Towards the Total Synthesis of Spirastrellolide E: Investigations into Advanced Southern Hemisphere Fragments

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Towards the Total Synthesis of Spirastrellolide E: Investigations into Advanced Southern Hemisphere Fragments

Abstract
This dissertation describes progress towards the synthesis of spirastrellolide E, a potent cytotoxic marine macrolide. In particular, the synthesis of advanced southern hemisphere fragments is reported. Chapter 1 details the isolation, structural determination, and biological activity of the spirastrellolide family, as well as synthetic efforts towards members of the family. Chapter 2 describes the evolution of the Smith group synthetic strategy towards the spirastrellolides, details the choice of target for a total synthesis effort, and describes a successful first generation approach to a relevant advanced southern hemisphere fragment. Key steps involve a convergent Type I Anion Relay Chemistry (ARC) union and a gold catalyzed directed spiroketalization. Chapter 3 then revises the overall retrosynthetic analysis by proposing a novel strategy for hemisphere union, involving a cross metathesis/epoxidation/epoxide ring opening cascade, and describes the synthesis of more than 500 mg of a revised southern hemisphere fragment. In addition, the mechanism of the key directed gold catalyzed spiroketalization is discussed in detail. A stereochemical rationale for diverging outcomes during spiroketalization is described.

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TOWARDS THE TOTAL SYNTHESIS OF SPIRASTRELLOLIDE E:
INVESTIGATIONS INTO ADVANCED SOUTHERN HEMISPHERE FRAGMENTS

Alexander Sokolsky

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Chemistry

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Degree of Doctor of Philosophy

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ABSTRACT

TOWARDS THE TOTAL SYNTHESIS OF SPIRASTRELLOLIDE E:
INVESTIGATIONS INTO ADVANCED SOUTHERN HEMISPHERE FRAGMENTS

Alexander Sokolsky
Professor Amos B. Smith, III

This dissertation describes progress towards the synthesis of spirastrellolide E, a potent cytotoxic marine macrolide. In particular, the synthesis of advanced southern hemisphere fragments is reported. Chapter 1 details the isolation, structural determination, and biological activity of the spirastrellolide family, as well as synthetic efforts towards members of the family. Chapter 2 describes the evolution of the Smith group synthetic strategy towards the spirastrellolides, details the choice of target for a total synthesis effort, and describes a successful first generation approach to a relevant advanced southern hemisphere fragment. Key steps involve a convergent Type I Anion Relay Chemistry (ARC) union and a gold catalyzed directed spiroketalization. Chapter 3 then revises the overall retrosynthetic analysis by proposing a novel strategy for hemisphere union, involving a cross metathesis/epoxidation/epoxide ring opening cascade, and describes the synthesis of more than 500 mg of a revised southern hemisphere fragment. In addition, the mechanism of the key directed gold catalyzed spiroketalization is discussed in detail. A stereochemical rationale for diverging outcomes during spiroketalization is described.
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CHAPTER 1

1.1 Isolation and Structural Determination of Spirastrellolide A and Congeners

In 2003, the Anderson group reported that the extracts of the sponge *spirastrella coccinea* displayed potent activity in a cell assay testing for mitotic arrest. The major bioactive component of this extract was isolated and termed spirastrellolide A. The authors originally proposed structure 1.1 (Figure 1-1) based on extensive 2D NMR analysis; however, in a subsequent report, the authors revised the skeletal connectivity based on improved mass spectral data; structure 1.2 ultimately proved to be correct (*vide infra*).

At the time of their initial report, Anderson and coworkers were able to identify the relative stereochemistry of the southern hemisphere spiroketal and one of the northern hemisphere rings based on ROESY spectroscopy. With the revision of the skeletal connectivity, the group was next able to clarify further the stereochemistry by determining the relative stereochemistry of the C(3)-C(7), C(9)-C(24) and C(27)-C(34) fragments (see Figure 1-1 for numbering). The relative configuration between the various domains, as well as the stereogenicity of the isolated C(46) carbinol, remained undetermined. It was not until the Anderson group isolated spirastrellolide B (1.3, Figure 1-2) in 2007 from the same sponge that advances were made on this structural dilemma. Spirastrellolide B differs from A both by lack of

\[ \text{Figure 1-1 Original and revised structure of spirastrellolide A (1.2)} \]
a chlorine atom at C(28) and saturation of the C(15)-C(16) bond. The lack of unsaturation in the macrocyclic core of spirastrellolide B permitted degradation via oxidative side chain removal, which, in turn, led to the formation of derivative 1.4, which lacked the flexible side chain and permitted the growth of X-ray quality crystals for structural analysis.

![Diagram of conversion of spirastrellolide B to a derivative for X-ray characterization](image)

**Figure 1-2 Conversion of spirastrellolide B to a derivative for X-ray characterization**

Structural determination via X-ray analysis of 1.4 defined the relative and absolute stereochemistry of the spirastrellolide core. The final stereochemical hurdle was the stereogenicity of the remote C(46) carbinol, which had been removed during oxidative cleavage of the side chain. This issue was finally addressed by the Anderson group's isolation of spirastrellolides C-G later in 2007. The structures of these novel macrolides (1.5 - 1.9, Figure 1-3) were shown to be very similar to that of spirastrellolides A and B, importantly, careful oxidative cleavage of the side chain in spirastrellolide D (1.6) permitted correlation to (R)-dimethyl malate, which unambiguously determined the last unknown structural detail at C(46).

From the initial isolation, spirastrellolide A (1.2) was recognized to have a very intriguing biological profile. In their original report, Anderson and coworkers noted the potent activity (IC50 100 ng/mL) in their anti-mitotic assay, but no effect on tubulin polymerization, a feature not typically observed for other natural products possessing anti-mitotic activity.
In addition, spirastrellolide A (1.2) was observed to accelerate entry of cells into mitosis from other stages of the cell cycle. This behavior lead the authors to suspect inhibition of Ser/Thr phosphatases, which was confirmed by in vitro assays. Importantly, spirastrellolide A (1.2) inhibits PP2A selectively (IC₅₀ 1 nM) over PP1 (IC₅₀ 50 nM) and PP2C (IC₅₀ >1 μM). Spirastrellolides C-E show similar activity. In addition, spirastrellolides A and B isolated from a different sponge by Matsunaga and coworkers revealed activity against HeLa cells (20 and 40 nM, respectively).

1.2 Early Approaches to Spirastrellolide Fragments for Structural Determination

The combination of intriguing biological activity and breath-taking structural complexity of spirastrellolide A (1.2) attracted the attention of a large number of synthetic chemists. Initial attempts focused on identifying the relative configuration of the fragments, in particular the C(3)-C(7) and C(9)-C(27) fragments, as their union would comprise an advanced southern hemisphere for a potential total synthesis. A number of groups thus targeted flexible approaches that would permit the synthesis of multiple diastereomers, with the eventual goal of correlating the ¹H and ¹³C NMR signals of synthetic analogues with the NMR chemical shifts reported for the natural product. In particular, the Paterson and De Brabander groups made notable early contributions in this vein. Their respective approaches are outlined below.
In 2005, the Paterson group reported approaches to the southern hemisphere of the putative stereostructure of spirastrellolide A. Their approach (Scheme 1-1) featured a convergent strategy uniting a C(1)-C(16) alkyne (1.11) with a C(17)-C(25) aldehyde (1.12).

The C(1)-C(16) alkyne 1.11 was further divided to isolate the C(1)-C(9) fragment (1.13), which was prepared as two enantiomers. In the forward sense, intermediate 1.14 could be taken forward to two enantiomeric methyl ketones (1.13), which could be transformed into two epimeric alkynes 1.18 in a 6 steps sequence (only one diastereomer shown in Scheme 1-1). The two diastereomeric alkynes were then coupled to aldehyde 1.12 and after two steps subjected to acid-
catalyzed spiroketalization with concomitant protecting group loss. Unfortunately, comparison of the two diastereomers to the natural product proved inconclusive.

The De Brabander Approach

In 2006, the De Brabander group reported a similar approach, also targeting two diastereomers of the C(1)-C(22) southern hemisphere varying in the stereogenicity of the C(3) and C(7) centers. Their synthesis is outlined in Scheme 1-2.

![Scheme 1-2 The De Brabander approach to southern hemisphere stereochemical determination](image)

The two enantiomers of methyl ketone 1.23 were synthesized from commercial dihydropyran in a 6 step sequence. The stereogenicity of C(7) was set by choice of a suitable allylation reagent in the synthesis of 1.22, while the desired cis relative configuration was achieved by a diastereoselective Michael addition to provide 1.23. Each congener was next coupled to the C(11)-C(22) aldehyde 1.24 through an aldol condensation. Diastereoselective reduction and terminal PMB removal then furnished two possible C(1)-C(22) diastereomers.
Unfortunately, comparison of the NMR chemical shifts of these less elaborate congeners also did not lead to good agreement with the natural product. The authors attributed the discrepancies to possible conformation effects in the fully elaborated macrolide.

1.3 Other approaches to spirastrellolide fragments

A number of other groups have reported approaches to various fragments of the spirastrellolides, which have not, to date, culminated in total syntheses. These are summarized below in chronological order of the first publication.

The Hsung Approach

In 2005, the Hsung group reported the first in a series of papers outlining a strategy towards the C(11)-C(23) fragment of spirastrellolid e A (1.2) based on their tethered ketal RCM strategy. After originally pursuing the incorrect diastereomer at C(22), the group settled on the route shown in Scheme 1-3.

Scheme 1-3 The Hsung approach to the C(11)-C(23) southern hemisphere fragment

Key intermediate 1.28, available in 11 steps from diethyl tartrate, underwent addition of vinylmagnesium bromide followed by ketalization with a functionalized alcohol to provide
In 2014, the Hsung group also published an approach towards the northern hemisphere metathesis (RCM), under the action of the second generation Grubbs catalyst. Addition of the intermediate, which formed the desired unsaturated spiroketal \( \text{1.30} \) upon ring-closing metathesis (RCM), under the action of the second generation Grubbs catalyst. Addition of the C(1)-C(11) fragment \( \text{1.32} \) to \( \text{1.31} \) via a Mukiyama aldol, reduction and protection then furnished the fully elaborated C(1)-C(23) fragment \( \text{1.34} \).

In 2014, the Hsung group also published an approach towards the northern hemisphere DEF ring system, as shown in Scheme 1-4.

![Scheme 1-4 Hsung approach to the northern hemisphere skeleton](image)

Scheme 1-4 Hsung approach to the northern hemisphere skeleton

In a similar fashion to their southern hemisphere synthesis, key intermediate \( \text{1.35} \) was condensed with alcohol \( \text{1.36} \) to form the corresponding ketal (\( \text{1.37} \)). Ring-closing metathesis, reduction of the resulting olefin and oxidative cyclization then provided a DEF ring system similar to that of the spirastrellolides.

The Forsyth Approach

In 2006, the Forsyth group reported a strategy towards the C(26)-C(40) fragment (northern hemisphere). As seen in Scheme 1-5, straightforward construction of intermediate \( \text{1.44} \) was followed by tandem sequential hetero-Michael additions of the requisite pendant alcohols onto the ynone and equilibration to the thermodynamic bis-spiroketal isomer to yield the desired core \( \text{1.45} \).
Scheme 1-5 The Forsyth approach to the C(26)-C(40) northern hemisphere fragment

Notably, the authors were not able to incorporate readily the chlorine substituent at C(28) due to competitive epoxide formation with the C(29) hydroxyl under the highly basic conditions (c.f. potassium tert-butoxide) of the double hetero Michael addition (1.44 → 1.45).

The Phillips Approach

In 2008, the Phillips group reported a highly convergent synthesis of the C(1)-C(23) fragment of the southern hemisphere of spirastrellolide B (which differs from A in the absence of the C(15)-C(16) unsaturation - see Scheme 1-6 for numbering). The synthesis begins with the straightforward construction of two complex fragments 1.47 and 1.49. The two fragments were then united through a novel intermolecular Kulinkovich cyclopropanation and the resulting cyclopropyl alcohol fragmented under radical conditions to furnish ketone 1.50, which represents the full carbon skeleton of the southern hemisphere. Acid catalyzed spiroketalization completed the synthesis of 1.51.
Scheme 1-6 The Phillips approach to a C(1)-C(23) southern hemisphere fragment

The Chandrasekhar Approach

Later in 2008, the Chandrasekhar group also published results towards a spirastrellolide B synthesis, focusing on the C(9)-C(25) fragment (Scheme 1-7).  

Scheme 1-7 The Chandrasekhar approach to a C(9)-C(25) southern hemisphere fragment
The group built up the C(17)-C(25) aldehyde 1.53 from glucose, then coupled the aldehyde to the C(9)-C(15) alkyne 1.56, followed by acid catalyzed spiroketalization to furnish 1.58. Of particular note is the intriguing protecting group scheme used for the C(22)-C(25) domain, featuring an acetal masked hemiketal.

**The Brimble Approach**

In 2010, the Brimble group reported studies directed towards the northern hemisphere of the spirastrellolide family; full details soon followed. The strategy centered on two key dithiane couplings: first, between dithiane 1.59 and epoxide 1.60; then, after a series of functional group manipulations, the derived aldehyde 1.62 and the dithiane 1.63. The resulting fragment, 1.64, representing the full C(25)-C(40) segment, was subjected to dithiane removal (Scheme 1-8) with concomitant cyclization to provide 1.65. Northern hemisphere fragment 1.66 was then available via a straightforward Barton reduction.

**Scheme 1-8 The Brimble approach to the C(25)-C(40) northern hemisphere fragment**
Finally, in 2014, the Rajesh group published studies aimed at the southern hemisphere of spirastrellolide B (Scheme 1-9).\(^{19}\)

![Scheme 1-9 The Rajesh approach to a C(1)-C(23)](image)

The group constructed key fragments 1.68, 1.70, and 1.72. Intermediates 1.70 and 1.72 were then coupled via an aldehyde alkynylation; fragment 1.68, in turn, was appended via selective cross metathesis to form the full C(1)-C(23) carbon skeleton of the spirastrellolide B southern hemisphere, albeit without spiroketal formation.

### 1.4 Total Syntheses of Members of the Spirastrellolide Family

As the above approaches to various fragments of spirastrellolide congeners were being reported, the Paterson\(^{8,20–22}\) and Furstner\(^{23–25}\) groups focused on the total synthesis of spirastrellolide A (1.2), with occasional reports of their progress. These efforts culminated in successful approaches towards spirastrellolide congeners - the synthesis of spirastrellolide A (1.2) was achieved first by Paterson\(^{26–29}\) followed a few years later by Furstner.\(^{30}\) In the intervening years, the Furstner group achieved the first\(^{31,32}\) and second\(^{33}\) generation synthesis of
spirastrellolide F (1.7). Finally, the Paterson group published a second generation synthesis of spirasterellolide A (1.2). The evolution and eventual success of these approaches are outlined below.

The Paterson Synthesis of Spirastrellolide A (1.2)

In 2005, the first reports from the Paterson laboratory targeted at spirastrellolide A (1.2) synthesis began to appear. The southern hemisphere approach was mentioned previously as an attempt to clarify the structural ambiguities present in the stereochemical information, still present at the time of their original report. The C(26)-C(39) northern hemisphere approach is summarized in Scheme 1-10.

Scheme 1-10 Synthesis of the C(27)-C(39) northern hemisphere fragment 1.83

The chlorine substituent at C(28) was installed at a very early stage by an enantioselective chloroallyl boration. The resulting allyl chloride 1.76 was taken on to phosphonate fragment 1.77, which was then coupled to ketal fragment 1.81 utilizing a Horner-Wadsworth-Emmons olefination/conjugate reduction sequence. With the full carbon skeleton in
place, acid catalyzed spiroketalization provided the fully functionalized northern hemisphere 1.83, albeit in low yield due to the chemical instability of spiroketalization precursor 1.82.

In an attempt to improve this route, Paterson realized that both fragments featured an asymmetric hydroxylation to set carbinol stereocenters possessing the same absolute configuration. The strategy towards the northern hemisphere was therefore amended in a manner that the two dihydroxylations were performed simultaneously at a late stage, thereby installing sensitive functionality (i.e., the acid-sensitive ketal) towards the end of the route. In addition, the group decided to move away from the δ lactone protecting group due to problems associated with stability. After some optimization, the group settled on a revised route shown in Scheme 1-12. Thus, construction of a structurally simpler chloride 1.87 by similar chemistry as employed in the first generation route was followed by a double asymmetric dihydroxylation, and then by an acid catalyzed spiroketalization to furnish the fully protected northern hemisphere fragment 1.89.

Scheme 1-11 An improved route to the northern hemisphere fragment

Although these original approaches to the spirastrellolide A (1.2) fragments were published in 2005-6, it was not until two years later that the group disclosed two communications describing the total synthesis of spirastrellolide A (1.2).26,27 The reason for this delay was made
clear with the publication of the full account in 2012 on the total synthesis spirastrellolide A in the Paterson laboratory.\textsuperscript{28,29} The latter publications detail the difficulties associated with the union of the northern and southern hemispheres of spirastrellolide A (1.2; Scheme 1-12 A). In particular, approaches that attempted to unite the two fully elaborated hemispheres via chemistry that does not generate additional unsaturation, (i.e., to avoid late stage chemoselectivity difficulties with the olefination present in the southern hemisphere spiroketal) proved unsuccessful due to the chemical instability of the northern hemisphere. Olefination proved similarly unsuccessful. As seen in Scheme 1-12, even very simple building blocks (1.91 and 1.92) did not lead to successful bond formation presumably due to the steric encumbrance of the northern hemisphere.

\[
\begin{align*}
A) & \quad \begin{array}{c}
\text{X = CH}_2\text{X (1.89)} \\
\text{or CHO (1.90)}
\end{array} \\
& \quad \text{X = CH}_2\text{X} \quad \text{X = CHO}
\end{align*}
\]

\[
\begin{align*}
B) & \quad \begin{array}{c}
\text{PMB} \\
\text{TES}
\end{array} \\
& \quad \text{25% yield}
\end{align*}
\]

Scheme 1-12 Hemisphere union attempts

It was at this stage that the Paterson group moved away from a synthetic strategy relying on the union of two fully elaborated hemispheres towards a more flexible strategy that built the southern hemisphere stepwise after initial addition of the C(17)-C(25) or C(17)-C(24) fragment to a fully elaborated northern hemisphere. Even with this revised synthetic plan, hemisphere union proved challenging, with a planned Julia olefination to forge the C(25)-C(26) bond proving
unsuccessful due to steric hinderence associated with the U-shaped northern hemisphere (Scheme 1-12 B). Fortunately, moving the site of fragment union one bond away from the northern hemisphere core to C(24) provided better results, with the C(24)-C(25) bond formation now being achieved by an sp$^2$-sp$^3$ Suzuki cross coupling (*vide infra*).

With these strategic considerations in mind, the revised Paterson retrosynthetic analysis is shown in Scheme 1-13. Initial removal of the sidechain leads to the macrocyclic core of spirastrellolide A (1.95), which was further disconnected by a retro-macrolactonization to provide the spirastrellolide A seco acid (1.96). A retro-spiroketalization/reduction/alkynylation sequence to install the southern hemisphere would then permit disconnection to aldehyde 1.98. The key C(24)-C(25) bond would then be forged by an sp$^2$-sp$^3$ Suzuki cross coupling between vinyl iodide 1.100 and northern hemisphere fragment 1.99.

Scheme 1-13 Revised retrosynthetic analysis
To implement this analysis, the authors required a large supply of advanced material, particularly challenging in the case of the northern hemisphere; thus the route to the earlier fragment 1.99 was revised, this time with the goal of improved scalability. The final route for the requisite Paterson northern hemisphere precursor 1.107 is summarized in Scheme 1-14.

Scheme 1-14 Revised northern hemisphere synthesis

Key changes include a modified aldehyde substrate for chloroallylation (1.101) for the preparation of key methyl ketone 1.103. After aldol coupling with aldehyde 1.86, an improved synthesis of diketone 1.87 was implemented, which, while longer, permitted for significantly improved material throughput. Double asymmetric Shapless dihydroxylation and spiroketalization as before now led to gram quantities of the northern hemisphere fragment precursor 1.107.

The southern hemisphere route at this juncture consisted of two fragments (1.99 and 1.100, Scheme 1-13) to be installed in a stepwise fashion. To this end, vinyl iodide fragment 1.100 was constructed via a nine step sequence, utilizing an Evans glycolate aldol with sensitive
aldehyde 1.109 (Scheme 1-15). Installation of the final stereocenter was then accomplished via
diastereoselective chelation-controlled reduction of the ketone available from the Grignard reaction
of Weinreb amide 1.111 with allylimagensium bromide.

![Scheme 1-15 Synthesis of vinyl iodide 1.100](image)

The remaining segment of the southern hemisphere (1.119) was constructed via a route
adapted from previous iterations of the Paterson fully elaborated southern hemisphere syntheses
(Scheme 1-16). Construction of tetrahydropyran containing aldehyde 1.116 was followed by a
diastereoselective aldol reaction to construct the carbon skeleton 1.117. Functional group
manipulation then furnished the key alkyne fragment 1.119.

![Scheme 1-16 Revised synthesis of southern hemisphere fragment](image)

Finally, the stannane ester 1.122 required for elaboration of the spirastrellolide side chain
was prepared in a straightforward manner (Scheme 1-17).
With the fragments readily available, the group turned to their assembly. The first order of business was the addition of the C(17)-C(24) vinyl iodide 1.100 to the northern hemisphere 1.99 (Scheme 1-18). To this end, northern hemisphere alcohol 1.89 was converted to the corresponding terminal olefin. Hydroboration of this olefin with 9-BBN for the proposed Suzuki reaction, followed by the addition of 1.100 in the presence of catalytic PdCl₂(dppf), Ph₃As as ligand and aqueous cesium carbonate as the base furnished the desired coupled product 1.123 in 83% yield (!), validating the hypothesis that moving the site of bond formation away from the crowded northern hemisphere would increase the ease of bond formation. This observation will become important to our own synthesis of a spirastrellolide southern hemisphere.

With the key bond formed, elaboration continued (Scheme 1-19). To set the stereocenters at C(23)-C(24), the Paterson group utilized a directed hydroboration/oxidation to furnish the desired stereodiad with 3:1 diastereoselectivity. The authors note that they believe the conformation of the molecule, rather than local substrate control, was responsible for this outcome. The hydroboration/oxidation sequence also conveniently converted the terminal olefin in 1.123 to the corresponding alcohol. After routine protecting group manipulation, selective
oxidation and addition of the remaining southern hemisphere fragment (1.114) permitted spiroketalization to provide the full core carbon skeleton of spirastrellolide A (1.126).

Scheme 1-19 Elaboration of the southern hemisphere

Macrolactonization of the seco-acid derived from 1.126 was next achieved employing the Yamaguchi protocol (Scheme 1-20) to furnish 1.28. Global deprotection/reprotection then set the stage for the attachment of the side chain, which was achieved using a cross metathesis reaction with a symmetrical allyl carbonate, followed by π-allyl palladium chemistry to install the remaining carbons in the form of vinyl stannane 1.122. Thus, the first total synthesis spirastrellolide A (1.2) methyl ester was achieved. The group later published a second generation approach,34 which improved on several of the fragment union steps, but did not significantly alter the overall strategy.
Scheme 1-20 Completion of spirastrellolide A (1.2)

The Furstner Total Synthesis of Spirastrellolide F

The Furstner group had also embarked on a total synthesis of spirastrellolide A (1.2) soon after the isolation report. As such, their approach also centered around disconnection of the molecule into fragments of known relative stereochemistry. This consideration is reflected in the original retrosynthetic analysis adopted by the Furstner group, shown in Scheme 1-21.
Scheme 1-21 Furstner group retrosynthetic analysis

With the above retrosynthetic approach in mind, the group reported approaches to the southern hemisphere spiroketal through union of 1.131 and 1.132 and northern hemisphere bis spiroketal fragment 1.133 (Scheme 1-21). The southern hemisphere synthesis is outlined in Scheme 1-22.

Scheme 1-22 Synthesis of an advanced southern hemisphere fragment
First, two key fragments were constructed: dithiane 1.136 and tetrahydropyranyl methyl ketone 1.139. Union of dithiane 1.136 to the diethyl tartrate derived aldehyde 1.142 was followed by a deprotection/acid catalyzed spiroketalization sequence to furnish advanced aldehyde 1.144 as a single diasteromer, which could be readily coupled with fragment 1.139 to furnish the southern hemisphere 1.145.

Attention then turned to the northern hemisphere (Scheme 1-23). A similar chloroallylation reaction as employed by Paterson to set the stereocenter of the C(28) chlorine substituent was performed to start the synthesis. The resulting allylic chloride was transformed into cyanohydrin 1.149 through a series of straightforward manipulations.

As a coupling partner for the cyanohydrin TMS ether 1.149, Furstner et al. constructed an oxazole bearing an alkyl iodide side chain via a [3+2] cycloaddition of 1.150 and 1.151. After standard functional group manipulations, union of fragments 1.153 and 1.149 generated the full carbon skeleton of the northern hemisphere (1.154), which was then converted to the desired
bisspiroketal by first reductive cleavage of the oxazole, revealing the β-hydroxy ketone moiety, and then by acid catalyzed spiroketalization to furnish 1.155. Furstner and coworkers also encountered the instability of the five membered ring in the bisspiroketal, as well as the corresponding ketal precursors, to acidic and basic conditions; furan formation predominated in all but the mildest of settings.

Fragments 1.145 and 1.155 were eventually available in significant amounts to initiate studies to unite the two hemispheres. The first approach chosen by Furstner and coworkers entailed esterification of the two hemispheres, followed by ring closing metathesis. However, in line with the results observed by the Paterson group, no bond formation was observed under a large variety of conditions, presumably due to the steric bulk of the northern hemisphere. The group therefore decided to construct ester 1.157 (Scheme 1-24), featuring a partially deconstructed northern hemisphere.

Scheme 1-24 Attempted ring closing metathesis

This congener indeed underwent ring closing metathesis, lending credence to the suggestion that steric bulk was the determining factor for difficulties associated with the original plan. Unfortunately, attempted formation of the bisspiroketal after formation of the macrocyclic core was met with failure (i.e., decomposition). The group therefore moved to the relay ring closing metathesis approach developed by Hoye,35 with the expectation of using the relay trigger to transfer the ruthenium carbene to the hindered northern hemisphere olefin. However, after
preparing the necessary substrate 1.158 (Scheme 1-25), the group found that only the ring expanded analogue 1.159 could be isolated.

Scheme 1-25 Preparation of a ring expanded analogue

At this stage, a reexamination of the overall strategy was required. A new retrosynthetic analysis was thus devised, similar in many ways to the ultimately successful strategy employed by Paterson (Scheme 1-26).

Scheme 1-26 Revised retrosynthetic analysis

Bond construction between the two hemispheres was moved to the C(24)-C(25) bond, and a Suzuki cross coupling reaction was chosen as the key bond-forming reaction. In contrast to the Paterson approach, the Furstner group elected to use a southern hemisphere vinyl triflate as the coupling partner to the northern hemisphere. It was also at this stage that the Furstner group
switched from pursuing spirastrellolide A (1.2) to the simpler spirastrellolide F (1.8), which differs from 1.2 in the absence of unsaturation at C(15)-C(16).

The new retrosynthetic analysis required an amended southern hemisphere 1.173, the synthesis of which is outlined in Scheme 1-27.

Scheme 1-27 Revised southern hemisphere synthesis

With the relative stereochemistry of the spirastrellolides unambiguously assigned at this stage, the requirement for strategic bond unions between regions of unknown stereochemistry was no longer in play, so a more convergent approach was possible. Thus, a Marshall propargylation between aldehyde 1.161 and an enantiopure propargylic mesylate furnished homo-propargylic alcohol 1.162, which, after oxidation to 1.163, was in turn coupled to fragment...
1.164 via a Mukiyama aldol reaction. Functional group interconversion then furnished alkyne 1.166. The challenging stereotetrad in fragment 1.170 also relied on a Mukiyama aldol reaction to construct intermediate alkyne 1.168, which was converted to the desired aldehyde 1.170 in five steps. Aldehyde 1.170 and alkyne 1.166 were then coupled and subjected to spioketalization under acidic conditions after oxidation state adjustment. Finally, installation of the vinyl triflate completed the new southern hemisphere fragment (1.173).

With both hemispheres (1.155 and 1.173) available in large amounts, the envisioned key Suzuki cross coupling reaction was evaluated. As expected from the studies of Paterson, both the cross coupling and subsequent macrolactonization operations proved facile (Scheme 1-28); the olefin hydrogenation to set the stereocenter at C(24), however, proved extremely challenging.

Scheme 1-28 Completion of spirastrellolide F

Through an unfortunate combination of circumstances, both faces of the terminal olefin are shielded: one by the adjacent ketal, the other by the northern hemisphere bis spioketal. The authors eventually found that an analogue of Crabtree's catalyst employed under forcing conditions (c.f. 200 bar H₂ pressure) provided the desired product 1.175. At this stage, the synthesis intercepted nicely with the spirastrellolide A (1.2) synthesis of Paterson and coworkers;
subsequent manipulations were thus performed in a straightforward manner to permit completion of the first total synthesis of spirastrellolide F (1.8).

The Second Generation Furstner Synthesis of Spirastrellolide F (1.8)

In 2011, the Furstner group published a second generation approach to spirastrellolide F (1.8) based on an alkyne metathesis/spiroketalization approach (Scheme 1-29). Furstner hypothesized that the earlier union of advanced southern and northern hemispheres was not the ideal route for the synthesis of spirastrellolide congeners. Earlier retrosynthetic analyses had focused on such a disconnection to isolate fragments of the spirastrellolides that at the time possessed unknown relative configuration. With the relative configuration established unequivocally after the first generation syntheses of the Paterson and Furstner groups, an alternative approach could now be investigated.

In particular, in their second generation synthesis, the Furstner group chose to disconnect the southern hemisphere spiroketal at a late stage via a gold catalyzed ring closure, leading back to alkynyl diol 1.178 (Scheme 1-29). Application of the Furstner group’s signature alkyne ring closing metathesis methodology would permit 1.178 to arise from the appropriate bis alkyne 1.179. Dialkyne 1.179, in turn, could be readily assembled from three fragments (1.155, 1.181, 1.180) via an esterification and a variant of the Suzuki cross coupling reaction that proved successful in the spirastrellolide F synthetic venture. Importantly, the fragments required for the revised analysis could be readily prepared from intermediates synthesized previously en route to spirastrellolide F, with northern hemisphere fragment 1.155 remaining unchanged and fragment 1.181 available by a minor modification of the established synthetic procedure.
Scheme 1-29 Second generation retrosynthetic analysis of spirastrellolide F

The requisite acid 1.180 (Scheme 1-30) was available by a simple three step homologation of intermediate 1.165 (Scheme 1-27), followed via conversion of the primary TBS-protected carbinol to the corresponding carboxylic acid.

Scheme 1-30 Synthesis of a modified alkyne fragment

With these intermediates in hand, construction of spirastrellolide F (1.8) proceeded by Suzuki cross coupling of the northern hemisphere 1.155 with fragment 1.81 (Scheme 1-29)
employing conditions developed previously and in turn esterification with fragment 1.180 to furnish 1.179 (Scheme 1-31).

![Scheme 1-31 Completion of a second generation synthesis of spirastrellolide F](image)

Alkyne metathesis proceeded smoothly utilizing methods developed earlier in the Furstner laboratory. Generation of the two pendant hydroxyls from the corresponding PMB ethers
then provided $\text{1.178}$, which was set up for a gold catalyzed spiroketalization, which was conveniently accomplished using a cationic JohnPhos ligated gold species. At this stage, the second generation route intercepted the first generation route. The group decided, however, to install the side chain in a different fashion, now relying on a Julia-Kociencki olefination with the appropriate sulfone ($\text{1.185}$) to complete the second generation Furstner synthesis of spirastrellolide F ($\text{1.8}$).

*The Furstner Synthesis of Spirastrellolide A ($\text{1.2}$)*

In 2013, the Furstner group, employing the lessons learned from the spirastrellolide F ($\text{1.8}$) synthesis reported completion of a total synthesis of spirastrellolide A ($\text{1.2}$)$^{30}$ (Scheme 1-32). The strategy and general retrosynthesis were not significantly different from those used in their earlier approaches. However, due to the presence of unsaturation in the southern hemisphere spiroketal, a somewhat different approach to the southern hemisphere was envisioned, with the unsaturation at C(15)-C(16) masked as a dithiane.

Towards this end, a Mukiyama aldol between tetrahydropyran possessing a TMS enol ether ($\text{1.163}$) and dithiane aldehyde $\text{1.186}$ (Scheme 1-32), followed by an Evans-Tischenko reduction and protecting group manipulations lead smoothly to the fully protected dithiane $\text{1.187}$, which was coupled to aldehyde $\text{1.142}$ to complete the carbon skeleton $\text{1.188}$. Spiroketalization and conversion of the eastern terminus to the desired vinyl triflate next provided $\text{1.190}$, which was in turn converted to acid $\text{1.191}$ in four steps, ready for union with the northern hemisphere.
The fragment union steps once again followed the precedent set in the spirastrellolide F synthesis (Scheme 1-31) and is shown in more detail in Scheme 1-33. Thus, Suzuki cross coupling as before furnished coupled product 1.193, which similarly underwent a macrolactonization/diastereoselective reduction sequence to 1.194. At this stage, the C(16) ketone was converted to the corresponding olefin by triflation and, in turn, a palladium catalyzed reduction, to provide spiro-olefin 1.195. Coupling of the side chain was then performed via a Julie-Kocienski olefination of the derived aldehyde 1.196 with sulfone 1.197. Global deprotection then furnished spirastrellolide A methyl ester (1.2) in a modest yield (32% over two steps).
1.5 Summary of Smith Group Approaches to Spirastrellolide Fragments at the Outset of Thesis Research

The Smith group has had a long-standing interest in the spirostrellolide family of natural products. Their intriguing cytotoxicity addressed the Smith group's interest in the construction of complex anti-cancer natural products, while the polyketide architecture seemed nearly perfect for exploiting Type II Anion Relay Chemistry (ARC), which was first reported by Smith et al. as a new synthetic paradigm in 2006. As such, studies in pursuit of a total synthesis of spirastrellolide A (1.2) commenced in 2004 soon after the original isolation of the natural product and the early development of ARC.
The first subtarget to succumb to synthesis in the Smith group was the southern hemisphere of spirastrellolide A (1,2), performed by graduate student Dae-Shik Kim and post-doctoral fellow Dr. Helmar Smits. At the time, difficulties associated with a cross metathesis approach towards hemisphere union were unknown, so the target chosen was 1.196, containing a terminal alkene. The Smith retrosynthetic analysis to this target is shown in Scheme 1-33 A.

**Scheme 1-34 Retrosynthetic analysis towards an advanced southern hemisphere fragment**

Attachment of the C(1)-C(9) and C(23)-C(25) fragments was envisioned to occur at a late stage, via dithiane addition to the termini of spiroketal-containing fragment 1.199. This fragment, in turn, was seen to arise from linear precursor 1.200, which was viewed as an excellent candidate for Type II Anion Relay Chemistry. This original approach, however, proved problematic given that the bifunctional linchpin 1.202 was recalcitrant to nucleophilic attack, a fact that is now understood to arise from a preferred conformation which embeds the epoxide into the
dithiane ring. A revised retrosynthesis was therefore implemented (Scheme 1-33 B), utilizing the simpler linchpin \textbf{1.206}, with the expectation that the methyl substituent could be installed at a later point in the synthesis.

This synthetic analysis was indeed converted to practice: deprotonation of dithiane \textbf{1.203}, addition to linchpin \textbf{1.206} and, after gegen-ion promoted Brook rearrangement, trapping with epoxide \textbf{1.201} furnished the three component adduct \textbf{1.205} in 77% yield (Scheme 1-34).

![Scheme 1-35 Synthesis of advanced spiroketal 1.204](image)

Double dithiane removal utilizing the mercury conditions of Corey and Erickson\textsuperscript{39} provided diketone \textbf{1.207}, which, upon \textit{anti} reduction led to partial hemiketalization; this mixture was subsequently treated with aqueous perchloric acid to permit complete spiroketalization, via a Ferrier reaction, that yielded \textbf{1.208} as a single diastereomer. After protection, the unsaturated spiroketal \textbf{1.204} was obtained in 34% yield over the 6 steps. Unfortunately, upon repeated attempts to install directly the C(14) methyl group success was not achieved. A three step sequence was therefore implemented (Scheme 1-35) involving allylic oxidation, displacement of the resulting hydroxyl group with bis(phenylsulfonyl)methane with inversion of configuration via a Mitsunobu\textsuperscript{40} reaction, and reduction. Frasier-Reid epoxidation\textsuperscript{41} to provide the key intermediate epoxide \textbf{1.199}. Treatment of this epoxide with the potassium anion of dithiane \textbf{1.197} proceeded smoothly to furnish coupled product \textbf{1.211}.
Scheme 1-36 Synthesis of advanced fragment 1.211

Standard functional group manipulations then led to aldehyde intermediate 1.212 (Scheme 1-37). All that remained to complete a potentially viable southern hemisphere skeleton was installation of the C(23)-C(25) fragment by dithiane addition to the aldehyde terminus of 1.212 (Scheme 1-36).

Scheme 1-37 Installation of the C(23)-C(25) fragment and completion of synthesis
Unfortunately, all attempts to achieve the correct stereochemistry at C(22) proved futile, with most conditions favoring the undesired isomer. Repeated attempts to reverse the diastereoselectivity of the addition lead, at best, to a 1:1 mixture of isomers. Ultimately, a three step oxidation/reduction sequence permitted the conversion of the undesired diastereomer to the correct diastereomer at C(22) (1.214, Scheme 1-36). An additional three steps then completed the synthesis of the proposed spirastrellolide A (1.2) southern hemisphere 1.196.

**Approach Towards the Northern Hemisphere of Spirastrellolides B (1.3) and E (1.6)**

In 2012, post-doctoral scholar Dr. Xiaozhao Wang in the Smith group achieved the synthesis of the northern hemisphere of spirastrellolide family members lacking a chlorine substituent.\(^{42}\) Retrosynthetically, the key step was the unraveling of the central [5,6,6]-bisspiroketal to a simple monoketal 1.216 via an alkyne bisfunctionalization tactic (Scheme 1-37). The requisite ketal 1.216 in turn, was envisioned to be constructed in a straightforward manner from the three fragments 1.217-9.

![Scheme 1-38 Retrosynthetic analysis of an advanced northern hemisphere fragment](image)

In a forward sense, addition of the lithium anion of 1.218 to epoxide 1.217 furnished the two component adduct 1.220 (Scheme 1-37). A three step conversion to the corresponding methyl ketone then provided 1.222, which was poised for a Mukiyama aldol reaction with aldehyde 1.219. The resulting product was obtained both in high yield and diastereomeric purity (>19:1). Protection of the free hydroxyl as the MOM ether then provided 1.223, substrate for the planned spiroketalization.
Scheme 1-39 Synthesis of spiroketalization precursor 1.223

Unfortunately, when 1.223 was converted to a mixture of ketals by the removal of the two PMB groups with DDQ, and subsequently treated with Au(I)Cl in THF, a low yield of a spiroketal that did not possess the desired [5,6,6] framework was isolated. Instead, the product, identified by extensive NMR studies, proved to be the related [5,5,7] bisspiroketal system (1.227, Scheme 1-40). Closer inspection revealed that alkyne activation by gold lead to nucleophilic attack at the incorrect C(9) terminus of the alkyne bond. Selective removal of only the C(14) PMB group under carefully controlled conditions, followed by alkyne activation in protic solvent lead exclusively to ketone 1.226, demonstrating that attack by nucleophiles was favored at C(9). This intermediated could also be converted to 1.227 by removal of the remaining PMB group and acid-catalyzed cyclization.

Scheme 1-40 Formation of an unexpected [5,5,7]-bisspiroketal

While the [5,5,7] system was of interest from the point of view of spirastrellolide A analogues, an approach towards the original [5,6,6] bisspiroketal was still clearly required. Reasoning that the attack of the C(14) hydroxyl onto the activated alkyne was slow relative to
attack of the C(7) hemiketal oxygen or external attack by solvent, a system where both of these pathways were disfavored was eventually identified (Scheme 1-41).

![Scheme 1-41 Completion of the advanced northern hemisphere fragment](image)

That is, while desired product formation under gold catalysis could not be achieved, platinum catalysis in the form of Ziese’s salt permitted alkyne functionalization at the desired C(10) acetylenic carbon to form ketal 1.230 as a mixture of diastereomers. This observation is consistent with the results of de Brabander and coworkers, which highlight the higher selectivity of platinum for 6-endo cyclizations relative to gold in such systems. Removal of the remaining hydroxyl protecting group then provided the desired [5,6,6] system 1.212 under acid catalysis, thereby completing the synthesis of the advanced northern hemisphere fragment of the spiroastrellolide family. Thus, by 2010, the Smith group had access to both northern and southern hemisphere fragments of several members of the spiroastrellolide family.

1.6 References Relevant for Chapter 1


2.1 Identification of a New Spirastrellolide Synthetic Target

In Chapter 1, in addition to a general overview of earlier spirastrellolide synthetic approaches and total syntheses, the successful completion by the Smith group of advanced intermediates for both the northern and southern hemispheres of spirastrellolide congeners was described. With approaches to both hemispheres established, the focus shifted to completion of a total synthesis of one of the spirastrellolide congeners. At this stage, a target needed to be defined. At the outset of Smith group efforts in the spirastrellolide field, as early as 2003, spirastrellolide A was the presumed target, as no others had yet been reported. Over the years, however, approaches to fragments relevant to spirastrellolides A, B, and E had been described. In addition, the synthesis of spirastrellolides A (1.2) and F (1.8) had been achieved by the Paterson and Furstner groups, respectively.1-3 After careful analysis of the approaches available to the Smith group, it became clear that spirastrellolides B and E were our most appropriate targets, as our northern hemisphere route lacked chlorine at C(28) (see Figure 2-1 for numbering). We therefore chose the more complex spirastrellolide E (1.6), possessing a southern hemisphere spiroketal olefin, as our target. No synthesis of this congener has been reported to date.

![Figure 2-1 Spirastrellolides A, B and E](image)
2.2 Examination of Smith Group Southern Hemisphere Approach

With this decision made, we examined the relevant synthetic routes to advanced northern and southern hemisphere fragments in preparation for the synthesis of ample material for hemisphere union studies. This analysis quickly identified the Smith southern hemisphere route (Scheme 2-1) as problematic from the point of view of rapid material advancement, as the sequence led only to a 0.2% overall yield, requiring a 33 step longest linear sequence.

Scheme 2-1 Summary of first generation southern hemisphere route

Careful examination of the published southern hemisphere route revealed a number of areas where significant improvements could be achieved. First, the inability to install the C(14) methyl group during the Type II ARC reaction required a costly three step sequence to correct (c.f., 2.5 → 2.6). Second, the configuration at C(22) in 2.8 could not be established...
stereoselectively after many attempts; at best a 1:1 ratio of the two diastereomers resulted upon addition of dithiane 2.10, with most conditions providing the undesired diastereomer as the major product. The conversion of the undesired diastereomer 2.11 to the desired configuration (i.e., 2.12) also necessitated a three step sequence to correct (i.e., oxidation to the corresponding ketone, reduction with concomitant cleavage of the primary pivalic ester and reprotction of the free primary alcohol).

A final consideration in revising the Smith southern hemisphere target lay in the information gathered by the Paterson and Furstner groups on the way to their successful total syntheses of spirastrellolide congeners.4,5 Specifically, attempts to unite the advanced southern and northern hemisphere fragments at the C(25)-C(26) linkage led to repeated failures due to the considerable steric hindrance imparted by the U-shape nature of the northern hemisphere bis-spiroketel (vide supra). As such, the original southern hemisphere fragment (2.13, Scheme 2-1), which possesses a terminal olefin poised for C(25)-C(26) bond formation via olefin metathesis, was deemed to have a very low chance of success. A strategy that forms the nearby C(24)-C(25) bond, as in previous successful syntheses of Paterson and Furstner, would be clearly preferable.

2.3 Revision of Synthetic Strategy and Choice of New Spirastrellolide Target

With these considerations in mind, a retrosynthetic analysis for spirastrellolide E was proposed (Scheme 2-2). For the hemisphere union strategy, we elected to pursue the method of Paterson, uniting hemispheres 2.14 and 2.15 via a Suzuki cross coupling between an sp^3 boronate derived from a northern hemisphere alkene and a vinyl iodide present in an advanced southern hemisphere fragment. Importantly, we chose to move away from a stepwise hemisphere construction strategy, as employed by Paterson, and attempt to unite an advanced southern hemisphere fragment 2.15, with the expectation of improving the convergence of the route. Such a disconnection would lead back to C(28)-C(40) northern hemisphere fragment 2.14, readily available from 2.17, the result of our earlier northern hemisphere efforts, and 2.15, a revised C(1)-C(24) southern hemisphere fragment.
Next, we turned to the development of a retrosynthesis for the new C(1)-C(24) southern hemisphere fragment 2.15. Encouraged by the success of our northern hemisphere synthesis, which crafted the central [5,6,6] spiroketal via a metal-catalyzed bis-cyclization of the corresponding alkyne, we envisioned that the central [6,6] spiroketal core of the southern hemisphere could similarly arise from cyclization of two pendant hydroxyls onto a central alkyne moiety (Scheme 2-3). A major concern, however, was the regioselectivity of the addition. Clearly, for our purposes, we required the attack of the C(21) hydroxyl on the C(15) acetylynic carbon (blue arrow, Scheme 2-3). However, both our own efforts on the northern hemisphere, as well as the efforts of many other researchers, have revealed strong directing effects of the specific conditions on the regioselectivity of metal-catalyzed spiroketalizations, with mixtures formed in a large number of cases.
Scheme 2-3 Possible modes of nucleophilic attack for a gold catalyzed spiroketalization

We were therefore drawn to the method of Aponick and coworkers (Scheme 2-4), in which a substrate propargylic alcohol directs the regioselectivity of a gold-catalyzed cyclization in 2.19 by the formation a hydrogen bond between an incoming hydroxyl and the C(3) propargyl hydroxyl in only one of the four possible hydroxyl approaches (Scheme 2-4, green arrow).

Conveniently from the perspective our proposed spirastrellolide synthetic strategy, rather than providing the expected saturated spiroketal, an unsaturated ketal is formed instead (2.22). The mechanism of this transformation will be discussed in greater detail in Chapter 3, However, in basic terms, addition of the C(9) hydroxyl of 2.19 to the gold-activated alkyne forms a vinyl gold complex (2.20), which readily eliminates with loss of a ligated gold hydroxide complex, leading to an intermediate allene. At this stage, two pathways to the product are possible. The allene can isomerize to the corresponding oxocarbenium (Path a), followed by a non-catalyzed addition of the remaining hydroxyl. Alternatively, gold catalyzed addition of a hydroxyl to a gold-activated allene followed by protodeauration could also lead to the desired spiroketal (Path b).

Scheme 2-4 Alcohol directed spiroketalization method of Aponick
The expected reaction course for our proposed substrate 2.23 is shown in Scheme 2-5. Thus, by analogy to the simple system reported by Aponick, we expected selective attack of the C(21) hydroxyl onto the C(17) terminus of the alkyne, proceeding via hydroxyl directed transition state 2.24, to produce vinyl gold intermediate 2.25, which after a second cyclization event, would furnish southern hemisphere fragment 2.15, or a close derivative.

Scheme 2-5 Expected spiroketalization of intermediate 2.23

From the retrosynthetic perspective, applying the gold catalyzed spiroketalization transformation to the southern hemisphere target 2.15 would lead to intermediate 2.23 (Scheme 2-6), which in turn can be further simplified into two complex fragments: aldehyde 2.27 and alkyne 2.26.

Scheme 2-6 Retrosynthetic analysis of revised southern hemisphere
Alkyne 2.26 is very similar to a fragment of the Paterson synthesis of spirastrellolide A (1.2), whereas aldehyde 2.27 is an ideal substrate to demonstrate the versatility of Anion Relay Chemistry (ARC). In particular, we envisioned a Type I ARC union of epoxides 2.29 and 2.30 around the central TES-dithiane linchpin 2.28. Notably, by changing the bonds formed via the ARC union protocol, the problematic C(14) methyl group is now installed as part of an appropriate epoxide. Also notable is installation of the C(22) hydroxyl in a stereoselective manner (vide infra).

2.4 Synthesis of the Requisite Fragments for ARC Union

With this route in mind, we began by preparing the requisite epoxides for the key strategic ARC union with the help of Martin Cattoen, a French summer exchange student. Epoxide 2.29, a known compound, was readily prepared by a modification of the reported procedure (Scheme 2-7).

Scheme 2-7 Synthesis of epoxide 2.29

To this end, commercially available (S)-diethyl malate was first methylated diastereoselectively exploiting the procedure of Seebach, to provide a 67% yield of an inseparable mixture of diastereomers in ratios ranging from 5:1 to 8:1 in favor of the desired isomer. Next, exhaustive reduction of the diester led to the triol, which, without purification, was treated with benzaldehyde dimethyl acetal in the presence of PPTS to provide intermediate 2.32. We found that use of stoichiometric PPTS, rather than the catalytic amount called for in the original procedure, gave optimal results. At this stage, the minor diastereomer could be separated, providing the desired benzilidene ketal as a single compound in 63% yield over the
two steps. Regioselective opening of ketal 2.32 was best achieved with lithium aluminum hydride in the presence of aluminum trichloride in a dichloromethane/diethyl ether mixture at reflux.\textsuperscript{12} Finally, Frasier-Reid epoxidation\textsuperscript{13} provided the desired epoxide 2.29 in near quantitative yield. Overall, epoxide 2.29 could be constructed in 6 steps and 38\% overall yield from (S)-diethyl malate. The sequence also proved scalable, with a single 25 g batch of (S)-diethyl malate providing more than 6 grams of the desired epoxide.

The second epoxide 2.28 for the ARC union could also be constructed readily on large scale (Scheme 2-8). Here, we chose to modify a route first reported by de Brabander.\textsuperscript{14} Starting with commercially available 3,4-dihydropyran, hydration under mild acidic conditions furnished lactol 2.34, which could be reacted with freshly prepared ethyl (triphenylphosphoranylidene) acetate\textsuperscript{15} to form $\alpha,\beta$-unsaturated ester 2.35 as an inconsequential mixture of olefin isomers (typically 10-12:1 as determined by NMR). Notably, choice of the ethyl ester provided critical in securing improved yields over the remainder of the synthetic sequence. Oxidation followed by Brown allylation\textsuperscript{16} then furnished the desired homoallylic alcohol 2.37 as a single enantiomer in 70\% yield over 2 steps. Importantly, the reaction could be run $>$20 g scale to provide the desired product in 61\% yield over 2 steps. Cyclization of alcohol 2.37 initially proved variable, as under the catalytic potassium tert-butoxide conditions, competitive formation of the tert-butyl ester was observed. Maintaining the reaction temperature below $-60 \, ^\circ C$ and quenching the reaction by dropwise addition of a saturated aqueous ammonium chloride solution, while maintaining the temperature at $-60 \, ^\circ C$ permitted the preparation of chromatographically homogeneous material. When these precautions were taken, the cyclized product 2.38 could be formed in $>$95\% yield on $>$10 g scale and importantly was of sufficient purity to be used in the next sequence of steps; namely, reduction of the ester and protection of the resulting primary hydroxyl as the TBS ether. The overall yield of 2.39 for the three operations from 2.37 was 82\%.
Dihydroxylation of the terminal olefin next provided the diol 2.40 in 97% overall yield as a 3:1 to 6:1 mixture of diastereomers, which could be separated by careful column chromatography to provide an improved diastereomeric ratio (c. 10-12:1) of the desired diastereomer. The stereochemistry of the major product was ultimately obtained by analysis of a later intermediate (vide infra, Scheme 3-7). Frasier-Reid epoxidation\(^{13}\) then provided epoxide 2.30 in preparation for the ARC union. Overall, epoxide 2.30 could be synthesized in 9 steps and 27% overall yield on multigram scale.

### 2.5 ARC Union and Further Elaboration

With both ARC epoxides in hand, optimization of the Type I Anion Relay Chemistry union began (Table 2-1). In a first trial, excess TES-dithiane (1.3 equiv) was deprotonated with \(n\)-butyllithium at room temperature for 5 minutes, then cooled to -45 °C and reacted with epoxide 2.29 in a 1:1 molar ratio. After 1 hour at this temperature, epoxide 2.30 was added as a solution in ether, followed by HMPA (2 equivalents) as a solution in ether. Pleasingly, this protocol provided a 50% yield of the desired three component adduct 2.41 (Table 2-1).

While this initial protocol proved successful in providing the desired product, there were a few drawbacks. First, addition to epoxide 2.29 was incomplete as evidenced by the observation of quenched intermediate 2.42 in the NMR spectrum of the unpurified reaction mixture. Second, because intermediate 2.42 was used in excess, none of the reaction components could be
recycled. As a consequence, the use of excess of **2.29** to assure complete conversion of intermediate **2.42** was unattractive. We therefore decided to use only one equivalent of epoxide **2.29**, but to use epoxide **2.30** in excess, as such a protocol would permit the unreacted epoxide **2.30** to be recovered and reused.

**Table 2-1 Optimization of the key ARC Union protocol**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dithiane eq</th>
<th><strong>2.29 eq</strong></th>
<th><strong>2.30 eq</strong></th>
<th>Solvent 1</th>
<th>Solvent 2</th>
<th>Temp</th>
<th>HMPA eq</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
<td>EtO</td>
<td>EtO</td>
<td>-45°C</td>
<td>-0.75</td>
<td>~50% <strong>2.41</strong></td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>1.0</td>
<td>1.3</td>
<td>THF</td>
<td>1:1 EtO/THF</td>
<td>--</td>
<td>--</td>
<td>~40% <strong>2.41</strong>, 21% <strong>2.42</strong>, 47% <strong>2.30</strong></td>
</tr>
<tr>
<td>3</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>THF</td>
<td>--</td>
<td>-78 to -55°C</td>
<td>--</td>
<td>~20% <strong>2.41</strong>, 40% <strong>2.42</strong>, 67% <strong>2.30</strong></td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>EtO</td>
<td>--</td>
<td>-40°C</td>
<td>--</td>
<td>incomplete addition</td>
</tr>
<tr>
<td>5</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>-40°C</td>
<td>--</td>
<td>~50% <strong>2.41</strong>, 22% <strong>2.42</strong>, 34% <strong>2.30</strong></td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>--</td>
<td>1.4</td>
<td>1:3 THF:EtO</td>
<td>3:1 THF:EtO</td>
<td>-45°C</td>
<td>--</td>
<td>~30% <strong>2.41</strong>, 42% <strong>2.42</strong>, 60% <strong>2.30</strong></td>
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<td>7</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>EtO</td>
<td>--</td>
<td>1.5</td>
<td>~60% <strong>2.41</strong>, 16% <strong>2.42</strong>, 8% <strong>2.30</strong></td>
</tr>
<tr>
<td>8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1.5</td>
<td>62% <strong>2.41</strong>, 16% <strong>2.42</strong>, 35% <strong>2.30</strong></td>
</tr>
<tr>
<td>9</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>4.0</td>
<td>--</td>
<td>62% <strong>2.41</strong>, 21% <strong>2.42</strong>, 40% <strong>2.30</strong></td>
</tr>
<tr>
<td>10</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.75</td>
<td>--</td>
<td>62% <strong>2.41</strong>, 16% <strong>2.42</strong>, 48% <strong>2.30</strong></td>
</tr>
</tbody>
</table>

*THF was added until complete addition to first epoxide was observed.

-- denotes the use of the above value.

When this modified protocol was implemented (Table 2-1, Entry 2), the desired product was isolated in 40% yield, with 21% of unreacted **2.42** after quenching the reaction mixture. Pleasingly, more than 50% of the unreacted epoxide **2.30** could be recovered by simple column chromatography. We next examined a variety of reaction factors. A temperature of ~45°C proved optimal for the first epoxide addition, as lower temperatures lead to poor conversion (Entry 3). The optimal solvent proved to be a mixture of ether:THF (3:1) for the first step and 9:1 ether:THF mixture overall (Entry 4-7). That is, at lower temperatures and solvent polarities, incomplete addition of the relative non-nucleophilic TES-dithiane anion to epoxide **2.29** was observed; at higher solvent polarities the highly basic anion of **2.42** was more readily quenched. Thus, identification of the ideal solvent polarity over the course of the ARC protocol proved highly
beneficial. With the optimized solvent combination, a 60% yield of the desired product could be obtained. Increasing the amount of epoxide \textbf{2.30} to 2 equivalents provided a consistent 62% yield of the desired product \textbf{2.41} (Entry 8). Interestingly, the amount of HMPA, proved less important (Entry 9-10).

It should be noted that the yields in Table 2-1 are approximate due to the formation of an inseparable and very difficult to characterize product, which, based on later observations (\textit{vide infra}), is believed to be the semi-symmetrical product \textbf{2.43} (Figure 2-1), which forms upon addition of intermediate \textbf{2.42} to excess epoxide \textbf{2.30}. The proton NMR signals of this product overlap with those of the product, so assignment of the exact relative amounts proved difficult; nonetheless, between 10-20% of \textbf{2.43} was typical. It was later discovered that this byproduct could be removed by conducting the addition to epoxide \textbf{2.30} below 0 °C. Performing the reaction under these conditions lead to a 63% yield of coupled product \textbf{2.41} as a single compound.

![Figure 2-2 Proposed byproduct from ARC union](image)

With three component adduct \textbf{2.41} in hand, we continued construction of the key aldehyde \textbf{2.27} (Scheme 2-9). First, dithiane removal was examined. The conditions for this transformation, as well as subsequent chemistry of the resulting ketone en route to \textbf{2.27}, were established by Dr. Xiaozhao Wang, who found that NBS in the presence of silver perchlorate and 2,6-lutidine\textsuperscript{17} provided a reliable 70-75% yield of hydroxy ketone \textbf{2.44}. Stereoselective \textit{anti}-Gribble-Evans\textsuperscript{18} reduction then provided the desired diol in 70% yield as a single diastereomer. At this stage, byproduct \textbf{2.43} could be separated as the corresponding diol. Continuing with the synthesis, bis-TBS protection of the diol was required. Upon reaction of the diol with TBSOTf in the presence of 2,6-lutidine, however, the C(13) TES group migrated to the adjacent carbinol (\textit{c.f., 2.45}, Scheme 2-9). The resulting products proved difficult to separate. It was therefore decided to
revise the protecting group scheme employing the MOM blocking group; this transformation was readily achieved with MOMBr in the presence of tetrabutylammonium iodide and Hunig's base at elevated temperatures in dichloroethane as solvent. However, from the perspective of the total synthesis of spirastrellolide E (1.6), we recognized that such a protecting group scheme would not be ideal, as the MOM group would be the last protecting group to be removed. Such deprotections are notoriously difficult, particularly in late stage settings. Nevertheless, we were eager to validate some of the later chemistry and chose to proceed with the MOM-based route. To this end, removal of the primary benzyl group and oxidation to the corresponding aldehyde provided advanced fragment 2.27 in preparation for alkynylation.

Scheme 2-9 Successful synthesis of aldehyde 2.27

The coupling partner for the proposed alkynylation was next constructed based on the synthesis of a similar fragment by the Paterson group in their approach to spirastrellolide A (1.2). Notably, the C(22) stereocenter, which had proven problematic in our previous spirastrellolide A and B southern hemisphere synthesis, is set with excellent selectivity (vide infra). The first task was the preparation of the sensitive aldehyde 2.48. The Paterson group had synthesized 2.48 by performing a titanium mediated hydromagnesiotation of 2-butyn-1-ol, followed by an iodine quench (Scheme 2-10). In our hands, this procedure proved difficult to scale up due to formation.

53
of an unidentified side product, which proved impractical to separate. In addition, yields tended to be variable. We therefore turned to a two step procedure involving protection of 2-butyn-1-ol as the corresponding TES ether, followed by a hydrozirconation/iodination protocol. Careful oxidation of the resulting product with Dess-Martin periodinane then provided aldehyde 2.48. Yields for the sequence, however, remained low, due partially to the sensitivity of the final product to light and concentration, as well as the volatility of the intermediates.

Scheme 2-10 Synthesis aldehyde 2.48 for aldol reaction

Nevertheless, the desired aldehyde 2.48 could be obtained on multi-gram scale and then reacted with the boron enolate of acylated oxazolidinone 2.50 (Scheme 2-11) to furnish the desired syn isomer 2.51 as a single diastereomer in 82% yield. Removal of the auxiliary by formation of the Weinreb amide proceeded smoothly. However, the desired product and the auxiliary proved inseparable. Subsequent protection of the free hydroxyl as the TES ether permitted separation of the desired product 2.53 from the auxiliary, which had now been converted to the TES-amide 2.54 under the reaction conditions. Importantly, the valuable auxiliary 2.55 could then be recovered by following a literature procedure.

Scheme 2-11 Synthesis of Weinreb amide 2.53
Next, Grignard addition of bromide 2.57 to 2.53 (Scheme 2-12) was planned. The desired bromide could be constructed in a straightforward manner from commercially available 3-butyl-1-ol involving TMS protection of the terminal alkyne, followed by the Appel conditions to install the primary bromide (Scheme 2-12).

![Scheme 2-12 Successful synthesis of alkyne fragment 2.26](image)

The bromide was originally purified by distillation, however, this lead to no conversion in the subsequent Grignard reaction due to the co-distillation of bromoform, a byproduct from the Appel reaction. When column chromatography was employed as the method of purification, the desired Grignard reaction proceeded in >90% yield. The resulting ketone 2.59 was then reduced diastereoselectively to the corresponding alcohol employing zinc borohydride, and the alcohol methylated with Meerwein's salt. Finally, removal of the TMS group was achieved employing potassium carbonate in ethanol, which lead to partial removal of the secondary TES ether. Reprotection provided alkyne 2.26 in 77% yield over 2 steps.

With both the aldehyde and alkyne fragments available, the critical alkynylation could now be explored (Figure 2-3). First, however, the stereochemistry of the resulting propargylic carbinol must be considered with respect to spiroketalization. In principle, this carbinol center would be removed to form the requisite unsaturation present in the spiroketal. A search of the
literature, however, suggested that the spiroketalization reaction would not be as simple and depends strongly on the configuration of the carbinol stereocenter to be removed.

**Figure 2-3 Proposed alkynylation**

In their original publication, Aponick and coworkers demonstrated that when syn and anti were subjected to a mixture of JohnPhos ligated gold (I) chloride and silver triflate, the resulting cationic gold catalyst displayed strikingly different reactivities with the anti and syn isomers (Scheme 2-13 A).

**Scheme 2-13 Literature examples of spiroketalization efficiency depending on substrate stereochemistry**
The *anti* product gave the desired spiroketal 2.63 in high yield; the *syn* product, on the other hand, gave a complex mixture of spiroketals, with the desired product (2.63) a minor component. Similarly, in a more complex setting, the Forsyth group\(^{23}\) reported that compound 2.66 (Scheme 2-13, B) behaved differently in a related gold catalyzed spiroketalization. Once again, the *anti* isomer underwent clean reaction to furnish the desired product (2.67), while the *syn* isomer lead to a mixture of spiroketals, with the [5,7] saturated spiroketal favored as a nearly 1:1 mixture of diastereomers.

With this precedent in mind, it seemed clear that the propargylic stereocenter would comprise an important factor in the reactivity and selectivity of our proposed gold catalyzed spiroketalization process. However, the details of the impact were unknown; and as such, we chose to prepare both diastereomers varying at C(15) and subject each to gold catalysis. A non-selective alkynylation was therefore pursued. Treatment of alkyne 2.26 with 1 equivalent of lithium diisopropylamide in THF, followed by cannulation into a solution of aldehyde 2.27 in THF smoothly provided a 75% combined yield of a mixture of diastereomers (1.7:1), with the *syn* product favored slightly (Scheme 2-14). Choice of base (i.e., LDA) proved critical to the success of this reaction, as the use of the more basic *n*-butyllithium led to exclusive lithium-halogen exchange prior to alkynylation.

![Scheme 2-14 Alkynylation and unsuccessful spiroketalization attempts](image)

With both alkyne isomers in hand, removal of the PMB group with DDQ provided spiroketalization precursors *syn* and *anti* 2.70, which were both subjected to gold catalysis. Unfortunately, the conditions of Aponick\(^{7}\), Forsyth\(^{23}\), Trost\(^{24}\) or several modifications thereof,
provided none of the desired spiroketal. The problem appeared to lie in the necessity for mildly acidic conditions to remove the C(13) TES ether during the reaction. Unfortunately, we were forced to use methanol at least as a cosolvent, with PPTS as a mild acid. Under these conditions, regardless of the gold source, slow decomposition of the substrate was observed.

### 2.6 A Second Approach to Southern Hemisphere

Undaunted, we reasoned that the use of a substrate possessing differential protection at the C(13), C(21) and C(22) hydroxyls would be more amenable to reaction optimization due to the possibility of isolating a triol spiroketalization precursor 2.71, which would not require any additional functional group manipulations during spiroketalization (Scheme 2-15).

![Scheme 2-15 Revised strategy for spiroketalization](image)

We therefore chose 2.71 as our new target (Scheme 2-16). Notably, in addition to the differential protection at C(13) and C(21), we chose to return to TBS protection at the C(9) and C(11) carbinols due to the aforementioned difficulties expected with selective MOM group removal at the late stages of the synthesis (vide supra).

Analysis of 2.71 is illustrated in Scheme 2-16. Spiroketalization and alkynylation were still envisioned as the end game, now requiring aldehyde 2.72. Importantly, this aldehyde could be constructed from the identical ARC components as our original intermediates by simply changing the order of addition, followed by dithiane removal and stereoselective reduction of the resulting ketone. This tactic serves as another illustration of the remarkable flexibility and utility of the ARC union protocol.
In the forward direction, ARC union with inverted order of addition proceed equally well under the conditions developed previously, providing intermediate 2.74 in 68% yield (Scheme 2-17). Dithiane removal was similarly successful with the optimal conditions from the first route. With the resulting product 2.75 readily available, simultaneous reduction of the hydroxy ketone and differentiation of the resulting diol was required. The Evans-Tischenko reduction with benzaldehyde was chosen to fulfill these goals. This strategy would permit the formation of a benzoate at C(13), a group that could be removed orthogonally with respect to both the C(21) PMB ether and the C(22) TES ether after union with 2.72 (Scheme 2-20).
After considerable optimization, we found that the reduction of 2.75 was best conducted via the portionwise addition of a freshly prepared samarium diiodide solution over the course of 8 hours in the presence of 15 equivalents of freshly distilled benzaldehyde, providing the desired anti-diol 2.76 in 84% yield as a single observable isomer. We were surprised to observe the formation of a second product, initially suspected to be the C(11) diastereomer. However, after careful separation and extensive NMR structural investigation, the byproduct was identified as 2.78 after TBS protection to assist purification. This byproduct has its origins in the initial ARC step where, at higher temperatures, excess TBS-dithiane can attack two equivalents of the excess epoxide 2.29 to form semi-symmetrical adduct 2.77, which is inseparable both at this stage and after dithiane removal.

Identification of 2.77 as a byproduct of the ARC step led us to reconsider the conditions for the ARC union in both the inverted and regular order of addition (vide supra). We reasoned that the symmetrical adduct was arising after introduction of epoxide 2.29 (Scheme 2-18). That is, immediately after Brook rearrangement the anion 2.42-Li is present in significantly larger quantities and should react with epoxide 2.29 significantly faster. We therefore reasoned that by lowering the temperature of the second epoxide addition, the rate of product formation would not be significantly influenced, while the rate of formation of byproduct 2.77 would decrease sufficiently such that double addition would not take place.

Scheme 2-18 Formation of byproduct 2.77
Indeed, when the second epoxide addition was maintained below 0 °C, the ARC product was isolated as a single compound in a similar yield as before. Importantly, when this chromatographically pure compound was carried through to the Evans-Tischenko reduction, a single diastereomer was obtained in 84% yield. The remaining hydroxyl was next protected as the TBS ether to yield 2.79 (Scheme 2-19). Removal of the primary benzyl group and careful oxidation with Dess-Martin periodinane (DMP)\textsuperscript{26} then provided aldehyde fragment 2.72. Two details are of note. First, oxidation to the aldehyde proved highly sensitive, as conditions other than DMP resulted in exclusive elimination of the benzoate to form the corresponding α,β-unsaturated congener, a fact that foreshadowed future difficulties (vide infra). Second, the decision to move away from TES protection at C(13) was highly beneficial in terms of yield - whereas in our previous sequence (see Scheme 2-9) yields were generally low due to partial loss of the labile C(13) TES ether, the late stage manipulations in Scheme 2-17 proceeded in uniformly high yield.

![Scheme 2-19 Completion of aldehyde 2.72](image)

Aldehyde 2.72 available from the above sequence was next coupled with the previously constructed alkyne 2.26, again utilizing a non-selective alkynylation protocol (Scheme 2-20). The diastereomers were readily separated by standard column chromatography and each isomer subjected to a two stage deprotection sequence, involving DIBAL-H mediated removal of the benzoyl group, following by oxidative removal of the PMB group. On small scale, this sequence readily provided samples of spiroketalization precursors syn-2.80 and anti-2.80. Note that the syn and anti designations are assigned here to match the syn and anti designations in the Aponick and Forsyth cases described in Scheme 2-13.
With the appropriate precursors in hand, we moved on to the critical gold catalyzed spiroketalization step (Scheme 2-21). Pleasingly, when anti-2.81 was treated with cationic JohnPhos ligated gold complex 2.82, a new product was isolated in 81% yield, which, after extensive 1D and 2D NMR analysis, proved to be the desired spiroketal 2.15.
The stereochemistry of the spiroketal core was confirmed by observation of a key nOe between the C(13) and C(21) protons (Figure 2-2); a similar nOe was observed by Patterson in a related system.28

![Figure 2-4 Key observed nOe confirming spiroketal stereochemistry](image)

Conversely, when syn-2.81 (Scheme 2-21) was subjected to the same spiroketalization conditions, none of the desired spiroketal was identified. Unfortunately, poor purity and instability to silica gel precluded the full structural characterization of this compound, though based on results that will be described in Chapter 3, we can now assign the structure to be 2.83 (Scheme 2-21).

In conclusion, the first synthesis of the proposed southern hemisphere fragment for spirastrellolide E, namely C(1)-C(24) spiroketal 2.15, has been achieved, proceeding in 19 steps (longest linear sequence) and a 2% overall yield. An account of the synthesis of 2.15 was published in a 2015 Tetrahedron Letters Special Issue to honor and remember Henry Wasserman, Yale University (1948-2013).29

![Figure 2-5 Southern hemisphere 2.15](image)

### 2.7 References Relevant to Chapter 2


Chapter 2 described the successful completion of a synthetic approach to the unsaturated southern hemisphere relevant to spirastrellolide E, a congener of the spirastrellolide family of antitumor agents. Upon completion of this sequence, our thoughts turned: 1) to optimization of the sequence with the ultimate goal of scaling up to 1 gram of the southern hemisphere for completion of spirastrellolide E (1.6), and 2) to the steps necessary for completion of a total synthesis of spirastrellolide E.

### 3.1 Examination and Further Revision of the Hemisphere Coupling Strategy

With southern hemisphere 3.2 complete and the northern hemisphere 3.1 being constructed by Dr. Roberto Forrestieri, thoughts first turned to the steps necessary to complete a total synthesis (Scheme 3-1). The initial plan was to involve a Suzuki cross coupling between southern hemisphere 3.2 and a boronate (3.1) derived from the northern hemisphere. Such a cross coupling would provide intermediate 3.3, based on the precedent of both the Furstner\(^1\) and Paterson\(^2\) groups. Next, the installation of the C(23) and C(24) hydroxyl and methyl substituents with control of stereochemistry would be required.

![Scheme 3-1 Examination of proposed hemisphere union](image)

Examination of intermediate 3.3, however, reveals an earlier underappreciated potential chemoselectivity problem – namely, the functionalization of the C(24)-C(25) olefin in the presence

66
of unsaturation in the southern hemisphere [6,6]-spiroketal. A review of the previous strategies to install the C(24-25) stereodiad was not promising. Thus, the Paterson group used a hydroboration/oxidation sequence to chemo- and stereo-selectively functionalize the C(24)-C(25) olefin prior to spiroketal formation (Scheme 3-2 A). Such a reaction applied to 3.3 would almost certainly not be selective (Scheme 3-2 B), as the C(15)-C(16) olefin is expected to be both more sterically accessible and more electron rich. Indeed, it is perhaps as a result of this observation that the Paterson group elected to construct the southern hemisphere in a stepwise fashion.

Scheme 3-2 Problematic application of Paterson conditions to intermediate 3.3

The Furstner synthesis alternatively utilized a difficult hydrogenation of an exo-olefin in their spirastrellolide F synthesis (Scheme 3-3 A), which would not be suitable for intermediate 3.3 due to the more hindered nature of the internal C(23,24) olefin. In Furstner's synthesis, even the relatively unhindered exo olefin required very forcing conditions. The lack of oxygenation at C(23) in our proposed intermediate 3.3, also raised a chemoselectivity concern with the more sterically accessible C(15)-C(16) olefin (Scheme 3-3 B). Undoubtedly, similar concerns led the Furstner group to first construct spirastrellolide F (1.8), lacking unsaturation in the southern hemisphere, and to mask the corresponding olefin in their spirastrellolide A (1.2) synthesis as a dithiane.
It quickly became clear that a new hemisphere coupling strategy would be required. We reasoned that masking and/or protecting the C(15)-C(16) olefin would be counterproductive, as spiroketal construction in 3.3 was the cornerstone of our southern hemisphere synthetic strategy. Instead, we sought a method that would permit functionalization of a C(24)-C(25) olefin chemoselectively. We were particularly intrigued by the possibility of using the C(23) hydroxyl, which we expected could be selectively deprotected, as a directing group for selective manipulation of the C(24)-C(25) olefin. Of the possible directed functionalizations, we chose the Sharpless asymmetric epoxidation\(^3\) due to the mild conditions and broad functional group compatibility. Although such a late stage oxidation is of considerably high risk, there are a large number of examples of the Sharpless epoxidation used in very complex settings. Figure 3-1 reveals a striking example from the Paterson synthesis of laulimalide A,\(^4\) in which a single olefin, out of a possible 7 olefins, was selectively epoxidized.
Figure 3-1 Application of highly selective Sharpless asymmetric epoxidation to laulimalide

With these considerations in mind, a revised hemisphere union, as outlined in Scheme 3-4, would be required. We reasoned that the C(25) methyl group could arise from the opening of an appropriate epoxide (3.12), which, in turn, would derive from a directed Sharpless asymmetric epoxidation of the appropriate allylic alcohol. In this manner, both the epoxidation and subsequent epoxide opening would be controlled by the C(23) hydroxyl. The requisite allylic alcohol (3.13) would result from a cross metathesis or ring closing metathesis of new northern and southern hemispheres 3.14 and 3.15.

Scheme 3-4 Revised retrosynthetic analysis for spirastrellolide E
We further reasoned that the difficulties with olefin metathesis at the C(25)-C(26) bond encountered by Paterson and Furstner would not be as relevant in our system, as the site of metathesis was now two bonds removed from the bulky northern hemisphere. Finally, we were cognizant of the potential incompatibility of typical conditions for nucleophilic methylation of epoxides with such an advanced system. Nevertheless, we were encouraged by a number of reports of such reactions in complex settings.\(^5\)\(^6\) In addition, we recognized that a number of possible substrates were amenable to the proposed strategy. In particular, applying the epoxidation/ring opening sequence after macrocyclic ring closure would also be possible and could address potential pitfalls encountered in the acyclic case of 3.13, as the spirastrellolide skeletons are well known to adapt distinctly different conformations upon macrocycle formation.\(^1\)\(^2\)

To pursue such a revised hemisphere union plan, a new southern hemisphere target would be required, possessing a terminal olefin. As the terminal carbon atom of the olefin would be lost during the olefin metathesis upon hemisphere union, the revised target was envisioned to be a C(1)-C(23) fragment \(i.e.,\) 3.15. Pleasingly, the retrosynthesis of this fragment, illustrated in Scheme 3-5, closely resembles our approach chosen for the previous southern hemisphere target (2.15, Scheme 2-6). Thus, spiroketalization and alkynylation leads back to aldehyde 3.17, which was used in the previous synthesis \(i.e.,\) 2.73, and a modified alkyne (3.18). Synthesis of alkyne 3.18 would thus be accomplished by a simple modification of the existing route, employing an Evans aldol reaction between the previously synthesized acylated oxazolidinone 3.19 (2.50 in Chapter 2) and acrolein.
Scheme 3-5 Retrosynthetic analysis of modified southern hemisphere

In a forward direction (Scheme 3-6), the planned Evans aldol reaction proceeded smoothly. Given that acrolein is a commodity chemical, it could be used in large excess (4-10 equiv).

Scheme 3-6 Synthesis of revised alkyne 3.18

Employing these conditions, the desired aldol product 3.20 was isolated in 61% yield (91% brsm) as a single diastereomer. Importantly, the unreacted 3.19 could be readily recycled. Moreover, 10 grams of 3.20 could be readily prepared in one run. Conversion to the corresponding Weinreb amide and TES protection, followed by Grignard addition as before then led to ketone 3.22.

At the stage of the requisite diastereoselective reduction of 3.22, we observed a reduced yield due to an alternate pathway involving attack of the product hydroxyl group onto the alkyne moiety. The products of this reaction were tentatively assigned as a mixture of 3.24 and 3.25,
which proved inseparable by column chromatography. However, after some optimization, the desired alcohol 3.23 could be obtained in a 61% yield by maintaining the reaction temperature below -60 °C. Pleasingly, methylation and removal of the alkynyl TMS group completed the synthesis of the new alkyne fragment 3.18. Importantly, use of 3.18 as the new alkyne fragment removed the least efficient step in the previous synthesis, namely the preparation of aldehyde 2.48 (Scheme 2-10) for the key aldol reaction. As an added bonus, the lack of hindrance near the TES carbinol in 3.23 permitted the alkynyl TMS group to be removed in an excellent yield of 94% without affecting this previously sensitive TES. As a result, the new alkyne fragment 3.18 could now be prepared in 22% overall yield from 3.19 in 7 steps on multigram scale.

With the new alkyne fragment readily available, alkynylation with aldehyde 3.17 (Scheme 3-7), previously prepared in the synthesis of 2.15 (Scheme 2-19) was performed, resulting, as before, in a ~1.5:1 ratio of the diastereomeric alcohols, syn-3.26 and anti-3.26, (89% combined yield), which were readily separated by column chromatography (Scheme 3-7). Attempts to remove the benzoyl group as before, via DIBAL-H reduction, on the larger scales involved in this route led to erratic results, with incomplete conversion observed in most cases.

![Scheme 3-7 Alkynylation and improved procedure for benzoyl group removal](image-url)
Reoptimization of this process led to the identification and use of freshly prepared ethyl magnesium bromide\(^7\) as the ideal reagent for the deprotection, proving reproducible 80-95% yields of the desired diols \textit{syn-3.27} and \textit{anti-3.27}. At this stage, we were able to confirm the assignment of the stereochemistry present in these diols utilizing the method of Rychnovsky\(^8\) by converting \textit{anti-3.27} to the corresponding bis acetonide \textit{3.28}, \textit{via} treatment with dimethoxypropane in the presence of PPTS (Scheme 3-8). The presence of acetonide methyl peaks corresponding both to a \textit{syn} acetonide (25, 25 ppm; C(9-11) diol) and an \textit{anti} acetonide (19, 30 ppm; C(13-15) diol) suggested the stereochemistry as shown for \textit{3.28} (Scheme 3-8). Finally, PMB removal employing excess DDQ (10 equiv) provided triols \textit{syn-3.29} and \textit{anti-3.29}.

\[\text{Scheme 3-8 Synthesis of revised spiroketalization precursors}\]

The stage was now set for spiroketalization. Using the previously optimized conditions, \textit{anti-3.29} readily underwent cyclization to furnish the desired spiroketal \textit{3.15} in 81% yield (Scheme 3-9). This transformation completed the synthesis of the revised C(1)-C(23) southern hemisphere fragment of spirastrellolide E in a longest linear sequence of 19 steps and an overall yield of 7.5%, a marked improvement over the route to \textit{2.15} (Chapter 2), which had proceeded with an overall yield of 2% over the same number of steps. Moreover, with an improved route to alkyne fragment \textit{3.17} available, the revised route proved to be significantly more scalable.
Scheme 3-9 Synthesis of a revised southern hemisphere fragment for spirastrellolide E

The *anti*-3.29 isomer, on the other hand, again provided a different product under the same reaction conditions. This time, however, we discovered that performing the reaction in methanol, instead of THF, permitted the isolation of spectroscopically pure material after simple filtration through a pad of silica gel to remove the gold catalyst. The pure sample, in turn permitted application of a series of detailed 1D (*¹H, *¹³C NMR and DEPT) and 2D (COSY, HSQC, NOESY, TOCSY) NMR studies. With NMR interpretation unhampered by extraneous signals, the structure of the byproduct could now be assigned as 3.30 (Figure 3-2).

Figure 3-2 Product from attempted spiroketalization of *syn*-3.29

3.2 Mechanistic Considerations for the Formation of 3.15 and 3.30

With the product of the minor diastereomer identified, a rationale for the formation of this compound could now be proposed. We will however first present a mechanism for the key spiroketalization reaction in more detail.
Figure 3-3 outlines the catalytic cycle as proposed by Aponick and coworkers in their original publication for systems that do not possess stereogenicity. In this system, there are two possible cycles, depending on which hydroxyl first attacks the gold-activated alkyne. In both cases, upon gold complexation with the triple bond, the attack of a hydroxyl group leads to a vinyl gold intermediate (3.32 or 3.36, Figure 3-3), depending on which hydroxyl attacks. In the case of the exo vinyl gold species 3.32, elimination of gold hydroxide leads to allene 3.33, most likely bound by gold. At this stage, both isomerization to vinyl gold (I) complex 3.34, followed by a non-catalyzed spiroketalization or direct oxyalkylation of a gold-activated allene are both possible to furnish 3.35. For endo vinyl gold (I) species 3.36, rearrangement to the oxocarbenium ion (3.37) precedes elimination to provide 3.38, which then undergoes a non-catalyzed addition of the pendent carbinol to the oxocarbenium ion.

This model accounts for observations made for many of the systems outlined in the original Aponick report, but does not provide information for situations in which stereogenicity is present, nor does it account for the role played by the directing carbinol in determining the regioselectivity of the reaction. The only published analysis of such a system comes from the work of Forsyth on the okadaic acids. As mentioned in Chapter 2, a similar stereochemistry-dependent spiroketalization was observed in their work. The rationale proposed is shown in
Figure 3-4. The authors invoke a kinetic preference for the 5-exo oxy-auration of the C(30) carbinol, attacking the C(33) terminus of the alkyne after complexation of the gold species. In the syn isomer of 3.39, this would lead to transition state A, which possesses a five-membered ring with all substituents in the equatorial orientation. Conversely, a similar 5-exo course of events in anti-3.39 would lead to transition state B, in which the C(32) hydroxyl group is now in an axial configuration. As a consequence, transition state C, featuring a 6-endo attack of the C(38) hydroxyl on the C(33) terminus of the alkyne, predominates. It appears unlikely, however, that a switch in the orientation of one hydroxyl group would lead to such drastic results, as the A-value for a hydroxyl group (~0.5 kcal/mol) is not sufficiently large for a full reversal of the course of the reaction.

Additional clues for deciphering the mechanism can be found in a publication by Aponick describing his detailed mechanism, supported by calculations, of the gold-catalyzed cyclization of mono-allylic diols. The Aponick system differs from the one under study in our case only in the substitution of an alkene for the alkyne, and attack of only one hydroxyl (Scheme 3-10); it is therefore reasonable to expect that the conclusions reached by Aponick are at least partially applicable to the cyclization of mono-propargylic triols.
Aponick's main conclusions are summarized in Figure 3-5. Of particular importance is the presence of a hydrogen bond between the allylic alcohol and the incoming nucleophilic carbinol, which is proposed to provide considerable stabilization to the favored transition state both by promoting attack of the carbinol on the weakly electrophilic alkene and facilitating the subsequent elimination to form a new olefin (3.46 to 3.47, Figure 3-5). The authors note that transition states that do not possess such a hydrogen bond are uniformly 5-10 kcal/mol higher in energy.

Also important is an examination of how the mechanism changes for the (R, Z)-3.42 (Figure 3-6). This system differs only in the orientation of the olefin, which, in combination with a preset stereochemical configuration of the allylic carbinol, is similar, in principle, to the syn and anti effects for the diols in our system. Figure 3-6 illustrates that in this case, the system maintains a conformation that permits the molecule to maintain the key hydrogen bond described above.
This observation is critical, as it suggests that the hydrogen bond between the incoming hydroxyl nucleophile and the directing carbinol is the dominant structural element in determining the three-dimensional structure of both the intermediates and transition states *en route* to products 3.43 and 3.44.

Finally, an early report by de Brabander and coworkers\textsuperscript{12} on the reactivity and selectivity of non-directed metal catalyzed spiroketalizations should be mentioned. The de Brabander group examined protected derivatives of simple alkynyl diol 3.51 (Figure 3-7).

Protection of one hydroxyl, as in 3.52, permitted observation of the preferred mode of attack between 6-exo and 7-endo, whereas protection of the alternative hydroxyl, as in 3.53, permitted observation of competition between 5-exo and 6-endo addition. In each case, initial
metal-catalyzed oxyalkylation was followed in the same pot by a subsequent acid-catalyzed
deprotection and spiroketalization to provide a mixture of spiroketaIs; their relative ratios were
then used to infer the original selectivity of oxy-auration.

Thus, for alcohol 3.52, 6-exo and 7-endo modes are possible. As seen in Table 3-1, gold
and palladium provide a mixture of the two possible products, while platinum is selective for 6-exo
cyclization.

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio 6-exo:7-endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl₂(1)</td>
<td>1.5</td>
<td>52</td>
<td>2.1</td>
</tr>
<tr>
<td>2</td>
<td>MeAuPPPh₂(1), TIOH(10)</td>
<td>0.5</td>
<td>40</td>
<td>1.3:1</td>
</tr>
<tr>
<td>3</td>
<td>AuClPPh₃AgOTf(5)</td>
<td>0.5</td>
<td>36</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>AuCl₃</td>
<td>0.5</td>
<td>41</td>
<td>2.2:1</td>
</tr>
<tr>
<td>5</td>
<td>PtCl₂</td>
<td>24</td>
<td>64</td>
<td>116:1</td>
</tr>
<tr>
<td>6</td>
<td>[Cl₂P(CH₂CH₂)₂(1)]</td>
<td>0.5</td>
<td>75</td>
<td>30:1</td>
</tr>
</tbody>
</table>

**Table 3-1 Selectivities in the cyclization of 3.52**

Protecting the other terminus allows for discrimination between a 5-exo and 6-endo
pathway. Table 3-2 demonstrates that platinum once again prefers formation of the six membered
ring, while gold shows a preference for 5-exo attack.

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio 5-exo:6-endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cl₂P(CH₂CH₂)₂(1)]</td>
<td>0.5</td>
<td>70</td>
<td>1.11</td>
</tr>
<tr>
<td>2</td>
<td>PdCl₂(PhCN)₂(3)</td>
<td>3</td>
<td>95</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>MeAuPPPh₃AgPF₆</td>
<td>0.5</td>
<td>92</td>
<td>3.7:1</td>
</tr>
<tr>
<td>4</td>
<td>MeAuPPPh₃AgPF₆</td>
<td>13</td>
<td>73</td>
<td>6.6:1</td>
</tr>
</tbody>
</table>

**Table 3-2 Selectivities in the cyclization of 3.53**

Combining the observations of the work described above, a mechanistic picture for our
spiroketalization can be proposed. With two nucleophilic carbinols and two termini of the alkyne,
there are four possible initial oxy-aurations for each enantiopure diastereomer (Figure 3-7). For the sake of clarity, the non-participating western portion is abbreviated as $R_w$ and the eastern portion as $R_e$.

Formation of a seven membered ring by attack of the C(21) carbinol onto the C(16) terminus of the alkyne (light red arrow) is a possibility as evidenced by the de Brabander study mentioned above. However, such a configuration would not permit the key hydrogen bond identified by Aponick to form.

**Figure 3-8 Possible modes of cyclization for 3.29**

Attack of the C(13) carbinol onto the C(17) terminus (light blue arrow) similarly does not permit for the formation of the key hydrogen bond; furthermore, the de Brabander study identifies 5-exo attack as the more likely course relative to 6-endo cyclization for cationic gold catalysts. This leads to two possible modes of attack for each diastereomer (bold red and blue arrows in Figure 3-8).

Figure 3-9 examines these options with the corresponding transition states. For diastereomer *anti*-**3.29**, attack of the C(21) alcohol onto the C(17) terminus leads to transition state **3.54** (Figure 3-9 A), which possesses both a favorable hydrogen bond and all substituents in the equatorial position, leading, ultimately, to **3.15**, as observed. Conversely, attack of the C(13) carbinol onto the C(16) terminus (Figure 3-9 B; transition state **3.56**), lacks this hydrogen bond, as the lone pair of the incoming nucleophile is perpendicular to the lone pair of the C(15) carbinol, and thus not observed. In diastereomer *syn*-**3.29**, C(21) carbinol attack onto the C(17)
terminus leads to transition state 3.58 (Figure 3-9 C). In order to maintain the favorable hydrogen bond, either the \( R_w \) or \( R_e \) substituent has to be axial. Alternatively, a non-constrained system, which could adopt a fully equatorial orientation, lacks the beneficial hydrogen bond. Finally, attack of C(13) onto C(16) of the alkyne (Figure 3-9 D; transition state 3.59) predominates experimentally to furnish, ultimately, 3.30, although this transition state also does not possess the stabilizing hydrogen bond.

![Figure 3-9 Analysis of possible transition states for isomers of 3.29](image)

To understand the preference for transition state 3.59 (Figure 3-9 D) over other modes of attack lacking a hydrogen bond, it is instructive to look at the alternatives (Figure 3-10). There are two other possibilities for attack of a carbinol onto the alkyne without formation of a hydrogen bond, namely C(13) hydroxyl onto C(17) or the C(21) hydroxyl onto C(16) (Figure 3-10 A and B). As mentioned above, attack of C(13) onto the C(17) terminus can be excluded, as de Brabander has demonstrated that 5-exo attack is preferred in unbiased systems. The lack of attack of C(21) onto the C(16) terminus of the alkyne in a 7-endo fashion, is harder to explain, as this course of
action is allowed, as again shown by de Brabander. However, the fact that syn-3.29 stops at the formation of the five membered ring product 3.30 suggests that seven membered ring formation is comparatively difficult. A possible transition state 3.62 is shown in Figure 3-10 B. Examination of a hand-held model of 3.62 confirms that formation of a hydrogen bond between the incoming C(21) oxygen and the C(15) carbinol is not favorable, but does not identify any unfavorable interactions. It is reasonable to assume, however, that, while formation of a seven membered ring may be somewhat competitive with six membered ring formation, five membered ring formation is significantly more facile, allowing attack of C(13) to be favored kinetically.

![Diagram](image_url)

**Figure 3-10 Examination of non-hydrogen bonded transition states for syn-3.29**

This transition state analysis, we believe, helps to explain the course of the spiroketalization observed for both diastereomers (i.e., anti-3.29 and syn-3.29). By combining the observations and conclusions of the Forsyth, Aponick and de Brabander groups a fuller picture of the spiroketalization is now available.
3.3 Epilogue: Optimization of Material Throughput for the Second Generation Route to Southern Hemisphere 3.15

At this stage, all that remained to complete a highly effective synthesis of the southern hemisphere of spirastrellolide E was a solution to the material throughput issue, namely, the fact that only one diastereomer of intermediate 3.29 provided the desired spirokeetal, while the other provided a product that was not directly useful for advancing southern hemisphere material for a total synthesis of spirastrellolide E (1.6) (Scheme 3-11). This section will summarize recent attempts to rectify this drawback at various stages of the synthetic route.

![Scheme 3-11 Material throughput problem at 3.29](image)

Our first attempt to address this issue came upon the completion of the synthesis of the original C(1)-C(24) southern hemisphere (2.15), described in Chapter 2, when the original dependence of spirokeetalization on the propargylic stereocenter was discovered. We reasoned that the simplest solution was to simply produce only one diastereomer of the propargylic alcohol via an enantio- or diastereo-selective alkynylation. However, a diastereoselective alkynylation seemed less promising, as the 1.5:1 ratio of products (Scheme 2-20) suggested the lack of substrate bias. Such an observation is to be expected, as alkynes, due to their rod-like shape, often provide poor stereoselectivities in the Felkin-Ahn model for addition to α-chiral aldehydes.
Nevertheless, we reasoned that by making the lithium species more sterically bulky, the diastereoselectivity would be improved. Table 3-3 summarizes these attempts.

We first attempted to use additives such as LiBr, HMPA and TMEDA (Entries 2-4). While the exact function of lithium bromide is unclear, HMPA and TMEDA are likely to create a bulkier lithium acetylide by formation of a chelate with the metal. Unfortunately, while these conditions provided better d.r. in the literature examples, in our case, elimination of the benzoate moiety to form α,β-unsaturated aldehyde 3.64 (Table 3-3, top) was observed instead.

![Chemical structure](image)

**Table 3-3 Attempts at improving alkynylation diastereoselectivity**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal</th>
<th>Metalation conditions</th>
<th>Reaction conditions</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>LDA, -78°C to -20°C</td>
<td>-78°C to -20°C</td>
<td>~90%, 1.9:1 d.r., no elimination</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Li</td>
<td>LDA, LiBr, 4 Å M.S.</td>
<td>&quot;</td>
<td>&gt;90%, 1.2:1 d.r. and elimination of alkene</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Li</td>
<td>LDA, HMPA</td>
<td>&quot;</td>
<td>complete elimination of alkene</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Li</td>
<td>LDA, TMEDA</td>
<td>-78°C to -30°C</td>
<td>35% elimination, &lt;5% conversion</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Ti(OiPr)₃</td>
<td>LDA, then C(Ti(OiPr)₃)</td>
<td>-45°C, 1h</td>
<td>60% overall yield, but ~1:1 d.r.</td>
<td>12</td>
</tr>
</tbody>
</table>

In general, conditions possessing either amine bases or Lewis acids favored this pathway. We next turned to a system reported by Trost using titanium as the metal (Entry 5); while conversion was observed, the d.r. did not improve.

We next moved to reagent controlled transformations, encouraged by results from our laboratory employing the Carreira alkynylation. Efforts towards this goal are summarized in Table 3-4. Application of the conditions that ultimately proved successful in the Smith group (+)-
18-epi-latrunculol synthetic venture\textsuperscript{16} (Entry 1) to our system lead to promising results, with a 23\% yield of a single diastereomer isolated after 3 days of reaction time. However, elimination to 3.64 was once again observed, with the aldehyde ultimately undergoing elimination over the 3 days. We reasoned that the cause of the elimination was the excess of the zinc metal present in the reaction mixture.

\begin{center}
\includegraphics[width=\textwidth]{diagram.png}
\end{center}

We also conducted a detailed examination of the reaction conditions and found that switching to the standard stoichiometric alkynylation conditions\textsuperscript{17} lead to no reaction, even at 55 °C; only slow elimination of the starting aldehyde was observed (Entry 2).

After examining in more detailed the reaction temperature, equivalents of the metal, ligand and

\begin{table}
\begin{center}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Metal & Base & Temp & Equivalencies & Result \\
\hline
1 & Zn & \textit{Et}_2N & r.t. & alkyl (1.8), Zn (10), ligand (11), base (11) & 23\%, 19:1 d.r., full elimination after 3 d \\
2 & Zn & \textit{Et}_2N & r.t. to 55 °C & alkyl (1.8), Zn (11), ligand (12), base (12) & N.R., 60\% 3.64 \\
3 & Zn & \textit{Et}_2N & 60 °C & alkyl (1.8), Zn (11), ligand (12), base (12) & 3.64 only product, <5\% conversion \\
4 & Zn & \textit{iPr}_2EtN & r.t. & alkyl (2), Zn (2), ligand (3), base (3) & 35\% yield, 19:1 d.r., ~10\% 3.64 \\
5 & Zn & \textit{iPr}_2EtN & 60 °C & alkyl (2), Zn (1.65), ligand (1.83), base (1.65) & <5\% conversion, 50\% 3.64 \\
6 & Zn & \textit{iPr}_2EtN & 60 °C & alkyl (2), Zn (8.25), ligand (9.15), base (8.25) & complete elimination, no product \\
7 & Zn & \textit{iPr}_2EtN & r.t. & alkyl (2), Zn (1.65), ligand (1.83), base (1.65) & zinc complex does not form \\
8 & Zn & lipasine & r.t. & alkyl (2), Zn (1.65), ligand (1.83) & no conversion, 40\% 3.64 \\
9 & Zn & \textit{iPr}_2EtN & r.t. & slow addition of aldehyde over 3 h & no conversion, 25\% 3.64 \\
10 & Zn & \textit{iPr}_2EtN & r.t. & reverse addition of aldehyde over 3 h & no conversion, 30\% 3.64 \\
11 & Zn & Cy$_3$NMe & r.t. & alkyl (2), Zn (1.65), ligand (1.83), base (1.65) & excellent d.r., but <5\% conversion \\
12 & Zn/Ti & no base & reflux & alkyl (2), Zn (1.8), BINOL (1.8) & no conversion, 28\% 3.64 \\
13 & In & Cy$_3$NMe & 40 °C & alkyl (2.0), InBr$_3$ (1.8), BINOL (1.8), base (1.8) & no conversion, 28\% 3.64 \\
14 & In & \textit{iPr}_2NMe & 45 °C & alkyl, InBr$_3$, BINOL base (2.0) & loss of PMB and TES groups \\
15 & Zn & \textit{iPr}_2NEt & r.t. & alkyl (2), Zn (2), ligand (2.2), base (2) & ~5\% conversion, 60\% 3.64 \\
\hline
\end{tabular}
\end{center}
\caption{Attempts an enantioselective alkynylation}
\end{table}
base for the generation of the alkynyl zinc species (Entry 3-5), we settled on conditions reported by Carreira in the total synthesis of bafilomycin A1, which in our hands provided a 35% yield of the desired isomer, again as a single diastereomer. Encouraged, we reexamined temperature, stoichiometry, choice of base, order and speed of addition (Entries 6-11), but to our dismay, no conversion was observed, with partial elimination the only observable byproduct. Lack of reproducibility is a well-known issue in Carreira alkynylation. In fact, a test reaction with isopropylaldehyde was found not to be reproducible after initial success, so fresh bottles of the main reagents were used. In addition, Zn(OTf)$_2$, which seems to be the main culprit in the lack of reproducibility, was prepared using the methods of Corey and Laprete, the latter using complete water and oxygen free conditions. These attempts did not produce any improvement. We also tried a number of other enantioselective alkynylation, including the Shibasaki method using indium (Entries 13-14) and the method of Marshall utilizing titanium (Entry 12). No desired product was observed in either case.

Undaunted, we turned to a later stage of the synthesis for the potential convergence of the two alkynylation diastereomers. In particular, we reasoned that the undesired product syn-3.26 could be converted into the desired anti-3.26 either by a Mitsunobu inversion or by an oxidation/reduction sequence (Scheme 3-12). Attempts to perform a Mitsunobu inversion were hampered by poor conversion, even under forcing conditions. Alternatively, while oxidation of syn-3.26 was facile, the ensuing reduction was once again hampered by elimination to furnish the α,β-unsaturated ketone 3.67.
We next reasoned that perhaps conditions could be found where the fully elaborated spirotetalization precursor \textit{syn-3.29} could be converted into the desired spirotetal. An examination of a range of conditions (Table 3-5) did not identify conditions for this transformation, with most conditions providing only \textit{3.30}, or decompositions when other metals were used.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{AuCl} or ([\text{Au}]^+), THF, DCM or MeOH</td>
<td>Only byproduct</td>
</tr>
<tr>
<td>\textit{HgCl}_2, MeCN</td>
<td>Decom.</td>
</tr>
<tr>
<td>\textit{PdCl}_2(MeCN)_2, DCM</td>
<td>Full conversion, no product</td>
</tr>
</tbody>
</table>

Table 3-5 Attempts to convert \textit{syn-3.29} to the desired spirotetal

At this stage, we postulated that the conversion of \textit{syn-3.29} into the desired spirotetal was being hindered by the hydrogen bond between the incoming C(21) hydroxyl and the C(15)
carbinol, as described above. Thus, removal of this possibility, or, alternatively, blocking the C(13) hydroxyl from attack would alleviate the difficulties we were observing. At the same time, the Aponick group published a paper with very similar logic, in which an acetonide blocking group was used to block attack of the undesired alcohol onto the alkyne. Importantly, the Aponick group demonstrated that a mixture of diastereomers underwent the spiroketalization with equal efficiency, together or separately (Scheme 3-13).

![Scheme 3-13 Aponick cyclization of acetonide alkynes](image)

Excited by this possibility, we constructed both the required acetonide and the related carbonate (Scheme 3-14). To date, however, conditions to convert either of these congeners into the desired spiroketal have not been found. Studies in this direction continue.

![Scheme 3-14 Synthesis of acetonide 3.70 and carbonate 3.71](image)
3.4 Summary

Chapter 3 has described our efforts to develop a viable synthesis for the southern hemisphere of spirastrellolide E methyl ester (1.6). Pleasingly, in the area of the overall spirastrellolide synthetic venture, a revised hemisphere union strategy was designed and validated, in conjunction with completion of a large scale synthesis (c. 500 mg) of the required southern hemisphere fragment (3.15). This sequence now proceeds in a 7.5% overall yield with a longest linear sequence of 19 steps. Also, in the area of the southern hemisphere, identification of the byproduct from spiroketalization (3.30) has lead to efforts to understand the origin and to determine appropriate conditions to minimize the formation of this byproduct.

Figure 3-11 Southern hemisphere 3.15

3.5 References Relevant for Chapter 3


4 CHAPTER 4 Experimental

4.1 General Methods

Reactions were carried out in oven- or flame-dried glassware under a nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. Diethyl ether, dichloromethane, THF, and toluene were obtained from a Pure Solve TM PS-400. Triethylamine and diisopropylamine were distilled from calcium hydride under ambient pressure. HMPA was distilled from calcium hydride under reduced pressure (~0.1 mm Hg). N,O-dimethylhydroxylamine hydrochloride was azeotroped with benzene three times before use. NBS was recrystallized from water before use in dithiane deprotections. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck precoated silica gel plates. Spots were visualized by dipping the plate in an ethanol solution of anisaldehyde or potassium permanganate and heating. In aqueous work-up, all organic solutions were dried over sodium sulfate, and filtered prior to rotary evaporation at water aspirator pressure. Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. MPLC purification was performed using an apparatus comprised of a solvent pump (Waters 510 HPLC pump, 10 mL/min), injection loop (5 mL), column (11 mm ID x 300 mm, ACE glass) packed with Silasorb silica gel (18-32 micron particle size, 60 Å pore size), and a refractive index detector (Waters R401). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. All reagents were purchased from commercial vendors and used as received, unless otherwise noted. Benzaldehyde and diiodomethane were distilled before use. n-butyllithium (2.5 M in hexanes) was titrated with diphenylphosphoric acid before use. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts for $^1$H and $^{13}$C NMR spectra are reported as δ values relative to the internal chloroform (δ 7.27 ppm for $^1$H and δ 77.16 ppm for $^{13}$C) or benzene (δ 7.16 ppm for $^1$H and δ 128.1 for $^{13}$C). High resolution mass spectra were measured at the University of Pennsylvania.
Mass Spectrometry Service Center on either a VG Micromass 70/70 H or VG ZAB-E spectrometer. Optical rotations were measured on a Jasco P-2000 polarimeter.

4.2 Experimental Details Relevant to Chapter 2

Synthesis of Epoxide 2.27

**Scheme 4-1 Synthesis of epoxide 2.29**

**Compound 2.31.** To a -78 °C solution of diisopropylamine (19.3 mL, 138 mmol, 2.1 eq) in THF (130 mL) was added n-BuLi (56.6 mL, 138 mmol, 2.5 M in hexanes, 2.1 eq) dropwise and the mixture was stirred at -78 °C for 40 min. A solution of diethyl malate (12.5 g, 65.7 mmol, 1.0 eq) in THF (13 mL) was then added dropwise, and the mixture stirred for 1.5 h at 0 °C, then recooled to -78 °C. A dark red color indicates successful formation of the dianion. Methyl iodide (6.13 mL, 98.5 mmol, 1.5 eq) was then added dropwise and the reaction mixture gradually warmed to room temperature overnight, then quenched with sat. aqueous sodium bicarbonate. The mixture was diluted with ethyl acetate and the layers separated. The aqueous layer was extracted five times with ethyl acetate and the combined organics were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (4:1 Hexanes:Ethyl acetate) to yield the title compound (9.15 g, 68%, 7:1 d.r.) as a slightly yellow oil. The spectral data of this compound were in agreement with literature reports.¹

**Compound 2.32.** A modification of a published procedure was followed.² To a suspension of lithium aluminum hydride (8.5 g, 223 mmol, 4.0 eq) in THF (220 mL)
at 0 °C was added a solution of diester 2.31 (11.4 g, 55.8 mmol, 1 eq) in THF (30 mL) dropwise over 30 minutes. The reaction was heated to reflux for 3h, then cooled to 0 °C and quenched by the successive addition of H₂O (8.5 mL), 15% NaOH (8.5 mL) and H₂O (27 mL). The resulting mixture was stirred under reflux for 2h, then dried over magnesium sulfate, filtered over Celite and concentrated to provide the crude triol (6.01 g, 90%)

A portion of the resulting residue (3.7 g, 31 mmol, 1.0 eq) was dissolved in dichloromethane (100 mL) and p-TsOH (6 g, 31 mmol, 1.0 eq) and benzaldehyde dimethyl acetal (6.2 mL, 40 mmol, 1.3 eq) were added. The reaction mixture was stirred at room temperature overnight, then quenched with triethylamine until smoking was no longer observed and concentrated. The residue was purified by flash column chromatography (3:1 → 2:1 Hexanes:Ethyl Acetate) to yield the title compound (4.5 g, 63% over 2 steps).

\[^1\text{H NMR} (\text{CDCl}_3, 500 \text{ MHz}): \delta = 7.51 (dd, J = 1.6, 7.7 \text{ Hz}, 2 \text{ H}), 7.42 - 7.34 (m, 3 \text{ H}), 5.55 (s, 1 \text{ H}), 4.16 (dd, J = 4.9, 11.3 \text{ Hz}, 1 \text{ H}), 3.87 (dd, J = 2.5, 11.9 \text{ Hz}, 1 \text{ H}), 3.72 (dd, J = 6.3, 12.1 \text{ Hz}, 1 \text{ H}), 3.62 (dd, J = 2.4, 5.0, 7.3 \text{ Hz}, 1 \text{ H}), 3.55 (t, J = 11.3 \text{ Hz}, 1 \text{ H}), 2.14 - 2.03 (m, 1 \text{ H}), 0.84 (d, J = 6.7 \text{ Hz}, 3 \text{ H}); \]^13\text{C NMR} (\text{CDCl}_3, 126 \text{ MHz}): \delta = 138.4, 129.2, 128.5, 126.3, 101.4, 83.5, 72.8, 63.4, 30.0, 12.3.; \text{IR (film)}: \tilde{\nu} = 3436, 2958, 1456, 1391 \text{ cm}^{-1}; \text{HRMS (ESI)}: \text{Calc. for C}_{12}\text{H}_{17}\text{O}_3 [M^\ast + \text{H}]^{+} 209.1178. \text{Found 209.1180}. [\alpha]_D^{20} = +9.5 (c =1 \text{ in CH}_2\text{Cl}_2)
magnesium sulfate were poured into the reaction mixture, which was then filtered and the filtrate concentrated. The resulting \textbf{2.33} was sufficiently pure to be carried onto the next step.

To a 0 °C suspension of NaH (60% dispersion in mineral oil, 1.7 g, 41.4 mmol, 3.0 eq) in THF (100 mL) was added the above solution of \textbf{2.33} in THF (50 mL). The reaction mixture was stirred for 1 h at 0 °C, then triisopropylsulfonil imidazole (6.9 g, 20.7 mmol, 1.3 eq) was added as a solid in one portion and stirring was continued for an additional 1 h. The reaction was quenched with sat. aqueous ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer extracted 3 times with diethyl ether. The combined organics were washed with water and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was taken up in diethyl ether and filtered through a plug of cotton and the filtrate reconcentrated. Purification by flash column chromatography (9:1 Hexanes:Ethyl Acetate) yielded the title compound (2.5 g, 94% over 2 steps) as a colorless oil.

\textbf{1H NMR} (CDCl$_3$, 500 MHz): $\delta = 7.40 - 7.30$ (m, 5 H), 4.55 (s, 2 H), 3.70 (dd, $J = 3.0, 10.9$ Hz, 1 H), 3.64 - 3.56 (m, 3 H), 3.53 (q, $J = 9.0$ Hz, 1 H), 2.03 (dtd, $J = 4.0, 7.1, 8.4$ Hz, 1 H), 0.91 (d, $J = 7.0$ Hz, 3 H); \textbf{13C NMR} (CDCl$_3$, 126 MHz): $\delta = 137.6, 128.7, 128.1, 127.9, 76.4, 74.8, 73.7, 64.9, 35.7, 13.8$; \textbf{IR} (film): 3388, 2877, 1454, 1363 cm$^{-1}$; \textbf{HRMS} (Cl): Calc. for C$_{12}$H$_{19}$O$_3$ [$M^+$] 211.1334. Found 211.1326; [$\alpha$]$_D^{20} = +18$ (c = 1 in CH$_2$Cl$_2$).

\textbf{1H NMR} (CDCl$_3$, 500 MHz): $\delta = 7.37 - 7.33$ (m, 4 H), 7.31 - 7.27 (m, 1 H), 4.53 (d, $J = 1.2$ Hz, 2 H), 3.53 (dd, $J = 5.4, 9.1$ Hz, 1 H), 3.48 (dd, $J = 6.0, 9.3$ Hz, 1 H), 2.91 (td, $J = 3.4, 6.9$ Hz, 1 H), 2.75 (t, $J = 4.5$ Hz, 1 H), 2.55 (dd, $J = 2.8, 5.0$ Hz, 1 H), 1.72 (spt, $J = 6.5$ Hz, 1 H), 1.02 (d, $J = 7.0$ Hz, 3 H); \textbf{13C NMR} (CDCl$_3$, 126 MHz): $\delta = 138.6, 128.5, 127.7, 73.3, 72.9, 54.4, 45.9, 36.8, 13.3$; \textbf{IR} (film): $\tilde{\nu} = 2858, 1454, 1361$ cm$^{-1}$; \textbf{HRMS} (Cl): Calc. for C$_{12}$H$_{16}$O$_2$ [$M^+$] 192.1150. Found 192.1141; [$\alpha$]$_D^{20} = -7.4$ (c = 1 in CH$_2$Cl$_2$).

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Construction of epoxide 2.28

Scheme 4-2 Synthesis of epoxide 2.30

**Compound 2.34.** To a 0 °C solution of pyran (25 mL, 0.28 mmol) was added 0.2 N aqueous HCl (60 mL) dropwise. The reaction mixture was stirred at 0 °C for 15 min., then at room temperature for 1 h. The resulting solution was then extracted with 3x100 mL dichloromethane. The combined organics were washed with sat. aqueous sodium bicarbonate and brine, dried over Na₂SO₄ and concentrated. The crude product was distilled (0.01 torr) to yield the title compound (19.9 g, 71%) as a colorless oil.

**¹H NMR** (CDCl₃, 500 MHz): δ = 4.95 - 4.87 (m, 1 H), 4.08 - 3.96 (m, 1 H), 3.55 (td, J = 5.8, 11.5 Hz, 1 H), 2.88 (s, 1 H), 1.96 - 1.74 (m, 2 H), 1.61 - 1.45 (m, 4 H); **¹³C NMR** (CDCl₃, 126 MHz): δ = 94.6, 64.0, 32.1, 25.4, 20.4; **IR** (film): ν = 3390, 2942, 1442 cm⁻¹; **HRMS** (ESI): Calc. for C₅H₃O [M-H⁺] 101.0603. Found 101.0605;

**Compound 2.35.** To a solution of triphenylphosphine (68.7 g, 262 mmol, 1.0 eq) in ethyl acetate (400 mL) was added a solution of ethyl bromoacetate (29 mL, 262 mmol, 1.0 eq) in ethyl acetate (100 mL). The reaction was stirred at reflux for 3 h until the solution solidified. The white precipitate was filtered and washed with ethyl acetate. The crude product was dissolved in dichloromethane and transferred to a separatory funnel. Sodium hydroxide (21 g, 526 mmol, 2.0 eq) in water (300 mL) was added and the mixture shaken vigorously. The layers were separated and the aqueous layer extracted with additional
dichromethane. The combined organics were washed with brine and dried over sodium sulfate. Concentration provided ethyl (triphenylphosphoranylidene)acetate (86.8 g, 95%) as a white solid, which was used without further purification in the Wittig olefination.

To this ylide in THF (1 L) was added a solution of 2.34 (19.9 g, 194 mmol) in THF (100 mL) dropwise. The mixture was then heated to reflux overnight, then cooled down and concentrated. The solid residue was stirred in a 7:3 mixture of ether:petroleum ether (50 mL) for 1h, then filtered to remove the triphenylphosphine oxide byproduct. The solid was washed with ether and the filtrate was concentrated. The residue was purified by flash column chromatograph (2:1 → 1:1 Hexanes:Ethyl Acetate) to yield the title compound as an oil in an inconsequential 14:1 ratio of E:Z olefin isomers (28.2 g, 84% total yield).

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 6.96$ (dt, $J = 15.6$, 7.0 Hz, 1 H), 5.82 (dt, $J = 15.7$, 1.3 Hz, 1 H), 4.53 - 4.60 (m, 1 H), 4.18 (q, $J = 7.1$ Hz, 2 H), 3.81 - 3.89 (m, 1 H), 3.46 - 3.54 (m, 1 H), 3.39 (dt, $J = 9.9$, 6.0 Hz, 1 H), 2.24 (q, $J = 7.0$ Hz, 2 H), 1.75 - 1.88 (m, 1 H), 1.67 - 1.72 (m, 1 H), 1.47 - 1.66 (m, 8 H), 1.28 (t, $J = 7.1$ Hz, 3 H); $^{13}$C NMR (CDCl$_3$, 126 MHz) $\delta = 166.8$, 148.9, 121.7, 62.6, 60.3, 32.2, 32.0, 24.4, 14.4; IR (film): $\tilde{\nu} = 3429, 2936, 1720, 1656, 1439$ cm$^{-1}$. HRMS (ESI): Calc. for C$_9$H$_{16}$O$_3$Na [M$^+$ + Na] 195.0997, found 195.0991.

**Compound 2.36.** To a suspension of PCC (42.4 g, 196 mmol, 1.3 eq) and Celite (40 g) in dichloromethane (500 mL) was added a solution of 2.35 (28.2 g, 164 mmol, 1.0 eq) in dichloromethane (100 mL) and the reaction mixture stirred for 4 h at room temperature. The reaction mixture was purified directly by flash column chromatography (3:1 Hexanes:Ethyl Acetate) to yield the title compound (22.9 g, 82%) as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 9.77$ (s, 1 H), 6.85 - 6.99 (m, 1 H), 5.83 (d, $J = 15.9$ Hz, 1 H), 4.18 (q, $J = 7.2$ Hz, 2H), 2.48 (t, $J = 7.2$ Hz, 2 H), 2.25 (q, $J = 7.2$ Hz, 2 H), 1.81 (quin, $J = 7.2$ Hz, 2 H), 1.05 (m, 8 H).
1.28 (td, \(J = 7.1, 1.9\) Hz, 3 H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 201.7, 166.5, 147.6, 122.4, 60.4, 43.1, 31.4, 20.5, 14.4\); \(\text{IR}\) (film): \(\tilde{\nu} = 2951, 2843, 2726, 1720, 1656, 1438, 1318, 1275\) cm\(^{-1}\).

**Compound 2.37.** To a solution of [(+)-ipc\(_2\)]BOMe (9.6 g, 30.3 mmol, 1.5 eq) in diethyl ether (80 mL) at -78 °C was added allylmagnesium chloride (2 M in THF, 12.8 mL, 25.7 mmol, 1.3 eq) dropwise. The reaction mixture was stirred at -78 °C for 10 minutes, then warmed to room temperature and stirred an additional 1 h, then recooled to -78 °C. A solution of compound 2.36 (4.0 g, 23.3 mmol, 1.0 eq) in diethyl ether (50 mL) was then added dropwise and the reaction mixture gradually warmed to room temperature overnight. The resulting mixture was cooled to 0 °C and quenched with successive addition of methanol (55 mL), pH 7 buffer (35 mL) and 30% H\(_2\)O\(_2\) (35 mL). The mixture was allowed to stir for 24 h at room temperature, then diluted with diethyl ether. The layers were separated and the aqueous layer extracted with additional diethyl ether. The combined organics were dried over Na\(_2\)SO\(_4\) and concentrated. The residue was purified by flash column chromatography (3:1 → 1:1 Hexanes:Ethyl Acetate) to yield the title compound (4.2 g, 85%) as a colorless oil.

\(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz) \(\delta = 6.96\) (dt, \(J = 15.7, 6.9\) Hz, 1 H), 5.82 (d, \(J = 16.4\) Hz, 2 H), 5.15 (s, 1 H), 5.10 - 5.13 (m, 1 H), 4.18 (q, \(J = 7.1\) Hz, 2 H), 3.67 (br. s, 1 H), 2.26 - 2.35 (m, 1 H), 2.23 (q, \(J = 7.3\) Hz, 2 H), 2.10 - 2.19 (m, 1 H), 1.86 (s, 1 H), 1.59 - 1.71 (m, 1 H), 1.46 - 1.58 (m, 3 H), 1.28 (t, \(J = 7.1\) Hz, 3 H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 167.1, 149.2, 134.7, 121.7, 118.5, 70.6, 70.6, 60.4, 42.1, 36.2, 32.2, 24.2, 14.4\); \(\text{IR}\) (film): \(\tilde{\nu} = 3437, 2933, 1725, 1656, 1437, 1273\) cm\(^{-1}\); \(\text{HRMS}\) (ESI): calc. for C\(_{12}\)H\(_{21}\)O\(_3\) \([M^+ + H]^+\) 213.1491, found 213.1496. \([\alpha]_D^{29} = -5.48\) (c 1.00, CH\(_2\)Cl\(_2\)).

**Compound 2.39.** To a solution of 2.37 (8 g, 37.7 mmol, 1.0 eq) in THF (160 mL) at -78 °C was added t-BuOK (1 M in THF, 22.6 mL, 22.6 mmol, 0.6 eq). The reaction mixture was then gradually warmed to -60 °C and stirred until starting
material had been consumed as determined by TLC analysis (1h). The mixture was then re-
cooled to -78 °C and quenched slowly with sat. aqueous ammonium chloride. After dilution with
ethyl acetate, the layers were separated and the aqueous layer extracted with ethyl acetate. The
combined organics were washed with brine, dried over Na₂SO₄ and concentrated to provide 2.38
of sufficient purity to be taken onto the next step without further purification.

To a suspension of LAH (1.68 g, 44.3 mmol, 1.2 eq) in diethyl ether (170 mL) at 0 °C was
added the above solution of 2.38 in diethyl ether (115 mL). The reaction was stirred at this
temperature for 1h, then quenched by the successive addition of H₂O (1.7 mL), 15% NaOH (1.7
mL), and H₂O (5.1 mL). The resulting suspension was stirred at room temperature for 2 h, then
filtered and the resulting solid was washed liberally with diethyl ether. The filtrated was dried over
Na₂SO₄ and concentrated.

The crude residue was dissolved in dichloromethane (80 mL) and cooled to 0 °C.
Imidazole (868 mg, 75 mmol, 2 eq), DMAP (225 mg, 0.38 mmol, 0.1 eq), and TBSCI (8.3 g, 54.8
mmol, 1.3 eq) were added successively as solids and the reaction mixture warmed to room
temperature and stirred for 1h, then quenched with water and diluted with dichloromethane. The
layers were separated and the aqueous layer extracted with dichloromethane. The combined
organics were dried over Na₂SO₄ and concentrated. The residue was purified by flash column
chromatography (20:1 Hexanes:Ethyl Acetate) to yield the title compound (8.77 g, 84% over three
steps) as a colorless oil.

\[
\begin{align*}
\text{H NMR (CDCl₃, 500 MHz): } & \quad \delta = 5.74 - 5.87 \text{ (m, 1 H)}, 5.06 \text{ (d, } J = 18.0 \text{ Hz, 1 H)}, 5.00 \text{ (d, } J = 9.7 \text{ Hz, 1 H)}, 4.15 \text{ (q, } J = 7.1 \text{ Hz, 2 H)}, 3.73 - 3.82 \text{ (m, 1 H)}, 3.34 - 3.43 \text{ (m, 1 H)}, 2.50 - 2.59 \text{ (m, 1 H)}, 2.36 - 2.43 \text{ (m, 1 H)}, 2.25 - 2.33 \text{ (m, 1 H)}, 2.10 - 2.19 \text{ (m, 1 H)}, 1.84 \text{ (d, } J = 13.5 \text{ Hz, 1 H)}, 1.49 - 1.69 \text{ (m, 3 H)}, 1.26 \text{ (t, } J = 7.1 \text{ Hz, 4 H)}, 1.16 - 1.24 \text{ (m, 1 H)}; \\
\text{C NMR (CDCl₃, 126 MHz): } & \quad \delta = 171.9, 135.2, 166.4, 77.7, 74.7, 60.6, 41.9, 40.9, 31.3, 30.8, 23.5, 14.3; \\
\text{IR (film): } & \quad \tilde{\nu} = 2936, 2860, 1742, 1642, 1437, 1346, 1288 \text{ cm}^{-1}. \\
\text{HRMS (ESI): Calc. for } C_{12}H_{20}O_3 \text{ [M'] 212.1212, found 212.1418.}
\end{align*}
\]
**H NMR** (CDCl₃, 500 MHz): δ = 5.89 - 5.79 (m, 1 H), 5.05 (dd, J = 1.5, 17.2 Hz, 1 H), 5.01 (td, J = 0.9, 10.2 Hz, 1 H), 3.79 - 3.73 (m, 1 H), 3.71 - 3.65 (m, 1 H), 3.43 (dt, J = 1.4, 5.2, 14.9 Hz, 1 H), 3.30 (dt, J = 1.8, 6.4, 11.0 Hz, 1 H), 2.33 - 2.26 (m, 1 H), 2.17 - 2.10 (m, 1 H), 1.84 - 1.78 (m, 1 H), 1.72 - 1.42 (m, 6 H), 1.18 (s, 3 H), 0.89 (d, J = 0.6 Hz, 10 H), 0.05 (d, J = 2.6 Hz, 6 H); **C NMR** (CDCl₃, 126 MHz): δ = 135.5, 116.4, 77, 74.5, 59.7, 41.2, 39.7, 31.9, 31.4, 26.1, 23.8, 18.5, -5.2, -5.2; **IR** (film): ν = 2933, 2857, 1643, 1472, 1439, 1387, 1254, 1198 cm⁻¹; **HRMS** (ESI): Calc. for C₁₆H₃₃O₂Si [M⁺ + H] 285.2250. Found 285.2260; [α]_D⁰ = -19 (c = 1 in CH₂Cl₂).

**Compound 2.40.** To a rapidly stirring mixture of K₂OsO₄·2H₂O (9.1 mg, 0.027 mmol, 0.01 eq), (DHQD)₂PYR (65 mg, 0.073 mmol, 0.03 eq), K₂CO₃ (1.02 g, 7.38 mmol, 3.0 eq), and K₃Fe(CN)₆ (2.43 g, 7.38 mmol, 3.0 eq) in H₂O/t-BuOH (8 mL/11 mL) at 0 °C was added a solution of 2.39 (700 mg, 2.46 mmol, 1.0 eq) in t-BuOH (3 mL). The reaction mixture was stirred at 0 °C overnight, then quenched by the addition of Na₂SO₃ (1.55 g, 12.3 mmol, 5.0 eq) and stirring for 4 h at room temperature. The mixture was diluted with H₂O/ethyl acetate and the layers separated. The aqueous layer was extracted with ethyl acetate and the combined layers dried over Na₂SO₄ and concentrated to give the crude diol as a ~6:1 mixture of diastereomers. Column chromatography (2:1 → 3:2 → 1:2 Hexanes:Ethyl Acetate) could improve the diastereomeric ratio to ~8-12:1. This mixture was used in the next step. An analytically pure sample of the major diastereomer was obtained by purification with an MPLC (elution with 3:2 hexanes:ethyl acetate).

Major isomer:

**H NMR** (CDCl₃, 500 MHz): δ = 3.98 - 3.93 (m, 1 H), 3.72 - 3.66 (m, 2 H), 3.59 (dd, J = 3.8, 11.1 Hz, 2 H), 3.57 - 3.52 (m, 1 H), 3.49 (dd, J = 5.8, 13.1 Hz, 1 H), 1.86 - 1.80 (m, 1 H), 1.75 - 1.63 (m, 3 H), 1.63 - 1.48 (m, 4 H), 1.33 - 1.19 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); **C NMR** (CDCl₃, 126 MHz): δ = 78.7, 75.1, 72.2, 66.8, 59.6, 39.5, 39.2, 32.2, 31.5, 26.1, 26.1, 23.5, 20.8.
Epoxide 2.30. To a 0 °C suspension of sodium hydride (60% dispersion in mineral oil, 900 mg, 22.4 mmol, 3.0 eq) in THF (25 mL) was added a solution of 2.40 (2.38 g, 7.47 mmol, 1.0 eq) in THF (50 mL) and the reaction mixture stirred at 0 °C for 0.5 h. Triisopropylsulfonyl imidazole (3.86 g, 11.2 mmol, 1.5 eq) was then added as a solid in one portion and stirring was continued for an additional 1h at 0 °C. The reaction mixture was then quenched with sat. aqueous ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer extracted 3x75 mL diethyl ether. The combined organics were washed with water and brine, dried over Na₂SO₄ and concentrated. The residue was taken up in diethyl ether and filtered through a plug of cotton, then reconcentrated to yield an oil, which was purified by flash column chromatography (9:1 Hexanes:Diethyl Ether) to yield the title compound (2.19 g, 97%) as a colorless oil.

¹H NMR (CDCl₃, 500 MHz): δ = 3.79 - 3.66 (m, 2 H), 3.57 - 3.50 (m, 1 H), 3.50 - 3.43 (m, 1 H), 3.09 (sxt, J = 4.2 Hz, 1 H), 2.79 (dd, J = 4.1, 5.0 Hz, 1 H), 2.49 (dd, J = 2.8, 5.1 Hz, 1 H), 1.87 - 1.81 (m, 1 H), 1.78 (ddd, J = 4.8, 9.1, 14.2 Hz, 1 H), 1.74 - 1.45 (m, 7 H), 1.22 (s, 2 H), 0.90 (s, 10 H), 0.06 (s, 6 H); ¹³C NMR (CDCl₃, 126 MHz): δ = 75.4, 74.5, 59.8, 50.0, 47.5, 40.1, 39.8, 32.1, 31.8, 26.1, 26.1, 23.8, 18.5, -5.2, -5.2; IR (film): ν = 2930, 2857, 1471 cm⁻¹; HRMS (ESI): Calc. for C₁₆H₃₂O₃NaSi [M⁺ + Na] 323.2011. Found 323.2009; [α]₂⁰°D = −8.5 (c = 3 in CH₂Cl₂).

ARC Adduct 2.41. To a solution of TES-dithiane 2.26 (67 mg, 0.286 mmol, 1.1 eq) in 1:1 THF:Diethyl Ether (0.6 mL) was added n-butyllithium (2.5 M in hexanes, 125 µL, 0.312 mmol, 1.2 eq) dropwise and the reaction mixture stirred at room temperature for 15
min, then cooled to -55 °C. A solution of epoxide 2.29 (50 mg, 0.260 mmol, 1.0 eq) in diethyl ether (0.6 mL) was added dropwise and the reaction mixture stirred for 1h at -45 °C. Completion of the first addition was verified by TLC (9:1 Hexanes:Diethyl ether). The reaction mixture was cooled to -78 °C. A solution of epoxide 2.30 (156 mg, 0.520 mmol, 2.0 eq) in diethyl ether (0.6 mL) was added slowly, followed by a solution of HMPA (70 µL, 0.39 mmol, 1.5 eq) in diethyl ether (0.6 mL) and the reaction mixture was taken out of the dry ice/acetone bath and allowed to warm to 0 °C and stir 1 h. The reaction was quenched with sat. aqueous ammonium chloride and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with 2x5 mL ethyl acetate and the combined layers washed with water (2x10 mL) and brine, then dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (5% to 10% diethyl ether in hexanes, then 9:1 → 7:1 Hexanes:Ethyl Acetate; alternatively the residue could be purified by MPLC, 9:1 Hexanes:Ethyl Acetate) to yield the title compound as a colorless oil (118 mg, 62%) along with recovered epoxide 2.30 (55 mg, 70% of theoretical recovery) and quenched intermediate 2.41 (18 mg, 16%).

¹H NMR (CDCl₃, 500 MHz): δ = 7.37 - 7.32 (m, 4 H), 7.31 - 7.28 (m, 1 H), 4.51 (d, J = 11.7 Hz, 2 H), 4.41 - 4.34 (m, 2 H), 3.79 - 3.67 (m, 2 H), 3.60 - 3.55 (m, 1 H), 3.53 (d, J = 2.4 Hz, 1 H), 3.48 - 3.40 (m, 2 H), 3.37 (dd, J = 5.9, 9.8 Hz, 1 H), 2.85 - 2.75 (m, 3 H), 2.74 - 2.65 (m, 1 H), 2.23 - 2.11 (m, 3 H), 2.02 - 1.96 (m, 2 H), 1.92 - 1.85 (m, 2 H), 1.84 - 1.78 (m, 1 H), 1.73 - 1.60 (m, 2 H), 1.58 - 1.47 (m, 5 H), 1.34 - 1.17 (m, 2 H), 0.99 (t, J = 8.6 Hz, 9 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.67 (q, J = 7.5 Hz, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ¹³C NMR (CDCl₃, 126 MHz): δ = 138.7, 128.4, 127.6, 75.0, 74.7, 73.2, 73.2, 71.0, 65.7, 59.9, 52.6, 47.5, 44.1, 41.7, 40.9, 39.9, 31.9, 31.7, 26.7, 26.3, 26.2, 25.1, 23.9, 18.5, 11.2, 7.3, 5.7, -5.1; IR (film): ˜ν = 3466, 2933, 1495, 1252 cm⁻¹; HRMS (ESI): Calc. for C₃₈H₇₀O₅NaSi₂S₂ [M⁺ + Na] 749.4101. Found 749.4109; [α]D²⁰ = + 12 (c = 0.5 in CH₂Cl₂).
**Compound 2.42**

| H NMR (CDCl$_3$, 500 MHz): δ = 7.37 - 7.34 (m, 4 H), 7.31 - 7.28 (m, 1 H), 4.50 (d, J = 1.9 Hz, 2 H), 4.15 (ddd, J = 3.5, 4.5, 7.7 Hz, 2 H), 3.40 (dd, J = 6.9, 9.3 Hz, 1 H), 3.29 (dd, J = 6.5, 9.3 Hz, 1 H), 2.93 - 2.76 (m, 4 H), 2.16 - 2.09 (m, 1 H), 2.09 - 2.04 (m, 1 H), 1.93 - 1.83 (m, 1 H), 1.80 (ddd, J = 4.3, 9.4, 13.8 Hz, 2 H), 0.99 (t, J = 7.5 Hz, 9 H), 0.94 (d, J = 7.2 Hz, 3 H), 0.65 (q, J = 7.7 Hz, 6 H); 13C NMR (CDCl$_3$, 500 MHz): δ = 138.7, 128.4, 127.6, 127.5, 73.3, 72.6, 69.9, 44.4, 39.5, 38.5, 30.8, 30.1, 26.3, 12.2, 7.2, 5.3; IR (film): ν = 2953, 2875, 1455, 1421, 1241 cm$^{-1}$; HRMS (ESI): Calc. for C$_{22}$H$_{39}$O$_2$S$_2$Si [M + H]$^+$ 427.2161. Found 427.2164; [α]$^0$ = +16 (c = 1 in CH$_2$Cl$_2$).

**Ketone 2.44.** To a solution of NBS (27 mg, 0.154 mmol, 2.0 eq), silver perchlorate (35 mg, 0.169 mmol) and 2,6-lutidine (36 µL, 0.308 mmol, 4.0 eq) in 10% aqueous acetone (6.9 mL) was added a solution of ARC adduct 2.41 (56 mg, 0.077 mmol, 1.0 eq) in acetone (1 mL) and the reaction mixture stirred vigorously for ~1 min, then quenched with sat. aqueous sodium bicarbonate (15 mL) and stirred for 30 minutes. The mixture was diluted with water and ethyl acetate and the layers were separated. The aqueous layer was extracted with 2x15 mL ethyl acetate and the combined organics were washed with brine, dried over Na$_2$SO$_4$, filtered through a plug of Celite and concentrated. The residue was purified by flash column chromatography (9:1 → 7:1 Hexanes:Ethyl Acetate) to yield the title compound (45 mg, 82%) as a colorless oil.

| H NMR (CDCl$_3$, 500 MHz): δ = 7.36 - 7.31 (m, 4 H), 7.28 (m, 1 H), 4.47 (q, J = 12.0 Hz, 2 H), 4.38 - 4.33 (m, 1 H), 4.33 - 4.28 (m, 1 H), 3.69 (m, 2 H), 3.61 - 3.54 (m, 1 H), 3.48 (m, 2 H), 3.42 (dd, J = 7.1, 9.2 Hz, 1 H), 3.28 (dd, J = 5.6, 9.8 Hz, 1 H), 2.63 - 2.49 (m, 4 H), 2.04 - 1.95 (m, 1 H), 1.86 - 1.80 (m, 1 H), 1.72 - 1.47 (m, 8 H), 1.22 (s, 3 H), 0.94 (t, J = 8.9 Hz, 12 H), 0.91 (s, 9 H), 0.59 (q, J = 8.1 Hz, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); 13C NMR (CDCl$_3$, 126 MHz): δ = 210.4, 138.7, 128.5, 127.7, 127.6, 75.0, 74.8, 73.2, 72.4, 70.0, 64.9, 59.7, 51.3, 47.5, 42.4, 39.8, 39.5, 31.8, 31.6, 26.1, 26.1, 23.8, 18.5, 12.8, 7.1, 5.1, -5.2; IR (film): ν = 3483, 2933, 1708, 1457, 1252, 102
1089 cm⁻¹; **HRMS (ESI)**: Calc. for C₃₅H₆₅O₆Si₂ [M⁺ + H] 637.4320. Found 637.4316; [α]D²⁰ = + 10 (c = 0.5 in CH₂Cl₂).

**Compound 2.46.** To a solution of Me₄NBH(OAc)₃ (111.5 mg, 0.424 mmol, 6.0 eq) in acetic acid/acetonitrile (1:2, 3.6 mL total) at -30 °C was added a solution of ketone 2.44 (45 mg, 70.6 µmol, 1.0 eq). The reaction mixture was stirred at -30 °C overnight, then quenched slowly with sat. aqueous sodium bicarbonate and diluted with ethyl acetate. The layers were separated and the organic layer dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (5:1 → 3:1 Hexanes:Ethyl Acetate) to yield the title compound (31.6 mg, 70%)

To a solution of the resulting diol (46 mg, 72 µmol, 1.0 eq), Hunig's base (205 µL, 1.08 mmol, 15 eq) and TBAI (29 mg, 72 µmol, 1.0 eq) in dichloroethane (1 mL) was added MOMBr (65 µL, 0.72 mmol, 10 eq) dropwise and the reaction mixture stirred at room temperature overnight, then quenched with sat. aqueous ammonium chloride and diluted with dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organics were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (6:1 Hexanes:Diethyl ether) to yield the title compound (45.7 mg, 85%) as a pale yellow oil.

**¹H NMR** (CDCl₃, 500 MHz): δ = 7.36 - 7.32 (m, 4 H), 7.30 - 7.26 (m, 1 H), 4.68 (s, 2 H), 4.66 (d, J = 2.3 Hz, 1 H), 4.50 (s, 2 H), 4.00 - 3.96 (m, 1 H), 3.92 - 3.86 (m, 1 H), 3.83 - 3.77 (m, 1 H), 3.71 (dd, J = 6.2, 7.0 Hz, 2 H), 3.48 - 3.39 (m, 3 H), 3.38 (s, 4 H), 3.34 (s, 3 H), 3.28 (dd, J = 7.1, 9.7 Hz, 1 H), 2.10 - 2.01 (m, 1 H), 1.87 - 1.78 (m, 1 H), 1.75 - 1.67 (m, 3 H), 1.66 - 1.46 (m, 8 H), 1.24 - 1.13 (m, 2 H), 0.97 (t, J = 9.1 Hz, 9 H), 0.93 (d, J = 6.9 Hz, 3 H), 0.90 (s, 9 H), 0.62 (q, J = 8.6 Hz, 6 H), 0.06 - 0.04 (s, 6 H); **¹³C NMR** (CDCl₃, 126 MHz): δ = 139.2, 138.9, 128.4, 127.6, 127.5,
Alcohol 4.1. To a solution of 2.46 (40 mg, 55.4 µmol, 1.0 eq) in THF (2.5 mL) was added Pd(OH)$_2$ on carbon (8 mg, 11.1 µmol, 0.2 eq). The flask was evacuated and backfilled with hydrogen; this was repeated three times. The solution was then stirred at room temperature for 30 minutes. The reaction mixture was filtered through a pad of Celite and concentrated. The residue was purified by MPLC (4:1 Hexanes:Ethyl Acetate) to yield the title compound (28 mg, 80%) as a colorless oil.

Aldehyde 2.25. To powdered 4 Å molecule sieves (30 mg) and alcohol 4.1 (20 mg, 37.2 µmol, 1.0 eq) in dichloromethane (500 µL) were added NMO (7 mg, 55.8 µmol, 1.5 eq) and TPAP (1.3 mg, 3.72 µmol, 0.1 eq) successively and the reaction mixture stirred at room temperature for 45 min, then filtered through a pad of silica gel, eluting with 9:1 Hexanes:Diethyl ether to afford the title compound (18 mg, 78%) directly as a colorless oil.
$^1$H NMR (C$_6$D$_6$, 500 MHz): $\delta$ = 9.80 (d, $J$ = 1.5 Hz, 1 H), 4.88 - 4.82 (m, 3 H), 4.80 - 4.78 (m, 1 H), 4.45 - 4.41 (m, 1 H), 4.28 - 4.21 (m, 1 H), 4.16 - 4.10 (m, 1 H), 3.92 (m, 2 H), 3.61 - 3.55 (m, 1 H), 3.54 - 3.48 (m, 1 H), 3.42 (s, 3 H), 3.36 (s, 3 H), 2.59 - 2.53 (m, 1 H), 2.03 - 1.67 (m, 8 H), 1.49 - 1.31 (m, 4 H), 1.28 - 1.20 (m, 2 H), 1.18 (d, $J$ = 7.0 Hz, 3 H), 1.15 - 1.09 (m, 18 H), 0.75 (q, $J$ = 7.6 Hz, 6 H), 0.23 (s, 3 H), 0.22 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): 96.7, 96.2, 74.5, 74.1, 73.4, 72.5, 70.6, 59.9, 55.9, 55.8, 52.1, 43.1, 42.4, 41.5, 40.0, 32.2, 31.8, 26.1, 23.9, 18.4, 10.0, 7.1, 5.3, -5.2; IR (film): $\tilde{\nu}$ = 2934, 2879, 1724, 1461, 1384, 1252 cm$^{-1}$; HRMS (ESI): Calc. for C$_{32}$H$_{68}$O$_3$NaSi$_2$ [M$^+$ + Na] 657.4194. Found 657.4194; $[\alpha]_D^{20}$ = $-$ 21 (c = 0.9 in CH$_2$Cl$_2$).

**Synthesis of Alkyne 2.24**

1. TESO
2. $\text{Cp}_2\text{ZrCl}_2$, DIBAL-H, then I$_2$
3. DMP, CH$_2$Cl$_2$
4. $n$-BuLi, THF, then BOTf
5. 1) MeNH(OMe)HCl, Et$_3$N, PhMe, 2) TESOTf
6. AlMe$_3$
7. Me$_3$OBF$_4$, proton sponge
8. TMS, 1) K$_2$CO$_3$, EtOH, 2) TESOTf

**Scheme 4-3 Synthesis of alkyne fragment 2.26**

**Compound 2.49** To a solution of 2-butyn-1-ol (5.0 g, 71.5 mmol, 1.0 eq), imidazole (7.3 g, 0.11 mol, 1.5 eq) and DMAP (440 mg, 3.6 mmol, 0.05 eq) in dichloromethane (250 mL) was added TESCl (14.5 mL, 85.8 mmol, 1.2 eq). The cloudy reaction mixture was stirred for 4 h at room temperature, then quenched with water. The layers were separated and the aqueous layer extracted with additional dichloromethane. The combined organic layers were
dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (100% hexanes → 5% diethyl ether in hexanes) to provide the title compound as a colorless free-flowing liquid (12.77 g, 97%).

$^1$H NMR (CDCl$_3$, 500MHz) δ = 4.28 (q, J = 2.3 Hz, 2 H), 1.85 (t, J = 2.4 Hz, 3 H), 0.99 (t, J = 8.5 Hz, 9 H), 0.66 (q, J = 8.6 Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 126MHz) δ = 81.0, 77.8, 51.7, 6.8, 4.6, 3.7; IR (film): $\tilde{\nu}_{\text{max}}$ = 2953, 2877, 2238 cm$^{-1}$; HRMS (ESI): Calc. for C$_{10}$H$_{21}$OSi \([M^+ + H]\) 185.1362. Found 185.1358.

**Compound 2.47.** To a 0 °C solution of Cp$_2$ZrCl$_2$ (6.97 g, 23.9 mmol, 1.1 eq) in THF (56 mL) was added DIBAL-H (1.0 M in hexanes, 24 mL, 24 mmol, 1.1 eq) dropwise and the reaction mixture stirred 0.5 h at 0 °C. A solution of 2.49 (4 g, 21.7 mmol, 1.0 eq) in THF (12 mL) was added dropwise and the reaction mixture warmed to room temperature and stirred for 1 h, then cooled to - 78 °C. A solution of iodine (7.16 g, 28.2 mmol, 1.3 eq) in THF (40 mL) was added slowly. The mixture was stirred at - 78 °C for 1.5 h, then quenched with sat. aqueous ammonium chloride and warmed to room temperature, then stirred for 1.5 h. The layers were separated, the aqueous layer extracted 2x10 mL diethyl ether, and the combined organics washed with sat. aqueous Na$_2$S$_2$O$_3$ and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (3:1 Hexanes:Ether → 3:1 Pentane:Ether → 2:1 Pentane:Ether) to yield the title compound (2.66 g, 62%) as a volatile oil that was not stored for prolonged periods of time due to decomposition. The spectral data for a diethyl ether solution (~25% w/w) of this compound matched the data reported in the literature for the pure compound.$^3$

**Compound 2.48.** The entirety of this reaction was performed in the dark. To a solution of 2.47 (3.28 g, 16.6 mmol, 1.0 eq) in dichloromethane (60 mL) was added Dess-Martin periodinane (9.13 g, 21.5 mmol, 1.3 eq) and the reaction mixture warmed to room temperature and stirred for 1 h, then recooled to 0 °C and quenched with sat. aqueous sodium bicarbonate (60 mL) and sat. aqueous Na$_2$S$_2$O$_3$ (60 mL). After stirring vigorously at room temperature for 1 h, the layers were separated and the aqueous layer extracted with diethyl ether
(3x20 mL). The combined organics were dried over Na$_2$SO$_4$ and concentrated under reduced pressure (c. 200 Torr). The residue was purified by flash column chromatography (9:1 Petroleum ether:Diethyl Ether) to yield the title compound (2.24 g, 69%) as a pale yellow oil. Due to instability, this compound was kept in the dark, never concentrated fully and used immediately in the next step. The spectral data matched those previously reported in the literature.$^3$

**Compound 4.2** Chloroacetic acid (4.72 g, 50 mmol, 1.0 eq) and 4-methoxybenzyl alcohol (6.25 mL, 50 mmol, 1.0 eq) were combined in a 500 mL round bottom flask and azeotroped twice with benzene, then dried under vacuum. Toluene (180 mL) was added and the reaction mixture cooled to 0 °C. Sodium hydride (4.4 g, 110 mmol, 2.2 eq, 60% in mineral oil) was then added portionwise. After addition was complete, the reaction mixture was heated to reflux and allowed to stir overnight. The following morning, the mixture was cooled to room temperature and quenched with water. The layers were separated and the aqueous layer was acidified to pH 1 by the addition of 3 M HCl, then extracted three times with dichloromethane (200 mL). The combined organics were dried over sodium sulfate and concentrated. The crude residue was purified by flash column chromatography (2:1 Hexanes:Ethyl Acetate + 1% formic acid → 1:2 Hexanes:Ethyl Acetate + 1% formic acid) to yield the title compound (8.51 g, 87%).

$^1$H NMR (CDCl$_3$, 500MHz) δ = 7.30 (d, $J$ = 7.9 Hz, 2 H), 6.91 (d, $J$ = 8.6 Hz, 2 H), 4.60 (s, 2 H), 4.12 (s, 2 H), 3.83 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 126MHz) δ = 159.8, 130.5, 130.0, 128.6, 114.2, 73.3, 66.4, 55.5; IR (film): $\tilde{\nu}_{\text{max}}$ = 3240, 2937, 2829, 1732, 1612, 1514 cm$^{-1}$; HRMS (ESI): Calc. for C$_{10}$H$_{12}$O$_4$Na [$M^+$ + Na] 291.0633, found 291.0634.

**Compound 2.50.** To a -78 °C solution of 4.2 (2.52 g, 12.8 mmol, 1.0 eq) in THF (45 mL) was added triethylamine (2.0 mL, 141. mmol, 1.1 eq) and pivalic chloride (1.65 mL, 13.4 mmol, 1.05 eq) dropwise. The reaction mixture was then gradually warmed to -20 °C over 1.5 h to form the corresponding mixed anhydride. In a separate flask, a solution of Evans auxiliary (2.5 g, 14.1 mmol, 1.1 eq) in THF (45 mL) was treated with n-butyllithium (2.5 M in hexanes, 5.9 mL, 14.7 mmol, 1.15 eq) dropwise at -78 °C, then stirred for an
additional hour at this temperature. The lithiated auxiliary was then canulated dropwise into the flask containing the anhydride. The reaction mixture was allowed to gradually warm to r.t. over c. 1h, then quenched with sat. aqueous ammonium chloride and diluted with H₂O/diethyl ether. The layers were separated and the aqueous layer extracted with diethyl ether (2x50 mL). The combined organics were washed with 1 M sodium hydroxide and brine, dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (3:1 → 2:1 Hexanes:Ethyl Acetate) to yield the title compound (3.79 g, 83%) as a white solid.

**M.P.** 64-65 °C; **¹H NMR** (CDCl₃, 500 MHz): δ = 7.38 - 7.32 (m, 4 H), 7.32 - 7.28 (m, 1 H), 7.22 (d, J = 7.1 Hz, 2 H), 6.91 (d, J = 9.1 Hz, 2 H), 4.74 - 4.67 (m, 3 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.63 (d, J = 11.4 Hz, 1 H), 4.28 (t, J = 8.4 Hz, 1 H), 4.23 (dd, J = 4.3, 9.0 Hz, 1 H), 3.82 (s, 3 H), 3.34 (dd, J = 2.9, 13.5 Hz, 1 H), 2.83 (dd, J = 9.5, 13.4 Hz, 1 H); **¹³C NMR** (CDCl₃, 126 MHz): δ = 170.4, 159.7, 153.5, 135.1, 130.0, 129.6, 129.4, 129.2, 127.6, 114.1, 73.3, 69.5, 69.5, 67.4, 55.4, 54.9, 37.9; **IR** (film): ν = 2918, 1779, 1714, 1612, 1585, 1514, 1393 cm⁻¹; **HRMS** (ESI): Calc. for C₂₀H₂₁NO₅Na [M⁺ + Na] 378.1317. Found 378.1314; [α]_D²⁰⁻⁶₁ (c = 2 in CH₂Cl₂).

**Compound 2.51.** To a solution of **2.50** (2.53 g, 7.13 mmol, 1.0 eq) and triethylamine (1.3 mL, 9.27 mmol, 1.3 eq) in toluene (9.5 mL) at -50 °C was added dibutyl boron triflate (1 M in dichloromethane, 7.84 mL, 7.84 mmol, 1.1 eq) and the reaction mixture stirred at -50 °C for 1.5 h. A solution of aldehyde **2.48** (2.24 g, 11.4 mmol, 1.6 eq) in toluene (9.5 mL) was then added dropwise at this temperature and the reaction mixture was allowed to gradually warm to -30°C and stir at this temperature for an additional 1.5 h. The reaction was then quenched by the successive careful addition of methanol (6 mL), pH 7 buffer (6 mL) and 30% hydrogen peroxide (6 mL). The mixture was stirred vigorously at room temperature for 1h. The layers were separated and the aqueous layer was extracted with diethyl ether (3x25 mL). The combined organics were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (2:1 → 1:1
Hexanes:Ethyl Acetate) to yield the title compound (3.23 g, 82%, single diastereomer) as an off-white foam.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.37 - 7.32 (m, 4 H), 7.32 - 7.29 (m, 1 H), 7.23 - 7.19 (m, 2 H), 6.94 - 6.90 (m, 2 H), 6.33 (qd, $J$ = 1.3, 8.9 Hz, 1 H), 5.20 (d, $J$ = 4.3 Hz, 1 H), 4.65 (d, $J$ = 11.2 Hz, 1 H), 4.63 - 4.58 (m, 2 H), 4.56 (d, $J$ = 11.1 Hz, 1 H), 4.29 (t, $J$ = 8.8 Hz, 1 H), 4.21 (dd, $J$ = 2.2, 9.1 Hz, 1 H), 3.80 (s, 3 H), 3.18 (dd, $J$ = 3.3, 13.5 Hz, 1 H), 2.67 (dd, $J$ = 9.7, 13.4 Hz, 1 H), 2.43 (d, $J$ = 1.5 Hz, 3 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 170.0, 160.0, 153.4, 138.4, 135.1, 130.5, 129.5, 129.2, 127.6, 114.1, 100.2, 79.1, 73.3, 70.5, 67.2, 60.5, 55.8, 55.4, 37.9, 28.9; IR (film): $\tilde{\nu}$ = 3465, 2920, 1778, 1705, 1611, 1513, 1455, 1390, 1354 cm$^{-1}$; HRMS (ESI): Calc. for C$_{24}$H$_{26}$NO$_6$NaI [M$^+$ + Na]$^+$ = 574.0703. Found 574.0702; $[\alpha]_D^{20}$ = -55 (c = 1.091 in CH$_2$Cl$_2$); $[\alpha]_D^{20}$ = -55 (c = 0.9 in CH$_2$Cl$_2$).

**Compound 2.53.** To a 0 °C suspension of N,N-dimethylhydroxylamine hydrochloride (995 mg, 10.2 mmol, 3.0 eq) in THF (9 mL) was added trimethylaluminum (2.0 M in toluene, 5.1 mL, 10.2 mmol, 3.0 eq) and the mixture stirred for 30 minutes at room temperature. The reaction mixture was then cooled to -20 °C and a solution of 2.51 (1.87 g, 3.40 mmol, 1.0 eq) in THF (9 mL) was added dropwise. The reaction mixture was transferred to a 0 °C ice bath and stirred for 1 h. The reaction was quenched by the careful dropwise addition of Rochelle’s salt (9 mL), followed by 1 h of vigorous stirring at room temperature. The mixture was diluted with water and diethyl ether and the layers were separated. The aqueous layer was extracted 3x5 mL dichloromethane and the combined organics dried over Na$_2$SO$_4$ and concentrated to yield a crude inseparable mixture of the desired Weinreb amide and Evans auxiliary.

This mixture was dissolved in dichloromethane (6 mL) and cooled to -78 °C. 2,6-lutidine (1.46 mL, 12.6 mmol, 3.7 eq) and TESOTf (1.69 mL, 7.48 mmol, 2.2 eq) were added dropwise and the reaction mixture was stirred for 1 h at -78 °C. The reaction was quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. The layers were separated and
the aqueous layer extracted with dichloromethane (3x15 mL). The combined organics were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography to yield the title compound (1.39 g, 74% over 2 steps) and TES-protected Evans auxiliary 2.54 (888 mg). The auxiliary could be recovered by stirring in a TFA/THF/H$_2$O (1:10:2.5) mixture overnight following a literature procedure.\(^4\)

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.28 (d, $J$ = 8.6 Hz, 2 H), 6.87 (d, $J$ = 8.6 Hz, 2 H), 6.21 (dd, $J$ = 1.5, 9.3 Hz, 1 H), 4.66 (d, $J$ = 12.0 Hz, 1 H), 4.63 (dd, $J$ = 9.8, 6.7 Hz, 1 H), 4.50 (d, $J$ = 12.0 Hz, 1 H), 3.81 (s, 3 H), 3.49 (br. s., 3 H), 3.17 (s, 3 H), 2.37 (d, $J$ = 1.0 Hz, 3 H), 0.96 (t, $J$ = 8.6 Hz, 9 H), 0.62 (q, $J$ = 7.9 Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 159.3, 140.4, 130.2, 129.7, 113.8, 97.6, 72.2, 71.9, 61.4, 55.4, 32.5, 29.8, 28.8, 6.8, 4.9; IR (film): $\tilde{\nu}$ = 2953, 1670, 1513 cm$^{-1}$; HRMS (ESI): Calc. for C$_{22}$H$_{36}$NO$_5$SiNa [M$^+$ + Na] 572.1305. Found 572.1307; $[\alpha]_D^{28}$ = +28 (c = 1.55 in CH$_2$Cl$_2$).

**Compound 2.54:** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.35 (t, $J$ = 7.2 Hz, 2 H), 7.28 (tt, $J$ = 1.2, 7.4 Hz, 1 H), 7.17 (d, $J$ = 7.0 Hz, 2 H), 4.13 - 4.06 (m, 2 H), 3.91 - 3.83 (m, 1 H), 3.00 (dd, $J$ = 3.4, 13.5 Hz, 1 H), 2.72 (dd, $J$ = 11.1, 13.5 Hz, 1 H), 1.06 (t, $J$ = 8.2 Hz, 9 H), 0.94 (q, $J$ = 7.0 Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 126 MHZ): $\delta$ = 161.6, 136.4, 129.3, 129.1, 129.1, 127.3, 68.1, 57.6, 42.2, 7.0, 7.0; IR (film): $\tilde{\nu}_{\text{max}}$ = 2953, 1670, 1513 cm$^{-1}$; HRMS (ESI): Calc. for C$_{16}$H$_{26}$NO$_2$Si [M$^+$ + H] 292.1733. Found 292.1733; $[\alpha]_D^{28}$ = −38 (c = 1 in CH$_2$Cl$_2$).

**Compound 2.56** To a -78 °C solution of 3-butyn-1-ol (7.0 g, 100 mmol) in THF (400 mL) was added $n$-butyllithium (88 mL, 220 mmol, 2.2 eq, 2.5 M solution in hexanes) and the resulting cloudy mixture stirred 1.5 h at -78 °C. Trimethylsilyl chloride (23.8 g, 220 mmol, 2.2 eq) was then added dropwise and the reaction mixture warmed to 0 °C and stirred and additional 2 h. 2 N HCl (30 mL) was then added dropwise and the reaction mixture stirred a final 30 minutes at 0 °C. The mixture was then extracted directly with diethyl ether.
(3x200 mL) and the combined extracts dried over sodium sulfate and concentrated to provide the title compound, which was used in the next step without any further purification.

$^1$H NMR (CDCl$_3$, 500MHz) $\delta$ = 3.72 (q, $J$ = 6.1 Hz, 2 H), 2.51 (dt, $J$ = 1.3, 6.3 Hz, 2 H), 0.17 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 126MHz) $\delta$ = 103.4, 87.2, 61.0, 24.4, 0.2; IR (film): $\tilde{\nu}_{max}$ = 3348, 2959, 2899, 2177 cm$^{-1}$. HRMS (Cl): Calc. for C$_6$H$_{11}$OSi [$M^+$ - Me] 127.0579, found 127.0564.

**Compound 2.57** To a -20 °C solution of compound 2.56 (6.46 g, 45.4 mmol, 1.0 eq) in dichloromethane (70 mL) were added triphenylphosphine (14.3 g, 54.5 mmol, 1.2 eq) and NBS (8.9 g, 49.9 mmol, 1.1 eq) as solids in one portion. The reaction mixture was allowed to warm to room temperature and stir under an argon atmosphere overnight, then diluted with diethyl ether (250 mL) and washed with saturated aqueous sodium bicarbonate solution and brine. The organics were dried over sodium sulfate and concentrated. The residue was suspended in hexanes and stirred for 15 minutes, then filtered and reconcentrated. Flash column chromatography (hexanes) provided the title compound a colorless free-flowing liquid (4.644 g, 50%).

$^1$H NMR (CDCl$_3$, 500MHz) $\delta$ = 3.44 (t, $J$ = 7.5 Hz, 2 H), 2.79 (t, $J$ = 7.5 Hz, 2 H), 0.17 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 126MHz) $\delta$ = 103.3, 87.1, 29.3, 24.4, 0.1; IR (film): $\tilde{\nu}_{max}$ = 2960, 2898, 2178, 1418 cm$^{-1}$; HRMS (Cl): Calc. for C$_6$H$_{10}$SiBr [$M^+$] 188.9735. Found 188.9726.

**Compound 2.59**. Grignard reagent derived from 2.57 was prepared according to a literature procedure.$^7$ To magnesium turnings (660 mg, 27.2 mmol, 5.0 eq) in refluxing THF (40 mL) was added dibromoethane (230 µL, 2.72 mmol, 0.5 eq) and the mixture refluxed an additional 10 minutes. A solution of 2.57 (3.35 g, 16.3 mmol, 3.0 eq, must be free of trace bromoform from the preceding Appel reaction) in THF (10 mL) was then added dropwise and the reaction mixture refluxed for an additional 1h. In a separate flask, a solution of 2.53 (2.99 g, 5.44 mmol, 1.0 eq) in THF (20 mL) was cooled to -78 °C. The solution of the Grignard was then cooled to room temperature and transferred to the solution of 2.53
dropwise via syringe and the resulting mixture stirred at -78 °C for 30 min, then at 0 °C for an additional 1.5 h. The reaction was quenched with sat. aqueous ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer extracted with additional diethyl ether. The combined organics were washed with water and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (9:1 Hexanes:Diethyl ether) to yield the title compound (3.06 g, 92%) as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 7.26 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 6.26 (qd, J = 1.4, 8.0 Hz, 1 H), 4.69 (d, J = 11.8 Hz, 1 H), 4.56 (dd, J = 3.9, 7.0 Hz, 1 H), 4.39 (d, J = 11.8 Hz, 1 H), 3.84 (s, 3 H), 3.68 (d, J = 3.6 Hz, 1 H), 2.93 - 2.77 (m, 2 H), 2.51 - 2.37 (m, 2 H), 2.34 (d, J = 1.5 Hz, 3 H), 0.92 (t, J = 8.1 Hz, 9 H), 0.54 (q, J = 8.2 Hz, 6 H), 0.15 (s, 9 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): δ = 210.3, 159.7, 140.9, 130.1, 129.0, 114.1, 106.1, 96.9, 86.2, 84.9, 73.5, 71.7, 55.4, 40.3, 28.5, 13.8, 6.8, 6.8, 6.8, 4.8, 0.2; IR (film): $\tilde{\nu}$ = 2956, 2912, 2877, 2176, 1718, 1637, 1586, 1514, 1250 cm$^{-1}$; HRMS (ESI): C$_{27}$H$_{43}$O$_4$Si$_2$INa [M$^+$ + Na] $\text{Found 637.1639; } [\alpha]_D^{20} = +56 \text{ (c = 0.92 in CH}_2\text{Cl}_2)$. Compound 2.60. Zinc borohydride solution was freshly prepared by adding a solution of zinc chloride (1 M in diethyl ether, 5.5 mL, 5.5 mmol, 1.0 eq) to a suspension of sodium borohydride (401 mg, 10.6 mmol, 1.93 eq) in diethyl ether (30 mL) and stirring the resulting mixture for 2 days. An aliquot of this solution (7 mL, 0.978 mmol, 1.2 eq) was then added to a -50 °C solution of 2.59 (500 mg, 0.815 mmol, 1.0 eq) in diethyl ether (10 mL). The reaction mixture was stirred at -50 °C for 30 min., then quenched by the careful addition of Rochelle's salt. The biphasic mixture was warmed to room temperature and stirred vigorously for 1h. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography to yield the title compound (313 mg, 62%) as a colorless oil. Performing this reaction on a larger scale resulted in a significant drop in yield. Higher yields (up to 73%) could be obtained on smaller scale (<300 mg).
\( ^1H \text{ NMR} \) (CDCl\(_3\), 500 MHz): \( \delta = 7.26 \) (d, \( J = 8.8 \) Hz, 2 H), 6.90 (d, \( J = 8.9 \) Hz, 2 H), 6.33 (dd, \( J = 1.4, 9.1 \) Hz, 1 H), 4.58 (q, \( J = 11.4 \) Hz, 2 H), 4.54 (dd, \( J = 4.5, 9.1 \) Hz, 1 H), 3.89 - 3.84 (m, 1 H), 3.82 (s, 3 H), 3.31 (dd, \( J = 4.9, 10.0 \) Hz, 1 H), 3.17 (d, \( J = 4.0 \) Hz, 1 H), 2.42 (d, \( J = 1.4 \) Hz, 3 H), 2.37 (m, 1 H), 1.88 - 1.80 (m, 1 H), 1.65 - 1.57 (m, 1 H), 0.96 (t, \( J = 8.7 \) Hz, 9 H), 0.60 (q, \( J = 8.0 \) Hz, 6 H), 0.17 (s, 9 H); \( ^{13}C \text{ NMR} \) (CDCl\(_3\), 126 MHz): \( \delta = 159.6, 140.6, 130.1, 129.9, 114.0, 107.4, 97.5, 84.9, 82.6, 73.6, 71.1, 70.5, 55.4, 32.5, 28.9, 16.2, 6.8, 4.8, 0.4; IR (film): \( \tilde{\nu} = 3495, 2955, 2876, 2172, 1640, 1612, 1586, 1514, 1249 \) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{27}\)H\(_{45}\)O\(_4\)NaSi\(_2\)I \([M^+ + Na]\) 639.1799. Found 639.1804; \([\alpha]\)\(_D\) = −25 (c = 1 in CH\(_2\)Cl\(_2\)).

**Compound 2.61.** To a solution of 2.60 (1 g, 1.62 mmol, 1.0 eq) in dichloromethane (30 mL) were added proton sponge (1.04 g, 4.86 mmol, 3.0 eq) and trimethyloxonium tetrafluoroborate (720 mg, 4.86 mmol) in one portion and the reaction mixture was stirred for 1 h at room temperature. The reaction was then quenched with brine and diluted with dichloromethane. The layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic layers were filtered through a pad of Celite and concentrated, then redissolved in ether and refiltered. The filtrate was concentrated and the residue purified by flash column chromatography (9:1 Hexanes:Diethyl ether) to yield the title compound (782 mg, 77%) as a colorless oil.

\( ^1H \text{ NMR} \) (CDCl\(_3\), 500 MHz): \( \delta = 7.28 \) (d, \( J = 8.9 \) Hz, 2 H), 6.88 (d, \( J = 8.5 \) Hz, 2 H), 6.23 (d, \( J = 9.3 \) Hz, 1 H), 4.62 (d, \( J = 10.2 \) Hz, 2 H), 4.41 (dd, \( J = 5.2, 9.1 \) Hz, 1 H), 3.82 (s, 3 H), 3.52 - 3.46 (m, 2 H), 3.33 (s, 3 H), 2.46 (s, 3 H), 2.42 - 2.30 (m, 2 H), 1.86 - 1.78 (m, 1 H), 1.74 - 1.66 (m, 1 H), 0.96 (t, \( J = 7.9 \) Hz, 9 H), 0.59 (q, \( J = 8.1 \) Hz, 6 H), 0.18 (s, 9 H); \( ^{13}C \text{ NMR} \) (CDCl\(_3\), 126 MHz): \( \delta = 159.3, 142.1, 130.9, 129.6, 113.8, 107.4, 96.6, 84.9, 81.9, 79.6, 73.9, 70.9, 57.7, 55.4, 29.4, 28.8, 16.3, 6.9, 5.1, 0.4; IR (film): \( \tilde{\nu} = 3495, 2955, 2876, 2173, 1729, 1640, 1614, 1586, 1514, 1463 \) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{28}\)H\(_{47}\)O\(_4\)Si\(_2\)I Na \([M^+ + Na]\) 653.1955. Found 653.1957; \([\alpha]\)\(_D\) = +4.9 (c = 1 in CH\(_2\)Cl\(_2\)).
**Alkyne 2.26.** To a solution of 2.61 (258 mg, 0.409 mmol, 1.0 eq) in ethanol (5 mL) was added potassium carbonate (170 mg, 3.0 eq) in one portion and the reaction mixture stirred at room temperature for 3 days, then concentrated. The residue was dissolved in diethyl ether and washed with water and brine, dried over Na$_2$SO$_4$ and concentrated. Crude NMR showed ~30% loss of TES group.

The crude residue was dissolved in dichloromethane (5 mL) and cooled to -78 °C. 2,6-lutidene (95 µL, 0.818 mmol, 2.0 eq) and TESOTf (92 µL, 0.409 mmol, 1.0 eq) were added and the reaction mixture stirred at -78 °C for 30 min, then quenched with sat. aqueous sodium bicarbonate, warmed to room temperature and diluted with dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organics were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (12:1 Hexanes:Diethyl ether) to yield the title compound (176 mg, 77% over two steps) as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 7.28$ (d, $J = 8.9$ Hz, 2 H), 6.88 (d, $J = 9.0$ Hz, 2 H), 6.22 (dd, $J = 1.5, 9.4$ Hz, 1 H), 4.64 (s, 2 H), 4.39 (dd, $J = 5.8, 9.4$ Hz, 1 H), 3.82 (s, 3 H), 3.52 (dd, $J = 3.1, 5.8$ Hz, 1 H), 3.46 (td, $J = 2.9, 9.2$ Hz, 1 H), 3.33 (s, 3 H), 2.46 (d, $J = 1.6$ Hz, 3 H), 2.37 - 2.25 (m, 2 H), 1.99 (t, $J = 2.7$ Hz, 1 H), 1.89 - 1.80 (m, 1 H), 1.69 - 1.63 (m, 1 H), 0.96 (t, $J = 8.1$ Hz, 9 H), 0.60 (q, $J = 8.0$ Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 159.2, 141.8, 130.9, 129.6, 113.8, 97.0, 84.4, 81.7, 79.8, 74.1, 71.2, 68.8, 57.6, 55.4, 29.3, 28.9, 14.8, 6.9, 5.1; IR (film): 2953, 2876, 2116, 1638, 1613, 1514, 1462, 1378, 1302, 1248 cm$^{-1}$; HRMS (ESI): Calc. for C$_{25}$H$_{39}$O$_4$NaSi [M$^+$ + Na] 581.1560. Found 581.1553; [$\alpha$]$_D^{20} = -1.7$ (c = 1 in CH$_2$Cl$_2$).

**Propargylic alcohols syn-2.23 and anti-2.23.** A stock solution of LDA (0.2 M in THF) was freshly prepared by adding n-butyllithium (2.5 M in hexanes, 220 µL, 0.5 mmol) to a solution of diisopropylamine (70 µL, 0.5 mmol) in THF (2.5 mL) at -78 °C and stirring for 40 minutes. An aliquot of this solution (435 µL, 87 µmol, 3.0 eq) was then added to a -78 °C solution of alkyne 2.24 (48.6 mg, 87 µmol, 3.0 eq) in THF (0.5 mL) and the reaction mixture allowed to gradually...
warm to -20 °C over ~30 min., then stirred at this temperature for 15 min and recooled to -78 °C.

In a separate flask, a solution of aldehyde 2.25 (18.4 mg, 29 µmol, 1.0 eq) in THF (0.5 mL) was cooled to -78 °C. The solution of alkyne anion was then transferred via cannula to the aldehyde solution and the mixture was transferred to a 0 °C ice bath and stirred for 1h, then quenched with sat. aqueous ammonium chloride and diluted with H2O/diethyl ether. The layers were separated and the aqueous layer extracted 2x5 mL diethyl ether. The combined organic layers were dried over Na2SO4 and concentrated. The residue was purified by MPLC (5:1 Hexanes:Ethyl Acetate) to yield the title compounds anti-2.23 (15.1 mg, ) and syn-30b (8.8 mg), as well as recovered alkyne 2.4 (33.3 mg, ~100%).

**anti-2.23:**

**1H NMR (CDCl3, 500 MHz):** δ = 7.27 (d, J = 8.1 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.22 (d, J = 9.2 Hz, 1 H), 4.84 - 4.60 (m, 7 H), 4.40 (dd, J = 5.5, 9.3 Hz, 1 H), 3.95 (m, 1 H), 3.92 - 3.87 (m, 1 H), 3.82 (s, 4 H), 3.78 - 3.68 (m, 3 H), 3.53 (br. s., 1 H), 3.44 (dd, J = 3.8, 5.4 Hz, 1 H), 3.41 - 3.35 (m, 8 H), 3.31 (s, 3 H), 2.45 (s, 3 H), 2.30 (t, J = 6.2 Hz, 2 H), 2.07 - 1.98 (m, 1 H), 1.87 - 1.78 (m, 3 H), 1.74 - 1.64 (m, 4 H), 1.63 - 1.48 (m, 8 H), 1.29 - 1.11 (m, 8 H), 0.97 (td, J = 7.9, 13.0 Hz, 18 H), 0.89 (s, 9 H), 0.65 (q, J = 7.9 Hz, 6 H), 0.59 (q, J = 7.9 Hz, 6 H), 0.05 (s, 6 H); **13C NMR (CDCl3, 126 MHz):** δ = 159.2, 142.1, 130.9, 129.6, 113.8, 96.8, 96.8, 96.2, 81.8, 80.6, 80.0, 74.5, 74.5, 74.1, 73.3, 72.5, 71.1, 63.5, 59.9, 57.6, 55.9, 55.8, 55.4, 43.3, 42.5, 42.3, 41.4, 40.0, 32.2, 31.8, 29.9, 29.6, 28.8, 26.1, 23.9, 18.4, 15.2, 12.0, 7.0, 6.9, 5.2, 5.1, -5.2; **IR (film):** ν = 3455, 2932, 2877, 1613, 1514, 1461, 1379 cm⁻¹; **HRMS (ESI):** Calc. for C57H105O12Si3Na [M⁺ + Na] 1215.5856. Found 1215.5857; [α]D 30 = +3.3 (c = 1 in CH2Cl2).
**syn-2.23:** ¹H NMR (CDCl₃, 500 MHz): δ = 7.28 (d, J = 8.8 Hz, 2 H), 6.88 (d, J = 9.1 Hz, 2 H), 6.22 (dd, J = 1.4, 9.4 Hz, 1 H), 4.72 - 4.60 (m, 6 H), 4.39 (dd, J = 5.7, 9.4 Hz, 1 H), 4.24 (d, J = 9.1 Hz, 1 H), 4.18 - 4.13 (m, 1 H), 3.92 - 3.85 (m, 2 H), 3.82 (s, 3 H), 3.71 (t, J = 6.6 Hz, 2 H), 3.50 - 3.46 (m, 1 H), 3.41 - 3.37 (m, 8 H), 3.31 (s, 3 H), 2.93 (d, J = 5.4 Hz, 1 H), 2.46 (d, J = 1.3 Hz, 3 H), 2.33 (t, J = 7.0 Hz, 2 H), 1.97 - 1.90 (m, 1 H), 1.87 - 1.79 (m, 2 H), 1.78 - 1.65 (m, 5 H), 1.54 (m, 8 H), 1.21 - 1.14 (m, 2 H), 1.01 - 0.92 (m, 21 H), 0.90 (s, 9 H), 0.65 (q, J = 8.0 Hz, 6 H), 0.59 (q, J = 8.0 Hz, 6 H), 0.05 (s, 6 H); ¹³C NMR (CDCl₃, 126 MHz): δ = 159.1, 142.1, 130.7, 129.6, 113.8, 96.9, 96.7, 95.7, 85.6, 81.8, 81.0, 79.9, 77.4, 77.2, 76.9, 74.6, 74.1, 72.4, 71.1, 70.2, 65.4, 60.0, 57.6, 55.9, 55.4, 46.2, 43.6, 43.1, 42.4, 40.0, 39.0, 32.2, 31.9, 29.8, 29.5, 28.8, 26.1, 23.9, 18.5, 15.4, 15.2, 11.4, 7.2, 6.9, 5.4, 5.1, -5.2; IR (film): ν = 3455, 2932, 2877, 1613, 1514, 1461, 1379 cm⁻¹; HRMS (ESI): Calc. for C₅₇H₁₀₅O₁₂Si₃Na [M⁺ + Na] 1215.5856. Found 1215.5857; [α]⁺[D] = +3.3 (c = 1 in CH₂Cl₂).

**Diols anti-2.70 and syn-2.70.** The following procedure of anti-2.70 is representative. To a solution of anti-2.23 (15.1 mg, 12.6 µmol, 1.0 eq) in dichloromethane/pH 7 buffer (9:1, 2.4 mL total) at 0 ºC was added DDQ (28 mg, 0.126 mmol, 10 eq) in one portion and the reaction mixture stirred for 1 h at 0 ºC, then quenched with sat. aqueous sodium bicarbonate. The layers were separated and the aqueous layer extracted with 2x3 mL dichloromethane. The combined organic layers were washed with sodium bicarbonate, dried over Na₂SO₄ and concentrated. The residue was purified (4:1 Hexanes:Ethyl Acetate) to yield the title compound (9.4 mg, 69%) as a colorless oil. Yields for syn-2.70 tended to be higher (~85%).
3.45 - 3.38 (m, 2 H), 3.37 (s, 3 H), 3.33 (m, 4 H), 3.16 (s, 3 H), 2.36 (dt, \( J = 1.5, 6.6 \text{ Hz} \), 2 H), 2.26 (d, \( J = 1.5 \text{ Hz} \), 3 H), 2.17 - 2.09 (m, 2 H), 2.03 - 1.95 (m, 1 H), 1.94 - 1.77 (m, 5 H), 1.76 - 1.57 (m, 4 H), 1.40 - 1.33 (m, 9 H), 1.15 (m, 1 H), 1.05 (t, \( J = 7.7 \text{ Hz} \), 9 H), 1.01 (s, 9 H), 0.95 (t, \( J = 7.7 \text{ Hz} \), 9 H), 0.72 (q, \( J = 8.0 \text{ Hz} \), 6 H), 0.56 (dq, \( J = 2.1, 8.0 \text{ Hz} \), 6 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ^{13}C \text{ NMR} (C_6D_6, 126 MHz): \( \delta = 142.4, 96.9, 96.8, 96.1, 85.3, 81.9, 79.4, 75.0, 74.3, 74.1, 73.7, 73.4, 72.7, 69.9, 65.8, 64.0, 60.1, 57.0, 55.6, 55.5, 44.8, 43.8, 43.1, 40.9, 40.4, 32.4, 32.0, 30.3, 30.1, 29.0, 28.3, 26.1, 24.1, 18.4, 15.4, 14.2, 11.4, 7.2, 6.9, 5.5, 5.2, -5.2; \text{ IR} \text{ (film)}: \tilde{\nu} = 3436, 2929, 1640, 1461, 1251 \text{ cm}^{-1}; \text{ HRMS} \text{ (ESI)}: \text{ Calc. for } C_{49}H_{97}O_{11}Si_{3}INa [M^+ + Na] 1095.5281. \text{ Found } 1095.5317; [\alpha]_D^{\theta} = +27 \text{ (c = 0.5 in CH}_{2}\text{Cl}_{2}).

\text{Revised Second Generation Route - Synthesis of Revised Alkyne 2.72}

\text{ARC Adduct 2.74.} \text{ To a solution of TBS-dithiane (1.78 g, 7.60 mmol, 1 eq) in a mixture of diethyl ether (6 mL) and THF (6 mL) at room temperature was added } n\text{-butyllithium (2.4 M in hexanes, 3.45 mL, 8.29 mmol, 1.2 eq) dropwise and the reaction mixture stirred at room temperature for 10 minutes, then cooled to -50 } \degree \text{C. A solution of epoxide 2.30 (2.08 g, 6.91 mmol, 1.0 eq) in diethyl ether (12 mL) was added slowly and the reaction mixture stirred for 1h at -45 } \degree \text{C, then cooled to -78 } \degree \text{C. A solution of epoxide 2.29 (1.99 g, 10.36 mmol, 1.5 eq) in diethyl ether (12 mL) was added slowly, followed by a solution of HMPA (900 \mu\text{L}, 5.18 mmol, 0.75 eq) in diethyl ether (12 mL). The reaction mixture turns yellow, indicating successful Brook rearrangement. The reaction mixture was then removed from the cooling bath, allowed to warm to 0 } \degree \text{C and stirred for 1h. The reaction was then quenched with sat. aqueous ammonium chloride and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with ethyl acetate (3x15 mL). The combined organics were washed with water (2x15 mL) and brine, dried over Na}_2\text{SO}_4 \text{ and concentrated. The residue was purified by flash column chromatography (9:1 } \rightarrow {7:1} \text{ Hexanes:Ethyl Acetate} \text{ to yield the title compound (1.14 g, 76%) a colorless oil.}
\(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz): \(\delta = 7.35 - 7.32\) (m, 4 H), 7.31 - 7.26 (m, 1 H), 4.52 (s, 2 H), 4.24 (quin, \(J = 5.6\) Hz, 1 H), 4.03 - 3.97 (m, 1 H), 3.73 (d, \(J = 7.2\) Hz, 2 H), 3.64 - 3.55 (m, 2 H), 3.50 (dd, \(J = 6.0, 9.2\) Hz, 1 H), 3.40 (dd, \(J = 6.3, 14.1\) Hz, 2 H), 2.98 - 2.71 (m, 4 H), 2.33 (ddd, \(J = 9.5, 15.8, 24.5\) Hz, 2 H), 2.12 - 2.02 (m, 2 H), 1.99 - 1.87 (m, 4 H), 1.84 - 1.72 (m, 2 H), 1.65 - 1.43 (m, 5 H), 1.25 - 1.14 (m, 2 H), 1.03 (d, \(J = 6.9\) Hz, 3 H), 0.90 (s, 18 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.06 (s, 6 H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 138.6, 128.5, 127.8, 127.7, 127.7, 127.6, 74.8, 74.6, 73.4, 73.0, 71.4, 67.3, 60.3, 51.7, 48.7, 46.7, 44.1, 40.0, 39.7, 32.4, 31.7, 26.9, 26.4, 26.3, 26.3, 24.8, 24.0, 18.5, 18.2, 14.5, -3.4, -4.0, -5.1, -5.1; \(\text{IR}\) (film): \(\tilde{\nu} = 3451, 2929, 2856, 1471, 1387, 1360, 1254\) cm\(^{-1}\); \(\text{HRMS}\) (ESI): Calc. for C\(_{38}\)H\(_{70}\)O\(_5\)Si\(_2\)S\(_2\)[M\(^+\) + Na] 749.4101. Found 749.4103; \(\alpha\)\(_D\)\(^{20}\) = +11 (c = 1 in CH\(_2\)Cl\(_2\)).

**Compound 4.3:** \(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz) \(\delta = 4.15 - 4.12\) (m, 1 H), 4.09 (t, \(J = 7.1\) Hz, 1 H), 3.79 - 3.74 (m, 1 H), 3.72 (s, 1 H), 3.42 - 3.34 (m, 2 H), 2.90 (tt, \(J = 3.0, 15.2\) Hz, 1 H), 2.84 - 2.77 (m, 3 H), 2.17 - 2.06 (m, 1 H), 1.92 - 1.86 (m, 1 H), 1.85 - 1.80 (m, 3 H), 1.79 - 1.69 (m, 1 H), 1.66 - 1.57 (m, 3 H), 1.56 - 1.45 (m, 3 H), 1.25 - 1.16 (m, 2 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.13 (s, 3 H), 0.09 (s, 3 H), 0.06 (s, 6 H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 126 MHz) \(\delta = 74.8, 74.0, 66.0, 60.4, 45.0, 44.1, 43.9, 40.0, 32.2, 31.8, 30.7, 30.4, 26.2, 26.1, 23.9, 18.5, 18.2, -4.1, -4.3, -5.1; \(\text{IR}\) (film): \(\tilde{\nu}_{\text{max}} = 2929, 2856, 1471, 1387, 1254\) cm\(^{-1}\); \(\text{HRMS}\) (ESI): Calc. for C\(_{26}\)H\(_{54}\)O\(_3\)S\(_2\)Si\(_2\)Na [M\(^+\) + Na] 557.2951, found 557.2958; \(\alpha\)\(_D\)\(^{20}\) = -7 (c = 1 in CH\(_2\)Cl\(_2\)).

**Ketone 2.75.** 10% aqueous acetone (380 mL) was added to solid NBS (1.76 g, 9.88 mmol, 2.0 eq; freshly recrystallized, slightly yellow NBS gives inferior yields) and silver perchlorate (2.05 mg, 9.88 mmol, 2.0 eq). The reaction mixture was stirred for 3 minutes. 2,6-lutidine (1.72 mL, 14.82 mmol, 3.0 eq) was added, followed immediately by a solution of ARC adduct 2.74 (3.59 g, 4.94 mmol, 1.0 eq) in acetone (10 mL). The reaction mixture was stirred for 1 minute, then quenched with sat. aqueous sodium bicarbonate (500 mL) and diluted with ethyl acetate (500 mL) and brine (100
The layers were separated and the aqueous layer extracted with ethyl acetate (2x500 mL). The combined organics were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (7:1 → 5:1 Hexanes:Ethyl Acetate) to yield the title compound (2.19 g, 70%) as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 7.37 - 7.28$ (m, 5 H), 4.51 (s, 2 H), 4.39 - 4.32 (m, 1 H), 4.06 - 4.00 (m, 1 H), 3.75 - 3.67 (m, 2 H), 3.56 - 3.47 (m, 3 H), 3.43 - 3.33 (m, 2 H), 2.68 - 2.53 (m, 4 H), 1.95 - 1.86 (m, 1 H), 1.85 - 1.69 (m, 2 H), 1.65 - 1.55 (m, 4 H), 1.54 - 1.47 (m, 2 H), 1.18 (dq, $J = 3.7$, 13.0 Hz, 2 H), 0.94 (d, $J = 6.9$ Hz, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 9 H).

$^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta =$ 210.6, 138.4, 128.5, 127.7, 74.7, 74.0, 73.4, 70.8, 66.1, 60.1, 52.4, 48.7, 45.0, 40.0, 38.5, 32.3, 31.7, 26.1, 26.1, 23.9, 18.5, 18.1, 13.9, -4.3, -4.5, -5.1; IR (film): $\tilde{\nu} =$ 3485, 2927, 1714, 1472 cm$^{-1}$; HRMS (ESI): Calc. for C$_{35}$H$_{64}$O$_6$NaSi$_2$ [M$^+ +$ Na] 659.4139. Found 659.4127; $[\alpha]_D^{20} = +34$ (c = 0.5 in CH$_2$Cl$_2$).

**Alcohol 2.76.** Samarium iodide (0.1 M in THF) was prepared freshly before each reaction by adding freshly distilled diiodomethane (500 µL, 1.25 mmol, 0.95 eq) to a rapidly stirring suspension of samarium metal (980 mg, 1.3 mmol, 1.0 eq) in THF (62 mL). The resulting mixture was stirred overnight and used only if a deep blue color developed after the first 30-45 minutes.

To a solution of ketone 2.75 (2.28 g, 3.58 mmol, 1.0 eq) and benzaldehyde (5.5 mL, 53.7 mmol, 15 eq) in THF (33 mL) at -10 °C was then added an aliquot of the samarium iodide solution (7.1 mmol, 7.1 mmol, 0.2 eq). An additional aliquot was added after 4 and 8 hours. After the final addition, the reaction mixture was allowed to stir at -10 °C overnight, then quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. The mixture was diluted with water and diethyl ether and the layers separated. The aqueous layer was extracted with diethyl ether (2x100 mL) and the combined organics washed with sat. aqueous sodium bicarbonate and brine, dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column
chromatography (9:1 Hexanes:Diethyl ether then 8:1 → 6:1 Hexanes:Ethyl Acetate) to yield the title compound as a pale yellow oil (2.153 mg, 81%) as a single detectable diastereomer by $^1$H NMR analysis.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 8.02$ (dd, $J = 1.2$, 8.2 Hz, 2 H), 7.58 (t, $J = 7.3$ Hz, 1 H), 7.44 (t, $J = 7.7$ Hz, 2 H), 7.31 (d, $J = 4.7$ Hz, 4 H), 7.27 - 7.24 (m, 1 H), 5.44 - 5.39 (m, 1 H), 4.49 (d, $J = 12.5$ Hz, 2 H), 4.14 - 4.08 (m, 1 H), 3.83 - 3.76 (m, 1 H), 3.70 (t, $J = 6.6$ Hz, 2 H), 3.60 - 3.55 (m, 2 H), 3.42 (dd, $J = 6.7$, 9.2 Hz, 1 H), 3.39 - 3.28 (m, 2 H), 2.27 - 2.18 (m, 1 H), 1.82 - 1.75 (m, 1 H), 1.75 - 1.64 (m, 4 H), 1.63 - 1.38 (m, 8 H), 1.21 - 1.12 (m, 2 H), 1.07 (d, $J = 6.9$ Hz, 3 H), 0.92 - 0.88 (m, 9 H), 0.72 (s, 9 H), 0.05 (s, 6 H), 0.02 (s, 3 H), -0.05 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 167.3$, 138.5, 133.2, 130.2, 130.0, 128.4, 127.7, 127.6, 74.6, 74.3, 73.7, 73.3, 72.0, 67.1, 63.9, 60.1, 44.9, 44.6, 40.6, 39.9, 38.1, 32.2, 31.8, 26.1, 25.9, 23.8, 18.5, 18.0, 14.2, -4.4, -4.6, -5.1; IR (film): $\tilde{\nu} = 3511$, 2927, 2855, 1698, 1640, 1453, 1277 cm$^{-1}$; HRMS (ESI): Calc. for C$_{42}$H$_{71}$O$_7$Si$_2$ [M$^+ + H$] 743.4738. Found 743.4732; [$\alpha$]$_D^{20} = -14$ (c = 0.4 in CH$_2$Cl$_2$).

**Compound 2.79.** To a -78 °C solution of alcohol 2.76 (358 mg, 0.482 mmol, 1.0 eq) and 2,6-lutidine (560 µL, 4.82 mmol, 10 eq) in dichloromethane (8 mL) was added TBSOTf (420 µL, 2.41 mmol, 5.0 eq) dropwise and the reaction mixture was warmed to room temperature and stirred 2h. The reaction was then quenched with sat. aqueous ammonium chloride and diluted with dichloromethane. The layers were separated and the aqueous layer extracted with dichloromethane. The combined aqueous layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatograph (14:1 Hexanes:Diethyl Ether) to yield the title compound (390 mg, 94% yield) as a colorless oil.

$^1$H NMR (C$_6$D$_6$, 500 MHz): $\delta = 8.41$ - 8.38 (m, 2 H), 7.44 (d, $J = 7.4$ Hz, 2 H), 7.32 - 7.27 (m, 5 H), 7.21 (tt, $J = 1.9$, 7.4 Hz, 1 H), 5.88 (ddd, $J = 1.7$, 4.9, 10.0 Hz, 1 H), 4.47 (d, $J = 12.0$ Hz, 1 H), 4.42 (d, $J = 12.1$ Hz, 1 H), 4.39 - 4.32 (m, 1 H), 4.24 - 4.18 (m, 1 H), 3.93 (t, $J = 6.6$ Hz, 2 H), 3.69 (tt, $J = 1.9$, 10.4 Hz, 1 H), 3.60 (d, $J = 6.3$ Hz, 2 H), 3.46 (dd, $J = 4.7$, 6.3 Hz, 1 H), 2.66 - 2.57 (m,
1 H), 2.31 - 2.25 (m, 1 H), 2.11 (t, \( J = 6.9 \) Hz, 2 H), 2.06 - 1.97 (m, 2 H), 1.95 - 1.88 (m, 1 H), 1.82 - 1.75 (m, 1 H), 1.75 - 1.70 (m, 1 H), 1.67 - 1.60 (m, 1 H), 1.56 - 1.50 (m, 1 H), 1.47 - 1.41 (m, 2 H), 1.31 - 1.20 (m, 2 H), 1.18 (d, \( J = 6.9 \) Hz, 3 H), 1.14 (s, 9 H), 1.13 (s, 9 H), 1.11 (s, 9 H), 0.34 (s, 3 H), 0.32 (s, 3 H), 0.31 (s, 3 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.21 (s, 3 H);

\( ^{13} \)C NMR (C\(_6\)D\(_6\), 500 MHz): \( \delta = 165.8, 139.2, 139.1, 132.6, 131.5, 130.0, 128.5, 128.4, 127.5, 74.5, 74.0, 73.6, 73.0, 72.4, 67.6, 66.8, 60.3, 47.8, 44.9, 40.5, 38.6, 37.6, 32.5, 32.1, 26.2, 26.1, 26.1, 24.0, 18.4, 18.2, 12.8, -3.6, -3.8, -4.1, -4.3, -5.1, -5.2; IR (film): \( \tilde{\nu} = 2929, 2856, 1719, 1471 \) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{48}\)H\(_{84}\)O\(_7\)Si\(_3\)Na [\( M^+ + Na \)] 879.5423. Found 879.5396; \( [\alpha]_D^{20} = + 14 \) (c = 1 in CH\(_2\)Cl\(_2\)).

**Compound 2.78** \(^1\)H NMR (CDCl\(_3\), 500MHz) \( \delta = 8.04 \) (dd, \( J = 1.3, 8.4 \) Hz, 2 H), 7.55 (tt, \( J = 1.1, 7.5 \) Hz, 1 H), 7.42 (t, \( J = 7.8 \) Hz, 2 H), 7.38-7.32 (m, 8 H), 7.31 - 7.26 (m, 2 H), 5.45 (ddd, \( J = 2.0, 4.5, 9.9 \) Hz, 1 H), 4.55 - 4.45 (m, 4 H), 3.94 (tt, \( J = 3.1, 8.9 \) Hz, 1 H), 3.88 (td, \( J = 3.3, 8.8 \) Hz, 1 H), 3.53 (dd, \( J = 6.1, 9.4 \) Hz, 1 H), 3.38 - 3.33 (m, 2 H), 3.34 - 3.28 (m, 1 H), 2.37 (dq, \( J = 4.7, 6.6 \) Hz, 1 H), 2.07 (s, 1 H), 2.02 (ddd, \( J = 2.7, 10.1, 14.5 \) Hz, 1 H), 1.72 (ddd, \( J = 4.2, 9.0, 13.0 \) Hz, 1 H), 1.60 (ddd, \( J = 2.0, 9.2, 14.5 \) Hz, 1 H), 1.49 (ddd, \( J = 2.9, 9.2, 13.6 \) Hz, 1 H), 0.98 (d, \( J = 6.9 \) Hz, 3 H), 0.91 (s, 12 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H), -0.03 (s, 3 H); \( ^{13} \)C NMR (CDCl\(_3\), 126MHz) \( \delta = 166.2, 138.8, 138.7, 132.8, 131.1, 129.8, 128.5, 128.3, 127.8, 127.6, 127.5, 127.5, 73.8, 73.1, 73.1, 72.9, 72.4, 70.2, 67.0, 41.2, 39.2, 38.2, 37.4, 26.1, 26.0, 18.1, 18.1, 12.9, 11.7, -3.9, -4.2, -4.6; IR (film): \( \tilde{\nu}_{\text{max}} = 3510, 2927, 2855, 1698, 1453 \) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{44}\)H\(_{68}\)O\(_7\)Si\(_3\)Na [\( M^+ + Na \)] 771.4452, found 771.4457; \( [\alpha]_D^{20} = + 0.4 \) (c = 0.2 in CH\(_2\)Cl\(_2\)).

**Aldehyde 2.72.** To a solution of 2.79 (431 mg, 0.503 mmol, 1.0 eq) in THF (30 mL) was added Pd(OH)$_2$ on carbon (71 mg, 0.100 mmol, 0.2 eq). The head space of the reaction was evacuated and back filled with hydrogen gas three times. The reaction mixture was then stirred under a balloon of hydrogen for 4h. Upon reaction completion, the mixture was filtered through a pad of Celite and concentrated. The crude residue was dissolved in dichloromethane (10 mL). Sodium bicarbonate (211 mg, 2.52 mmol, 5.0 eq) was added as a solid, followed by DMP (213 mg, 0.503
mmol, 1.0 eq). The reaction mixture was stirred for 1h, then cooled to 0 °C and quenched by the addition of a 1:1 mixture of sat. sodium bicarbonate:sat. sodium thiosulfite (20 mL total). After stirring for an additional 1h at room temperature, the layers were separated and the aqueous layer extracted with additional dichloromethane. The combined organics were dried over Na₂SO₄ and concentrated. The crude residue was purified by flash column chromatography (12:1 → 9:1 Hexanes:Diethyl ether) to afford the title compound as a colorless oil (352 mg, 91% over 2 steps). The de-benzylation could also be run utilizing Pd/C in ethyl acetate as solvent with similar results, but higher reproducibility due to the greater stability of the catalyst.

**Compound 4.4: **

**¹H NMR (C₆D₆, 500 MHz):** δ = 8.30 - 8.26 (m, 2 H), 7.21 - 7.16 (m, 3 H), 5.65 (ddd, J = 1.4, 7.0, 9.9 Hz, 1 H), 4.28 - 4.22 (m, 1 H), 4.06 (q, J = 7.8 Hz, 1 H), 3.89 - 3.80 (m, J = 3.5 Hz, 2 H), 3.63 - 3.55 (m, 1 H), 3.49 (d, J = 4.7 Hz, 3 H), 2.14 (ddd, J = 1.7, 10.3, 14.3 Hz, 1 H), 2.00 (t, J = 7.0 Hz, 2 H), 1.96 - 1.87 (m, 4 H), 1.79 (ddd, J = 2.1, 9.8, 13.7 Hz, 1 H), 1.70 (ddt, J = 4.7, 6.9, 13.6 Hz, 1 H), 1.66 - 1.60 (m, 1 H), 1.51 (ddd, J = 2.0, 9.4, 13.9 Hz, 1 H), 1.46 - 1.39 (m, 1 H), 1.35 (br. s., 2 H), 1.22 - 1.14 (m, 2 H), 1.07 (d, J = 6.9 Hz, 3 H), 1.04 (s, 9 H), 1.03 (s, 9 H), 1.00 (s, 9 H), 0.24 (s, 3 H), 0.21 (s, 3 H), 0.18 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), 0.11 (s, 3 H); **¹³C NMR (C₆D₆, 126 MHz):** δ = 166.8, 132.9, 131.0, 130.1, 128.6, 74.5, 73.9, 73.6, 67.5, 66.6, 64.0, 60.4, 47.6, 44.7, 40.6, 40.3, 39.4, 32.5, 32.1, 30.1, 26.2, 24.0, 18.4, 18.2, 13.3, -3.6, -3.8, -4.2, -4.4, -5.1, -5.2; **IR (film):** ν = 3441, 2928, 2856, 1718, 1472, 1387, 1275, 1254 cm⁻¹; **HRMS (ESI):** Calc. for C₄₁H₇₅O₇NaSi₃ [M⁺ + Na] 789.4953. Found 789.4957; [α]D³⁰ = + 21 (c = 0.5 in CH₂Cl₂).

**¹H NMR (CDCl₃, 500 MHz):** δ = 9.80 (d, J = 1.5 Hz, 1 H), 8.06 (ddd, J = 0.1, 1.3, 8.6 Hz, 2 H), 7.59 (tt, J = 1.2, 7.4 Hz, 1 H), 7.46 (t, J = 7.9 Hz, 1 H), 5.62 (ddd, J = 2.3, 4.6, 9.8 Hz, 1 H), 3.98 - 3.91 (m, 1 H), 3.86 - 3.78 (m, 1 H), 3.76 - 3.67 (m, 2 H), 3.45 - 3.35 (m, 2 H), 3.00 - 2.93 (m, 1 H), 2.04 (ddd, J = 2.2, 9.9, 14.3 Hz, 1 H), 1.86 - 1.79 (m, 1 H), 1.78 - 1.64 (m, 3
Coupled products anti-2.80 and syn-2.80. To a -78 °C solution of alkyne 2.26 (194 mg, 0.348 mmol, 2.0 eq) in THF (1.75 mL) was added a cold LDA solution (0.5 M in THF, 700 µL, 0.348 mmol, 2.0 eq) dropwise and the reaction mixture gradually warmed up to -30 °C and stirred at this temperature for 30 min, then recooled to -78 °C and transferred to a solution of aldehyde 2.72 (133 mg, 0.174 mmol, 1.0 eq) in THF at -78 °C (1.75 mL) via cannula. The reaction mixture was stirred at -78 °C for 30 min, then gradually warmed to -20 °C and quenched with sat. aqueous ammonium chloride. After warming to room temperature, the biphasic mixture was diluted with water and diethyl ether. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organics were dried over Na₂SO₄ and concentrated. The residue was purified by MPLC (9:1 Hexanes:Ethyl acetate) to yield the title compounds anti-2.80 and syn-2.80 (191 mg total yield, 1.4:1 d.r., 89%) as well as recovered alkyne 2.26 (97 mg, 100% of theoretical).
2 H), 1.73 - 1.65 (m, 1 H), 1.65 - 1.59 (m, 1 H), 1.54 - 1.47 (m, 1 H), 1.42 (d, J = 6.9 Hz, 3 H), 1.38 - 1.27 (m, 4 H), 1.21 - 1.06 (m, 3 H), 1.05 - 1.00 (m, 36 H), 0.62 (q, J = 8.0 Hz, 6 H), 0.25 (s, 3 H), 0.21 (s, 3 H), 0.17 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): 159.2, 142.0, 133.3, 130.9, 130.1, 129.6, 128.6, 113.8, 96.6, 85.5, 81.8, 79.8, 74.6, 74.3, 74.1, 73.5, 71.1, 67.2, 66.9, 66.3, 62.7, 60.4, 57.6, 55.4, 48.2, 47.1, 44.4, 44.2, 40.4, 39.9, 32.5, 31.9, 29.6, 28.8, 26.1, 23.9, 18.5, 18.1, 14.9, 10.7, 6.9, 5.1, -3.5, -3.9, -4.3, -4.5, -5.1; IR (film): $\tilde{\nu} = 3419, 2928, 2856, 1718, 1613, 1514, 1462, 1381 \text{ cm}^{-1}; [\alpha]_D^{20} = +24 (c = 0.5 \text{ in CH}_2\text{Cl}_2)$.

**syn-2.80**: $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 8.08 (d, J = 7.0 Hz, 2 H), 7.56 (tt, J = 1.1, 7.2 Hz, 1 H), 7.44 (t, J = 7.8 Hz, 2 H), 7.26 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.20 (dd, J = 1.5, 9.4 Hz, 1 H), 5.47 (dd, J = 5.3, 9.1 Hz, 1 H), 5.50 - 5.45 (m, 1 H), 4.60 (d, J = 12.0 Hz, 2 H), 4.37 (dd, J = 5.5, 9.4 Hz, 2 H), 3.99 - 3.91 (m, 1 H), 3.81 (s, 4 H), 3.79 – 3.67 (m, 3 H), 3.44 (dd, J = 3.4, 5.6 Hz, 1 H), 3.41 – 3.37 (m, 2 H), 3.36 – 3.32 (m, 1 H), 3.28 (s, 3 H), 2.45 (d, J = 1.3 Hz, 3 H), 2.38 (d, J = 6.9 Hz, 1 H), 2.31 – 2.24 (m, 1 H), 2.22 – 2.08 (m, 2 H), 1.95 (ddd, J = 1.9, 9.9, 14.6 Hz, 1 H), 1.82 – 1.65 (m, 6 H), 1.63 – 1.43 (m, 7 H), 1.36 – 1.28 (m, 1 H), 1.21 – 1.14 (m, 1 H), 1.08 (d, J = 7.0 Hz, 5 H), 0.94 (t, J = 8.0 Hz, 11 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.58 (q, J = 7.8 Hz, 6 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 6 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ = 159.3, 142.0, 132.8, 130.9, 129.9, 129.6, 128.4, 113.8, 96.9, 86.0, 81.7, 80.5, 79.7, 74.5, 74.1, 73.5, 73.0, 71.1, 67.1, 66.4, 64.6, 60.3, 57.6, 55.4, 47.1, 44.4, 43.4, 40.2, 38.1, 32.4, 31.9, 29.4, 28.8, 26.1, 24.1, 23.8, 18.5, 18.1, 15.0, 12.2, 6.9, 5.1, -3.7, -3.9, -4.3, -4.4, -5.1; IR (film): $\tilde{\nu} = 3455, 2929, 2856, 1719, 1613, 1514, 1463, 1381 \text{ cm}^{-1}; [\alpha]_D^{20} = +5 (c = 0.5 \text{ in CH}_2\text{Cl}_2)$.

**Triols anti-2.81 and syn-2.81.** The following procedure for anti-2.81 is representative. To a -78 °C solution of anti-2.80 (42.5 mg, 32.1 µmol, 1.0 eq) in dichloromethane (500 µL) was added DIBAL-H (1.0 M in toluene, 160 µL, 0.160 mmol, 5.0 eq) dropwise and the reaction mixture stirred
at -78 °C until complete (~30 minutes). The reaction was then quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. Ethyl acetate was added and the mixture poured into a sat. aqueous solution of Rochelle’s salt and stirred vigorously at room temperature until a clear biphasic solution is obtained (~1h). The layers were then separated and the aqueous layer extracted with ethyl acetate. The combined organics were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatograph (6:1 → 7:1 Hexanes:Ethyl Acetate) to yield the desired diol (30 mg, 77%) as a colorless oil.

To a solution of the above diol in dichloromethane/pH 7 buffer (9:1, 11 mL total volume) at 0 °C was added DDQ (1 g, 4.5 mmol, 10 eq) as a solid in one portion and the reaction mixture stirred at 0 °C for 45 minutes, then quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (3:1 Hexanes:Ethyl Acetate) to yield the title compound **anti-2.81** (261 mg, 60%, 2 steps) as a colorless oil.

**anti-2.81: $^1$H NMR** (CD$_6$D$_6$, 500 MHz): δ = 6.52 (dd, J = 1.5, 9.2 Hz, 1 H), 4.79 (d, J = 5.9 Hz, 1 H), 4.60 (dd, J = 3.2, 9.2 Hz, 1 H), 4.52 (t, J = 8.2 Hz, 1 H), 4.40 - 4.36 (m, 1 H), 4.32 - 4.22 (m, 1 H), 4.22 - 4.12 (m, 2 H), 3.90 (q, J = 7.1 Hz, 2 H), 3.80 (dt, J = 1.8, 6.6 Hz, 1 H), 3.62 (t, J = 10.2 Hz, 1 H), 3.52 (dt, J = 3.2, 7.5 Hz, 1 H), 3.49 - 3.44 (m, 1 H), 3.41 - 3.36 (m, 1 H), 3.20 (s, 3 H), 2.49 (d, J = 8.1 Hz, 1 H), 2.45 - 2.40 (m, 2 H), 2.28 (d, J = 1.4 Hz, 3 H), 2.20 (tt, J = 4.7, 9.0 Hz, 1 H), 2.09 - 1.89 (m, 5 H), 1.77 (m, 3 H), 1.70 - 1.60 (m, 2 H), 1.52 (ddd, J = 2.5, 9.6, 14.4 Hz, 1 H), 1.45 - 1.40 (m, 1 H), 1.39 - 1.33 (m, 2 H), 1.20 - 1.11 (m, 1 H), 1.11 - 1.07 (m, 12 H), 1.04 (s, 9 H), 0.97 (t, J = 7.6 Hz, 9 H), 0.92 (s, 9 H), 0.57 (dq, J = 2.1, 7.9 Hz, 6 H), 0.30 (s, 3 H), 0.29 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); $^{13}$C NMR (CD$_6$D$_6$, 126 MHz): δ = 142.6, 96.9, 85.8, 81.3, 79.5, 75.2, 74.8, 73.6, 72.6, 70.0, 69.9, 67.3, 66.5, 60.4, 60.1, 57.2, 45.8, 44.9, 44.7, 40.5, 39.8, 32.7, 31.9, 29.0, 28.5,
26.3, 26.2, 26.0, 24.1, 18.6, 18.4, 18.1, 14.4, 14.2, 13.9, 7.1, 5.3, -3.5, -4.1, -4.3, -4.6, -5.0, -5.0; IR (film): \( \tilde{\nu} = 3441, 2935, 1640, 1464, 1251 \text{ cm}^{-1} \); HRMS (ESI): Calc. for C\(_{51}\)H\(_{103}\)O\(_9\)Si\(_4\)I \([M^+ + Na]\) 1121.5622. Found 1121.5627; \([\alpha]\)\(_D^{20}\) = + 27 (c = 0.37 in CH\(_2\)Cl\(_2\)).

**syn-2.81:** \(^1\)H NMR (C\(_6\)D\(_6\), 500 MHz): \( \delta = 6.52 \) (dd, \( J = 1.4, 9.3 \) Hz, 1 H), 4.92 (d, \( J = 6.4 \) Hz, 1 H), 4.59 (dd, \( J = 3.3, 9.3 \) Hz, 1 H), 4.24 - 4.14 (m, 3 H), 3.80 (dt, \( J = 2.2, 6.6 \) Hz, 2 H), 3.61 (t, \( J = 10.7 \) Hz, 1 H), 3.51 - 3.44 (m, 2 H), 3.38 - 3.33 (m, 1 H), 3.18 (s, 3 H), 2.42 - 2.36 (m, 2 H), 2.28 (d, \( J = 1.4 \) Hz, 3 H), 2.18 (ddd, \( J = 4.4, 9.1, 13.6 \) Hz, 1 H), 2.06 - 1.82 (m, 6 H), 1.76 (d, \( J = 2.6 \) Hz, 2 H), 1.71 - 1.58 (m, 2 H), 1.52 (ddd, \( J = 2.0, 9.9, 11.4 \) Hz, 1 H), 1.45 - 1.29 (m, 6 H), 1.21 (d, \( J = 6.8 \) Hz, 3 H), 1.18 (m, 2 H), 1.06 (s, 9 H), 1.03 (s, 9 H), 0.97 (t, \( J = 8.1 \) Hz, 9 H), 0.94 (s, 9 H), 0.57 (dq, \( J = 2.2, 7.9 \) Hz, 6 H), 0.27 (s, 3 H), 0.26 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 3 H); \(^{13}\)C NMR (C\(_6\)D\(_6\), 126 MHz): \( \delta = 142.5, 96.8, 85.9, 81.3, 79.4, 75.0, 74.7, 73.5, 72.3, 69.9, 69.7, 66.5, 66.3, 60.2, 57.0, 45.9, 45.9, 44.8, 40.4, 39.6, 32.6, 31.8, 28.9, 28.4, 26.2, 26.1, 25.9, 24.0, 18.4, 18.3, 18.0, 14.2, 12.8, 6.9, 5.2, -3.7, -4.2, -4.4, -4.7, -5.1, -5.1; IR (film): \( \tilde{\nu} = 3428, 2928, 2856, 1640, 1462, 1254 \text{ cm}^{-1} \); HRMS (ESI): Calc. for C\(_{51}\)H\(_{104}\)O\(_9\)Si\(_4\)I \([M^+ + H]\) 1099.5802. Found 1099.5814; \([\alpha]\)\(_D^{20}\) = + 29 (c = 1 in CH\(_2\)Cl\(_2\)).

**Southern Hemisphere 2.15.** Triol anti-2.81 (10.4 mg, 9.46 \( \mu \text{mol, 1.0 eq} \)) was dissolved in dichloromethane (300 \( \mu \text{L} \)) over activated 4 Å molecular sieves. A stock solution of cationic gold catalyst 2.82 (0.01 M in THF) was also prepared. The two solutions were degassed by three cycles of freeze/pump/thaw and allowed to warm up to room temperature under nitrogen. An aliquot of the catalyst solution (73 \( \mu \text{L}, 0.095 \text{ mmol, 0.1 eq} \)) was then added to the reaction mixture, which was stirred for 2 h at room temperature, then quenched with triethylamine (3 drops). The crude reaction mixture was filtered through a plug of silica gel, eluting with diethyl ether. The filtrate was concentrated and the residue purified by flash
column chromatography (24:1 Hexanes:Ethyl Acetate) to yield the fully protected southern
hemisphere (8.3 mg, 81%) as a pale yellow oil.

\[ ^1H \text{NMR} \ (C_6D_6, 500 \text{ MHz}) \]: \( \delta = 6.81 \ (dd, J = 1.4, 9.0 \text{ Hz}, 1 \text{ H}), 5.55 \ (dd, J = 2.3, 10.0 \text{ Hz}, 1 \text{ H}), 5.48 \ (dd, J = 1.3, 10.0 \text{ Hz}, 1 \text{ H}), 4.90 \ (dd, J = 2.3, 9.0 \text{ Hz}, 1 \text{ H}), 4.35 - 4.26 \ (m, 2 \text{ H}), 3.83 \ (dt, J = 2.2, 6.7 \text{ Hz}, 3 \text{ H}), 3.75 \ (dd, J = 2.3, 9.2 \text{ Hz}, 1 \text{ H}), 3.59 \ (t, J = 10.2 \text{ Hz}, 1 \text{ H}), 3.52 - 3.44 \ (m, 2 \text{ H}), 3.22 \ (s, 3 \text{ H}), 2.41 \ (d, J = 1.3 \text{ Hz}, 3 \text{ H}), 2.25 - 2.17 \ (m, 1 \text{ H}), 2.09 - 1.97 \ (m, 2 \text{ H}), 1.96 - 1.85 \ (m, 2 \text{ H}), 1.74 - 1.63 \ (m, 4 \text{ H}), 1.61 - 1.52 \ (m, 4 \text{ H}), 1.50 - 1.26 \ (m, 6 \text{ H}), 1.09 \ (s, 12 \text{ H}), 1.08 - 1.04 \ (m, 18 \text{ H}), 1.02 \ (s, 9 \text{ H}), 0.68 \ (dq, J = 3.3, 8.3 \text{ Hz}, 6 \text{ H}), 0.33 \ (s, 3 \text{ H}), 0.32 \ (s, 3 \text{ H}), 0.27 \ (s, 3 \text{ H}), 0.26 \ (s, 3 \text{ H}), 0.14 \ (s, 3 \text{ H}), 0.13 \ (s, 3 \text{ H}); \]

\[ ^13C \text{NMR} \ (C_6D_6, 126 \text{ MHz}) \]: \( \delta = 143.6, 134.1, 129.1, 95.2, 94.0, 76.2, 74.6, 74.2, 74.1, 72.3, 69.1, 68.1, 67.6, 60.4, 55.4, 48.5, 45.9, 42.3, 40.5, 34.0, 33.3, 32.4, 32.2, 32.0, 30.1, 28.4, 26.3, 26.2, 26.1, 24.1, 23.8, 23.0, 18.5, 18.4, 18.3, 17.2, 14.3, 7.1, 5.5, -3.0, -3.6, -3.9, -5.1; \]

IR (film): \( \tilde{\nu} = 2928, 2856, 1741, 1640, 1462, 1379, 1254 \text{ cm}^{-1}; [\alpha]_D^0 = +16.5 \ (c = 0.5 \text{ in CH}_2\text{Cl}_2). \]

**Compound 2.83** To a solution of triol \textit{syn-2.81} (7.4 mg, 6.73 \mu mol, 1.0 eq) in THF (300 \mu L) over 4 A molecular sieves was added the catalyst (1 mg, 1.35 \mu mol, 0.2 eq). After stirring at room temperature for 2 hours, the mixture was filtered directly through a plug of silica gel and analyzed by NMR.

\[ ^1H \text{NMR} \ (CDCl}_3, 500\text{MHz} ) \delta = 6.55 \ (d, J = 9.9 \text{ Hz}, 1 \text{ H}), 4.70 \ (d, J = 9.0 \text{ Hz}, 1 \text{ H}), 4.39 \ (q, J = 7.0 \text{ Hz}, 2 \text{ H}), 4.34 - 4.28 \ (m, 1 \text{ H}), 4.27 - 4.23 \ (m, 1 \text{ H}), 4.13 - 4.08 \ (m, 1 \text{ H}), 3.82 \ (t, J = 6.8 \text{ Hz}, 2 \text{ H}), 3.63 - 3.54 \ (m, 2 \text{ H}), 3.50 - 3.42 \ (m, 1 \text{ H}), 3.36 \ (s, 3 \text{ H}), 3.27 \ (q, J = 6.9 \text{ Hz}, 1 \text{ H}), 2.46 \ (d, J = 7.8 \text{ Hz}, 2 \text{ H}), 2.32 \ (s, 3 \text{ H}), 2.00 \ (t, J = 6.1 \text{ Hz}, 2 \text{ H}), 1.97 - 1.85 \ (m, 3 \text{ H}), 1.77 \ (t, J = 9.4 \text{ Hz}, 1 \text{ H}), 1.65 \ (m, 3 \text{ H}), 1.47 - 1.15 \ (m, 16 \text{ H}), 1.16 - 1.10 \ (m, 2 \text{ H}), 1.08 \ (s, 9 \text{ H}), 1.07 \ (s, 9 \text{ H}), 1.02 \ (s, 9 \text{ H}), 0.98 \ (t, J = 8.0 \text{ Hz}, 12 \text{ H}), 0.59 \ (q, J = 7.8 \text{ Hz}, 6 \text{ H}), 0.29 \ (s, 3 \text{ H}), 0.26 \ (s, 9 \text{ H}), 0.13 \ (s, 3 \text{ H}), 0.12 \ (s, 3 \text{ H}); \]

\[ ^13C \text{NMR} \ (C_6D_6, 126\text{MHz} ) \delta = 158.9, 142.8, 98.7, 96.8, 81.9, 80.6, 75.4, 74.7, 73.9, 70.0, 67.9, 67.1, 65.9, 60.5, 57.3, 48.5, 45.4, 44.2, 42.4, 40.5, 32.8, 32.0, 30.7, 30.2, 29.9, 28.5, 127 \]
4.3 Experimental Details Relevant to Chapter 3

Synthesis of Alkyne Fragment 3.18

Compound 3.20 A modification of a literature procedure was followed. To a solution of compound 3.19 (7.15 g, 20.1 mmol, 1.0 eq) and triethylamine (4.8 mL, 34.2 mmol, 1.7 eq) in toluene (54 mL) at -50 °C was added dibutyl boron triflate (1 M in DCM, 30.2 mL, 30.2 mmol, 1.5 eq) and the reaction mixture stirred at -50 °C for 1.5 h, then recooled to -78 °C. A solution of freshly distilled acrolein (5.4 mL, 80.4 mmol, 4 eq) was then added dropwise at this temperature and the reaction mixture was allowed to stir at -78 °C for one hour, then warmed up to 0 °C and allowed to stir an additional 1 h. The reaction was then quenched by the successive careful addition of methanol (25 mL), pH 7 buffer (25 mL) and 30% hydrogen peroxide (25 mL). The mixture was stirred vigorously at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with diethyl ether (3x75 mL). The combined organics were dried over Na2SO4 and concentrated. The residue was purified by flash column chromatography (2:1 → 1:1 Hexanes:Ethyl Acetate) to yield recovered 3.19 (2.38 g, 33%) the title compound (5.03 g, 61%, 91% brsm, single diastereomer) as a white solid.

M.P. = 86-88 °C; 1H NMR (CDCl3, 500 MHz): 5 = 7.37 - 7.28 (m, 5 H), 7.20 (d, J = 6.5 Hz, 2 H), 6.89 (d, J = 9.2 Hz, 2 H), 5.95 (ddd, J = 5.8, 10.5, 17.2 Hz, 1 H), 5.35 (td, J = 1.4, 17.3 Hz, 1 H),
5.26 (d, J = 3.8 Hz, 1 H), 5.24 (td, J = 1.3, 10.5 Hz, 1 H), 4.68 - 4.62 (m, 2 H), 4.57 (d, J = 11.3 Hz, 1 H), 4.40 (dd, J = 1.7, 3.6 Hz, 1 H), 4.23 - 4.16 (m, 2 H), 3.79 (s, 3 H), 3.22 (dd, J = 3.3, 13.5 Hz, 1 H), 2.71 - 2.62 (m, 2 H); \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \(\delta = 170.5, 159.9, 153.5, 136.6, 135.2, 130.3, 129.5, 129.2, 129.1, 127.6, 117.2, 114.0, 79.4, 73.8, 73.2, 67.0, 55.7, 55.4, 37.9; IR (film): \(\tilde{\nu} = 3463, 2935, 1776, 1707, 1612, 1514, 1392 \text{ cm}^{-1}\); HRMS (ESI): Calc. for C\(_{23}\)H\(_{25}\)NO\(_6\)Na [M\(^+\) + Na] 434.1580. Found 434.1565; \([\alpha]_{D}^{20} = -34 \text{ (c = 1 in CH}_{2}\text{Cl}_2)\).

Compound 4.5. To a 0 °C suspension of freshly azeotroped N,O-dimethylhydroxylamine hydrochloride (3.58 g, 36.6 mmol, 3.0 eq) in THF (36 mL) was added trimethylaluminum (2.0 M in toluene, 18.3 mL, 36.6 mmol, 3.0 eq) and the mixture stirred for 30 minutes at room temperature. The reaction mixture was then cooled to -20 °C and a solution of 3.20 (5.03 g, 12.2 mmol, 1.0 eq) in THF (36 mL) was added dropwise. The reaction mixture was transferred to a 0 °C ice bath and stirred for 1 h. The reaction was quenched by the careful dropwise addition of Rochelle’s salt (36 mL), followed by 1 h of vigorous stirring at room temperature. The mixture was diluted with water and diethyl ether and the layers were separated. The aqueous layer was extracted 3x20 mL dichloromethane and the combined organics dried over Na\(_2\)SO\(_4\) and concentrated. The mixture was purified with flash column chromatography (2:1 → 1:1 Hexanes:Ethyl Acetate) to yield the title compound (2.81 g, 78%) and recovered auxiliary (1.55 g).

\(^{1}\)H NMR (CDCl\(_3\), 500MHz) \(\delta = 7.28 \text{ (d, } J = 9.0 \text{ Hz, 2 H)}, 6.88 \text{ (d, } J = 8.6 \text{ Hz, 2 H)}, 5.85 \text{ (ddd, } J = 6.2, 10.6, 17.1 \text{ Hz, 1 H)}, 5.36 \text{ (d, } J = 17.2 \text{ Hz, 1 H)}, 5.21 \text{ (d, } J = 10.5 \text{ Hz, 1 H)}, 4.67 \text{ (d, } J = 11.4 \text{ Hz, 1 H)}, 4.43 \text{ (d, } J = 11.4 \text{ Hz, 1 H)}, 4.40 \text{ (q, } J = 5.7 \text{ Hz, 1 H)}, 4.31 \text{ (br. s., 1 H)}, 3.81 \text{ (s, 3 H)}, 3.59 \text{ (s, 3 H)}, 3.20 \text{ (s, 3 H)}; \(^{13}\)C NMR (CDCl\(_3\), 126MHz) \(\delta = 159.6, 136.0, 129.9, 129.3, 117.5, 114.0, 73.6, 71.9, 61.5, 55.4; IR (film): \tilde{\nu}_{\text{max}} = 3541, 2937, 1662, 1612, 1513 \text{ cm}^{-1};\) HRMS (ESI): Calc. for C\(_{15}\)H\(_{22}\)NO\(_5\) [M\(^+\)H'] 296.1498, found 296.1484; \([\alpha]_{D}^{20} = +34 \text{ (c = 2 in CH}_2\text{Cl}_2)\).
**Compound 3.21** Weinreb amide 4.3 (9.48 g, 32.1 mmol, 1.0 eq) was then dissolved in dichloromethane (300 mL) and cooled to -78 °C. 2.6-lutidine (11.2 mL, 96 mmol, 3.0 eq) and TESOTf (10.9 mL, 48.2 mmol, 1.5 eq) were added dropwise and the reaction mixture was stirred for 1 h at -78 °C. The reaction was quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer extracted with dichloromethane (3x100 mL). The combined organics were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (4:1 → 3:1 → 2:1 Hexanes:Ethyl Acetate) to yield the title compound (10.2 g, 77%) as a pale yellow oil.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.29 (d, $J$ = 8.6 Hz, 2 H), 6.86 (d, $J$ = 8.7 Hz, 2 H), 5.84 (ddd, $J$ = 6.8, 10.3, 17.2 Hz, 1 H), 5.26 (d, $J$ = 17.1 Hz, 1 H), 5.12 (d, $J$ = 10.4 Hz, 1 H), 4.63 (d, $J$ = 11.8 Hz, 1 H), 4.51 (d, $J$ = 11.8 Hz, 1 H), 4.47 (t, $J$ = 6.9 Hz, 1 H), 4.35 - 4.26 (m, 1 H), 3.81 (s, 3 H), 3.50 (br. s., 3 H), 3.14 (br. s., 3 H), 0.95 (t, $J$ = 8.2 Hz, 9 H), 0.62 (q, $J$ = 7.7 Hz, 6 H); $^13$C NMR (CDCl$_3$, 126MHz) $\delta$ = 159.3, 137.3, 129.6, 116.7, 113.7, 75.7, 72.2, 55.4, 6.9, 5.0; IR (film): $\tilde{\nu}$ = 2954, 1668, 1608, 1513, 1462 cm$^{-1}$; HRMS (ESI): Calc. for C$_2$H$_{35}$NO$_5$SiNa [M$^+$ + Na] 432.2182. Found 432.2173; $[\alpha]_D^{28}$ =+9 (c = 1 in CH$_2$Cl$_2$).

**Compound 3.22.** To magnesium turnings (1.7 g, 70.8 mmol, 3.0 eq) in refluxing THF (50 mL) was added dibromoethane (400 µL, 4.73 mmol, 0.2 eq) and the mixture refluxed 10 minutes. A solution of freshly prepared (4-bromobut-1-yn-1-yl)trimethylsilane (2.55) (9.7 g, 47.3 mmol, 2.0 eq) in THF (100 mL) was then added dropwise and the reaction mixture refluxed an additional 1h. In a separate flask, a solution of 3.21 (9.68 g, 23.6 mmol, 1.0 eq) in THF (50 mL) was cooled to -78 °C. The Grignard solution was then cooled to room temperature and transferred to the solution of 3.21 dropwise via cannula and the resulting mixture stirred at -78 °C for 30 min, then at room temperature for an additional 1.5 h. The reaction was quenched with sat. aqueous ammonium chloride and diluted with diethyl ether. The layers were separated and the aqueous layer extracted with additional diethyl ether. The combined organics were washed with water and brine, dried over Na$_2$SO$_4$ and concentrated. The
Residue was purified by flash column chromatography (9:1 Hexanes:Diethyl Ether → 2:1 Hexanes:Ethyl Acetate) to yield recovered starting material (1.5 g, 15%) the title compound (7.99 g, 71%, 85% brsm) as a colorless oil.

\[^1\text{H} \text{NMR}\] (CDCl\(_3\), 500 MHz): \(\delta = 7.26\) (d, \(J = 9.5\) Hz, 2 H), 6.88 (d, \(J = 9.3\) Hz, 2 H), 5.88 (ddd, \(J = 6.2, 10.8, 17.1\) Hz, 1 H), 5.25 (d, \(J = 17.2\) Hz, 1 H), 5.14 (d, \(J = 10.5\) Hz, 1 H), 4.60 (d, \(J = 11.7\) Hz, 1 H), 4.42 (d, \(J = 11.6\) Hz, 1 H), 4.38 (dd, \(J = 4.8, 6.0\) Hz, 1 H), 3.82 (s, 3 H), 2.87 (dd, \(J = 7.0, 8.7\) Hz, 1 H), 2.69 (ddd, \(J = 6.4, 8.3, 18.0\) Hz, 1 H), 2.43 (ddd, \(J = 2.8, 6.7, 8.2\) Hz, 2 H), 0.93 (t, \(J = 8.0\) Hz, 9 H), 0.58 (q, \(J = 8.4\) Hz, 6 H), 0.14 (s, 9 H); \[^{13}\text{C} \text{NMR}\] (CDCl\(_3\), 126 MHz): \(\delta = 209.3, 159.6, 137.1, 129.9, 129.5, 116.4, 114.0, 106.2, 87.5, 84.8, 75.0, 73.1, 55.4, 40.1, 13.8, 6.9, 6.9, 4.9, 4.9, 0.2; IR (film): \(\tilde{\nu} = 2956, 2177, 1720, 1637, 1612, 1514, 1250\) cm\(^{-1}\); HRMS (ESI): C\(_{26}\)H\(_{42}\)O\(_4\)Si\(_2\)Na [\(M^+ + Na\)] 497.2519. Found 497.2517; \([\alpha]_D^{20} = +15\) (c = 1 in CH\(_2\)Cl\(_2\)).

**Compound 3.23.** The reaction was typically run by separating the available 3.22 into batches of roughly 500 mg, then combining for purification. Zinc borohydride solution was freshly prepared by adding a solution of zinc chloride (1 M in diethyl ether, 5.5 mL, 5.5 mmol, 1.0 eq) to a suspension of sodium borohydride (401 mg, 10.6 mmol, 1.93 eq) in diethyl ether (30 mL) and stirring the resulting mixture for 2 days. Batches of 3.22 (530 mg, 1.12 mmol, 1.0 eq and 611 mg, 1.29 mmol, 1.0 eq) were then dissolved in ether (6 mL) and cooled to -50 °C. An aliquot of the zinc borohydride solution (9 mL, 1.54 mmol, 1.2 eq batch 1, 10.3 mL, 1.54 mmol, 1.2 eq batch 2) was then added. The reaction mixture was stirred at -50 °C for 30 min., then quenched by the careful addition of Rochelle’s salt (c. 10 mL). The biphasic mixture was warmed to room temperature and stirred vigorously for 1h. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over Na\(_2\)SO\(_4\) and concentrated. The two residues were combined and purified by flash column chromatography (9:1 → 7:1 Hexanes:Diethyl Ether) to yield the title compound (708 mg, 61%) as a colorless oil.
\(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz): \(\delta = 7.28\) (d, \(J = 7.3\) Hz, 2 H), 6.90 (d, \(J = 8.5\) Hz, 2 H), 6.03 (ddd, \(J = 5.2, 10.6, 17.2\) Hz, 1 H), 5.34 (d, \(J = 17.2\) Hz, 1 H), 5.26 (d, \(J = 10.6\) Hz, 1 H), 4.59 (s, 2 H), 4.39 (t, \(J = 4.8\) Hz, 1 H), 3.82 (s, 4 H), 3.47 (d, \(J = 2.5\) Hz, 1 H), 3.29 (ddd, \(J = 4.7, 7.8, 17.2\) Hz, 1 H), 2.45 - 2.36 (m, 1 H), 2.33 (s, 1 H), 1.97 - 1.88 (m, 1 H), 1.64 - 1.58 (m, 1 H), 0.95 (t, \(J = 8.3\) Hz, 9 H), 0.59 (q, \(J = 7.6\) Hz, 6 H), 0.16 - 0.14 (m, 9 H); \(^13\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 159.6, 136.3, 130.3, 129.8, 116.4, 114.0, 107.8, 84.4, 82.1, 74.3, 73.3, 70.5, 55.4, 32.5, 15.9, 6.9, 4.8, 0.3; IR (film): \(\tilde{\nu} = 3495, 2955, 2876, 2172, 1640, 1612, 1586, 1514, 1249\) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{26}\)H\(_{44}\)O\(_4\)NaSi\(_2\) \([M^+ + Na]\) 499.2676. Found 499.2675; \([\alpha]_D^{20} = -50\) (c = 1 in CH\(_2\)Cl\(_2\)).

**Compound 4.6.** To a solution of 3.23 (1.58 g, 3.3 mmol, 1.0 eq) in dichloromethane (30 mL) were added proton sponge (2.13 g, 9.9 mmol, 3.0 eq) and trimethyloxonium tetrafluoroborate (1.47 g, 9.9 mmol, 3.0 eq) in one portion and the reaction mixture was stirred for 1 h at room temperature. The reaction was then quenched with brine and diluted with dichloromethane. The layers were separated and the aqueous phase extracted three times with dichloromethane. The combined organic layers were filtered through a pad of Celite and concentrated, then redissolved in ether and refiltered. The filtrate was concentrated and the residue purified by flash column chromatography (9:1 Hexanes:Diethyl ether) to yield the title compound (1.33 mg, 82%) as a colorless oil.

\(^1\text{H NMR}\) (CDCl\(_3\), 500 MHz): \(\delta = 7.30\) (d, \(J = 8.6\) Hz, 2 H), 6.88 (d, \(J = 8.7\) Hz, 2 H), 5.92 (ddd, \(J = 6.2, 10.6, 17.1\) Hz, 1 H), 5.28 (d, \(J = 17.2\) Hz, 1 H), 5.15 (d, \(J = 10.5\) Hz, 1 H), 4.69 (d, \(J = 11.4\) Hz, 1 H), 4.63 (d, \(J = 11.4\) Hz, 1 H), 4.19 (t, \(J = 6.4\) Hz, 1 H), 3.81 (s, 3 H), 3.58 (dd, \(J = 2.3, 6.0\) Hz, 1 H), 3.48 (td, \(J = 2.5, 9.5\) Hz, 1 H), 3.31 (s, 3 H), 2.38 - 2.33 (m, 2 H), 1.86 - 1.77 (m, 1 H), 1.75 - 1.67 (m, 1 H), 0.95 (t, \(J = 8.6\) Hz, 9 H), 0.59 (q, \(J = 7.9\) Hz, 6 H), 0.16 (s, 9 H); \(^13\text{C NMR}\) (CDCl\(_3\), 126 MHz): \(\delta = 159.2, 138.1, 131.3, 129.4, 115.9, 113.7, 113.7, 107.7, 84.6, 81.9, 79.8, 74.3, 73.7, 57.4, 55.4, 29.2, 16.3, 7.0, 5.1, 5.1, 0.3; IR (film): \(\tilde{\nu} = 2955, 2876, 2173, 1729, 1640, 1614, 1586, 1514, 1463\) cm\(^{-1}\); HRMS (ESI): Calc. for C\(_{27}\)H\(_{46}\)O\(_2\)Si\(_2\)Na \([M^+ + Na]\) 513.2832. Found 513.2836; \([\alpha]_D^{20} = -26\) (c = 1 in CH\(_2\)Cl\(_2\)); \([\alpha]_D^{20} = -26\) (c = 1 in CH\(_2\)Cl\(_2\)).
Alkyne 3.18. To a solution of 3.24 (2.02 g, 4.12 mmol, 1.0 eq) in ethanol (50 mL) was added potassium carbonate (1.71 g, 12.3 mmol, 3.0 eq) in one portion and the reaction mixture stirred at room temperature for 3 days, then diluted with diethyl ether and washed with water and brine, then dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (12:1 Hexanes:Diethyl ether) to yield the title compound (1.63 g, 94%) as a colorless oil.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta = 7.29$ (d, $J = 8.7$ Hz, 2 H), 6.88 (d, $J = 8.7$ Hz, 2 H), 5.92 (ddd, $J = 6.3$, 10.5, 17.1 Hz, 1 H), 5.27 (td, $J = 1.5$, 17.2 Hz, 1 H), 5.15 (td, $J = 1.4$, 10.4 Hz, 1 H), 4.68 (d, $J = 11.5$ Hz, 1 H), 4.63 (d, $J = 11.4$ Hz, 1 H), 4.20 (t, $J = 6.1$ Hz, 1 H), 3.82 (s, 3 H), 3.78 - 3.74 (m, 1 H), 3.57 (dd, $J = 2.5$, 6.0 Hz, 1 H), 3.44 (td, $J = 2.6$, 9.4 Hz, 1 H), 3.31 (s, 3 H), 2.32 - 2.27 (m, 2 H), 1.92 (t, $J = 2.6$ Hz, 1 H), 1.88 - 1.79 (m, 2 H), 1.76 (d, $J = 2.7$ Hz, 1 H), 0.94 (t, $J = 8.0$ Hz, 9 H), 0.59 (q, $J = 8.4$ Hz, 6 H); $^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta = 159.2$, 138.1, 131.2, 129.4, 115.9, 113.7, 84.8, 81.8, 80.0, 74.4, 73.7, 68.3, 57.4, 55.4, 29.2, 15.0, 7.0, 5.1; IR (film): 2953, 2876, 2116, 1638, 1613, 1514, 1462, 1378, 1302, 1248 cm$^{-1}$; HRMS (ESI): Calc. for C$_{24}$H$_{38}$O$_4$NaSi [$M^+ + Na$] 441.2437. Found 441.2421; $\left[\alpha\right]_D^{39} = -29$ (c = 1 in CH$_2$Cl$_2$).

Completion of the Revised Southern Hemisphere 3.15

Coupled products anti-3.26 and syn-3.26. To a -40 °C solution of alkyne 3.18 (294 mg, 0.702 mmol, 2.6 eq) in THF (3 mL) was added a n-butyllithium (2.4 M in hexanes, 260 µL, 0.67 mmol, 2.5 eq) dropwise and the reaction mixture gradually warmed up to -20 °C and stirred at this temperature for 30 min, then recooled to -78 °C and transferred to a precooled -78 °C of aldehyde 3.17 (205 mg, 0.268 mmol, 1.0 eq) in THF (3 mL) via cannula. The reaction mixture was stirred at -78 °C for 30 min, then gradually warmed to -20 °C and quenched with sat. aqueous ammonium chloride. After warming to room temperature, the biphasic mixture was diluted with water and diethyl ether. The layers were separated and the aqueous layer extracted with diethyl ether. The combined organics were dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash column chromatography (9:1 Hexanes:Ethyl acetate) to yield recovered alkyne (151 mg, 83%
recovery) and a mixture of propargylic alcohols (282 mg, 89%, c. 1.4:1 ratio favoring anti). The diastereomers could be separated using flash column chromatography (7% Ethyl Acetate in Hexanes).

**anti-3.26:** $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta =$ 8.25 - 8.20 (m, 2 H), 7.33 (d, $J =$ 8.6 Hz, 2 H), 7.16 - 7.11 (m, 3 H), 6.80 (d, $J =$ 8.7 Hz, 2 H), 6.02 (ddd, $J =$ 6.1, 10.6, 17.1 Hz, 1 H), 5.68 (t, $J =$ 8.2 Hz, 1 H), 5.33 (td, $J =$ 1.4, 17.2 Hz, 1 H), 5.10 (td, $J =$ 1.5, 10.5 Hz, 1 H), 4.75 (d, $J =$ 11.5 Hz, 1 H), 4.68 (d, $J =$ 11.7 Hz, 1 H), 4.64 (s, 1 H), 4.30 (t, $J =$ 6.2 Hz, 1 H), 4.22 (q, $J =$ 7.6 Hz, 1 H), 4.05 (q, $J =$ 7.4 Hz, 1 H), 3.83 (t, $J =$ 6.8 Hz, 2 H), 3.69 (ddd, $J =$ 2.2, 6.3 Hz, 1 H), 3.58 (td, $J =$ 2.3, 9.4 Hz, 2 H), 3.50 - 3.41 (m, 1 H), 3.29 (s, 3 H), 3.24 (s, 3 H), 2.69 (d, $J =$ 4.8 Hz, 1 H), 2.50 - 2.37 (m, 2 H), 2.24 - 2.01 (m, 4 H), 1.97 (s, 2 H), 1.92 - 1.83 (m, 2 H), 1.79 - 1.71 (m, 1 H), 1.70 - 1.63 (m, 1 H), 1.62 - 1.55 (m, 1 H), 1.52 - 1.44 (m, 1 H), 1.43 - 1.25 (m, 8 H), 1.03 - 0.98 (m, 36 H), 0.62 (q, $J =$ 8.0 Hz, 6 H), 0.22 (s, 3 H), 0.18 (s, 3 H), 0.14 (s, 3 H), 0.13 - 0.12 (m, 3 H), 0.11 (s, 3 H), 0.08 (s, 3 H): $^{13}$C NMR (C$_6$D$_6$, 500 MHz) $\delta =$ 167.0, 159.6, 138.5, 133.0, 131.6, 130.8, 130.2, 129.5, 128.6, 128.2, 127.8, 115.6, 113.7, 85.8, 82.1, 81.1, 80.3, 74.7, 74.5, 74.4, 73.9, 73.6, 67.4, 66.6, 63.3, 60.4, 57.2, 54.7, 47.7, 44.8, 44.5, 40.5, 40.0, 32.5, 32.1, 30.1, 30.0, 29.8, 26.2, 24.0, 18.5, 18.2, 15.6, 10.8, 7.1, 5.3, -3.6, -3.8, -4.2, -4.4, -5.1, -5.1; IR (film): $\tilde{\nu} =$ 3419, 2928, 2856, 1718, 1613, 1514, 1462, 1381 cm$^{-1}$; HRMS (ESI): Calc. for C$_{65}$H$_{114}$O$_{11}$Si$_{4}$Na [$M^+ + Na$] 1205.7336. Found 1205.7341; [\alpha]$_D^{20} =$ + 5 (c = 1 in CH$_2$Cl$_2$).

**syn-3.26:** $^1$H NMR (CDCl$_3$, 500 MHz): $\delta =$ 8.08 (d, $J =$ 7.0 Hz, 2 H), 7.56 (tt, $J =$ 1.1, 7.2 Hz, 1 H), 7.44 (t, $J =$ 7.8 Hz, 2 H), 7.26 (d, $J =$ 8.6 Hz, 2 H), 6.87 (d, $J =$ 8.8 Hz, 2 H), 6.20 (dd, $J =$ 1.5, 9.4 Hz, 1 H), 5.47 (dd, $J =$ 5.3, 9.1 Hz, 1 H), 5.50 - 5.45 (m, 1 H), 4.60 (d, $J =$ 12.0 Hz, 2 H), 4.37 (dd, $J =$ 5.5, 9.4 Hz, 2 H), 3.99 - 3.91 (m, 1 H), 3.81 (s, 4 H), 3.79 - 3.67 (m, 3 H), 3.44 (dd, $J =$ 8.2 Hz, 2 H).
3.4, 5.6 Hz, 1 H), 3.41 - 3.37 (m, 2 H), 3.36 - 3.32 (m, 1 H), 3.28 (s, 3 H), 2.45 (d, J = 1.3 Hz, 3 H), 2.38 (d, J = 6.9 Hz, 1 H), 2.31 - 2.24 (m, 1 H), 2.22 - 2.08 (m, 2 H), 1.95 (ddd, J = 1.9, 9.9, 14.6 Hz, 1 H), 1.82 - 1.65 (m, 6 H), 1.63 - 1.43 (m, 7 H), 1.36 - 1.28 (m, 1 H), 1.21 - 1.14 (m, 1 H), 1.08 (d, J = 7.0 Hz, 5 H), 0.94 (t, J = 8.0 Hz, 11 H), 0.90 (s, 9 H), 0.89 (s, 9 H), 0.87 (s, 9 H), 0.58 (q, J = 7.8 Hz, 6 H), 0.07 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.05 (s, 3 H), 0.02 (s, 6 H); \(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \(\delta = 159.3, 142.0, 132.8, 130.9, 129.9, 129.6, 128.4, 113.8, 96.9, 86.0, 81.7, 80.5, 79.7, 74.5, 74.1, 73.5, 73.0, 71.1, 67.1, 66.4, 64.6, 60.3, 57.6, 55.4, 47.1, 44.4, 43.4, 40.2, 38.1, 32.4, 31.9, 29.4, 28.8, 26.1, 24.1, 23.8, 18.5, 18.1, 15.0, 12.2, 6.9, 5.1, -3.7, -3.9, -4.3, -4.4, -5.1; IR (film): \(\nu = 3455, 2929, 2856, 1719, 1613, 1514, 1463, 1381, 1251 \text{ cm}^{-1}.\ [\alpha]^{20}_D = +5 (c = 0.5 \text{ in CH}_2\text{Cl}_2).\)

**Diols anti-3.27 and syn-3.27.** The following procedure for anti-3.27 is representative. To a 0 °C solution of anti-3.26 (536 mg, 0.453 mmol, 1.0 eq) in diethyl ether (3.9 mL) was ethyl magnesium bromide (3 M in diethyl ether, 1.5 mL, 4.53 mmol, 10 eq). The reaction mixture was then warmed to room temperature and stirred for 2 h, at which point TLC analysis showed no further reaction. The mixture was therefore re-cooled to 0 °C and quenched by the dropwise addition of saturated aqueous ammonium chloride. The mixture was then diluted with diethyl ether and water and the layers separated. The aqueous layer was extracted with additional diethyl ether and the combined organics dried over Na\(_2\)SO\(_4\) and concentrated. The crude residue was purified by flash column chromatography (9:1 \(\rightarrow\) 6:1 \(\rightarrow\) 4:1 Hexanes:Ethyl Acetate) to provide the title compound (505 mg, >95%) as well as recovered anti-3.27 (10 mg, 2%).

**anti-3.27: \(^1\)H NMR (C\(_6\)D\(_6\), 500 MHz): \(\delta = 7.36\) (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.9 Hz, 2 H), 6.07 (ddd, J = 6.0, 10.6, 17.1 Hz, 1 H), 5.38 (td, J = 1.8, 17.2 Hz, 1 H), 5.15 (td, J = 1.6, 10.4 Hz, 1 H), 4.79 (d, J = 11.3 Hz, 2 H), 4.74 (d, J = 11.6 Hz, 1 H), 4.46 (dt, J = 3.5, 8.4 Hz, 1 H), 4.33 (t, J = 6.5 Hz, 1 H), 4.21 - 4.10 (m, 3 H), 3.89 (q, J = 7.5 Hz, 1 H), 3.82 - 3.74 (m, 2 H), 3.72 (dd, J =
2.1, 6.4 Hz, 1 H), 3.66 (td, J = 2.7, 9.4 Hz, 1 H), 3.59 (t, J = 11.2 Hz, 1 H), 3.48 - 3.41 (m, 1 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 2.58 - 2.44 (m, 2 H), 2.20 - 2.09 (m, 2 H), 2.01 - 1.86 (m, 4 H), 1.78 - 1.70 (m, 3 H), 1.64 (m, 3 H), 1.50 (ddd, J = 2.3, 9.7, 13.4 Hz, 1 H), 1.37 (s, 4 H), 1.18 - 1.11 (m, 1 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.06 - 0.99 (m, 27 H), 0.91 (s, 9 H), 0.65 (q, J = 8.0 Hz, 6 H), 0.27 (s, 3 H), 0.25 (s, 3 H), 0.12 (s, 3 H), 0.12 (s, 3 H), 0.09 (s, 3 H), 0.08 (s, 3 H); 13C NMR (C6D6, 500 MHz): δ = 159.6, 138.6, 131.6, 129.5, 115.7, 113.9, 85.7, 82.3, 81.2, 80.4, 74.8, 74.7, 74.0, 73.6, 72.2, 69.8, 66.8, 66.5, 60.2, 57.3, 54.7, 45.8, 44.8, 44.6, 40.4, 39.8, 32.6, 31.8, 30.0, 26.2, 26.1, 25.9, 24.0, 18.4, 18.2, 18.0, 15.7, 13.5, 7.1, 5.3, -3.6, -4.2, -4.4, -4.7, -5.1, -5.2; IR (film): ν = 3434, 2928, 2856, 1612, 1513. HRMS (ESI): Calc. for C58H111O10Si4 [M+H]+ 1079.7254. Found 1079.7251; [α]D20 = +6 (c = 0.75 in CH2Cl2).

syn-3.27: 1H NMR (C6D6, 500 MHz): δ = 7.36 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 9.0 Hz, 2 H), 6.07 (ddd, J = 6.1, 10.6, 17.0 Hz, 1 H), 5.38 (td, J = 2.5, 16.4 Hz, 1 H), 5.15 (td, J = 1.4, 10.6 Hz, 1 H), 4.86 (d, J = 6.8 Hz, 1 H), 4.78 (d, J = 11.6 Hz, 1 H), 4.73 (d, J = 11.4 Hz, 1 H), 4.34 (t, J = 6.1 Hz, 1 H), 4.26 - 4.20 (m, 1 H), 4.17 (t, J = 8.2 Hz, 2 H), 3.84 - 3.75 (m, J = 3.4 Hz, 2 H), 3.72 (dd, J = 2.5, 6.3 Hz, 1 H), 3.62 (qd, J = 2.6, 10.5 Hz, 2 H), 3.50 - 3.43 (m, 1 H), 3.33 (s, 3 H), 3.27 (s, 3 H), 2.54 - 2.41 (m, 2 H), 2.19 - 2.08 (m, 2 H), 1.92 (m, 4 H), 1.86 - 1.72 (m, 3 H), 1.71 - 1.57 (m, 2 H), 1.52 (ddd, J = 2.1, 9.5, 13.7 Hz, 1 H), 1.45 - 1.32 (m, 4 H), 1.18 (d, J = 6.8 Hz, 3 H), 1.12 (t, J = 7.0 Hz, 3 H), 1.05 (s, 9 H), 1.04 (s, 9 H), 1.02 (s, 9 H), 0.95 (s, 9 H), 0.66 (q, J = 8.1 Hz, 6 H), 0.26 (s, 3 H), 0.25 (s, 2 H), 0.14 (s, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H); 13C NMR (C6D6, 126 MHz): δ = 159.5, 138.6, 131.5, 129.5, 128.5, 115.7, 114.0, 86.1, 82.2, 81.3, 80.4, 74.7, 73.9, 73.6, 72.2, 69.6, 66.6, 66.4, 65.8, 60.3, 57.2, 54.7, 46.1, 45.9, 44.8, 40.4, 39.8, 32.6, 31.8, 29.9, 26.2, 26.1, 25.9, 24.0, 18.4, 18.2, 18.0, 15.7, 15.4, 12.9, 7.1, 5.3, -3.7, -4.2, -4.3, -4.7, -5.1, -5.2; IR (film): ν = 3436, 2928, 2856, 1613, 1514, 1472 cm⁻¹; [α]D20 = -1.8 (c = 0.73 in CH2Cl2).
Bisacetal 3.28. Diol syn-3.27 (16 mg, 14.8 µmol, 1.0 eq) was dissolved in a 2:1 mixture of DMF and 2,2-dimethoxypropane (300 µL total volume). Catalytic TsOH was added and the reaction mixture stirred overnight, then quenched with saturated aq. sodium bicarbonate and diluted with ethyl acetate. The layers were separated and the aqueous layer extracted with additional ethyl acetate. The combined organics were dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (4:1 → 2:1 → 1:1 Hexanes:Ethyl Acetate) to yield the desired compound (5 mg, ~50%).

¹H NMR (C₆D₆, 500 MHz): δ = 7.16 (d, J = 8.7 Hz, 2 H), 6.80 (d, J = 8.7 Hz, 2 H), 5.99 (ddd, J = 4.9, 10.6, 17.2 Hz, 1 H), 5.53 (td, J = 1.8, 17.2 Hz, 1 H), 5.18 (td, J = 1.8, 10.6 Hz, 1 H), 4.50 (d, J = 11.2 Hz, 1 H), 4.40 (d, J = 10.9 Hz, 1 H), 4.31 (d, J = 10.5 Hz, 4 H), 3.81 (dt, J = 1.8, 10.3 Hz, 1 H), 3.74 - 3.67 (m, 1 H), 3.66 - 3.56 (m, 2 H), 3.50 - 3.45 (m, 1 H), 3.44 (d, J = 4.7 Hz, 2 H), 3.32 (s, 3 H), 3.13 (s, 3 H), 3.09 (s, 2 H), 2.89 (d, J = 6.6 Hz, 1 H), 2.38 - 2.30 (m, 1 H), 2.29 - 2.21 (m, 1 H), 1.97 - 1.88 (m, 1 H), 1.88 - 1.83 (m, 1 H), 1.82 - 1.69 (m, 5 H), 1.64 - 1.57 (m, 3 H), 1.56 (s, 3 H), 1.53 (s, 3 H), 1.50 - 1.41 (m, 5 H), 1.39 - 1.34 (m, 4 H), 1.33 (s, 3 H), 0.90 (d, J = 6.7 Hz, 3H); ¹³C NMR (C₆D₆, 126 MHz): δ = 159.8, 138.9, 130.6, 129.8, 115.5, 114.1, 100.4, 99.8, 98.6, 84.9, 81.4, 80.5, 79.8, 75.2, 74.1, 73.5, 71.9, 70.6, 67.4, 63.4, 62.1, 57.9, 57.6, 54.5, 48.1, 43.4, 40.8, 39.7, 39.6, 37.8, 32.5, 32.2, 29.7, 25.0, 24.9, 24.7, 24.6, 19.3, 14.8, 12.7; IR (film): ʋ = 3454, 2933, 1612, 1513, 1379 cm⁻¹; HRMS (ESI): Calc. for C₄₀H₆₂O₁₀Na [M⁺ + Na]: 725.4241. Found 725.4252; [α]D²⁰ = −6 (c = 0.4 in CH₂Cl₂).

Triols anti-3.29 and syn-3.29. The following procedure for anti-3.29 is representative. To a solution of diol anti-3.27 (105 mg, 97.2 µL, 1.0 eq) in DCM/pH 7 buffer (9:1, 15 mL total volume) at 0 °C was added DDQ (221 mg, 0.97 mmol, 10 eq) as a solid in one portion and the reaction mixture stirred at 0 °C for 45 minutes, then quenched with sat. aqueous sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was
purified by flash column chromatography (3:1 Hexane:Ethyl Acetate) to yield the title compound (91 mg, 97%) as a colorless oil.

**anti-3.29: **$^1$H NMR (C$_6$D$_6$, 500 MHz): $\delta = 6.07$ (ddd, $J = 7.1$, 10.3, 17.3 Hz, 1 H), 5.31 (d, $J = 17.2$ Hz, 1 H), 5.13 (td, $J = 0.8$, 10.4 Hz, 1 H), 4.89 (d, $J = 5.4$ Hz, 1 H), 4.60 (t, $J = 8.4$ Hz, 1 H), 4.54 - 4.50 (m, 1 H), 4.48 (br. s, 1 H), 4.38 - 4.32 (m, 1 H), 4.32 - 4.28 (m, 1 H), 4.27 - 4.22 (m, 1 H), 3.90 (dt, $J = 2.4$, 6.5 Hz, 2 H), 3.76 - 3.68 (m, 2 H), 3.60 - 3.48 (m, 2 H), 3.31 (s, 3 H), 2.64 - 2.52 (m, 3 H), 2.34 - 2.25 (m, 1 H), 2.25 - 2.17 (m, 1 H), 2.14 - 1.98 (m, 4 H), 1.91 - 1.80 (m, 3 H), 1.80 - 1.68 (m, 2 H), 1.62 (ddd, $J = 2.1$, 9.8, 11.6 Hz, 1 H), 1.54 - 1.38 (m, 3 H), 1.31 - 1.21 (m, 1 H), 1.20 - 1.16 (m, 12 H), 1.13 (s, 9 H), 1.10 (t, $J = 8.0$ Hz, 9 H), 1.03 (s, 9 H), 0.72 (q, $J = 7.9$ Hz, 6 H), 0.40 (s, 3 H), 0.38 (s, 3 H), 0.25 (s, 3 H), 0.24 (s, 3 H), 0.20 (s, 3 H), 0.19 (s, 3 H); $^{13}$C NMR (C$_6$D$_6$, 126 MHz): $\delta = 139.3$, 116.0, 85.9, 81.1, 79.4, 75.0, 74.7, 74.0, 73.5, 72.3, 69.7, 67.2, 66.4, 60.2, 56.7, 45.8, 44.8, 44.6, 40.4, 39.9, 32.6, 31.8, 28.7, 26.2, 26.1, 25.9, 24.0, 18.4, 18.2, 18.0, 14.3, 13.7, 7.0, 5.4, -3.6, -4.2, -4.3, -4.7, -5.1, -5.2; IR (film): $\tilde{\nu} = 3441$, 2935, 1640, 1464, 1251 cm$^{-1}$; HRMS (ESI): Calc. for C$_{50}$H$_{102}$O$_9$Si$_4$Na [M$^+$ + Na]$^+$ 981.6499. Found 981.6494; $[\alpha]_{D}^{20} = +22$ (c = 0.75 in CH$_2$Cl$_2$).

**syn-3.29: **$^1$H NMR (C$_6$D$_6$, 500 MHz): $\delta = 5.98$ (ddd, $J = 7.5$, 11.0, 17.8 Hz, 1 H), 5.21 (d, $J = 17.2$ Hz, 1 H), 5.04 (d, $J = 10.4$ Hz, 1 H), 4.89 (d, $J = 7.1$ Hz, 1 H), 4.41 (dd, $J = 3.4$, 7.1 Hz, 1 H), 4.26 - 4.21 (m, 1 H), 4.18 (t, $J = 9.3$ Hz, 2 H), 3.80 (dt, $J = 3.0$, 6.8 Hz, 2 H), 3.60 (d, $J = 9.0$ Hz, 2 H), 3.50 - 3.43 (m, 1 H), 3.42 - 3.38 (m, 1 H), 3.20 (s, 3 H), 2.43 (dq, $J = 2.4$, 6.9 Hz, 2 H), 2.17 (ddd, $J = 5.2$, 9.4, 14.3 Hz, 1 H), 2.12 - 1.88 (m, 6 H), 1.88 - 1.79 (m, 1 H), 1.83 (ddt, $J = 1.3$, 6.2, 15.4 Hz, 1 H), 1.76 (s, 1 H), 1.71 - 1.58 (m, 3 H), 1.52 (ddd, $J = 2.6$, 9.1, 11.4 Hz, 1 H), 1.45 - 1.29 (m, 4 H), 1.19 (d, $J = 6.8$ Hz, 3 H), 1.16 - 1.10 (m, 1 H), 1.06 (s, 9 H), 1.03 (s, 9 H), 1.00 (t, $J$
1H NMR (C\textsubscript{6}D\textsubscript{6}, 500 MHz) \(\delta = 6.49\) (ddd, \(J = 7.8, 10.0, 17.5\) Hz, 1 H), 5.68 (dd, \(J = 2.5, 10.0\) Hz, 1 H), 5.55 (dd, \(J = 1.6, 10.0\) Hz, 1 H), 5.39 (d, \(J = 17.3\) Hz, 1 H), 5.26 (dd, \(J = 1.7, 10.2\) Hz, 1 H), 4.82 (dd, \(J = 1.5, 7.8\) Hz, 1 H), 4.40 - 4.34 (m, 1 H), 4.33 - 4.27 (m, 1 H), 4.00 - 3.87 (s, 3 H), 3.79 (ddd, \(J = 3.0, 6.5, 9.6\) Hz, 1 H), 3.70 (t, \(J = 9.5\) Hz, 1 H), 3.63 (dt, \(J = 5.4, 10.6\) Hz, 1 H), 3.58 - 3.51 (m, 1 H), 3.40 - 3.33 (m, 4 H), 2.23 - 1.93 (m, 8 H), 1.85 - 1.66 (m, 4 H), 1.58 - 1.40 (m, 4 H), 1.34 - 1.25 (m, 2 H), 1.24 - 1.11 (m, 36 H), 0.99 (d, \(J = 7.1\) Hz, 3 H), 0.83 (dq, \(J = 4.4, 7.9\) Hz, 6 H), 0.36 (s, 3 H), 0.35 (s, 3 H), 0.33 (s, 3 H), 0.33 (s, 3 H), 0.24 (s, 3 H), 0.23 (s, 3 H); 13C NMR (C\textsubscript{6}D\textsubscript{6}, 126 MHz) \(\delta = 140.4, 133.5, 129.5, 115.4, 93.8, 77.0, 74.5, 74.2, 73.7, 73.5, 72.3, 69.1, 67.1, 65.8, 60.5, 55.1, 48.1, 45.2, 43.0, 40.5, 34.5, 34.3, 32.3, 32.0, 26.2, 26.1, 24.1, 23.5, 18.5, 18.3, 18.3, 17.1, 15.5, 7.2, 5.7, -3.1, -3.4, -3.7, -4.1, -5.1; \textbf{IR} (film): \(\tilde{\nu} = 2928, 1658, 1472 \text{ cm}^{-1} \); \([\alpha]_{D}^{20} = + 14 \) (c = 0.67 in CH\textsubscript{2}Cl\textsubscript{2}).
Compound 3.30 To a solution of triol syn-3.29 (4.5 mg, 4.7 µmol, 1.0 eq) in methanol (200 µL) over 4 Angstrom molecular sieves was added the catalyst (0.7 mg, 0.94 µmol, 0.2 eq) and the reaction mixture stirred for 1.5 h at room temperature, then filtered through a plug of silica gel and analyzed directly by NMR spectroscopy. No yield was determined.

\(^{1}H\) NMR (C\(_6\)D\(_6\), 500MHz, cryoprobe) \(\delta = 6.04\) (ddd, \(J = 7.0, 10.3, 17.3\) Hz, 1 H), 5.24 (td, \(J = 1.2, 17.3\) Hz, 1 H), 5.04 (qd, \(J = 1.0, 10.3\) Hz, 1 H), 4.55 (dd, \(J = 3.1, 6.9\) Hz, 1 H), 4.42 (t, \(J = 7.3\) Hz, 2 H), 4.38 (dt, \(J = 3.5, 9.2\) Hz, 1 H), 4.33 - 4.29 (m, 1 H), 4.27 - 4.22 (m, 1 H), 4.11 (d, \(J = 4.5\) Hz, 1 H), 3.81 (dt, \(J = 2.0, 6.7\) Hz, 3 H), 3.66 (dt, \(J = 3.5, 7.3\) Hz, 1 H), 3.59 (t, \(J = 10.9\) Hz, 1 H), 3.49 - 3.43 (m, 1 H), 3.43 - 3.39 (m, 1 H), 3.38 (s, 3 H), 2.58 - 2.50 (m, 1 H), 2.49 - 2.43 (m, 2 H), 2.05 - 1.96 (m, 5 H), 1.95 - 1.85 (m, 3 H), 1.80 - 1.73 (m, 2 H), 1.73 - 1.59 (m, 6 H), 1.43 - 1.38 (m, 1 H), 1.28 - 1.15 (m, 1 H), 1.07 (m, 27 H), 1.02 (q, \(J = 7.4\) Hz, 6 H), 0.29 (s, 3 H), 0.26 (s, 9 H), 0.13 (s, 3 H), 0.12 (s, 3 H); \(^{13}C\) NMR (C\(_6\)D\(_6\), 126MHz, cryoprobe) \(\delta = 158.8, 139.8, 115.7, 98.8, 81.7, 80.4, 75.2, 74.6, 73.9, 67.9, 67.1, 65.7, 60.2, 56.7, 48.4, 45.4, 44.1, 42.3, 40.5, 32.7, 31.9, 29.4, 26.1, 24.0, 20.1, 18.5, 18.3, 15.4, 9.4, 7.1, 5.2, -3.6, -3.8, -4.0, -4.3, -5.9; IR (film): \(\tilde{\nu}_{\text{max}} = 3439, 2928, 2856, 1684, 1652, 1506, 1463\) cm\(^{-1}\); \([\alpha]_{B}^{20} = +33\) (c = 0.33 in CH\(_2\)Cl\(_2\)).

Miscellaneous Procedural and Spectral Information

Aldehyde 3.64: \(^{1}H\) NMR (C\(_6\)D\(_6\), 500MHz) \(\delta = 9.42\) (s, 1 H), 6.35 (dt, \(J = 1.3, 7.2\) Hz, 1 H), 4.15 - 4.08 (m, 1 H), 3.92 (quin, \(J = 6.0\) Hz, 1 H), 3.78 (dt, \(J = 2.2, 6.7\) Hz, 2 H), 3.54 (tt, \(J = 2.2, 10.1\) Hz, 1 H), 3.48 - 3.41 (m, 1 H), 2.38 (t, \(J = 6.4\) Hz, 2 H), 1.91 (qd, \(J = 6.8, 13.7\) Hz, 1 H), 1.83 (dt, \(J = 3.3, 7.2\) Hz, 2 H), 1.8 (s, 3H), 1.79 - 1.73 (m, 1 H), 1.67 (ddd, \(J = 1.6, 6.8, 13.5\) Hz, 1 H), 1.63 - 1.59 (m, 1 H), 1.55 (dd, \(J = 2.7, 9.0, 13.9\) Hz, 1 H), 1.43 - 1.26 (m, 4 H), 1.21 - 1.07 (m, 2 H), 1.01 (s, 9 H), 1.00 (s, 9 H), 0.96 (s, 9 H), 0.18 (s, 3 H), 0.14 (s, 3 H), 0.11 (s, 9 H), 0.01 (s, 3 H); \(^{13}C\) NMR (C\(_6\)D\(_6\), 126MHz) \(\delta = 193.7, 148.8, 141.0, 74.8, 73.7, 69.4, 66.8, 32.7, 31.9, 29.4, 26.1, 24.0, 20.1, 18.5, 18.3, 15.4, 9.4, 7.1, 5.2, -3.6, -3.8, -4.0, -4.3, -5.9;
60.2, 47.0, 45.4, 40.4, 36.8, 32.5, 31.9, 26.1, 25.9, 24.0, 18.4, 18.2, 18.1, 9.7, -3.9, -4.2, -4.3, -5.2; IR (film) $\tilde{\nu}_{\text{max}} = 2929, 2857, 1693, 1663, 1472 \text{ cm}^{-1}$; HRMS (ESI): Calc. for $C_{34}H_{71}O_5Si_3$ $[M^+ + H]$ 643.4609, found 643.4608; $[\alpha]^B_\text{D} = +7.5 \ (c = 1.0 \text{ in CH}_2\text{Cl}_2)$.

**Ketone 3.66.** Coupled product *syn*-3.26

(95 mg, 80 µmol, 1.0 eq) in dichloromethane (1 mL) was added sodium bicarbonate (65 mg, 0.80 mmol, 10 eq) and DMP (68 mg, 0.16 mmol, 2.0 eq) in one portion. The reaction mixture was stirred at room temperature for 2 h, then quenched by the addition of saturated aqueous sodium bicarbonate (4 mL) and saturated aqueous sodium thiosulfate (4 mL). After vigorous stirring for an additional 1 h, the layers were separated and the aqueous layer extracted with additional dichloromethane. The combined organics were dried over Na$_2$SO$_4$ and concentrated. The crude residue was purified by flash column chromatography (12:1 → 9:1 Hexanes:Ethyl Acetate) to provide the title compound (75 mg, 79%) as a colorless oil.

$^1$H NMR (C$_6$D$_6$, 500MHz) $\delta = 8.31 - 8.25 \ (m, 2 \text{ H}), 7.33 \ (m, 3 \text{ H}), 7.14 \ (d, J = 2.0 \text{ Hz}, 3 \text{ H}), 6.83 \ (d, J = 8.4 \text{ Hz}, 2 \text{ H}), 6.10 \ (dd, J = 5.8, 10.1 \text{ Hz}, 1 \text{ H}), 5.98 \ (ddd, J = 6.0, 10.7, 17.0 \text{ Hz}, 1 \text{ H}), 5.34 \ (d, J = 17.3 \text{ Hz}, 1 \text{ H}), 5.12 \ (d, J = 10.5 \text{ Hz}, 1 \text{ H}), 4.72 \ (d, J = 11.6 \text{ Hz}, 1 \text{ H}), 4.70 \ (d, J = 11.5 \text{ Hz}, 1 \text{ H}), 4.28 \ (t, J = 6.1 \text{ Hz}, 1 \text{ H}), 4.25 - 4.14 \ (m, 2 \text{ H}), 3.82 \ (t, J = 6.6 \text{ Hz}, 2 \text{ H}), 3.68 \ (dd, J = 2.0, 6.2 \text{ Hz}, 1 \text{ H}), 3.57 \ (t, J = 10.2 \text{ Hz}, 1 \text{ H}), 3.52 - 3.44 \ (m, 2 \text{ H}), 3.32 \ (m, 4 \text{ H}), 3.23 \ (s, 3 \text{ H}), 2.51 - 2.33 \ (m, 2 \text{ H}), 2.20 \ (dt, J = 2.3, 13.1 \text{ Hz}, 1 \text{ H}), 2.10 - 2.00 \ (m, 1 \text{ H}), 1.96 \ (t, J = 6.8 \text{ Hz}, 2 \text{ H}), 1.90 - 1.75 \ (m, J = 7.1 \text{ Hz}, 4 \text{ H}), 1.68 - 1.58 \ (m, 2 \text{ H}), 1.53 \ (dt, J = 1.8, 11.9 \text{ Hz}, 1 \text{ H}), 1.44 - 1.39 \ (m, 1 \text{ H}), 1.37 - 1.30 \ (m, 2 \text{ H}), 1.27 \ (d, J = 7.0 \text{ Hz}, 3 \text{ H}), 1.06 \ (s, 9 \text{ H}), 1.04 - 0.99 \ (m, 27 \text{ H}), 0.64 \ (q, J = 7.7 \text{ Hz}, 6 \text{ H}), 0.24 \ (s, 3 \text{ H}), 0.22 \ (s, 3 \text{ H}), 0.18 \ (s, 3 \text{ H}), 0.17 \ (s, 3 \text{ H}), 0.14 \ (s, 3 \text{ H}), 0.13 \ (s, 3 \text{ H});$ $^{13}$C

NMR (C$_6$D$_6$, 126MHz) $\delta = 186.6, 165.7, 159.6, 138.2, 132.8, 131.4, 131.0, 130.1, 129.5, 128.5, 116.0, 113.6, 100.2, 95.4, 81.8, 81.0, 80.1, 74.6, 74.4, 74.0, 73.6, 72.4, 67.5, 66.8, 60.3, 57.1, 54.7, 52.2, 47.5, 44.9, 40.4, 38.7, 32.5, 32.0, 28.6, 26.2, 26.1, 24.0, 18.4, 18.2, 18.2, 15.7, 11.0,
7.1, 5.3, -3.7, -3.8, -4.1, -4.2, -5.1, -5.1; IR (film): $\tilde{\nu}_{\text{max}} = 2928, 2856, 2210, 1723, 1675, 1513, 1472 \text{ cm}^{-1}$; [$\alpha$]$^D_{\text{D}} = -18$ (c = 1.0 in CH$_2$Cl$_2$).

**Acetal 3.70.** To a solution of triol syn-3.29 (28 mg, 29 µmol, 1.0 eq) in 2,2-dimethoxypropane (370 µL) was added PPTS (0.37 mg, 1.5 µmol, 0.05 eq, stock solution in THF). The reaction mixture was then stirred at 36 °C for 4 h. TLC analysis at this stage indicated full conversion. The reaction mixture was concentrated and purified by MPLC (5:1 Hexanes:Diethyl Ether) to provide the title compound (20 mg, 69%) as a colorless oil.

$^1$H NMR (C$_6$D$_6$, 500MHz) $\delta = 5.96$ (ddd, $J = 7.2, 10.3, 17.3$ Hz, 1 H), 5.20 (d, $J = 18.4$ Hz, 1 H), 5.02 (d, $J = 11.0$ Hz, 1 H), 4.38 (dd, $J = 3.7, 7.1$ Hz, 1 H), 4.33 (d, $J = 10.3$ Hz, 1 H), 4.26 - 4.16 (m, 2 H), 3.84 (t, $J = 6.8$ Hz, 2 H), 3.77 - 3.71 (m, 1 H), 3.62 - 3.56 (m, 1 H), 3.55 - 3.51 (m, 1 H), 3.51 - 3.44 (m, 1 H), 3.41 - 3.35 (m, 1 H), 3.17 (s, 3 H), 2.43 - 2.38 (m, 3 H), 2.07 - 1.99 (m, 1 H), 1.98 - 1.83 (m, 7 H), 1.80 - 1.67 (m, 3 H), 1.66 - 1.58 (m, 3 H), 1.44 - 1.25 (m, 11 H), 1.24 - 1.14 (m, 2 H), 1.07 (s, 9 H), 1.04 (s, 18 H), 1.00 (t, $J = 8.2$ Hz, 9 H), 0.63 (q, $J = 7.2$ Hz, 6 H), 0.26 (s, 6 H), 0.20 (s, 3 H), 0.16 (s, 9 H); $^{13}$C NMR (C$_6$D$_6$, 126MHz) $\delta = 139.2, 115.9, 98.4, 85.3, 79.5, 79.4, 75.2, 74.5, 74.1, 73.8, 71.6, 67.3, 67.2, 67.1, 65.8, 60.3, 56.6, 48.4, 45.6, 42.9, 40.5, 40.4, 32.6, 31.9, 30.4, 30.1, 28.9, 26.2, 26.2, 26.1, 25.9, 24.0, 22.9, 19.8, 18.5, 18.3, 18.3, 15.4, 14.4, 14.2, 13.2, 7.0, 5.4, -3.2, -3.7, -3.8, -4.0, -5.1; IR (film): $\tilde{\nu}_{\text{max}} = 3364, 2927, 2856, 1644, 1471 \text{ cm}^{-1}$; [$\alpha$]$^D_{\text{D}} = +16$ (c = 0.3 in CH$_2$Cl$_2$).

**Carbonate 3.71** A solution of diol syn-3.27 (34 mg, 31 µmol, 1.0 eq) and carbonyl diimidazole (51 mg, 0.31 mmol, 10 eq) in benzene (600 µL) was heated in a sealed tube to 65 °C for 2.5 hours. The mixture was filtered directly through a plug of silica gel and the filtrated evaporated. The crude residue was dissolved in a dichloromethane/pH 7 buffer mixture (9:1, total volume 4 mL) and cooled to 0 °C.
DDQ (70 mg, 0.31 mmol, 10 eq) was added in one portion and the reaction mixture stirred at 0 °C for 30 minutes, then quenched by the addition of saturated aqueous sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer extracted with additional dichloromethane. The combined organics were washed with water and brine, dried over Na₂SO₄ and concentrated. The crude residue was purified by flash column chromatography (9:1 → 6:1 Hexanes:Ethyl Acetate) to provide the title compound (30 mg, >95%) as a colorless oil.

¹H NMR (C₆D₆, 500MHz) δ = 5.94 (ddd, J = 7.2, 10.5, 17.4 Hz, 1 H), 5.21 (td, J = 1.3, 17.3 Hz, 1 H), 5.05 (d, J = 10.4 Hz, 1 H), 4.38 (dd, J = 3.6, 7.3 Hz, 1 H), 4.24 - 4.18 (m, 2 H), 4.12 (dt, J = 2.0, 10.3 Hz, 1 H), 3.80 (t, J = 6.6 Hz, 2 H), 3.58 (t, J = 9.6 Hz, 1 H), 3.54 - 3.50 (m, 1 H), 3.49 - 3.43 (m, 1 H), 3.38 - 3.31 (m, 1 H), 3.18 (s, 3 H), 2.35 (tt, J = 1.8, 7.3 Hz, 2 H), 2.07 - 1.83 (m, 7 H), 1.78 (ddd, J = 2.3, 10.9, 13.6 Hz, 1 H), 1.72 - 1.57 (m, 5 H), 1.44 - 1.28 (m, 4 H), 1.26 - 1.17 (m, 2 H), 1.06 (s, 9 H), 1.03 - 0.96 (m, 27 H), 0.70 (d, J = 6.7 Hz, 3 H), 0.63 (q, J = 8.2 Hz, 6 H), 0.26 (s, 3 H), 0.25 (s, 3 H), 0.19 (s, 3 H), 0.18 (s, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H); ¹³C NMR (C₆D₆, 126MHz) δ = 147.0, 139.1, 116.2, 89.2, 79.6, 79.2, 75.6, 75.0, 74.6, 74.1, 73.9, 73.8, 66.8, 65.9, 65.7, 60.2, 56.6, 48.1, 45.3, 41.4, 40.3, 38.1, 32.4, 31.7, 30.1, 28.3, 26.2, 26.0, 24.0, 18.4, 18.2, 18.1, 15.5, 14.1, 12.6, 7.0, 5.3, -3.8, -3.9, -4.1, -4.5, -5.1; IR (film): vₘₐₓ = 3375, 2926, 2854, 1765, 1644, 1422 cm⁻¹; HRMS (ESI): Calc. for C₅₁H₁₀₁O₁₀Si₄ [M⁺ + H] 985.6472, found 985.6498; [α]₂₀° = + 7 (c = 0.33 in CH₂Cl₂).

4.4 References Relevant to Chapter 4


About the Author

Alexander (Sasha) Sokolsky was born in the former USSR in 1988. Shortly thereafter, the USSR became Russia and the Sokolsky family began a stepwise migration abroad to the United States, with Sasha himself moving in 1996. He attended school in the suburbs of Philadelphia, where a three year experience with chemistry convinced him to explore a major in the field.

This interest then took him to the University of Rochester in upstate New York, where he continued his chemistry education. He was incredibly lucky to land a REU spot at the University of Rochester, working with Professor Robert K. Boeckman, Jr. on the synthesis of apoptolidin. This research continued into the following academic year. The following summer, Sasha decided to pursue a more industrial experience and secured an internship at GlaxoSmithKline, working with the MDR Boston team on Encoded Library Technology. The experience was so rewarding, he continued on for a second summer. In between, as a junior, he was recruited to work on a joint project between Dr's Richard Eisenberg and Alison Frontier involving the use of electrophilic iridium complexes as catalysts for the Nazarov cyclization.

Having run out of chemistry classes to take by the middle of his junior year, Sasha was encouraged by Dr. Tom Krugh, his academic advisor, to pursue a 4+1 Masters program available to University of Rochester students. Submatriculation allowed him to complete this program in four years, continuing work in the Eisenberg group while taking every organic graduate class the department had to offer. In 2010, he was awarded a combined M.S./B.S. degree with highest distinction.

He then moved on to the University of Pennsylvania to pursue a Ph.D. degree in chemistry, working under Professor Amos B. Smith, III on a variety of projects spanning methods development for Anion Relay Chemistry and synthetic efforts towards the spirastrellolide family of natural products. After completing his degree in February 2015, he will move on to a Research Investigator position at Incyte Corporation in Wilmington, Delaware.
Appendix
Figure A 1 $^1$H NMR spectrum of compound 2.32
Figure A $^{13}$C NMR spectrum of compound 2.32
Figure A 3 Infrared spectrum of compound 2.32
Figure A 4 $^1$H NMR spectrum of compound 2.33
Figure A $^{13}$C NMR spectrum of compound 2.33
Figure A.6 Infrared spectrum of compound 2.33
Figure A7 $^1$H NMR spectrum of compound 2.29
Figure A $^{13}$C NMR spectrum of compound 2.29
Figure A 9 Infrared spectrum of compound 2.29
Figure A 1H NMR spectrum of compound 2.34
Figure A 11 $^{13}$C NMR spectrum of compound 2.34
Figure A3 $^1$H NMR spectrum of compound 2.35
Figure A \(^{13}\text{C}\) NMR spectrum of compound 2.35
Figure A.15 Infrared spectrum of compound 2.35
Figure A

$^{1H}$ NMR spectrum of compound 2.36
Figure A $^{13}$C NMR spectrum of compound 2.36
Figure A.18 Infrared spectrum of compound 2.36
Figure A 19 $^1$H NMR spectrum of compound 2.37
Figure A: $^{13}$C NMR spectrum of compound 2.37
Figure A21: Infrared Spectrum of compound 2.37
Figure A22 $^1$H NMR spectrum of compound 2.38
Figure A 23 $^{13}$C NMR spectrum of compound 2.38
Figure A.24 Infrared Spectrum of compound 2.38
Figure A 25 $^1$H NMR spectrum of compound 2.39
Figure A 26$^{13}$C NMR spectrum of compound 2.39
Figure A.27 Infrared Spectrum of compound 2,39
Figure A 28 $^1$H NMR spectrum of compound 2.40
Figure A 29 $^{13}$C NMR spectrum of compound 2.40
Figure A 30 Infrared spectrum of compound 2.40
Figure A 31 $^1$H NMR spectrum of compound 2.30
Figure A \( ^{13}\)C NMR spectrum of compound 2.30
Figure A.33 Infrared Spectrum of compound 2.30
Figure A34: H NMR spectrum of compound 2.41
Figure A $^{13}$C NMR spectrum of compound 2.41
Figure A 36 Infrared spectrum of compound 2.41
Figure A 37-1 H NMR spectrum of compound 2.42
Figure A 38 $^{13}$C NMR spectrum of compound 2.42
Figure A 39 Infrared spectrum of compound 2.42
Figure A 40 $^1$H NMR spectrum of compound 2.44
Figure A 41 $^{13}$C NMR spectrum of compound 2.44
Figure A 42 Infrared spectrum of compound 2.44
Figure A43 $^1$H NMR spectrum of compound 2.46
Figure A 44 $^{13}$C NMR spectrum of compound 2.46
Figure A.45. Infrared spectrum of compound 2.46.
Figure A 46 $^1$H NMR spectrum of compound 4.1
Figure A 47 $^{13}$C NMR spectrum of compound 4.1.
Figure A 48. Infrared spectrum of compound 4.1.
Figure A 49 $^1$H NMR spectrum of compound 2.27
Figure A 50 $^{13}$C NMR spectrum of compound 2.27
Figure A 51 Infrared spectrum of compound 2.27
Figure A52 $^1$H NMR spectrum of compound 2.49
Figure A $^{13}$C NMR spectrum of compound 2.49
Figure A 54 Infrared spectrum of compound 2.49
Figure A55 $^1$H NMR spectrum of compound 4.2
Figure A $^13$C NMR spectrum of compound 4.2
Figure A.57: Infrared spectrum of compound 4.2.
Figure A.58 1H NMR spectrum of compound 2.50
Figure A 59 $^{13}$C NMR spectrum of compound 2.50
Figure A 60 Infrared spectrum of compound 2.50
Figure A 61 $^1$H NMR spectrum of compound 2.51
Figure A 62 $^{13}$C NMR spectrum of compound 2.51
Figure A 63 Infrared spectrum of compound 2.51
Figure A.64 $^1$H NMR spectrum of compound 2.54
Figure A 66: Infrared spectrum of compound 2.54
Figure A 67 $^1$H NMR spectrum of compound 2.53
Figure A $^{13}$C NMR spectrum of compound 2.53
Figure A 69 Infrared spectrum of compound 2.53
Figure A 70 $^1$H NMR spectrum of compound 2.56
Figure A $^{13}$C NMR spectrum of compound 2.56
Figure A 72 Infrared spectrum of compound 2.56
Figure A 1H NMR spectrum of compound 2.57
Figure A $^{13}$C NMR spectrum of compound 2.57
Figure A.75: Infrared Spectrum of compound 2.57
Figure A76: 1H NMR spectrum of compound 2.59
Figure A: $^{13}$C NMR spectrum of compound 2.59
Figure A 78 Infrared Spectrum of compound 2.59
Figure A 79 $^1$H NMR spectrum of compound 2.60
Figure 80: $^{13}$C NMR spectrum of compound 2.60

[Diagram showing the NMR spectrum with various peaks labeled]
Figure A 82 $^1$H NMR spectrum of compound 2.61
Figure A: $^{13}$C NMR spectrum of compound 2.61.
Figure A 84 Infrared spectrum of compound 2.61
Figure A 13C NMR spectrum of compound 2.26

ppm

5.09
6.94
14.82
28.89
29.31
55.41
57.64
68.80
71.22
74.11
76.91
77.16
77.42
79.76
81.71
84.44
97.03
113.78
129.62
130.92
141.84
159.23
Figure A.87 Infrared Spectrum of compound 2.26
Figure A 88 $^1$H NMR spectrum of compound anti-2.23
Figure A 89 $^{13}$C NMR spectrum of compound anti-2.23
Figure A. Infrared spectrum of compound anti-2,23.
Figure A 91 $^1$H NMR spectrum of compound syn-2.23
Figure A 92 $^{13}$C NMR spectrum of compound syn-2.23
Figure A 93 Infrared spectrum of compound syn-2.23
Figure A 94 \(^1\)H NMR spectrum of compound \textit{anti-2.70}
Figure A 95 $^{13}$C NMR spectrum of compound anti-2.70
Figure A 96 Infrared spectrum of compound anti-2.70
Figure A 97 $^1$H NMR spectrum of compound 2.74
Figure A 98 $^{13}$C NMR spectrum of compound 2.74
Figure A 99 Infrared spectrum of compound 2.74
Figure A100: 1H NMR spectrum of compound 4.3
Figure A 101 $^{13}$C NMR spectrum of compound 4.3
Figure A102. Infrared spectrum of compound 4.3.
Figure A 103 $^1$H NMR spectrum of compound 2.75
Figure A 104 $^{13}$C NMR spectrum of compound 2.75
Figure A 105 Infrared spectrum of compound 2.75
Figure A 106 $^1$H NMR spectrum of compound 2.76
Figure A 107 $^{13}$C NMR spectrum of compound 2.76
Figure A.108 Infrared spectrum of compound 2,76.
Figure A 109 $^1$H NMR spectrum of compound 2.79
Figure A $^{13}$C NMR spectrum of compound 2.79
Figure A 111 Infrared spectrum of compound 2.79
Figure A 112 $^1$H NMR spectrum of compound 2.78
Figure A 113 $^{13}$C NMR spectrum of compound 2.78
Figure A 114 Infrared spectrum of compound 2.78
Figure A115 $^1$H NMR spectrum of compound 4.4
Figure A $^{13}$C NMR spectrum of compound 4.4
Figure A.117 Infrared spectrum of compound 4.4
Figure A 118 $^1$H NMR spectrum of compound 2.72
Figure A 119 $^{13}$C NMR spectrum of compound 2.72
Figure A 120 Infrared spectrum of compound 2.72
Figure A 121 $^1\text{H}$ NMR spectrum of compound $\textit{anti}$-2.80
Figure A 122 $^{13}$C NMR spectrum of compound anti-2.80
Figure A. Infrared spectrum of compound anti-2.80
Figure A 124 $^1$H NMR spectrum of compound syn-2.80
Figure A $^{13}$C NMR spectrum of compound syn-2.80
Figure A 126 Infrared spectrum of compound syn-2.80
Figure A 127 $^1$H NMR spectrum of compound anti-2.81
Figure A 128 $^{13}$C NMR spectrum of compound anti-2.81
Figure A 129 Infrared spectrum of compound anti-2.81
Figure A. 130 H NMR spectrum of compound syn-2.81
Figure A 13C NMR spectrum of compound syn-2.81
Figure A.132 Infrared spectrum of compound syn-2.81
Figure A.133 $^1$H NMR spectrum of southern hemisphere 2.15
Figure A 13C NMR spectrum of southern hemisphere 2.15
Figure A.35 COSY spectrum of southern hemisphere 2.15
Figure A.136 HSQC spectrum of southern hemisphere 2.15.
Figure A 137 Infrared spectrum of southern hemisphere 2.15
Figure A 138 $^1$H NMR spectrum of compound 2.83
Figure A 13C NMR spectrum of compound 2.83
Figure A. Infrared spectrum of compound 2.83
Figure A 141 $^1$H NMR spectrum of compound 3.20
Figure A 1H NMR spectrum of compound 3.20
Figure A 143: Infrared spectrum of compound 3.20
Figure A144: $^{1}H$NMR spectrum of compound 4.5.
Figure A $^{13}$C NMR spectrum of compound 4.5
Figure A 146 Infrared spectrum of compound 4.5.
Figure A 147 $^1$H NMR spectrum of compound 3.21
Figure A 1^13C NMR spectrum of compound 3.21
Figure A 149 Infrared spectrum of compound 3.21
Figure A 1H NMR spectrum of compound 3.22
Figure A 151 $^{13}$C NMR spectrum of compound 3.22
Figure A 152 Infrared spectrum of compound 3.22
Figure A 153 $^1$H NMR spectrum of compound 3.23
Figure A 154 $^{13}$C NMR spectrum of compound 3.23
Figure A 155: Infrared spectrum of compound 3.23
Figure A156 $^1$H NMR spectrum of compound 4.6
Figure A $^{13}$C NMR spectrum of compound 4.6
Figure A.158 Infrared spectrum of compound 4.6
Figure A 159 $^1$H NMR spectrum of compound 3.18
Figure A 160 $^{13}$C NMR spectrum of compound 3.18
Figure A 161 Infrared spectrum of compound 3.18
Figure A 162 $^1$H NMR spectrum of compound $anti$.3.26
Figure A 163 $^{13}$C NMR spectrum of compound anti-3.26
Figure A 164 Infrared spectrum of compound \textit{anti-3.26}
Figure A 1H NMR spectrum of compound syn-3.26
Figure A 166 $^{13}$C NMR spectrum of compound syn-3.26
Figure A 167 Infrared spectrum of compound syn-3.26
Figure A 1H NMR spectrum of compound anti-3.27
Figure A $^{13}$C NMR spectrum of compound *anti*-3.27
Figure A 170 Infrared spectrum of compound anti-3.27
Figure A 171 $^1$H NMR spectrum of compound syn-3.27
Figure A 172 $^{13}$C NMR spectrum of compound syn-3.27
Infrared spectrum of compound syn-3.27
Figure A 174 $^1$H NMR spectrum of compound 3.28
Figure A 175 $^{13}$C NMR spectrum of compound 3.28
Figure A 176 Infrared spectrum of compound 3.28
Figure A 177 $^1$H NMR spectrum of compound $anti$-3.29
Figure A 178 $^{13}$C NMR spectrum of compound anti-3.29
Figure A 179 Infrared spectrum of compound anti-3.29
Figure A 180 $^1$H NMR spectrum of compound syn-3.29
Figure A 13C NMR spectrum of compound syn-3.29
Figure A. IR spectrum of compound syn-3.29
Figure A183 $^1$H NMR spectrum of southern hemisphere 3.15
Figure A 184 $^{13}$C NMR spectrum of southern hemisphere 3.15
Figure A185 Infrared spectrum of southern hemisphere 3.15
Figure A 186 $^1$H NMR spectrum of compound 3.30
Figure A $^{13}$C NMR spectrum of compound 3.30
Figure A 188 COSY spectrum of compound 330
Figure A189 HSQC spectrum of compound 3.30
Figure A 190 Infrared spectrum of compound 3.30
Figure A 191 $^1$H NMR spectrum of compound 3.64
Figure A 192 $^{13}$C NMR spectrum of compound 3.64
Figure A 193: Infrared spectrum of compound 3.64
Figure A 194 $^1$H NMR spectrum of compound 3.66
Figure A 195 $^{13}$C NMR spectrum of compound 3.66
Figure A 196 infrared spectrum of compound 3.66

Infrared spectrum of compound 3.66.
Figure A 197 $^1$H NMR spectrum of compound 3.17
Figure A 198 $^{13}$C NMR spectrum of compound 3.17
Figure A 199 Infrared spectrum of compound 3.71
Figure A 200 $^1$H NMR spectrum of compound 3.70
Figure A 201 $^{13}$C NMR spectrum of compound 3.70
Figure A. 202 infrared spectrum of compound 3.70.