 - 2.1 (1H, m), 1.2 - 2.0 (8H, m), 1.08 (3H, s), 0.95 - 1.05 (1H, m), 0.96 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz).

HRMS (Cl) calcd. for C₁₈H₃₃O₄ 313.2379. Found 313.2388.

**Epoxide 207:**

IR 3446, 2958 cm⁻¹.

¹H NMR (CDCl₃) δ 5.34 (1H, br s), 4.31 (1H, d, J = 5.4 Hz), 3.5 - 3.65 (2H, m), 3.36 (3H, s), 3.34 (3H, s), 3.24 (1H, dd, J = 4.5, 7.5 Hz), 2.4 - 2.5 (1H, m), 1.6 - 2.15 (6H, m), 1.68 (3H, d, J = 1.5 Hz), 1.45 - 1.6 (1H, m), 1.26 (3H, s), 0.87 (3H, d, J = 6.9 Hz), 0.78 (3H, d, J = 6.9 Hz).
\[^{13}\text{C}\ \text{NMR (CDCl}_3\text{)}\ \delta\ 136.5, 121.9, 107.2, 66.1, 61.5, 60.3, 55.0, 54.8, 41.5, 36.6, 35.6, 29.0, 27.2, 24.2, 22.9, 21.3, 16.3, 14.5.\]

HRMS (Cl) calcd. for C\(_{18}H_{33}O_4\) 313.2379. Found 313.2372.

1-Methyl-(4\(R\))-isopropyl-(5\(R\))-(6\(R\))-[7-(8\(S\))-methoxy-(9\(R\))-methyl-10-[4'-nitrobenzoyloxy]-butane]-(11\(R\))-methoxy-9,11-oxido-1-cyclohexene (##).

To a stirred solution of 208 (62 mg, 0.19 mmol) in CH\(_2\)Cl\(_2\) (2 mL) was added Et\(_3\)N (25 mg, 35 \(\mu\)L, 0.25 mmol) followed by PNBCl (37 mg, 0.20 mmol). After 24 h at ambient temperature, the reaction directly subjected to PLC, eluting with 20\% Et\(_2\)O/petroleum ether, to give 210 (78 mg, 0.17 mmol, 89\%) as an off-white solid. Crystals suitable for x-ray crystallography were obtained by recrystallization in Et\(_2\)O. X-ray coordinates for 210 can be found in Appendix 4.

IR 2924, 2853, 1722 cm\(^{-1}\).
$^1$H NMR (C$_6$D$_6$) δ 7.85 (2H, m), 7.63 (2H, m), 5.36 (1H, br s), 4.4 - 4.65 (3H, m),
3.20 (3H, s), 3.15 - 3.25 (1H, m), 3.02 (3H, s), 2.25 (1H, t, $J = 7.7$ Hz), 1.4 - 2.1
(11H, m), 1.24 (3H, s), 0.96 (3H, d, $J = 6.8$ Hz), 0.91 (3H, d, $J = 6.8$ Hz).
HRMS (Cl) calcd. for C$_{25}$H$_{36}$NO$_7$ 462.2492. Found 462.2478.

2-Methyl-3-Z-iodo-propenol (222).

\[
\begin{align*}
\text{MeMgBr, Et}_2\text{O, CuI} & \quad 0^\circ\text{C to 25$^\circ$C} \\
\text{I}_2, 0^\circ\text{C to 25$^\circ$C} & \quad 221 \quad \text{222}
\end{align*}
\]

To a stirred solution of CuI (2.3 g, 0.012 mol) in Et$_2$O (120 mL) with was
added MeMgBr (100 mL, 0.30 mol, 3.0 M in Et$_2$O) at -15°C. After 20 min,
propargyl alcohol (221) (6.7 g, 7.0 mL, 0.12 mol) via syringe pump over 30 min
at -15°C. The reaction was allowed to warm to ambient temperature over 2 h.
After 16 h at ambient temperature, the reaction recooled to 0°C, and I$_2$ (39 g,
0.15 mol) was added. After 15 min, the reaction was warmed to ambient
temperature for 50 min, carefully quenched with HCl (300 mL, 10% in H$_2$O) and
extracted with Et$_2$O (4 x 300 mL). The dried (MgSO$_4$) extract was concentrated
in vacuo and purified by chromatography over silica gel, eluting with 50% Et$_2$O /
petroleum ether, to give 222 (12.2 g, 0.062 mmol, 52%) as a yellow oil.
IR 3334, 2913 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.96 (1H, s), 4.23 (2H, s), 1.96 (3H, s), 1.59 (OH, br s).

HRMS (Cl) calcd. for \(\text{C}_4\text{H}_7\text{IO}\) 197.9542. Found 197.9538.

1-Methyl-(4R)-isopropyl-(5R)-dimethyl acetal-(6R)-[9-methyl-9-Z-butene-10-ol]-1-cyclohexene (223).

To 57 (227 mg, 1.01 mmol) was added 9-BBN (2.4 mL, 1.2 mmol, 0.5 M in THF) and heated in a sealed tube to 50°C. After 18 h, the reaction was allowed to cool to ambient temperature. Then, NaOH (1.0 mL, 3 mmol, 3 M in H\(_2\)O) was added followed by a solution of the iodide 222 (410 mg, 2.7 mmol) in THF (800 \(\mu\)L) via cannula then freshly prepared Pd(PPh\(_3\))\(_4\) (170 mg, 0.147 mmol). The mixture was heated to 65°C in a sealed tube in the dark. After 2 days, the reaction was allowed to cool to ambient temperature, diluted with saturated aqueous NaCl (20 mL) and extracted with Et\(_2\)O (4 x 25 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting
with 30% Et<sub>2</sub>O / petroleum ether, to give 223 (105 mg, 0.355 mmol, 35%) as a yellow oil.

IR 3418, 2957 cm<sup>-1</sup>.  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 5.3 - 5.4 (2H, m), 4.15 (1H, d, J = 5.6 Hz), 4.06 (1H, d, J = 12.0 Hz), 3.95 (1H, d, J = 12.0 Hz), 3.37 (3H, s), 3.34 (3H, s), 2.4 - 2.5 (1H, m), 2.1 - 2.3 (2H, m), 1.5 - 2.1 (5H, m), 0.86 (3H, d, J = 6.6 Hz), 0.77 (3H, d, J = 6.6 Hz).

HRMS (Cl) calcd. for C<sub>18</sub>H<sub>31</sub>O<sub>3</sub> 295.2273. Found 295.2267.

1-Methyl-<i>(4R)</i>-isopropyl-<i>(5R)</i>-<i>(6R)</i>-[7-(8S)-methoxy-(9S)-methyl-10-butanol]-<i>(11R)</i>-methoxy-9,11-oxido-1-cyclohexene (225).

![Chemical structure of 223 and 225 with reaction conditions]

To a stirred solution of (+)-DET (67 mg, 0.325 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) with one scoop of powdered 4 Å molecular sieves (approx 500 mg) at -20°C was added Ti(O<sub>i</sub>-Pr)<sub>4</sub> (72.2 mg, 75 µL, 0.254 mmol) and TBHP (360 µL, 1.8 mmol, 5 M in isooctane). After 30 min, a solution of 223 (74 mg, 0.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub>
(160 µL) was added dropwise via cannula. An additional amount of CH₂Cl₂ (2 x 80 µL) was added to rinse the allylic alcohol flask. The reaction was then allowed to warm to -8°C. After 19 h, the reaction was warmed to 0°C poured into a stirred solution of ferrous sulphate heptahydrate (3.2 g), tartaric acid (1.0 g) and H₂O (10 mL) at 0°C. After 20 min, the two phases were separated and the aqueous layer was extracted with Et₂O (4 x 20 mL). Then, the combined organic extracts were poured into a stirred, precooled solution (0°C) of NaCl (5 g) and NaOH (30 g) in H₂O (100 mL) and stirred at 0°C for 1.5 h. Then, the two phases separated and the aqueous layer was extracted with Et₂O (4 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40% Et₂O / petroleum ether (2 - 4% Et₃N), to give the acetal 225 (49 mg, 0.16 mmol, 63%) as a colorless oil.

[α]D²³ +31° (c 0.97).

IR 3450, 2928 cm⁻¹.

¹H NMR (C₆D₆) δ 5.33 (1H, br s), 4.82 (1H, d, J = 5.7 Hz), 3.91 (1H, d, J = 11.6 Hz), 3.76 (1H, d, J = 11.6 Hz), 3.3 - 3.4 (1H, m), 3.22 (3H, s), 2.93 (3H, s), 2.3 - 2.4 (2H, m), 1.7 - 2.0 (5H, m), 1.63 (3H, s), 1.49 (3H, s), 1.25 - 1.35 (1H, m), 0.91 (3H, d, J = 6.8 Hz), 0.84 (3H, d, J = 6.8 Hz).

¹³C NMR (C₆D₆) δ 136.8, 121.5, 103.2, 88.6, 78.5, 66.8, 57.3, 56.0, 45.2, 37.2, 36.6, 31.0, 29.9, 27.0, 25.2, 24.6, 21.9, 15.9.

HRMS (Cl) calcd. for C₁₈H₃₂O₄ 313.2379. Found 313.2376.
1-Methyl-(4R)-isopropyl-(5R)-(6R)-(7-(8S)-methoxy-(9R)-methyl-10-butanal]- (11R)-methoxy-9,11-oxido-1-cyclohexene (235).

To a stirred solution of 225 (415 mg, 1.33 mmol) in CH₂Cl₂ (21 mL) was added Dess-Martin periodinane¹⁰ (842 mg, 1.97 mmol) at ambient temperature. After 30 min, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) followed by saturated aqueous Na₂S₂O₃ (10 mL) and stirred until the solution was clear. The layers were allowed to separate and the aqueous layer was extracted with Et₂O (4 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo to give crude 235 as a colorless oil.

IR 2931, 1731 cm⁻¹.

¹H NMR (C₆D₆) δ 9.80 (1H, br s), 5.30 (1H, br s), 5.06 (1H, d, J = 5.7 Hz), 3.3 - 3.4 (1H), 3.31 (3H, s), 2.93 (3H, s), 2.4 - 2.5 (1H, m), 1.7 - 2.1 (6H, m), 1.61 (3H, s), 1.37 (3H, s), 1.25 - 1.35 (1H, m), 0.94 (3H, d, J = 6.8 Hz), 0.85 (3H, d, J = 6.8 Hz).
$^{13}$C NMR (CD$_3$D$_6$) δ 201.2, 135.9, 103.7, 85.8, 57.3, 56.4, 36.4, 45.7, 36.6, 36.3, 30.4, 30.2, 26.9, 24.7, 22.2, 22.0, 21.9, 16.0.

HRMS (Cl) calcd. for C$_{18}$H$_{31}$O$_4$ 311.2222. Found 311.2214.

1-Methyl-(4R)-isopropyl-(5R)-(6R)-(7-(8S)-methoxy-(9S)-methyl-11-phenylsulfonyl-10-E-pentene]-(12R)-methoxy-9,12-oxido-1-cyclohexene (236).

\[
\text{PhSO}_2\text{Me, } n\text{-BuLi, CIPO(OEt)$_2$, THF} \rightarrow \text{237}
\]

To a stirred solution of PhSO$_2$Me (282 mg, 1.81 mmol) in THF (16 mL) was added $n$-BuLi (1.59 mL, 3.98 mmol, 2.5 M in hexanes) at 0°C. After 30 min, CIPO(OEt)$_2$ (310 mg, 260 μL, 1.80 mmol) was added to the yellow slurry. After stirring at 0°C for 30 min, the reaction was cooled to -78°C and a solution of crude 235 (412 mg, 1.33 mmol) in THF (4.2 mL) was added via cannula. An additional amount of CH$_2$Cl$_2$ (2 x 1 mL) was added to rinse the aldehyde flask. After 10 min, the reaction was allowed to warm to 0°C for 1 h followed by ambient temperature for 1.5 h. Then, the reaction was quenched with saturated aqueous NH$_4$Cl (100 mL) and extracted with Et$_2$O (4 x 150 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over
silica gel, eluting with 15 - 30% Et₂O / petroleum ether, to give 237 (377 mg, 0.842 mmol, 63%) as a colorless oil.

[α]D²³ +34° (c 0.88).

IR 2931 cm⁻¹.

¹H NMR (CDCl₃) δ 7.9 - 8.0 (2H, m), 7.6 (1H, d, J = 15.1 Hz), 6.8 - 6.9 (4H, m), 5.21 (1H, br s), 4.65 (1H, d, J = 3.4 Hz), 3.60 (1H, d, J = 10.8 Hz), 3.12 (3H, s), 3.01 (3H, s), 2.2 - 2.3 (1H, m), 1.8 - 1.9 (2H, m), 1.2 - 1.8 (11H, m), 0.69 (3H, d, J = 6.8 Hz), 0.60 (3H, d, J = 6.8 Hz).

HRMS (Cl) calcd. for C₂₅H₃₇O₅S 449.2362. Found 449.2359.

1-Methyl-(4R)-isopropyl-(5R)-(6R)-(7-(8S)-methoxy-(9S)-methyl-11-phenylsulfonyl-pentane)-(12R)-methoxy-9,12-oxido-1-cyclohexene (##).

![Chemical Structure](image)

Procedure 1: To a stirred solution of 237 (42 mg, 0.094 mmol) in PhH (0.5 mL) was added [(Ph₃P)CuH]₆ (80 mg, 0.041 mmol) and heated to reflux. An additional amount of [(Ph₃P)CuH]₆ (90 mg, 0.046 mmol) was added during the
course of the reaction in which the solution was allowed to concentrate. After 3.5 h, the reaction slurry was allowed to cool to ambient temperature, diluted with Et₂O, filtered through silica gel (Et₂O rinse), concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give 229 (34 mg, 0.076, 80%) as a colorless oil.

Procedure 2: To a stirred solution of 237 (26 mg, 0.058 mmol) in MeCN (0.25 mL) was added NaBH₄ (52 mg, 1.4 mmol). After 2 h at ambient temperature, the reaction was heated to reflux for 8 h. The solution was allowed to concentrate during the course of the reaction. The reaction was quenched with H₂O (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give 229 (16 mg, 0.36 mmol, 61%) as a colorless oil.

\([\alpha]_D^{23} +15^\circ \text{ (c 2.86).}\]

IR 2928 cm⁻¹.

\(^1\text{H} \text{NMR (C}_6\text{D}_6) \delta 7.8 - 7.9 \text{ (2H, m), 6.8 - 6.9} \text{ (3H, m), 5.28} \text{ (1H, br s), 4.71} \text{ (1H, d, J = 4.5 Hz), 3.40} \text{ (1H, dt, J = 4.0, 13.1 Hz), 3.1 - 3.3} \text{ (5H, m), 2.95} \text{ (3H, s), 2.3 - 2.45} \text{ (1H, m), 2.15} \text{ (1H, dt, J = 4.9, 13.1 Hz), 1.5 - 2.0} \text{ (10H, m), 1.3 - 1.4} \text{ (1H, m), 1.13} \text{ (3H, s), 0.95} \text{ (3H, d, J = 6.9 Hz), 0.74} \text{ (3H, d, J = 6.9 Hz).}\]

\(^{13}\text{C} \text{NMR (C}_6\text{D}_6) \delta 140.6, 135.9, 133.0, 129.1, 121.5, 103.4, 86.9, 78.3, 57.2, 56.5, 52.6, 44.9, 36.8, 35.6, 30.2, 29.4, 28.7, 26.6, 25.2, 24.5, 22.0, 21.7, 15.6.\]

1-Methyl-(4R)-isopropyl-(5R)-(6R)-(7-(8S)-methoxy-(9S)-methyl-11-phenylsulfonyl-pentane)-(12S)-methoxy-9,12-oxido-1-cyclohexene (239).

To a stirred solution of TMSCl (30 mg, 35 μL, 0.276 mmol) in MeCN (0.3 mL) was added NaI (50.4 mg, 0.336 mmol) at 0°C. After 30 min, 2-methyl-2-butene (133 mg, 200 μL, 1.89 mmol) was added and stirred at 0°C. After 10 min, a solution of 229 (24.5 mg, 0.054 mmol) in MeCN (0.3 mL) was added via cannula. An additional amount of MeCN (2 × 100 μL) was added to rinse the acetal flask. After 10 min at 0°C, the reaction was quenched with DBU (111 mg, 100 μL, 0.728 mmol). After 1 h, the reaction was warmed to ambient temperature for 15 min, quenched with saturated aqueous NH₄Cl (10 mL), extracted with Et₂O (4 × 15 mL). The dried (MgSO₄) extract was diluted with Et₃N (2 mL), concentrated in vacuo and purified by PLC, eluting with 50% Et₂O / petroleum ether, to give 239 (15.6 mg, 0.347 mmol, 64%) as a colorless oil.

IR 2958 cm⁻¹.

¹H NMR (CDCl₃) δ 7.8 - 7.9 (2H, m), 6.8 - 6.9 (3H, m), 5.30 (1H, br s), 3.98 (1H, s), 3.4 - 3.6 (2H, m), 3.2 - 3.3 (1H, m), 2.94 (3H, s), 2.91 (3H, d), 2.5 - 2.6 (3H,
m), 2.19 (1H, d, J = 7.4 Hz), 1.5 - 1.7 (5H, m), 1.61 (3H, s), 1.4 - 1.6 (1H, m), 0.99 (3H, d, J = 6.8 Hz), 0.95 (3H, d, J = 6.8 Hz), 0.93 (3H, s).

HRMS (Cl) calcd. for C_{25}H_{39}O_{3}S 451.2518. Found 451.2507.

(1S)-Iodo-1-methyl-(4R)-isopropyl-(5R)-(6R)(7-(8S)-(9S)-methyl-11-phenylsulfonylel-pentane]-8,9,(12R)-bis-oxiode-cyclohexane (238).

To a stirred solution of TMSCl (20.5 mg, 24 µL, 0.189 mmol) in MeCN (200 µL) was added NaI (33 mg, 0.22 mmol) at 0°C. After 20 min, 1-pentene (25.6 mg, 40 µL, 0.36 mmol) was added and stirred an additional 5 min. Then, a solution of 228 (17 mg, 0.038 mmol) in MeCN (200 µL) was added via cannula. An additional amount of MeCN (2 x 100 µL) was added to rinse the acetal flask. After 1 h at 0°C, the reaction was quenched with saturated aqueous NaHCO₃ (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give 238 (5.0 mg, 0.0094 mmol, 25%) as
a pale yellow oil. Compound 238 was found to be quite labile, especially on silica gel.

IR 2957 cm\(^{-1}\).

\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta 7.8 - 7.9 \) (2H, m), \(6.8 - 6.9 \) (3H, m), \(5.29 \) (1H, d, \(J = 1.6 \) Hz), \(3.2 - 3.4 \) (2H, m), \(3.17 \) (1H, d, \(J = 2.6 \) Hz), \(3.02 \) (1H, dt, \(J = 4.7, 13.1 \) Hz), \(2.1 - 2.3 \) (3H, m), \(1.84 \) (3H, s), \(1.4 - 1.8 \) (7H, m), \(1.0 - 1.2 \) (1H, m), \(0.8 - 0.9 \) (1H, m), \(0.81 \) (3H, d, \(J = 6.8 \) Hz), \(0.78 \) (3H, s), \(0.72 \) (3H, d, \(J = 6.8 \) Hz).

HRMS (CI) calcd. for C\(_{23}\)H\(_{34}\)IO\(_4\)S 533.1223. Found 533.1214.
1-Methyl-(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-11-phenylsulfonylethylpentane]-8,9,(12R)-bis-oxido-1-cyclohexene (230) and 1-Methyl-(4R)-isopropyl-6-(7-(8S)-(9S)-methyl-11-phenylsulfonylethylpentanol]-8,12-oxido-5,6-cyclohexadiene (240) and 1-Methyl-(4R)-isopropyl-6-(7-(8S)-(9S)-methyl-11-phenylsulfonylethylpentanol]-12-hydroxy-8,12-oxido-6-cyclohexene (241).

To a stirred solution of PTSA (41.7 mg, 0.22 mmol) in MeCN (0.4 mL) was added NaI (67 mg, 0.45 mmol) at ambient temperature. After 10 min, the slurry was cooled to 0°C and a solution of 229 (20.5 mg, 0.0455 mmol) in MeCN (0.2 mL) was added via cannula. An additional amount of MeCN (2 x 100 μL)
was added to rinse the acetal flask. After 1 h, the reaction was quenched with DBU (255 mg, 250 µL, 1.67 mmol). After 15 min at 0°C, the reaction was allowed to warm to ambient temperature for 1 h, quenched with saturated aqueous NH₄Cl (10 mL) and extracted with Et₂O (4 x 15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et₂O / petroleum ether, to give sequentially the desired compound 230 (8.9 mg, 0.022 mmol, 48%) as a colorless oil, the enol ether 240 (4.1 mg, 0.010 mmol, 22%) as a colorless oil and the lactol 241 (3.0 mg, 0.0071 mmol, 16%) as a colorless oil.

**Ketal 230:**

IR 2958 cm⁻¹.

¹H NMR (C₅D₅) δ 7.8 - 7.9 (2H, m), 6.8 - 6.9 (3H, m), 5.37 (1H, d, J = 1.3 Hz), 5.34 (1H, br s), 3.3 - 3.5 (2H, m), 3.09 (2H, dt, J = 5.0, 13.0 Hz), 2.3 - 2.5 (1H, m), 2.23 (1H, dt, J = 4.1, 13.0 Hz), 2.0 - 2.1 (1H, m), 1.6 - 1.9 (3H, m), 1.1 - 1.6 (6H, m), 0.93 (3H, s), 0.79 (3H, d, J = 6.8 Hz), 0.54 (3H, d, J = 6.8 Hz).

HRMS (Cl) calcd. for C₂₃H₃₃O₄S 405.2030. Found 405.2101.

**Enol ether 240:**

IR 3499, 2926 cm⁻¹.

¹H NMR δ (C₆D₆) 7.75 - 7.9 (2H, m), 6.8 - 7.0 (3H, m), 6.04 (1H, s), 3.98 (1H, dd, J = 2.3, 12.3 Hz), 3.1 - 3.35 (3H, m), 2.38 (1H, dd, J = 2.3, 12.3 Hz), 1.1 - 2.3 (10H, m), 0.9 - 1.1 (2H, m), 0.86 (3H, d, J = 6.3 Hz), 0.85 (3H, d, J = 6.3 Hz), 0.78 (3H, s).
HRMS (Cl) calcd. for C_{23}H_{33}O_{4} 405.2100. Found 405.2103.

**Lactol 241:**

IR 3485, 2925 cm\(^{-1}\).

\(^1H\) NMR (CD\(_6\)) \(\delta\) 7.8 - 7.9 (2H, m), 6.8 - 6.95 (3H, m), 5.00 (1H, s), 3.7 - 3.85 (1H, m), 3.4 - 3.1 (2H, m), 2.37 (1H, dt, J = 3.7, 13.5 Hz), 1.7 - 1.9 (2H, m), 1.65 - 1.7 (1H, m), 1.4 - 1.6 (2H, m), 0.8 - 1.4 (10H, m), 0.78 (3H, d, J = 6.5 Hz), 0.73 (3H, s), 0.70 (3H, d, J = 6.5 Hz).

HRMS (Cl) calcd. for C\(_{23}\)H\(_{35}\)O\(_5\)S 423.2205. Found 423.2198.

**1-Methyl(4R)-isopropyl-(5R)-(6S)-(7-(8S)-(9S)-methyl-11-phenylsulfonyl-9-pentanol)-(12S)-allyl-8,12-oxido-1-cyclohexene (231)**

\[ \begin{array}{c}
\text{230} \\
\text{231}
\end{array} \]

To a stirred solution of 230 (27.0 mg, 0.0668 mmol) in CH\(_2\)Cl\(_2\) (1.6 mL) with allyltrimethylsilane (165) (79.1 mg, 110 \(\mu\)L, 0.692 mmol) was added TiCl\(_4\) (121 mg, 70 \(\mu\)L, 0.638 mmol) at -78°C. After 10 min, the reaction was briefly (1 min) removed from the cooling bath, quenched with saturated aqueous NaHCO\(_3\)
(10 mL) and extracted with Et$_2$O (4 x 15 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30 - 50% Et$_2$O / petroleum ether, to give 231 (19.7 mg, 0.440 mmol, 66%) as a colorless oil.

IR 3521, 2927 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) $\delta$ 7.8 - 7.9 (2H, m), 6.8 - 7.0 (3H, m), 5.7 - 5.9 (1H, m), 5.24 (1H, br s), 5.02 (1H, s), 4.98 (1H, d, J = 8.1 Hz), 3.2 - 3.5 (3H, m), 2.78 (1H, d, J = 11.3 Hz), 2.37 (1H, bs), 2.0 - 2.2 (3H, m), 1.5 - 2.0 (4H, m), 1.49 (3H, s), 1.0 - 1.5 (5H, m), 0.88 (3H, s), 0.84 (3H, d, J = 6.5 Hz), 0.77 (3H, d, J = 6.5 Hz).

HRMS (Cl) calcd. for C$_{26}$H$_{39}$O$_4$S 447.2569. Found 447.2567.
1-Methyl-(4R)-isopropyl-(5R)-[(12S)-14,15-butandiol]-\((6S)\)-(7-(8S)-(9S)-methyl-11-phenylsulfonyl-9-pentanol]- 8,12-oxido-1-cyclohexene (242)

\[
\text{AD mix } \beta^*: \quad K_3\text{Fe(CN)}_6 (6.996 \text{ g, 0.0215 mol}), \quad K_2\text{CO}_3 (2.936 \text{ g, 0.0212 mol}), \\
(DHQD)_2\text{PHAL} (152 \text{ mg, 0.195 mmol}), \quad K_2\text{OsO}_4\cdot 2\text{H}_2\text{O} (25.5 \text{ mg, 0.0692 mmol})
\]

were vigorously stirred until a homogeneous powder was observed.

To a stirred solution of 231 (11.5 \text{ mg, 0.0258 mmol}) in \(\text{t-BuOH} (350 \mu\text{L})\) and \(\text{H}_2\text{O} (350 \mu\text{L})\) was added AD mix \(\beta^*\) (27 \text{ mg}). After 2 h at ambient temperature, the reaction was diluted with \(\text{H}_2\text{O} (0.5 \text{ mL})\) and quenched with \(\text{Na}_2\text{SO}_3 (500 \text{ mg})\). After 10 min, the reaction was further diluted with saturated aqueous \(\text{NaCl} (10 \text{ mL})\) and extracted with \(\text{EtOAc} (4 \times 15 \text{ mL})\). The dried (\(\text{Na}_2\text{SO}_4\)) extract was concentrated \textit{in vacuo} and purified by chromatography over a small plug of silica gel, eluting with 70\% \(\text{Et}_2\text{O} / \text{petroleum ether to EtOAc}\), to give 242 (9.0 \text{ mg, 0.19 mmol, 73\%}) as a colorless oil. \(^1\text{H}\) NMR of the crude reaction mixture showed an approximately 3 to 1 mixture at C-4 which was inseperable by chromatography.
IR 3437, 2927 cm$^{-1}$.

$^1$H NMR (C$_6$D$_6$) $\delta$ 7.8 - 7.95 (2H, m), 6.9 - 7.0 (3H, m), 5.31 (1H, br s), 4.0 - 4.2 (1H, m), 3.94 (1H, t, $J = 6.3$ Hz, minor), 3.80 (1H, t, 8.3 Hz, major), 3.1 - 3.6 (4H, m), 2.92 (1H, d, $J = 11.1$ Hz), 2.79 (1H, m, minor), 2.05 - 2.3 (3H, m), 1.85 - 2.0 (3H, m), 1.55 - 1.8 (5H, m), 1.52 (3H, s), 1.1 - 1.3 (3H, m), 0.86 (3H, s), 0.83 (3H, d, $J = 6.4$ Hz), 0.79 (3H, d, $J = 6.4$ Hz).

HRMS (CI) calcd. for C$_{26}$H$_{41}$O$_6$S 481.2624. Found 481.2613.
1-Methyl-(4R)-isopropyl-(5R)-[(12S)-14-propanoic acid]-(6S)-[7-(8S)-(9S)-methyl-11-phenylsulfonyl-9-pentanol]-8,12-oxido-1-cyclohexene (232).

![Chemical Structure](image)

To a stirred solution of 242 (11.0 mg, 0.0229 mmol) in THF (0.3 mL) and H$_2$O (0.3 mL) was added NaIO$_4$ (8.5 mg, 0.040 mmol) at ambient temperature. An additional portion of NaIO$_4$ (3.0 mg, 0.014 mmol) was added during the course of the reaction. After 40 min, the excess NaIO$_4$ was quenched with ethylene glycol (10 µL).

To the stirred reaction mixture was added t-BuOH (0.5 mL) followed sequentially by NaH$_2$PO$_4$ (1.0 mL, 0.39 mmol, 0.39 M in H$_2$O), 2-methyl-2-butene (66 mg, 100 µL, 0.94 mmol) and NaClO$_2$ (0.5 mL, 0.16 mmol, 0.32 M in H$_2$O). After 40 min at ambient temperature, the reaction was diluted with saturated aqueous NaCl (10 mL) and extracted with EtOAc (4 x 15 mL). The dried (Na$_2$SO$_4$) extract was concentrated in vacuo and purified by PLC, eluting with 80% EtOAc / petroleum ether to EtOAc, to give 232 (6.4 mg, 0.014 mmol, 60%) as a colorless oil.

340
IR 2500 - 3500, 3437, 2927, 1728 cm\(^{-1}\).

\(^1\)H NMR (C\(_6\)D\(_6\)) \(\delta\) 7.9 - 8.0 (2H, m), 6.9 - 7.1 (3H, m), 5.21 (1H, br s), 3.8 - 4.0 (1H, m), 3.1 - 3.3 (3H, m), 2.81 (1H, d, \(J = 11.5\) Hz), 2.42 (1H, dd, \(J = 2.7, 14.5\) Hz), 2.1 - 2.3 (3H, m), 1.94 (1H, dt, \(J = 5.2, 12.6\) Hz), 1.76 (1H, br s), 1.0 - 1.7 (9H, m), 0.80 (3H, s), 0.79 (3H, d, \(J = 6.5\) Hz), 0.71 (3H, d, \(J = 6.5\) Hz).


3 *Enol Ether 259*: To a stirred solution of cyclohexanone (41.0 mL, 442 mmol) and CH(OMe)_3 (52.0 mL, 475 mmol) at 0°C was added portion wise PTSA (0.74 g, 3.90 mmol). The reaction was warmed slowly to ambient temperature. After 48 h, the reaction mixture was distilled (135 - 140°C, 760 mm Hg) and redistilled (140 - 144°C, 760 mm Hg) to yield 259 (15 g, 134 mmol, 30%) as a colorless liquid.

4 Ratio determined by ^1^H NMR of crude reaction mixture.


6 The distilled product often had a pale orange color; however, this color appears to have no effect on subsequent transformations.

7 Jones reagent was prepared from CrO_3 (87.5 g, 0.875 mol) in concentrated H_2SO_4 (60 mL) and H_2O (190 mL).


9 The diasteromers 99a and 99b could be seperated by PLC of the mixture, eluting with 15 % Et_2O / petroleum ether.


12 This reagent was kindly supplied by Professor Jack C. Gilbert's laboratory.

13 *Weinreb amide 128 Preparation:* To a stirred solution of HN(Me)OMe-HCl (300 mg, 3.08 mmol) in CH2Cl2 (10 mL) was added propionyl chloride (277 mg, 0.26 mL, 3.0 mmol) at 0°C. After 10 min, py (538 mg, 0.55 mL, 6.8 mmol) was added. After 30 min at 0°C, the reaction was warmed to ambient temperature. After 16 h, the reaction mixture was diluted with Et2O (25 mL), extracted with CuSO4 (25 mL, 1 M in H2O) and saturated aqueous NaCl (25 mL). The dried (Na2SO4) extracted was concentrated *in vacuo* and purified by Kügelrohr distillation (oven temperature 175 °C, 760 mm Hg) to yield 128 (0.17 g, 0.15 mmol, 48%) as a colorless liquid.


Appendices
Appendix 1

X-ray Experimental for C_{21}H_{29}NO_{6} (74):

Crystals grew in clusters of colorless needles from petroleum ether. The data crystal was cut from a cluster of crystals and had approximate dimensions; 0.17 x 0.31 x 0.80 mm. The data were collected at 193 K on a Siemens P3 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with MoKα radiation (λ = 0.71073 Å). Details of crystal data, data collection and structure refinement are listed in Supplementary Table 1. Four reflections (1,3,1; 2,-5,0; -1,-2,-4; -1,3,-1) were remeasured every 96 reflections to monitor instrument and crystal stability. A smoothed curve of the intensities of these check reflections was used to scale the data. The scaling factor ranged from 0.936 to 1.00. The check reflections showed a gradual decrease in intensity as data collection progressed. The data were corrected for Lp effects but not absorption. Data reduction and decay correction were performed using the SHELXTL/PC software package.¹ The structure was solved by direct methods and refined by full-matrix least-squares¹ on F^2 with anisotropic thermal parameters for the non-H atoms. The hydrogen atoms bound to carbon were calculated in idealized positions (C-H 0.96 Å) with isotropic temperature factors set to 1.2xUeq of the attached atom. The function, \[ \Sigma w(|F_o|^2 - |F_c|^2)^2 \], was minimized, where \( w = 1/[(\sigma(F_o))^2 + (0.0343^*P)^2] \) and \( P = (|F_o|^2 + 2|F_c|^2)/3 \). The absolute configuration was determined by internal comparison. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1990).² Other computer programs used in this work are listed elsewhere.³ All figures were generated.
using SHELXTL/PC.\textsuperscript{1} Tables of positional and thermal parameters, bond lengths, angles and torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary material.

**Supplementary Table 1. Crystallographic Data\textsuperscript{a} for C\textsubscript{21}H\textsubscript{29}NO\textsubscript{6}.**

<table>
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<th>Formula</th>
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<td>c, Å</td>
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<td>V, Å\textsuperscript{3}</td>
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<td>R\text{int} (F\textsuperscript{2})</td>
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\textsuperscript{a}Data are reported to 3 significant figures.
### Supplementary Table 1. Crystallographic Data (continued).

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<tr>
<th>Parameter</th>
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<td>Transmission factor range</td>
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<td>( R_w(F^2) )</td>
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<tr>
<td>( R(F) )</td>
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<td>Goodness of fit, ( S^d )</td>
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<td>Parameters</td>
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<td>Max (</td>
<td>\Delta/\sigma</td>
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<tr>
<td>Min, max peaks ((e^{-}/\text{Å}^3))</td>
<td>-0.21, 0.17</td>
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</table>

Data were collected on a Siemens P3 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using graphite monochromatized Mo K\( \alpha \) radiation \((\lambda = 0.71073\text{Å})\). Data were collected using \( \omega \) scans with a scan range of \( 1^\circ \) in \( \omega \). Lattice parameters were obtained from the least-squares refinement of 28 reflections with \( 17.7^\circ < 2\theta < 18.2^\circ \).

\[ R_w = \left\{ \sum w(|F_o|^2 - |F_c|^2)^2/\sum w(|F_o|^4) \right\}^{1/2} \]

where the weight, \( w \), is defined as follows:

\[ w = 1/(\sigma^2(|F_o|^2) + (0.0343*P)^2); P = [1/3*(\text{Maximum of (0 or }|F_o|^2) + 2/3*|F_c|^2)]. \]

* The conventional \( R \) index based on \( F \) where the 1303 observed reflections have \( F_o > 4(\sigma(F_o)) \).

\[ S = \left\{ \sum w(|F_o|^2 - |F_c|^2)^2/(n - p) \right\}^{1/2}, \text{ where } n \text{ is the number of reflections and } p \text{ is the number of refined parameters.} \]
Supplementary Table 2. Fractional coordinates and equivalent isotropic thermal parameters (Å²) for the non-hydrogen atoms of C$_{21}$H$_{29}$NO$_{6}$.

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<th>Atom</th>
<th>x</th>
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<td>0.1804(9)</td>
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<td>0.4720(3)</td>
<td>0.084(3)</td>
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<tr>
<td>O24</td>
<td>0.5675(5)</td>
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<td>0.41581(14)</td>
<td>0.0465(12)</td>
</tr>
<tr>
<td>C25</td>
<td>0.6830(8)</td>
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<td>0.4642(2)</td>
<td>0.071(2)</td>
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<tr>
<td>C26</td>
<td>0.5769(8)</td>
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<td>0.2980(2)</td>
<td>0.056(2)</td>
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<tr>
<td>C27</td>
<td>0.4757(8)</td>
<td>-0.0481(3)</td>
<td>0.2949(3)</td>
<td>0.070(2)</td>
</tr>
<tr>
<td>C28</td>
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<td>0.0616(4)</td>
<td>0.2467(2)</td>
<td>0.086(3)</td>
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</tbody>
</table>

For anisotropic atoms, the U value is U$_{eq}$, calculated as U$_{eq}$ = 1/3 $\Sigma_i \Sigma_j U_{ij}$ a$_i^*$$a_j^*$, where A$_{ij}$ is the dot product of the i-th and j-th direct space unit cell vectors.


Appendix 2

X-ray Experimental for C₃₄H₅₆O₆SSi (99a):

Crystals grew as colorless needles in large clusters by slow evaporation from hexanes and diethyl ether. The data crystal was a needle of approximate dimensions; 0.13 x 0.21 x 1.00 mm. The data were collected at -75 °C on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with MoKα radiation (λ = 0.71073 Å). Details of crystal data, data collection and structure refinement are listed in Supplementary Table 1. Three reflections (2,2,1; 2,1,3; 2,5,3) were remeasured every 97 reflections to monitor instrument and crystal stability. A smoothed curve of the intensities of these check reflections was used to scale the data. The scaling factor ranged from 0.936 to 1.00 with the intensities of the check reflections showing a smooth, gradual decrease in intensity. The data were corrected for Lp effects but not for absorption. Data reduction and decay correction were performed using the SHELXTL/PC software package.¹ The structure was solved by direct methods and refined by full-matrix least-squares¹ on F² with anisotropic thermal parameters for the non-H atoms. The hydrogen atoms were calculated in idealized positions (C-H 0.96 Å) with isotropic temperature factors set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydroxyl hydrogen atom on O3I was found in a ΔF map and refined with an isotropic temperature factor without constraint. The function, \[ \Sigma w(|F_o|^2 - |F_c|^2)^2, \] was minimized, where \( w = 1/[(\sigma(F_o))^2 + (0.0445*P)^2 + (1.2027P)] \) and \( P = (|F_o|^2 + 2|F_c|^2)/3 \). The absolute configuration was determined by internal comparison. The Flack x parameter² refined to -0.06(13) for this
configuration and, therefore, corroborating the initial assignment. The data were corrected for secondary extinction effects. The correction takes the form: $F_{\text{corr}} = kF_C/[1 + 7.8(5) \times 10^{-6} \times F_C^2 \lambda^3/(\sin \theta)]^{0.25}$ where $k$ is the overall scale factor.

Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1990). Other computer programs used in this work are listed elsewhere. All figures were generated using SHELXTL/PC. Tables of positional and thermal parameters, bond lengths, angles and torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary material.
Supplementary Table 1. Crystallographic Data\textsuperscript{a} for C\textsubscript{34}H\textsubscript{56}O\textsubscript{6}SSi.

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<td>( a, \text{\AA} )</td>
<td>11.704(3)</td>
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<tr>
<td>( b, \text{\AA} )</td>
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<tr>
<td>( c, \text{\AA} )</td>
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<td>( V, \text{\AA}^3 )</td>
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</tr>
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<td>( Z )</td>
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</tr>
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<td>( F(000) )</td>
<td>1352</td>
</tr>
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<td>Space Group</td>
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<td>( T, ^\circ C )</td>
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<tr>
<td>( 2\theta ) range ((^\circ))</td>
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<td>Scan speed ((^\circ/min))</td>
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<td>((1.0^\circ \omega \text{ scan}))</td>
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<tr>
<td>( \rho_{\text{calc}}, \text{g/cc} )</td>
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<td>( R_{\text{int}} (F^2) )</td>
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Supplementary Table 1. Crystallographic Data (continued).

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<td>Crystal size, mm</td>
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<tr>
<td>Transmission factor range</td>
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<tr>
<td>(R_w(F^2))(^b)</td>
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</tr>
<tr>
<td>(R(F))(^c)</td>
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<tr>
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<tr>
<td>Parameters</td>
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<tr>
<td>Max (</td>
<td>\Delta/\sigma</td>
</tr>
<tr>
<td>Min, max peaks ((\text{e}^7/\text{Å}^3))</td>
<td>-0.31, 0.45</td>
</tr>
</tbody>
</table>

\(^a\) Data were collected on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using graphite monochromatized Mo K\(\alpha\) radiation (\(\lambda = 0.71073\text{Å}\)). Data were collected using \(\omega\) scans with a scan range of 1° in \(\omega\). Lattice parameters were obtained from the least-squares refinement of 48 reflections with 8.8 < 2\(\theta\) < 19.8°.

\(^b\) \(R_w = [\Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|^4)]^{1/2}\) and where the weight, \(w\), is defined as follows:

\[ w = 1/(\sigma^2(|F_o|^2) + (a*P)^2 + b*P) \]

\(P = [1/3*(\text{Maximum of } (0 \text{ or } |F_o|^2) + 2/3*|F_c|^2)]\). The parameters \(a\) and \(b\) were suggested during refinement and are 0.0445 and 1.2027, respectively.

\(^c\) The conventional \(R\) index based on \(F\) where the 4030 observed reflections have \(F_o > 4(\sigma(F_o))\).

\(^d\) \(S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}\), where \(n\) is the number of reflections and \(p\) is the number of refined parameters.
Supplementary Table 2. Fractional coordinates and equivalent isotropic thermal parameters (Å²) for the non-hydrogen atoms of C₃₄H₅₆O₆SSi.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
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<tbody>
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<td>C1</td>
<td>0.6523(3)</td>
<td>0.7075(3)</td>
<td>0.2837(2)</td>
<td>0.0333(13)</td>
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<tr>
<td>C2</td>
<td>0.6675(3)</td>
<td>0.7829(3)</td>
<td>0.3170(2)</td>
<td>0.0386(14)</td>
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<tr>
<td>C3</td>
<td>0.6338(4)</td>
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<td>C4</td>
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<tr>
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<td>0.6152(3)</td>
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<td>0.0309(13)</td>
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<tr>
<td>C6</td>
<td>0.5994(3)</td>
<td>0.6193(3)</td>
<td>0.3100(2)</td>
<td>0.0285(12)</td>
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<tr>
<td>C7</td>
<td>0.6970(4)</td>
<td>0.7026(3)</td>
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<td>0.047(2)</td>
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<tr>
<td>C8</td>
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<td>0.7013(3)</td>
<td>0.4807(2)</td>
<td>0.046(2)</td>
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<td>C9</td>
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<td>0.0368(9)</td>
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<td>Si13</td>
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<td>C14</td>
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<td>0.4112(5)</td>
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<td>C18</td>
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<td>C20</td>
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<td>S21</td>
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<tr>
<td>O22</td>
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<tr>
<td>O23</td>
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<tr>
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<tr>
<td>C25</td>
<td>0.4362(4)</td>
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<tr>
<td>C26</td>
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<tr>
<td>C27</td>
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<tr>
<td>C28</td>
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<td>0.1109(2)</td>
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<tr>
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<td>O37</td>
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<td>0.29135(13)</td>
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355
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<td>0.8747(3)</td>
<td>0.1981(2)</td>
<td>0.045(2)</td>
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</table>

For anisotropic atoms, the $U$ value is $U_{eq}$, calculated as $U_{eq} = 1/3 \Sigma_i \Sigma_j U_{ij} a_i^* a_j^*$, where $A_{ij}$ is the dot product of the $i^{th}$ and $j^{th}$ direct space unit cell vectors.


Appendix 3

X-ray Data for C$_{20}$H$_{30}$O$_3$ (130):

Crystals grew as long colorless needles by slow evaporation from diethyl ether-hexanes. The data crystal was a needle of approximate dimensions; 0.10 x 0.12 x 1.04 mm. The data were collected at -80 °C on a Siemens P3 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with MoK$\alpha$ radiation ($\lambda$ = 0.71073Å). Details of crystal data, data collection and structure refinement are listed in Supplementary Table 1. Four reflections (-2,1,-1;0,-2,-1;2,1,-1;1,2,0) were remeasured every 96 reflections to monitor instrument and crystal stability. A smoothed curve of the intensities of these check reflections was used to scale the data. The scaling factor ranged from 1.000 - 1.031. The data were corrected for Lp effects but not for absorption. Data reduction, decay correction, structure solution and refinement were performed using the SHELXTL/PC software package.$^1$ The structure was solved by direct methods and refined by full-matrix least-squares on F$^2$ with anisotropic displacement parameters for the non-H atoms. The hydrogen atoms were calculated in idealized positions (C-H 0.96Å) with isotropic temperature factors set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, $\sum w((|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.0292*P)^2 + (0.7292P)]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. The absolute configuration was determined by internal comparison and could not be determined from the X-ray data. The Flack x parameter$^{22}$ refined to 2(5) for this configuration. The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_o/[1 + 1.6(2) \times 10^{-5} \times F_c^2 \lambda^3/(\sin\theta)]^{0.25}$ where k is the overall scale factor.
Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992). Other computer programs used in this work are listed elsewhere. All figures were generated using SHELXTL/PC. Tables of positional and thermal parameters, bond lengths, angles and torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary material.
### Supplementary Table 1. Crystallographic Data\textsuperscript{a} for C\textsubscript{20}H\textsubscript{30}O\textsubscript{3}.

<table>
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<th>Property</th>
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<td>a, Å</td>
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<td>b, Å</td>
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<td>c, Å</td>
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</tr>
<tr>
<td>V, Å(^3)</td>
<td>1793.6(15)</td>
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<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>F(000)</td>
<td>696</td>
</tr>
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<td>Crystal System</td>
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<td>Space Group</td>
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</tr>
<tr>
<td>T, °C</td>
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<tr>
<td>2θ range (°)</td>
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</tr>
<tr>
<td>Scan speed (°/min)</td>
<td>4 - 8</td>
</tr>
<tr>
<td>(1.2° ω scan)</td>
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</tr>
<tr>
<td>(\rho_{\text{calc}}), g/cc</td>
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<tr>
<td>Reflections measured</td>
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<tr>
<td>R(_{\text{int}}) ((F^2))</td>
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Supplementary Table 1. Crystallographic Data (continued).

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<td>Crystal size, mm</td>
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<tr>
<td>Transmission factor range</td>
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<td>( R_w(F^2) )(^b)</td>
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<td>( R(F) )(^c)</td>
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<td>Goodness of fit, S(^d)</td>
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<td>Parameters</td>
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<tr>
<td>Max</td>
<td>Δ</td>
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<tr>
<td>Min, max peaks((e^-/Å^3))</td>
<td>-0.24, 0.24</td>
</tr>
</tbody>
</table>

\(^a\) Data were collected on a Siemens P3 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using graphite monochromatized Mo K\( \alpha \) radiation (\( \lambda = 0.71073\) Å). Data were collected using \( \omega \) scans with a scan range of 1.2\(^\circ\) in \( \omega \). Lattice parameters were obtained from the least-squares refinement of 50 reflections with 8.3 < 2\( \theta \) < 18.7\(^\circ\).

\(^b\) \( R_w = \) \( \{ \sum w(|F_o|^2 - |F_c|^2)^2/\sum w(|F_o|^4) \}^{1/2} \) and where the weight, \( w \), is defined as follows:

\( w = 1/\{ \sigma^2(|F_o|^2) + (a*P)^2 + b*P \} \);

\( P = [1/3*(\text{Maximum of } 0 \text{ or } |F_o|^2) + 2/3*|F_c|^2] \). The parameters \( a \) and \( b \) were suggested during refinement and are 0.0292 and 0.7292, respectively.

\(^c\) The conventional \( R \) index based on \( F \) where the 849 observed reflections have \( F_o > 4(\sigma(F_o)) \).

\(^d\) \( S = \) \( \{ \sum w(|F_o|^2 - |F_c|^2)^2/(n - p) \}^{1/2} \), where \( n \) is the number of reflections and \( p \) is the number of refined parameters.
Supplementary Table 2. Fractional coordinates and equivalent isotropic thermal parameters (Å²) for the non-hydrogen atoms of C_{20}H_{30}O_{3}.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.7299(9)</td>
<td>-0.0006(8)</td>
<td>0.3730(7)</td>
<td>0.033(4)</td>
</tr>
<tr>
<td>C2</td>
<td>0.7623(9)</td>
<td>0.0259(9)</td>
<td>0.4591(7)</td>
<td>0.038(4)</td>
</tr>
<tr>
<td>C3</td>
<td>0.6823(9)</td>
<td>0.0891(9)</td>
<td>0.5269(6)</td>
<td>0.038(4)</td>
</tr>
<tr>
<td>C4</td>
<td>0.5762(8)</td>
<td>0.1532(8)</td>
<td>0.4766(6)</td>
<td>0.031(3)</td>
</tr>
<tr>
<td>C4A</td>
<td>0.5138(8)</td>
<td>0.0641(10)</td>
<td>0.4122(7)</td>
<td>0.033(4)</td>
</tr>
<tr>
<td>C4B</td>
<td>0.3987(9)</td>
<td>0.1109(8)</td>
<td>0.3664(7)</td>
<td>0.031(4)</td>
</tr>
<tr>
<td>O5</td>
<td>0.3517(5)</td>
<td>0.0257(6)</td>
<td>0.3000(5)</td>
<td>0.037(3)</td>
</tr>
<tr>
<td>C6</td>
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<td>0.0679(10)</td>
<td>0.2067(7)</td>
<td>0.039(4)</td>
</tr>
<tr>
<td>C6A</td>
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<td>0.034(4)</td>
</tr>
<tr>
<td>C7</td>
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<td>0.1127(8)</td>
<td>0.2554(6)</td>
<td>0.035(4)</td>
</tr>
<tr>
<td>C7A</td>
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<td>0.0243(8)</td>
<td>0.3362(6)</td>
<td>0.030(3)</td>
</tr>
<tr>
<td>O8</td>
<td>0.4251(6)</td>
<td>0.2111(5)</td>
<td>0.3124(4)</td>
<td>0.033(2)</td>
</tr>
<tr>
<td>C9</td>
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<td>-0.0602(8)</td>
<td>0.3078(6)</td>
<td>0.047(4)</td>
</tr>
<tr>
<td>C10</td>
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<td>0.2169(10)</td>
<td>0.5439(6)</td>
<td>0.041(4)</td>
</tr>
<tr>
<td>C11</td>
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<td>0.1351(9)</td>
<td>0.6056(6)</td>
<td>0.055(5)</td>
</tr>
<tr>
<td>C12</td>
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<td>0.3088(10)</td>
<td>0.6015(7)</td>
<td>0.055(4)</td>
</tr>
<tr>
<td>C13</td>
<td>0.4237(9)</td>
<td>-0.0393(8)</td>
<td>0.1521(6)</td>
<td>0.051(4)</td>
</tr>
<tr>
<td>C14</td>
<td>0.2699(9)</td>
<td>0.1200(8)</td>
<td>0.1645(7)</td>
<td>0.036(4)</td>
</tr>
<tr>
<td>C15</td>
<td>0.2556(10)</td>
<td>0.1726(9)</td>
<td>0.0834(7)</td>
<td>0.043(4)</td>
</tr>
<tr>
<td>C16</td>
<td>0.3508(11)</td>
<td>0.1958(11)</td>
<td>0.0113(8)</td>
<td>0.049(5)</td>
</tr>
<tr>
<td>O17</td>
<td>0.4584(7)</td>
<td>0.1804(8)</td>
<td>0.0225(5)</td>
<td>0.062(3)</td>
</tr>
<tr>
<td>C18</td>
<td>0.2986(9)</td>
<td>0.2372(9)</td>
<td>-0.0804(7)</td>
<td>0.046(4)</td>
</tr>
<tr>
<td>C19</td>
<td>0.3962(9)</td>
<td>0.2705(11)</td>
<td>-0.1486(6)</td>
<td>0.082(6)</td>
</tr>
</tbody>
</table>

For anisotropic atoms, the U value is U_{eq}, calculated as U_{eq} = 1/3 \sum_{j} U_{ij} a_{i}^{*} a_{j}^{*} A_{ij} where A_{ij} is the dot product of the i^{th} and j^{th} direct space unit cell vectors.


Appendix 4

X-ray Experimental for C_{25}H_{35}NO_{7} (210):

Crystals grew as large colorless prisms from diethyl ether. The data crystal was a block of approximate dimensions; 0.34 x 0.38 x 0.49 mm. The data were collected at 173 K on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using a graphite monochromator with MoKα radiation (λ = 0.71073 Å). Details of crystal data, data collection and structure refinement are listed in Supplementary Table 1. Three reflections (3,3,-4; 4,2,4; 3,3,5) were remeasured every 97 reflections to monitor instrument and crystal stability. A smoothed curve of the intensities of these check reflections was used to scale the data. The scaling factor ranged from 0.985 to 1.02. The data were corrected for Lp effects but not absorption. Data reduction and decay correction were performed using the SHELXTL/PC software package. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 with anisotropic thermal parameters for the non-H atoms. The hydrogen atoms were calculated in idealized positions (C-H 0.96 Å) with isotropic temperature factors set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The function, Σw(|F_o|^2 - |F_c|^2)^2, was minimized, where w = 1/[(σ(F_o))^2 + (0.0421*P)^2 + (0.786P)] and P = (|F_o|^2 + 2|F_c|^2)/3. The absolute configuration was determined by internal comparison. The Flack x parameter refined to 0.3(8) for this configuration. The data were corrected for secondary extinction effects. The correction takes the form: F_{corr} = kF_c/[1 + 7.9(5)×10^{-6} F_c^2 λ^3/(sinθ)]^{0.25} where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-
ray Crystallography (1990).³ Other computer programs used in this work are listed elsewhere.⁴ All figures were generated using SHELXTL/PC.¹ Tables of positional and thermal parameters, bond lengths, angles and torsion angles, figures and lists of observed and calculated structure factors are located in the supplementary material.
Supplementary Table 1. Crystallographic Data\textsuperscript{a} for C\textsubscript{25}H\textsubscript{35}NO\textsubscript{7}.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C\textsubscript{25}H\textsubscript{35}NO\textsubscript{7}</td>
</tr>
<tr>
<td>fw</td>
<td>461.54</td>
</tr>
<tr>
<td>a, Å</td>
<td>25.093(2)</td>
</tr>
<tr>
<td>b, Å</td>
<td>9.134(1)</td>
</tr>
<tr>
<td>c, Å</td>
<td>10.858(1)</td>
</tr>
<tr>
<td>β, °</td>
<td>97.083(6)</td>
</tr>
<tr>
<td>V, Å\textsuperscript{3}</td>
<td>2469.7(4)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>F(000)</td>
<td>992</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space Group</td>
<td>C2</td>
</tr>
<tr>
<td>T, °C</td>
<td>-100</td>
</tr>
<tr>
<td>2θ range (°)</td>
<td>4 - 60</td>
</tr>
<tr>
<td>Scan speed (°/min)</td>
<td>5 - 10</td>
</tr>
<tr>
<td>(1.0° ω scan)</td>
<td></td>
</tr>
<tr>
<td>ρ\textsubscript{calc}, g/cc</td>
<td>1.24</td>
</tr>
<tr>
<td>Reflections measured</td>
<td>9786</td>
</tr>
<tr>
<td>Unique reflections</td>
<td>5038</td>
</tr>
<tr>
<td>Decay Correction</td>
<td>0.985 - 1.02</td>
</tr>
<tr>
<td>R\textsubscript{int} (F\textsuperscript{2})</td>
<td>0.0306</td>
</tr>
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</table>
Supplementary Table 1. Crystallographic Data (continued).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>$\mu$, cm$^{-1}$</td>
<td>0.90</td>
</tr>
<tr>
<td>Crystal size, mm</td>
<td>0.34x0.38x0.49</td>
</tr>
<tr>
<td>Transmission factor range</td>
<td>N/A</td>
</tr>
<tr>
<td>$R_w(F^2)^b$</td>
<td>0.0984</td>
</tr>
<tr>
<td>$R(F)^c$</td>
<td>0.0418</td>
</tr>
<tr>
<td>Goodness of fit, $S^d$</td>
<td>1.017</td>
</tr>
<tr>
<td>Parameters</td>
<td>299</td>
</tr>
<tr>
<td>Max $</td>
<td>\Delta/\sigma</td>
</tr>
<tr>
<td>Min, max peaks</td>
<td>-0.18, 0.22</td>
</tr>
</tbody>
</table>

$^a$ Data were collected on a Siemens P4 diffractometer, equipped with a Nicolet LT-2 low-temperature device and using graphite monochromatized Mo K$\alpha$ radiation ($\lambda = 0.71073\ \text{Å}$). Data were collected using $\omega$ scans with a scan range of 1° in $\omega$. Lattice parameters were obtained from the least-squares refinement of 48 reflections with $15.7 < 2\theta < 24.4^\circ$.

$^b$ $R_w = \{ \Sigma w(|F_o|^2 - |F_c|^2)^2/\Sigma w(|F_o|^4) \}^{1/2}$ and where the weight, $w$, is defined as follows:

$$w = 1/\{ \sigma^2(|F_o|^2) + (a*P)^2 + b*P \}; \ P = [1/3*(\text{Maximum of } (0 \text{ or } |F_o|^2) + 2/3*|F_c|^2)].$$

The parameters 0.0421 and 0.7860 were suggested during refinement and are $x$ and $y$, respectively.

$^c$ The conventional R index based on F where the 4037 observed reflections have $F_o > 4(\sigma(F_o))$.

$^d$ $S = [\Sigma w(|F_o|^2 - |F_c|^2)^2/(n - p)]^{1/2}$, where $n$ is the number of reflections and $p$ is the number of refined parameters.
Supplementary Table 2. Fractional coordinates and equivalent isotropic thermal parameters (Å²) for the non-hydrogen atoms of C$_{25}$H$_{33}$NO$_7$.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>0.40613(7)</td>
<td>0.0066(3)</td>
<td>0.6717(2)</td>
<td>0.0362(6)</td>
</tr>
<tr>
<td>C2</td>
<td>0.44447(7)</td>
<td>0.0397(3)</td>
<td>0.7618(2)</td>
<td>0.0411(7)</td>
</tr>
<tr>
<td>C3</td>
<td>0.43338(7)</td>
<td>0.0942(3)</td>
<td>0.8871(2)</td>
<td>0.0415(7)</td>
</tr>
<tr>
<td>C4</td>
<td>0.37710(7)</td>
<td>0.1400(3)</td>
<td>0.8965(2)</td>
<td>0.0323(6)</td>
</tr>
<tr>
<td>C4A</td>
<td>0.33728(6)</td>
<td>0.0344(2)</td>
<td>0.8226(2)</td>
<td>0.0256(5)</td>
</tr>
<tr>
<td>C5</td>
<td>0.27912(7)</td>
<td>0.0781(2)</td>
<td>0.8356(2)</td>
<td>0.0264(5)</td>
</tr>
<tr>
<td>O6</td>
<td>0.24111(4)</td>
<td>0.0326(2)</td>
<td>0.73450(10)</td>
<td>0.0250(3)</td>
</tr>
<tr>
<td>C7</td>
<td>0.22393(6)</td>
<td>0.1322(2)</td>
<td>0.6346(2)</td>
<td>0.0244(5)</td>
</tr>
<tr>
<td>C8</td>
<td>0.26664(7)</td>
<td>0.1308(2)</td>
<td>0.5441(2)</td>
<td>0.0253(5)</td>
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<tr>
<td>C9</td>
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<td>0.1578(2)</td>
<td>0.6069(2)</td>
<td>0.0281(5)</td>
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<tr>
<td>C9A</td>
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<tr>
<td>C10</td>
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<tr>
<td>C11</td>
<td>0.36762(8)</td>
<td>0.1630(3)</td>
<td>1.0337(2)</td>
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</tr>
<tr>
<td>C12</td>
<td>0.40200(11)</td>
<td>0.2885(4)</td>
<td>1.0927(3)</td>
<td>0.0598(10)</td>
</tr>
<tr>
<td>C13</td>
<td>0.37614(10)</td>
<td>0.0260(4)</td>
<td>1.1139(2)</td>
<td>0.0531(9)</td>
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<tr>
<td>O14</td>
<td>0.26473(5)</td>
<td>0.0062(2)</td>
<td>0.94053(11)</td>
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<tr>
<td>C15</td>
<td>0.21767(8)</td>
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<tr>
<td>C16</td>
<td>0.21142(8)</td>
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<tr>
<td>C17</td>
<td>0.17466(7)</td>
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<tr>
<td>O18</td>
<td>0.12884(5)</td>
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<tr>
<td>C19</td>
<td>0.09050(7)</td>
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<td>0.6192(2)</td>
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<tr>
<td>O20</td>
<td>0.09296(6)</td>
<td>-0.1306(2)</td>
<td>0.5614(2)</td>
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<tr>
<td>C21</td>
<td>0.04313(7)</td>
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<td>0.6832(2)</td>
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<tr>
<td>C22</td>
<td>0.04319(9)</td>
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<td>0.7576(2)</td>
<td>0.0449(8)</td>
</tr>
<tr>
<td>C23</td>
<td>-0.00223(10)</td>
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<td>0.8144(3)</td>
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<td>C24</td>
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<td>C25</td>
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<td>N27</td>
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<td>0.0707(4)</td>
<td>0.8024(2)</td>
<td>0.1078(14)</td>
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<td>0.44967(12)</td>
<td>0.0305(4)</td>
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<tr>
<td>C31</td>
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<td>0.1934(3)</td>
<td>0.3312(2)</td>
<td>0.0398(7)</td>
</tr>
</tbody>
</table>

For anisotropic atoms, the U value is $U_{eq}$, calculated as $U_{eq} = 1/3 \sum_{i} \sum_{j} U_{ij} a_{i}^{*} a_{j}^{*}$, $A_{ij}$ where $A_{ij}$ is the dot product of the $i^{th}$ and $j^{th}$ direct space unit cell vectors.


Vita

Rich Garrett Carter was born in Dallas, Texas on August 27, 1971, the son of Peter and Susan Carter. He graduated magna cum laude from Gettysburg College in Gettysburg, Pennsylvania in May of 1993, with a Bachelor of Science in Chemistry and is a member of the Phi Beta Kappa Society.

In September of 1993, he began graduate studies at the University of Texas at Austin under the supervision of Professor Philip D. Magnus.

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