EFFORTS TOWARDS THE TOTAL SYNTHESIS OF AMPHIDINOLIDE B

by

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Studies towards the total synthesis of the cytotoxic marine macrolide Amphidinolide B have been disclosed. Catalytic asymmetric AAC methodology has been applied to efficiently generate the C$_{11}$- and the C$_{18}$- stereocenters in the requisite fragments 114 and 120 through β-lactones 102 and 81 respectively.

An efficient route to install the C$_{14}$-C$_{15}$ trisubstituted alkene was realized through a stannylcupration reaction. The Stille and Suzuki cross-coupling methodologies were investigated for the formation of the C$_{13}$-C$_{15}$ diene of amphidinolide B. Iodide 90 was coupled with boronic
ester 114 via an efficient Suzuki reaction to form a C\textsubscript{7}-C\textsubscript{20} fragment 115. Fragment was further homologated and coupled to sulfone 65 to complete a C\textsubscript{1}-C\textsubscript{20} synthon of amphidinolide B.
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<table>
<thead>
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<th>Description</th>
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<tr>
<td>DCC</td>
<td>1,3-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>(DHQ)$_2$PHAL</td>
<td>dihydroquinine 1,4-phthalazinediyl diether</td>
</tr>
<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>2-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1’-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammoniumfluoride</td>
</tr>
<tr>
<td>TBSOTf</td>
<td>tert-butyldimethylsilyl triflate</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TMSCI</td>
<td>trimethylsilylchloride</td>
</tr>
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</table>
I am thankful to God Almighty for giving me the strength to pursue graduate school to obtain an advanced degree.

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1.0 THE FIRST GENERATION APPROACH

1.1 BACKGROUND

1.1.1 Isolation

The amphidinolides are a series of macrocyclic natural products which have shown to have potential cytotoxic activity. These have been isolated as secondary metabolites from marine dinoflagellates of the genus *Amphidinium*, which are symbionts of the Okinawan flatworm *Amphiscolops* sp. [1] Amphidinolide B (I) is among the most biologically significant and structurally interesting molecules in this class of macrolides.

![Figure 1. Amphidinolide B (I)](image)
Amphidinolide B was first discovered in 1987 by the research group of Kobayashi in the
strain Y-5 from the cultured dinoflagellate of the flatworm *Amphiscolops Breviviridis*. Later,
Shimizu and coworkers isolated three amphidinolide B congeners, namely amphidinolides B1,
B2 (2) and B3 (3) from a free-swimming dinoflagellate *Amphidinium operculatum* ver nov
*Gibbosum*. [1] Amphidinolide B1 was shown to be identical in all respects to amphidinolide B
whereas 2 was shown to be its C$_{18}$- epimer and 3, the C$_{22}$- stereoisomer of 1 (Figure 2). More
recently, a strain Y-71 of the genus *Amphidinium* has been shown to yield a relatively large
amount of amphidinolide B.

![Figure 2. The amphidinolide B congeners](image)

Structural investigations concurrent with the isolation efforts of amphidinolide B were
undertaken by both the groups of Kobayashi and Shimizu which lead to proof of relative
stereochemistry through an X-ray crystal structure. [2] Subsequently, absolute stereochemistry
was also determined via chemical degradation studies leading to the C$_{22}$–C$_{26}$ subunit, and by
comparing its spectral and HPLC data with those of the same compound that was independently
synthesized. [3]
1.1.2 **Structural Features and Biological Activity**

The family of amphidinolides exhibits structural diversity including variations in the ring size of the macrolactone from 19 [amphidinolide E] to 27 [amphidinolide G]. The amphidinolide B group of molecules i.e. 1, 2 and 3 shares its 26-membered lactone feature with the structurally similar amphidinolide H-type macrolides.

Amphidinolide B possesses a very unique arrangement of functionality in its backbone. The top half of the molecule i.e. the C$_{14}$–C$_{26}$ portion bears four hydroxyl groups in addition to a C$_{20}$-ketone carbon and can be termed as the “hydrophilic” domain of the molecule. On the other hand, the C$_1$–C$_{13}$ or the “hydrophobic” portion of the molecule contains relatively fewer oxygen bearing carbons, save for the C$_8$–C$_9$ epoxide and an ester linkage. The molecule features a total of nine stereogenic centers which include a tertiary alcohol center at C$_{16}$, the C$_{21}$–C$_{22}$ syn diol relationship, in addition to two isolated methyl bearing stereocenters. Perhaps the most interesting structural features from a synthetic standpoint are the presence of a potentially acid sensitive exocyclic 1, 3-diene unit in the C$_{13}$–C$_{15}$ portion and the C$_8$–C$_9$ allylic epoxide moiety.

Amphidinolide B has been shown to have a rectangular shape as revealed in the X-ray crystal structure, this shape being dictated by the presence of a 2 Å hydrogen bond between the C$_{21}$-hydroxyl and the epoxide oxygen linking the C$_8$–C$_9$ bond (Figure 1). The solution conformation in chlorinated solvents seems to be close to the crystal conformation as indicated by the matching of spin-spin coupling constants and those calculated from dihedral angles obtained from crystal structure. This may hold some significance to the exceptional levels of cytotoxicity exhibited by this molecule.
Biological assays have placed amphidinolide B as among of the most cytotoxic in the family of amphidinolides. It displays IC\textsubscript{50} values of 0.14 ng/mL against the L1210 murine leukemia cell line, 0.12 \(\mu\)g/mL against the human colon tumor HCT 116 cell line and 4.2 ng/mL against the KB cancer cell line. The importance of the C\textsubscript{21}- hydroxyl group is revealed by the fact that the epimer at that carbon, amphidinolide D, is 100 times less cytotoxic than amphidinolide B (Table 1). The presence of the epoxide was found to be critical owing to the fact that the epoxide-opened derivative of \(1\) obtained by methanolysis was found to have \(1/600^{th}\) of its activity against the L1210 cell line. Amphidinolide H, which has a very similar X-ray crystal structure as \(1\), exhibits similar levels of cytotoxicity thus stressing the link between conformation and bioactivity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC\textsubscript{50} (a/\mu)g mL(^{-1}) (L1210)</th>
<th>(KB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphidinolide B (1)</td>
<td>0.00014</td>
<td>0.0042</td>
</tr>
<tr>
<td>amphidinolide D</td>
<td>0.019</td>
<td>0.08</td>
</tr>
<tr>
<td>amphidinolide H</td>
<td>0.0004</td>
<td>0.00052</td>
</tr>
<tr>
<td>epoxide-opened derivative of 1</td>
<td>0.081</td>
<td>-</td>
</tr>
</tbody>
</table>

\(a\) 50\% inhibition concentration. \(b\) Murine lymphoma cell \(c\) Human epidermoid carcinoma cells

Although assays have been performed to determine its biological activity, there have been no reports about the mechanism of action of amphidinolide B. Sparse amounts available
from natural sources and the lack of a total synthesis of the compound have severely hindered such studies. The synthetic community at large has been interested, for almost ten years, in achieving a total synthesis of this molecule. To date, a complete synthesis has not been reported; however, many partial syntheses have been communicated.

1.1.3 Previous Approaches to the Total Synthesis of Amphidinolide B

Chakraborty reported the first approach towards the total synthesis of amphidinolide B (1) in his stereoselective synthesis of the upper fragment 4 (Figure 3). This was achieved via an aldol bond construction across the C_{18}–C_{19} bond between aldehyde 5 and methyl ketone 6. The C_{16}- stereocenter in aldehyde 5 was formed by Sharpless asymmetric epoxidation of allylic alcohol 7, and Sharpless dihydroxylation of unsaturated ester 8 (syn:anti 3:1) set the syn-diol relationship across the C_{21}–C_{22} bond. [5] Key steps in the synthesis of lower fragment 9 include a Nozaki-Hiyama-Kishi reaction to couple aldehyde 10 and vinyl iodide 11 (syn:anti 3:7); an Evans’s alkylation reaction was used to set the C_{11}- stereocenter in aldehyde fragment 10 and a Wittig reaction subsequently formed the E-enoate ester. [6]
Figure 3. Chakraborty's approach to the synthesis of fragments of amphidinolide B

Nishiyama published his synthesis of the upper fragment 12 that involves the addition of the anion of dithiane 14 to iodide 13, wherein the C\textsubscript{16}- stereocenter in iodide 13 is set by an alkynyl opening of the methylketone derived from ester 15 and aldehyde 16 is homologated to dithiane 14 (Figure 4). [7] A Claisen rearrangement and a Wittig reaction were used in the synthesis of lower fragment 17. The methyl bearing C\textsubscript{11}- stereocenter in fragment 18 was set by Evan’s alkylation protocol and (D)-erythrose-derived diol 19 served as the source for the C\textsubscript{8}- and C\textsubscript{9}- stereocenters. [8]
Figure 4. Nishiyama’s approach to amphidinolide B fragments

Around the same time as Nishiyama’s investigations, independent studies were conducted by Lee who synthesized upper fragment 20 by the addition of a vinyl-lithium species generated from 22 to aldehyde 21 in which the C₁₆⁻ stereocenter is generated via a Sharpless epoxidation and subsequent opening with a methylcuprate (Figure 5). [9] The C₁₈⁻ stereocenter is set by a regioselective opening of epoxide 25 by cuprate derived from vinyl bromide 24. A later publication in 2000 describes the synthesis of lower fragment 26 wherein the C₁₁⁻ methyl bearing stereocenter is set using Myers’ chiral auxiliary. [10] A Sharpless epoxidation reaction on allylic alcohol 27 formed the C₈–C₉ epoxide functionality and subsequent homologation via a Horner-Wadsworth-Emmons reaction completed fragment 26.
Figure 5. Lee's retrosynthesis of fragments of amphidinolide B

In his 1998 publication, Pattenden disclosed his approach of making the C_{14}–C_{26} fragment 28, in which the requisite trisubstituted alkene functionality was installed in aldehyde 29 before its aldol coupling with ketone partner 30 with 3:2 diastereoselectivity (Figure 6). Vinyl iodide 29 was made by silyl-stannation of terminal alkyne 31 followed by introduction of the methyl group via a cuprate reaction. The C_{16}-stereocenter was formed by opening of epoxide derived form alcohol 32 and pentane-2,4-diol served as the precursor for ketone 30. Notable steps in the synthesis of lower fragment 33 include a Julia olefination between epoxy aldehyde 34 and sulfone 35. (R)-Methylglutarate 36, containing the preexisting C_{11}-stereocenter, served as the precursor to aldehyde 34. An intermolecular macrolactonization reaction linked the C_{1}–C_{13} fragment 28 to the C_{14}–C_{26} fragment 33; however, efforts to effect an intramolecular Stille reaction for the construction of the C_{13}–C_{14} bond were unsuccessful.
Figure 6. Pattenden's approach to the synthesis of amphidinolide B

Published in 1999, Kobayashi’s synthetic approach to the synthesis of the C\textsubscript{14}–C\textsubscript{26} fragment 37, shares common features with Chakraborty’s and Pattenden’s in that the aldol disconnection is used for the C\textsubscript{18}–C\textsubscript{19} bond construction (Figure 7). [13] The C\textsubscript{16}- tertiary alcohol stereocenter in aldehyde 38 is set using Sharpless’ asymmetric dihydroxylation, so also is the syn-diol relationship of the C\textsubscript{21}–C\textsubscript{22} bond in ketone 39. Lower fragment 40 is made by the addition of alkyne 42 to aldehyde 41. [14] (2S,4S)-Pentane-2,4-diol served as the common precursor for methyl ketone 39 and aldehyde 41.
Also in 1999, Myles synthesized the aldehyde equivalent of the upper fragment synthon 43 by coupling phosphonate ester 44 made from gereniol epoxide 45 with aldehyde 46 (Figure 8). [15] Lower fragment 47 is the product of a Julia olefination of ester 48 and sulfone 49. [16] Alcohol 50 derived from L-lactate was used as the common precursor for aldehyde 46 and ester 48.
Since 2004, there has been renewed interest in the synthetic community in realizing the goal of a total synthesis of one of the amphidinolide B-type molecules. Carter has recently reported an efficient synthesis of a C$_9$–C$_{29}$ fragment 51 by employing a highly diastereoselective aldol reaction between the lithium enolate of ketone 53 and aldehyde 52 to set the C$_{18}$-stereocenter (Figure 9). [17] The 1, 1- disubstituted alkene in 53 was formed by dehydration of the alcohol formed by the allylation of methyl ketone 54 by allyl silane 55. Methyl ketone 53 was formed from aldehyde 56 by application of Evans’ aldol reaction and the C$_{16}$-tertiary alcohol center is set by Seebach alkylation methodology.

Figure 8. Myles' approach towards the synthesis of amphidinolide B
More recently, Crews has reported the synthesis of three major fragments of amphidinolide B (Figure 10). [18] Fragment 57 was formed from methyl ketone 59 by a Horner-Wadsworth-Emmons reaction in which the C\textsubscript{16}\textsuperscript{-} stereocenter was set via Sharpless epoxidation followed by hydride opening. Synthesis of fragment 58 utilizes a stereoselective methallylsilane addition into aldehyde 60 followed by a Johnson ortho ester Claisen rearrangement. Key steps in making fragment 61 include a diastereoselective methylation of aldehyde 62 by Seebach’s protocol and rhenium oxo catalysis to effect 1, 3-isomerization of the allylic alcohol in the resulting adduct.
1.2  APPLICATION OF THE AAC METHODOLOGY TO THE TOTAL SYNTHESIS OF AMPHIDINOLIDE B

In the Nelson group, catalytic asymmetric methodology has been developed to prepare highly enantioenriched \( \beta \)-lactones from a wide range of aldehydes. [19] The use of substoichiometric amounts (10–15 mol %) of chiral aluminum triamine catalyst 63 in the asymmetric acyl-halide aldehyde cyclocondensation (AAC) provides optically active \( \beta \)-lactones (Eq 1). These easily prepared \( \beta \)-lactones serve as masked aldol adducts and have been employed as useful synthons in natural product syntheses. [20]
A variety of stereochemical relationships can be accessed from these optically active β-lactones. Addition of hard nucleophiles such as alkyl Grignard reagents and metal amides into the carbonyl of the β-lactones affords products with a hydroxyl-bearing stereocenter (Figure 11). Soft nucleophiles such as cuprates, on the other hand, open the β-lactones at the C₄ position in an S_N₂ fashion to yield products with alkyl-bearing stereocenters. Apart from accessing 1, 3-stereochemical relationships in compounds possessing carbonyl functional groups, these reactions can be used to set isolated stereocenters as well.

Amphidinolide B possesses an isolated methyl bearing stereocenter at C₁₁ and a hydroxyl-bearing stereocenter at C₁₈ which could potentially be synthesized via our AAC methodology. We decided to undertake the synthesis of this natural product to investigate the
challenges associated with it as well as to explore the applicability of our methodology in the context of a complex molecule synthesis.

1.3 RETROSYNTHETIC ANALYSIS

Our retrosynthetic analysis of amphidinolide B is based on the novel approach of creating strategic stereocenters using our AAC methodology. Recognizing the lability of the allyl-epoxide moiety in amphidinolide B, we elected to incorporate this functional group late in the synthesis. The major disconnections in the molecule are across the C₁–O bond via macrolactonization and the C₆–C₇ bond by Julia olefination reactions respectively, to arrive at precursors, aldehyde 64 and the corresponding sulfone fragment 65 (Figure 12). We envisioned that the diene moiety in fragment 64 could be installed via a Stille or Suzuki reaction between a vinyl metal (stannane or boronate) fragment 66- the “upper fragment” synthon and triflate 67. Further disconnection at the C₂₁–C₂₂ bond in fragment 66 showed that it could be made via a Horner–Wadsworth–Emmons olefination reaction between enantioenriched aldehyde 69 and phosphonate ester 68.
1.4 SYNTHESIS OF THE C7–C13 FRAGMENT

1.4.1 Retrosynthetic analysis

We envisioned that the C_{11}-methyl bearing stereocenter in the “lower left” triflate fragment 67 could be made by application of our AAC methodology. We aimed to prepare triflate 67 from carboxylic acid 71 via intermediate diol 70. Carboxylic acid 71 can be made from β-lactone 72 via a cuprate ring opening reaction (Figure 13). Lactone 72 would be the product of cyclocondensation on aldehyde 73 which in turn is produced from enantiomerically...
enriched β-lactone 74. Although the stereochemical information in aldehyde 73 would be ultimately destroyed in the formation of triflate 67, it is required in order to obtain good diastereoselectivity in the subsequent cyclocondensation reaction. Previous studies have shown that an optically active β-silyloxy aldehyde gives rise to double diastereoselection in the AAC reaction [21] and we decided to prepare the (S)-enantiomer of aldehyde 73 since it would be matched with chiral (S,S)-catalyst 63.

Figure 13: Retrosynthetic analysis of the C7-C13 fragment

### 1.4.2 Synthesis of Triflate 67

In order to execute the above mentioned scheme, β-lactone 74 was prepared by an asymmetric AAC reaction with acetaldehyde in 89% yield and greater than 98% enantiomeric excess (Scheme 1). Ring-opening of 74 with N,O-dimethylhydroxylamine and dimethylaluminum chloride followed by protection of the resulting alcohol with a tert-butyldimethylsilyl group gave Weinreb amide 75 in an overall 60% yield. Amide 75 was efficiently reduced by diisobutylaluminum hydride to give aldehyde 76 in 91% yield. Subsequent
cyclocondensation reaction of aldehyde 76 with acetyl bromide using optically active catalyst 63 afforded β-lactone 72 in a yield of 82% and excellent syn:anti diastereoselection of 35:1 as determined by 500 MHz $^1$H NMR analysis. Cuprate mediated ring-opening of β-lactone 72 proceeded in 71% yield to give carboxylic acid 71 which then underwent a one-step reduction-oxidation sequence, developed by Brown, [22] to afford aldehyde 77 in 85% yield. Horner-Wadsworth-Emmons olefination [23] of aldehyde 77 followed by diisobutylaluminum hydride mediated over-reduction and deprotection of the tert-butylsilyl group produced diol 70 in 62% overall yield over two steps. Selective protection of the primary alcohol in diol 70 with a triisopropylsilyl group proceeded smoothly followed by oxidation of the secondary alcohol by PCC to afford ketone 78 in 80% yield over two steps. Ketone 78 was then converted into triflate 67 with N-phenyltriflimide in 76% yield, [24] thus completing the synthesis of the “lower left” fragment of amphidinolide B.
Scheme 1. Synthesis of the C_{7}–C_{13} subunit

**Reagents and Conditions**: (a) MeO(Me)NH•HCl, Me_{2}AlCl. (b) TBSCl, iPr_{2}NEt, DMAP. (c) DIBAL-H. (d) AcBr, 10mol% 63, iPr_{2}NEt, –50 °C. (e) MeMgBr, CuBr•Me_{2}S. (f) BH_{3}; then PCC. (g) i. NaH, (PrO)_{2}P(O)CH_{2}CO_{2}Et; ii. DIBAL-H. (h) i. TIPSCl, im, Et_{3}N; ii. PCC. (i) KHMDS, PhNTf_{2}, –78 °C, THF.

1.5 SYNTHESIS OF THE C_{1}–C_{6} SULFONE FRAGMENT

The requisite sulfone fragment 65 was synthesized from \( \gamma \)-butyrolactone in a short sequence commencing with reduction to the lactol and in situ Wittig olefination with phosphonium salt 79 to obtain alcohol 80 in 70% yield (Scheme 2). [25,26] Subsequently, a Mitsunobu reaction was used to introduce the phenyltetrazole thiol group (DIAD, PPh_{3}, DMF) which was then oxidized to the sulfone functionality with ammonium molybdate and 30% hydrogen peroxide. The tert-butyl carboxylate was then exchanged for the more labile
trimethylsilyl ethyl protecting group by removal of the tert-butyl group by TFA and esterification with trimethylsilyl ethanol to make sulfone 65 (64% for 4 steps).

Scheme 2. Synthesis of C_1–C_6 Subunit

Scheme 2. Synthesis of C_1–C_6 Subunit

\[ \text{Conditions: (a) } \text{Bu}_2\text{AlH, CH}_2\text{Cl}_2; \text{ ii. } \text{79, THF. (b) phenyltetrazolethiol, DIAD, PPh}_3, \text{DMF; ii. } \text{H}_2\text{O}_2; (\text{NH}_4)_6\text{Mo}_7\text{O}_{24}.7\text{H}_2\text{O, 30% } \text{H}_2\text{O}_2; \text{ iii. TFA, CH}_2\text{Cl}_2/\text{anisole; iv. } 2\text{-trimethylsilyl ethanol, DCC, DMAP, CH}_2\text{Cl}_2. \]

1.6 SUMMARY

Towards the synthesis of amphidinolide B, an asymmetric synthesis of triflate fragment 67 was achieved by employing the AAC methodology. Sulfone fragment 65 was also made in a short sequence starting from \( \gamma \)-butyrolactone. An efficient synthesis of the C_{14}–C_{26} fragment and formation of the C_{13}–C_{15} diene unit were identified as the next important goals in the project.
EXPERIMENTAL SECTION

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $\alpha$ (c g/100 mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. $^1$H NMR spectra were recorded on Bruker DPX 301/302 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard (CHCl$_3$: $\delta$ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. $^{13}$C NMR spectra were recorded on Bruker DPX 301/302 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with solvent as internal standard (deuterochloroform $\delta$ 77.0). Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer. Analytical thin layer chromatography was performed as previously described on 230-240 mesh silica gel. [27] Analytical gas liquid chromatography was performed on a Varian 3900 gas chromatograph with a flame ionization detector and split mode capillary injection system, using Chiraldex™–TA column (20 m x 0.25 m). Analytical high performance on a Hewlett Packard 1100 liquid liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm), using Diacel Chiralcel™ OD-H column (250 x 4.6 mm). HPLC grade isopropanol and hexanes were used as eluting solvents.

All experiments were carried out under a nitrogen atmosphere in oven or flame-dried glassware using standard inert atmosphere techniques for the manipulation of solvents and
reagents. Anhydrous solvents were obtained by passing through successive alumina columns on a solvent purification system.

**((S)-4-Methyl-oxetan-2-one (74) [28]):** To a solution of 3.684 g of triamine ligand precursor to catalyst 63 (6.81 mmol) in 100 mL of CH$_2$Cl$_2$ was added 3.74 mL of trimethylaluminum (7.49 mmol) (2 M solution in hexanes) and was stirred for 2 h. The solution was cannulated into a solution of 36.0 g of tetraethylammonium bromide in 100 mL of CH$_2$Cl$_2$, cooled to $-78^\circ$C, and 20.2 mL of diisopropylethylamine (115.6 mmol) was added to it followed by the slow addition of 9.5 mL of acetyl bromide (129.2 mmol). To the resulting pale yellow solution was added 4.2 mL of acetaldehyde (68.0 mmol). The reaction mixture was stirred overnight at $-78^\circ$C, poured into 500 mL of cold hexanes and filtered through a short plug of silica gel with ether. The filtrate was concentrated to afford 5.2 g of lactone 61 (89%, crude) as a pale yellow oil. Separation of enantiomers by chiral GC [chiraldex G-TA column, flow rate 0.6 mL/min, method: 80 $^\circ$C for 5.0 min, ramp @ 5 $^\circ$C /min to 100 $^\circ$C for 10 min, ramp @ 5 $^\circ$C /min to 160 $^\circ$C for 30 min. $T_r$ 10.94 min ($R$) and 11.84 min ($S$) determined enantiomeric excess to be 98.4%; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.73–4.67 (m, 1H), 3.58 (dd, $J$ = 5.7, 16.2 Hz, 1H), 3.06 (dd, $J$ = 4.2, 16.3 Hz, 1H), 1.57 (d, $J$ = 6.1 Hz, 3H).

**(S)-3-Hydroxy-N-methoxy-N-methyl-butyramide (74a) [28]:** To a 0 $^\circ$C solution of 11.8 g of N$_2$O-dimethylhydroxylamine hydrochloride (12.0 mmol) in 280 mL of CH$_2$Cl$_2$, was added 120 mL of dimethylaluminum chloride (1 M solution in hexanes) (0.12 mmol) and the resulting solution was allowed to stir at ambient temperature for 2 h. To the clear solution was added, a solution of
lactone 74 in 20 mL of CH$_2$Cl$_2$, slowly via syringe. The resulting pale yellow solution was stirred overnight and quenched with 360 mL of pH 8 phosphate buffer (3 mL/mmol of Me$_2$AlCl). The organic layer was separated, filtered through celite, and the aqueous layer extracted with CH$_2$Cl$_2$ (5 x 200 mL). The organics were combined, dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by flash chromatography (10–40% EtOAc/Hex) to afford 6.26 g of the title compound (71%) as a pale yellow oil: $[\alpha]_D = +48.0$ (c 2.50, CHCl$_3$) $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.17 (ddq, $J = 2.6, 6.4, 9.0$ Hz, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.65 (d, $J = 16.4$ Hz, 1H), 2.43 (dd, $J = 9.5, 16.8$ Hz, 1H), 1.22 (d, $J = 6.3$ Hz, 3H).

(S)-(tert-Butylidimethylsilanyloxy)-N-methoxy-N-methylbutyramide (75): To a 0 °C solution of 3 g of Weinreb amide 74a (20.5 mmol) in CH$_2$Cl$_2$ (41 mL), was added 3.58 mL (20.5 mmol) of diisopropylethylamine, followed by 0.50g (4.1 mmol) of dimethylaminopyridine (DMAP) and 5.26 g (35.0 mmol) of tert-butylidimethylchlorosilane. The reaction mixture was allowed to warm to ambient temperature and stirred for 24 h, and quenched with 20 mL of a saturated solution of NaHCO$_3$. It was extracted with CH$_2$Cl$_2$ (5 x 30 mL) and the combined organic layers washed with brine (25 mL) and dried over Na$_2$SO$_4$. After concentrating the solution the crude product was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to give 4.55 g (85%) of the title compound as a colorless oil: $[\alpha]_D = +22$ (c 1.2, CHCl$_3$); IR (thin film): 2957, 2930, 2896, 2856, 1655, 1472, 1386, 1255, 1135, 1004, 836 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.32 (app. sextet, $J = 6.0$ Hz, 1H), 2.73 (dd, $J = 14.0, 7.2$ Hz, 1H), 3.66 (s, 3H), 3.13 (s, 3H), 2.30 (dd, $J = 14.5, 5.4$ Hz, 1H), 1.17 (d, $J = 6.1$ Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (75
MHz, CDCl$_3$): $\delta$ 172.2, 66.0, 61.2, 41.6, 31.7, 25.7, 24.0, 18.0, –4.8, –5.0; EI-MS $e/\nu$ 246 (M$^+–$Me), 204 (M$^+–$tBu), 159, 129, 115; HRMS calcd for C$_{11}$H$_{24}$NO$_3$Si: 246.1525, found 246.1515.

(3S)-3-tert-Butyldimethylsilanyloxy)butyraldehyde (76): To a –78 °C solution of 0.500 g of Weinreb amide 75 (1.91 mmol) in 10 mL of CH$_2$Cl$_2$, was added 2.1 mL (2.1 mmol) of diisobutylaluminumchloride (1.0 M solution in hexanes) slowly. The reaction was stirred for 45 min at –78 °C and quenched with 0.1 M HCl (5 mL). The layers were separated, the organic layer filtered through celite and the aqueous layer washed with CH$_2$Cl$_2$ (5 x 20 mL). The combined organics were dried over Na$_2$SO$_4$, concentrated and purified by flash chromatography on silica gel (2% EtOAc in hexanes) to afford 0.352 g (91%) of aldehyde 76 as a colorless oil: $[\alpha]_D^\circ$ = +16.1 (c 1.20, CHCl$_3$); IR (thin film): 3002, 2957, 2930, 1724, 1265, 837, 738 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.78 (t, $J = 2.1$ Hz, 1H), 4.34 (app. sextet, $J = 6.2$ Hz, 1H), 2.73 (ddd, $J = 15.7$, 6.9, 2.7 Hz, 1H), 2.30 (ddd, $J = 15.6$, 5.0, 1.8 Hz, 1H), 1.22 (d, $J = 6.1$ Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 202.0, 64.5, 53.0, 25.7, 24.1, 18.0, –4.4, –4.9; EI-MS $e/\nu$ 145 (M$^+–$tBu), 101 (M$^+–$tBu–CH$_3$CHO), 75; HRMS calcd for C$_6$H$_{12}$O$_2$Si: 145.0685, found 145.0681.

(4S,2'S)-4-[2-(tert-Butyldimethylsilanyloxy)propyl]-oxetan-2-one (72): To a solution of 0.164 g of triamine ligand precursor to catalyst 63 (0.30 mmol) in 5.8 mL of CH$_2$Cl$_2$ was added 0.166 mL of trimethylaluminum (0.33 mmol) (2 M solution in hexanes) and was stirred for 2 h. The solution was cooled to –50 °C, and 0.90 mL of diisopropylethylamine (5.2 mmol) was added to it followed by the slow addition of 0.42 mL of
acetylbromide (5.7 mmol). To the resulting pale yellow solution was added 0.613 g of aldehyde 76 (3.03 mmol) in 1.8 mL of CH$_2$Cl$_2$. The reaction mixture was stirred overnight at –50 °C, poured into cold hexanes and filtered through a short plug of silica gel with 30% EtOAc in hexanes. The filtrate was concentrated and the crude product purified by medium pressure chromatography (0–10% EtOAc in hexanes) to afford 0.607 g of lactone 72 (82%) as a colorless oil: [α]$_D$ = +8.3 (c 0.5, CHCl$_3$); IR (thin film): 2956, 2930, 2887, 2857, 1831, 1124, 836 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 4.71–4.63 (m, 1H), 3.98 (app. sextet, J = 6.1 Hz, 1H), 3.53 (dd, J = 16.3, 5.7 Hz, 1H), 3.14 (dd, J = 16.3, 4.3 Hz, 1H), 2.11 (dd, J = 13.7, 6.4, 6.4 Hz, 1H), 1.80 (ddd, J = 13.7, 7.1, 5.1 Hz, 1H), 1.20 (d, J = 6.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 168.2, 68.7, 65.3, 43.6, 43.3, 25.7, 23.4, 17.9, –4.0, –4.5; EI-MS e/v 229 (M$^+$–Me), 187 (M$^+$–i-Bu), 145, 115, 101, 88; HRMS calcd for C$_8$H$_{15}$O$_3$Si: 187.0790, found 187.0800.

(3R,5S)-5-(tert-Butyldimethylsilanyloxy)-3-methylhexanoic acid (71): To a –50 °C solution of 0.44 g of CuBr (3.1 mmol) in 20 mL of THF and 5 mL of dimethylsulfide, was added 2.1 mL of methylmagnesiumbromide (6.2 mmol) (3 M solution in ether) slowly to give a yellow suspension. The suspension was allowed to warm to –30 °C and stirred at that temperature for 30 min. The reaction mixture was cooled back to –50 °C, and 0.500 g of lactone 72 (2.05 mmol) in 5 mL of THF was added to it, and then it was maintained at –50 °C for 45 min. 0.39 mL (3.07 mmol) of trimethylsilylchloride was added to it and the reaction mixture was allowed to warm to ambient temperature. It was quenched with 20 mL of 0.1 M HCl and solid NH$_4$Cl. After separation of the layers, the organic layer was washed with 10 mL of saturated NH$_4$Cl solution and the aqueous layer extracted with ether (5 x 30 mL).
The combined organics were dried over Na$_2$SO$_4$, concentrated and the crude product purified by flash chromatography (5% EtOAc in hexanes) to yield 0.378 g of carboxylic acid 71 as a pale yellow, viscous oil: [α]$_D$ = +23.4 (c 0.58, CHCl$_3$); IR (thin film): 3583, 2958, 2929, 2857, 1709, 1462, 1256, 1065, 835 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 3.94–3.84 (m, 1H), 2.41–2.32 (m, 1H), 2.22–2.14 (m, 2H), 1.52 (ddd, $J =$ 13.5, 8.4, 4.5 Hz, 1H), 1.22 (ddd, $J =$ 12.7, 8.3, 4.0 Hz, 1H), 1.14 (d, $J =$ 6.0 Hz, 3H), 0.98 (d, $J =$ 6.3 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 179.4, 66.3, 46.6, 42.3, 26.6, 25.8, 24.3, 19.6, 18.0, –4.1, –4.8; EI-MS e/v 245 (M$^+$–Me), 227 (M$^+$–Me–H$_2$O), 203 (M$^+$–tBu), 185 (M$^+$–tBu–H$_2$O), 159, 143, 129, 111; HRMS calcd for C$_{12}$H$_{25}$O$_3$Si: 245.1573, found 245.1565.

(3R,5S)-5-(tert-Butyldimethylsilanyloxy)-3-methylhexanal (77): To a solution of 0.868 g of carboxylic acid 77 (3.38 mmol) in 16 mL of THF was added 2.5 mL of a 2.0 M solution of BH$_3$.Me$_2$S (5.0 mmol) in 16 mL of THF. The solution was refluxed for 2 h, cooled and the solvent evaporated in vacuo. The residue was dissolved in 16 mL of CH$_2$Cl$_2$, and refluxed with 1.79 g of pyridinium chlorochromate (8.34 mmol) for 3 h. The reaction mixture was cooled, diluted with CH$_2$Cl$_2$, and filtered through a short plug of silica. The filtrate was concentrated, and the crude product purified by flash chromatography on silica gel (2% EtOAc in hexanes) to afford 0.684 g of aldehyde 77 as a colorless oil: [α]$_D$ = +41.6 (c 0.85, CHCl$_3$); IR (thin film): 2957, 2929, 2857, 2710, 1728, 1472, 1255, 1134, 1070, 836 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 9.73 (t, $J =$ 2.4 Hz, 1H), 3.93–3.83 (m, 1H), 2.38 (ddd, $J =$ 14.8, 8.7, 2.5 Hz, 1H), 2.33–2.19 (m, 2H), 1.48 (ddd, $J =$ 14.8, 8.8, 4.1 Hz, 1H), 1.25–1.17 (m, 1H), 1.13 (d, $J =$ 6.0, 3H), 0.96 (d, $J =$ 6.2, 3H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (75 MHz,
CDCl$_3$: $\delta$ 202.9, 66.1, 51.6, 46.8, 25.8, 24.8, 24.4, 19.7, 18.0, –4.1, –4.8; EI-MS $e/\nu$ 243 ($M^+–H$), 187 ($M^+–$t-Bu), 159, 145, 115; HRMS calcd for C$_{13}$H$_{27}$O$_2$Si: 243.1780, found 243.1783.

(5R,7S)-7-(tert-Butyldimethylsilanyloxy)-5-methyl-oct-2-enoic acid ethyl ester (77a): To a 0 °C suspension of 0.15g of NaH (3.95 mmol) in THF (14 mL), was added 0.86 mL of diisopropyl(ethoxycarbonylmethyl) phosphonate (3.59 mmol). This was stirred at 0 °C for 20 min and 0.624 g of aldehyde 77 dissolved in THF (4 mL) was added to it. The reaction mixture was allowed to warm to ambient temperature, and then, 5 mL H$_2$O was added, the layers separated and the aqueous layer washed with EtOAc (3 x 10 mL). The organics were combined and concentrated and the crude material was purified by flash chromatography (2% EtOAc in hexanes) to yield 0.645 g (80%) of ester 77a as a yellow oil: $[\alpha]_D = +12.9$ (c 0.50, CHCl$_3$); IR (thin film): 3020, 2958, 2929, 2857, 1712, 1653, 1463, 1256, 1215, 836, 757 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.93 (ddd, $J = 15.3, 7.4, 7.4$ Hz, 1H), 5.82 (dd, $J = 15.5, 1.4, 1.4$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.90–3.86 (m, 1H), 2.19 (dddd, $J = 13.0, 7.3, 7.3, 1.3$ Hz, 1H), 2.03 (dddd, $J = 14.0, 7.4, 7.4, 1.3$ Hz, 1H), 1.80–1.90 (m, 1H), 1.50 (dd, $J = 13.4, 8.8, 4.4$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 6.0$ Hz, 3H), 1.17–1.08 (m, 1H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.7, 148.0, 122.5, 66.3, 60.1, 46.8, 40.3, 28.8, 26.0, 24.5, 19.5, 18.1, 14.3, –3.9, –4.7; EI-MS $e/\nu$ 257 ($M^+–$t-Bu), 228 ($M^+–$Bu–C$_2$H$_4$), 211, 159, 149, 115, 109, 95; HRMS calcd for C$_{13}$H$_{25}$O$_3$Si: 257.1572, found 257.1568.
**(5R,7S)-5-Methyl-oct-2-ene-1, 7-diol (70):** To a solution of 0.402 g of ester 77a (1.3 mmol) in CH₂Cl₂ (10 mL) at ambient temperature, was added 6.4 mL of diisobutylaluminum chloride (6.4 mmol) (1 M in hexanes), and stirred for 2 h. The reaction mixture was quenched with 0.1 M HCl, extracted with CH₂Cl₂ (3 x 20 mL) and the organic layer filtered through celite. After evaporation of solvents in vacuo, the crude product was purified by chromatography on silica (20–40% EtOAc in hexanes) to yield 0.200 g (77%) of diol 70 as a colorless oil: [α]₁ₒ = +22.5 (c 0.45, CHCl₃); IR (thin film): 3334, 963, 2920, 1459, 1376, 1127, 1085, 1003, 970 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.66–5.51 (m, 2H), 4.00 (br s, 2H), 3.84–3.77 (m, 1H), 3.22 (br s, 1H), 2.74 (br s, 1H), 1.92 (dd, J = 6.4, 6.4 Hz, 2H), 1.72–1.61 (m, 1H), 1.48 (ddd, J = 13.6, 8.9, 4.4 Hz, 1H), 1.12 (d, J = 6.1 Hz, 3H), 1.05 (ddd, J = 13.6, 9.3, 4.0 Hz, 1H), 0.86 (d, J = 6.6, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 131.0, 130.8, 65.5, 63.1, 45.8, 40.1, 29.5, 24.2, 19.5; EI-MS e/ν 140 (M⁺–H₂O), 122 (M⁺–2H₂O), 107, 93; HRMS calcd for C₉H₁₆O: 140.1201, found 140.1198.

**(4R,2S)-4-Methyl-8-isopropylsilyloxy-oct-6-en-2-ol (70a):** To a 0 °C solution of 0.230 g of diol 70 (1.46 mmol) in CH₂Cl₂ (10 mL), was added 0.2 mL of triethylamine (1.46 mmol), followed by 0.1 g of imidazole (1.46 mmol) and 0.34 mL (1.46 mmol) of triisopropylchlorosilane. The reaction mixture was stirred for 2 h, and quenched with 5 mL of a saturated solution of NaHCO₃. It was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers washed with brine (5 mL) and dried over MgSO₄. After concentrating the solution, the crude product was purified by flash chromatography on silica gel (5–10% EtOAc in hexanes) to give 0.390 g (85%) of alcohol 70a as a colorless oil; [α]₁ₒ = +8.2 (c 1.0, CHCl₃); IR (thin film): 3356, 2960, 2943, 1463, 1377, 1104,
1055, 882, 680 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.71–5.51 (m, 2H), 4.21 (dd, \(J = 4.7, 1.1\) Hz, 2H), 3.95–3.85 (m, 1H), 2.07 (ddd, \(J = 13.6, 6.8, 6.8\) Hz, 1H), 1.93 (ddd, \(J = 14.0, 7.0, 7.0\) Hz, 1H), 1.77–1.68 (m, 1H), 1.50 (ddd, \(J = 13.8, 9.4, 4.6\) Hz, 1H), 1.27–1.15 (m, 1H), 1.19 (d, \(J = 6.2\) Hz, 3H), 1.10–1.05 (m, 21H), 0.91 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 131.0, 129.8, 65.8, 64.0, 46.3, 40.3, 29.6, 24.4, 19.3, 18.0 12.0; EI-MS e/\(\nu\) 271 (M\(^{+}\)–iPr), 187, 141, 131, 123; HRMS calcd for C\(_{15}\)H\(_{31}\)O\(_2\)Si: 271.2093, found 271.2093.

\((4R)-4\)-Methyl-8-triisopropylsilyloxy-oct-6-en-2-one (78): To a solution of 0.380 g (1.23 mmol) of alcohol 70a in CH\(_2Cl_2\) (10 mL), was added 0.313 g of pyridiniumchlorochromate (1.45 mmol) at ambient temperature, and the reaction refluxed for 3 h. The reaction mixture was diluted with CH\(_2Cl_2\) and filtered through a short plug of silica gel. The filtrate was concentrated and purified by flash chromatography (5% EtOAc in hexanes) to afford 0.355 g (94%) of ketone 78 as a colorless oil \([\alpha]_D = +6.2\) (c 1.2, CHCl\(_3\)): IR (thin film): 2943, 2891, 2866, 1717, 1463, 1366, 1128, 1102, 972, 882 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.65–5.48 (m, 2H), 4.17 (d, \(J = 4.0\) Hz, 2H), 2.45 (dd, \(J = 15.7, 4.8\) Hz, 1H), 2.20–1.90 (m, 4H), 2.08 (s, 3H), 1.06–1.00 (m, 21H), 0.87 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 208.6, 131.4, 128.0, 63.6, 50.1, 39.3, 30.3, 29.1, 19.6, 17.9, 11.9; EI-MS e/\(\nu\) 297 (M\(^{+}\)–CH\(_3\)), 269 (M\(^{+}\)–iPr), 239 (M\(^{+}\)–iPr –2CH\(_3\)), 213, 171, 131; HRMS calcd for C\(_{15}\)H\(_{29}\)O\(_2\)Si: 269.1936, found 269.1934.
(3R)-Trifluoromethanesulfonic acid 3-methyl-1-methylene-7-triisopropylsilanyloxyhept-5-enyl ester (67): To a –78 °C solution of 1.43 mL of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.71 mmol) in THF (8 mL) was added a solution of 0.149 g of ketone 78 in THF (2 mL), dropwise via syringe. The resulting solution was stirred at –78 °C for 15 min, and then a solution of 0.188 g (0.53 mmol) of N-phenyltriflimide in THF (2 mL) was cannulated into the reaction mixture which was then allowed to warm to 0 °C. 5 mL of a saturated NaHCO₃ solution was added to it, the layers were separated, and the aqueous layer washed with ether (2 x 5 mL). The combined organics were dried over Na₂SO₄, concentrated and purified by column chromatography over silica gel (0.5% CH₂Cl₂ in hexanes, 2% Et₃N) to afford 0.161 g (76%) of the title compound as a colorless oil; [α]D = −3.5 (c 1.0, CHCl₃); IR (thin film): 2943, 2866, 1463, 1419, 1211, 1141, 937, 883 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.70–5.54 (m, 2H), 5.14 (d, J = 3.4 Hz, 1H), 4.92 (d, J = 3.4 Hz, 1H), 4.23–4.20 (m, 2H), 5.14 (d, J = 6.6 Hz, 1H), 2.16–1.83 (m, 4H), 2.14–1.04 (m, 21H), 0.96 (d, J = 6.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 155.8, 132.0, 127.2, 118.6 (JCF = 318 Hz), 105.4, 63.7, 40.7, 38.7, 30.3, 18.8, 18.0, 12.0; EI-MS e/ν 401 (M⁺–Pr), 251 (M⁺–Pr–CF₃SO₃H), 209, 157, 131, 121; HRMS calcd for C₁₆H₂₈O₄F₃: 401.1429, found 401.1442.

(E)-tert-Butyl-6-(1-phenyl-1H-tetrazol-5-ylthio)-2-methylhex-2-enoate (80a): To a 0 °C solution of 0.500 g of alcohol 80 (2.5 mmol) and 0.890 g of N-phenyltetrazolethiol (5.9 mmol, 2.0 equiv) in 12.5 mL of DMF added 1.314 g of
triphenylphosphine (5.0 mmol, 2.0 equiv) and 1mL of DIAD (5.0 mmol, 2.0 equiv). The resulting yellow solution was warmed to ambient temperature and stirred overnight. The reaction mixture was quenched with brine (10 mL) and diluted with ether. After separation of layers, the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organics were dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford 0.880 g of the title compound (98%) as a colorless oil: IR (thin film): 2977, 2931, 1703, 1649, 1500, 1388, 1254, 1157, 761 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.58–7.55 (m, 5H), 6.17 (br t, J = 6.2 Hz, 1H), 3.41 (t, J = 7.4 Hz, 2H), 2.32 (dt, J = 7.4, 7.4 Hz, 2H), 2.00 (tt, J = 7.4, 7.4 Hz, 2H), 1.78 (s, 3H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 167.2, 154.1, 138.6, 133.6, 130.5, 130.1, 129.8, 123.8, 80.2, 32.7, 28.0, 27.4, 21.3, 12.5; HRMS calcd for C₁₈H₂₄N₄O₂S: 380.1619, found 380.1603.

(E)-tert-Butyl-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl)-2-methylhex-2-enoate (80b): To a solution of 0.660 g of ammonium molybdate (5.32 mmol, 20 mol %) in 2 mL of EtOH added 3.0 mL of a 30% solution of hydrogen peroxide to produce a yellow solution. This was added to a solution of 0.960 g of sulfide 80a (2.66 mmol) in 10 mL of EtOH. The reaction mixture was stirred overnight and then was diluted with 50 mL of ether and 20 mL of brine was added to it. After separation of the layers, the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organics were dried over MgSO₄ and then the solvents were evaporated in vacuo to yield 0.900 g of the title compound (86%) as a white solid: m.p: 94–96 °C; IR (thin film): 3068, 2978, 2933, 1704, 1650, 1498, 1366, 1228, 1155, 1080, 763 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.66–7.61 (m, 2H), 7.60–7.56 (m, 3H) 6.56 (br t, J = 7.4
Hz, 1H), 3.72 (br t, J = 7.7 Hz, 2H), 2.35 (dt, J = 7.3, 7.3 Hz, 2H), 2.07 (tt, J = 7.4, 7.4 Hz, 2H), 1.77 (s, 3H), 1.46 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 166.9, 153.4, 137.1, 133.0, 131.5, 131.4, 129.7, 125.1, 80.3, 55.3, 28.0, 26.8, 21.3, 12.5; HRMS calcd for C\(_{18}\)H\(_{24}\)N\(_4\)O\(_4\)S: 392.1518, found 392.1515.

\(\text{(E)-6-(1-Phenyl-1H-tetrazol-5-ylsulfonyl)-2-methylhex-2-enoic acid (80c):}\) To a 0 °C solution of 0.620 g ester 80b (1.58 mmol) in 12 mL of a 5:1 mixture of CH\(_2\)Cl\(_2\) and anisole, added 2.7 mL of TFA (23.0 mmol, 15.0 equiv) dropwise via a syringe. After stirring at 0 °C for 1 h the solvents were evaporated \textit{in vacuo} to give a light brown solid which was recrystallized from CH\(_2\)Cl\(_2\) in hexanes to yield 0.480 g of carboxylic acid 80c (90%) as a white solid: m.p: 118–119 °C; IR (thin film): 2931, 2665, 1682, 1643, 1498, 1318, 1300, 1151, 764 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 7.72–7.69 (m, 2H), 7.66–7.61 (m, 3H), 6.83 (tq, J = 7.3, 1.3 Hz, 1H), 3.77 (br t, J = 7.7 Hz, 2H), 2.47 (dt, J = 7.3, 7.3 Hz, 2H), 2.19 (tt, J = 7.6, 7.6 Hz, 2H), 1.88 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): δ 172.5, 153.4, 141.0, 132.9, 131.5, 129.7, 129.4, 125.0, 55.3, 27.1, 21.2, 12.2; HRMS calcd for C\(_{14}\)H\(_{16}\)N\(_4\)O\(_4\)S: 336.0892, found 336.0871.

\(\text{(E)-2-(trimethylsilyl) ethyl 6-(1-phenyl-1H-tetrazol-5-ylsulfonyl)-2-methylhex-2-enoate (65):}\) To a solution of 0.200 g of carboxylic acid 80c (0.59 mmol) and 0.26 mL of trimethylsilylethanol (1.78 mmol, 3.0 equiv) in 8 mL of THF, added 0.25 g of DCC (1.2 mmol, 2.0 equiv) and 0.073 g of DMAP (0.59 mmol, 1.0 equiv). The resulting solution was stirred at ambient temperature for 3 d and worked up by
the addition of 5 mL of brine and 25 mL of ether. After separation of layers the aqueous layer was extracted with ether (3 x 10 mL). The combined organics were dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash chromatography (10–30% EtOAc in hexanes) to afford 0.220 g of the title compound as a colorless oil: IR (thin film): 2953, 1706, 1650, 1498, 1340, 1251, 1153, 859 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.68–7.54 (m, 5H), 6.65 (br t, J = 7.3 Hz, 1H), 4.22 (br t, J = 8.3 Hz, 2H), 3.73 (br t, J = 9.6 Hz, 2H), 2.39 (dt, J = 7.3, 7.3 Hz, 2H), 2.11 (tt, J = 7.5, 7.5 Hz, 2H), 1.83 (s, 3H), 1.00 (br t, J = 8.8 Hz, 2H), 0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 167.6, 153.2, 137.9, 132.8, 131.4, 130.2, 129.6, 124.9, 62.8, 55.2, 26.7, 21.1, 17.2, 12.5, –1.5; HRMS calcd for (M⁺+Na) C₁₀H₂₈N₄O₄SiSNa: 459.1498, found 459.1497.
2.0 THE DIENE PROBLEM: SOLUTION IN A MODEL SYSTEM

2.1 INTRODUCTION

We recognized that synthesis of the C_{13}–C_{15} portion of amphidinolide B (1) containing a 1, 3-exocyclic diene unit was potentially a challenging task, considering that there was no efficient way of making it in the literature. In Pattenden’s attempt at making 1, he disclosed that a final macrolactonization step involving an intramolecular copper-mediated Stille reaction was unsuccessful. [12] The presence of a trisubstituted alkene at C_{14}–C_{15} makes a sterically congested reaction partner in any coupling reaction to form the C_{13}–C_{14} bond. Since this was a relatively unexplored area in the synthesis of 1, we decided to take up the task of forming the C_{13}–C_{15} diene in an efficacious manner.

2.2 INSTALLATION OF THE C_{16} AND C_{18} STEREOCENTERS

2.2.1 Retrosynthetic analysis of fragment 68

We envisioned the formation of the C_{18}- stereocenter strategically via an asymmetric AAC reaction. Thus, β-ketophosphonate 68 would be formed via a phosphonate anion opening of β-lactone 81 (Figure 14). An AAC reaction would be used to form the enantioenriched β-
lactone 81 from aldehyde 82. The C_{16}- tertiary alcohol would be formed via a Sharpless asymmetric epoxidation of allylic alcohol 83.

![Figure 14: Retrosynthetic analysis of fragment 68](image)

The synthesis of aldehyde 82 closely resembled a strategy that Pattenden used for a similar substrate in his partial synthesis [11] (Scheme 3). It commenced with the Sharpless epoxidation [29] of known allylic alcohol 83 [30] to afford epoxide 84 in 83% yield and 88% ee. Hydride-mediated opening of epoxide 84 with lithium aluminum hydride gave diol 85 in 56% yield. A three step sequence of protection of the diol, selective removal of the primary silyl group followed by Dess-Martin oxidation [31] afforded aldehyde 82 in an overall yield of 64%. Aldehyde 82 was then subjected to an AAC reaction with acetyl bromide in the presence of Al(III) triamine catalyst 63 to give 1, 3-syn β-lactone 81 in 88% yield and 95% de, thus correctly setting the C_{18} stereocenter. [26]
Scheme 3: Installation of the C₁₆⁻ and C₁₈⁻ stereocenters

![Scheme 3: Installation of the C₁₆⁻ and C₁₈⁻ stereocenters](image)

*aConditions: (a) 30 mol % Ti(O\textsuperscript{i}Pr\textsubscript{4}), (+)-DIPT, \textsuperscript{t}BuOOH, CH\textsubscript{2}Cl\textsubscript{2}. (b) LiAlH\textsubscript{4}, Et\textsubscript{2}O, 0 °C. (c) TBSOTf, 2,6-lutidine, 0 C-RT. (d) DDQ, THF-H\textsubscript{2}O. (e) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}. (f) 10 mol % 63, MeCOBr, \textsuperscript{i}Pr\textsubscript{2}NEt, –50 °C.

### 2.3 INSTALLATION OF THE C₁₄⁻C₁₅ TRISUBSTITUTED ALKENE

With β-lactone 81 in hand, we decided to elaborate it into a suitable compound that would enable studies toward the formation of the C₁₄⁻C₁₅ trisubstituted alkene as well as the diene unit in 1 (Scheme 4). Amine-mediated ring-opening of 81 afforded Weinreb amide 86 in 91% yield in which the free hydroxyl group was protected as the tert-butylidemethylsilyl ether and the alkynyl silyl group was selectively cleaved with KOH/MeOH in an overall 88% yield. Terminal alkyne 87 thus contained the requisite functionality for further manipulation along the C₁₄⁻C₁₅ bond.
In order to carbometalate terminal alkyne 87, we investigated the stannylcupration reaction discovered by Lipshutz in the late 1980’s. [32] Although this is a synthetically very useful route to vinylstannanes, evidence in the literature suggests that the regioselectivity of stannylcupration of terminal alkynes is variable under kinetic and thermodynamic control. [33] In order to carbostannylate a terminal alkyne, the intermediate vinyl cuprate species has to be quenched with an electrophilic alkylating agent. Such reactions have literature precedent, [34] although to the best of our knowledge, not with an alkyne bearing a neopentyl substituent.

Higher order stannylcuprate reagents were prepared following Oehlschlager’s procedure, [33] and alkyne 87 was treated with them at −50 °C (Scheme 5). The intermediate vinyl cuprates 87a were quenched with excess methyl iodide at −50 °C to afford vinyltributylstannane 88 and vinyltrimethylstannane 89. The use of alkyltributylstannyl cuprate gave a better yield of 88 (83%) compared to the bis(stannyl)cuprate (64%). Carbostannylation with
trimethylstannylcuprate was found to be less efficient than tributylstannylcuprate in terms of reactivity with alkyne 87. However, use of the more reactive mixed alkyl(trimethylstannyl)cuprate reagent in excess afforded trimethylstannane 89 in 64% yield. Proof of regiochemistry of carbostannylation was obtained by conversion of stannane 88 to vinyl iodide 90 with molecular iodine (98%) and subsequent DEPT and nOe studies.

**Scheme 5: Carbostannylation studies on alkyne 87**

\[ \text{Scheme 5: Carbostannylation studies on alkyne 87} \]

\[ \text{Conditions: (a) i. Cuprate, } -50 \degree \text{C, THF; ii. excess } \text{MeI, } -50 \degree \text{C–RT.} \text{ (b) } \text{I}_2, \text{CH}_2\text{Cl}_2. \]

<table>
<thead>
<tr>
<th>Cuprate used</th>
<th>yield of 88 or 89</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{nBu}_3\text{Sn})_2\text{Cu(CN)Li}_2)</td>
<td>72%</td>
</tr>
<tr>
<td>((\text{nBu}_3\text{Sn})(\text{Bu})\text{Cu(CN)Li}_2)</td>
<td>83%</td>
</tr>
<tr>
<td>((\text{Me}_3\text{Sn})_2\text{Cu(CN)Li}_2)</td>
<td>41%</td>
</tr>
<tr>
<td>((\text{Me}_3\text{Sn})(\text{Bu})\text{Cu(CN)Li}_2)</td>
<td>64%</td>
</tr>
</tbody>
</table>
2.4 STILLE COUPLING STUDIES

2.4.1 Standard conditions

Having shown that we could synthesize the requisite trisubstituted vinylstannane in the model “upper fragment” 87, we wanted to explore its ability to engage in a Stille coupling reaction with triflate 67 to form the C_{13}–C_{14} bond in amphidinolide B. Stannane 88 and triflate 67 were subjected to the original Stille reaction conditions developed by Scott and Stille, with 15 mol% loading of palladium, triphenylphosphine as the ligand and lithium chloride as an additive. However, no desired product was observed (Eq 2) indicating that modified reaction conditions would have to be applied.

$$\begin{align*}
\text{OTBS} & \quad \text{N} \quad \text{OMe} \\
\text{TBSO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{nBu}_3\text{Sn} \\
\text{Me} & \quad \text{OTBS}
\end{align*}$$

$$\begin{align*}
\text{Pd}_2(\text{dba})_3, \text{PPh}_3, \text{LiCl}, \text{THF}, \text{reflux}
\end{align*}$$

2.4.2 Coupling under modified Stille conditions

As the next trial of forming the C_{13}–C_{15} diene in a model system, the Corey-modified protocol of the Stille reaction that was originally developed for sterically congested
I-substituted vinylstannanes, was investigated. [36] In order to serve preliminary coupling studies, known triflate 92 derived from phenol was prepared (Scheme 6). [37] Both stannanes 88 and 89 were subjected to cuprous chloride-accelerated Stille reactions with triflate 92. The reaction of tributylstannane 88 yielded 30% of recovered stannane 88 along with 7% of homocoupled product 93 of the vinyl stannane and some unidentifiable material. Trimethylstannane 89 proved to be better in terms of reactivity in that all the starting material stannane was consumed to afford 19% yield of the desired coupled product 94 as well as 20% of homocoupled product 93.

Scheme 6: The Corey-modified Stille trials on model system

Homocoupling of vinylstannanes in the presence of cuprous chloride has precedent in the literature. [38] Identifying reaction conditions that would retain the reactivity of the stannane and at the same time prevent self-coupling was important for the success of our Stille reaction.
Hence, we decided to test the Farina-modified Stille coupling strategy of using triphenylarsine ligands that tend to dissociate more readily from the palladium during the course of the reaction. When vinylstannane 88 was reacted with model triflate 92 in the presence of 10 mol% Pd_{2}(dba)\textsubscript{3} and 40 mol% Ph\textsubscript{3}As with lithium chloride as an additive in N-methylpyrrolidinone (NMP), the desired product 94 was formed in 21% yield, and starting material stannane 88 was recovered in 20% yield along with other unidentified material (Scheme 7). We were, however, pleased to find that trimethylstannane 89 underwent the reaction, under the same conditions, to completion to afford desired product 94 in 60% yield.

**Scheme 7: The Farina-modified Stille reaction trials on model system**

Application of these successful conditions to triflate 67 was our next priority. Disappointingly, under identical conditions, when stannane 89 was reacted with triflate 67 the only product recovered was destannylated compound 95 (Eq 3).
2.4.3 Summary of Stille coupling studies

Table 2 summarizes the trials performed to study the coupling of stannanes 88 and 89 with phenyl trifluoromethanesulfonate 92 and triflate 67 under various modified Stille conditions.
Table 2: Modified Stille coupling studies

<table>
<thead>
<tr>
<th>stannane employed</th>
<th>triflate partner</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>PhOTf</td>
<td>Pd(PPh$_3)_4$, CuCl, LiCl, DMSO, 60° C</td>
<td>88 + dimer 30% 7%</td>
</tr>
<tr>
<td>89</td>
<td>PhOTf</td>
<td>Pd(PPh$_3)_4$, CuCl, LiCl, DMSO, 60° C</td>
<td>coupled product + 19% dimer 20%</td>
</tr>
<tr>
<td>88</td>
<td>PhOTf</td>
<td>Pd$_2$(dba)$_3$, Ph$_3$As, LiCl, NMP, 65° C</td>
<td>coupled + 88 product 20% 21%</td>
</tr>
<tr>
<td>89</td>
<td>PhOTf</td>
<td>Pd$_2$(dba)$_3$, Ph$_3$As, LiCl, NMP, 65° C</td>
<td>coupled product 60%</td>
</tr>
<tr>
<td>89</td>
<td>PhOTf</td>
<td>Pd$_2$(dba)$_3$, Ph$_3$As, LiCl, NMP, 65° C</td>
<td>destannylated product 95 68%</td>
</tr>
</tbody>
</table>

2.5 SUZUKI COUPLING STUDIES

2.5.1 Attempted transmetalation of vinyl iodide fragment 90

Our first strategy in investigating the Suzuki coupling strategy was to convert iodide 90 into a boronic acid/ester that could potentially couple with the same triflate fragment 67. Although we could effect the formation of vinyllithium 90a from iodide 90, we were unable to
transmetalate the intermediate vinyllithium species with trialkoxyborates (Scheme 8). This result prompted us to explore other avenues to investigate the Suzuki coupling strategy.

Scheme 8: Attempted conversion of iodide 90 to boronic acid

2.5.2 Attempted modification of triflate fragment 67

The next step towards making substrates suitable for testing the Suzuki coupling strategy was to modify triflate fragment 67 suitably so that it could function as the transmetalating partner instead of undergoing oxidative addition during the coupling reaction. Since iodide 90 was available directly from stannane 88, it could be used as the electrophile undergoing oxidative addition onto palladium in the cross-coupling reaction.

We decided to apply Miyaura’s one-pot procedure of converting a vinyl triflate into a vinyl boronic ester using (bispinacolato)diboron and dichlorobis(triphenylphosphine) palladium as a catalyst and potassium phenoxide as a base. [40] Disappointingly, we observed no desired
product from this reaction (Eq 3). Although we do not have adequate proof of this hypothesis, we speculated that a reason for this could be a competing intramolecular Heck-type reaction that could occur in a 5-exo-dig manner after oxidative addition of triflate 67 on catalytic palladium(0). This was perceived as a counter-productive pathway in the previously performed Stille reaction studies, and could well be the reason that no desired coupled product was observed in the trials employing triflate 67 as the electrophilic partner.

![Chemical reaction diagram]

(3)

2.5.3 Synthesis of model boronic acid/ester compounds

In order to expedite our studies on the formation of the C\(_{13}\)--C\(_{14}\) linkage in amphidinolide B, we decided to synthesize a model boronic ester that would closely resemble fragment 67. A rapid synthesis of triflate 96 from commercially available \(S\)--(-)-citronellal was then initiated (Scheme 9). Thus, kinetic enolization of the methyl ketone derived from \(S\)--(-)-citronellal [41] and trapping with \(N\)-phenyl triflimide gave triflate 96 which then smoothly underwent transformation to boronic ester 97 following Miyaura’s protocol in 70% yield.
Scheme 9: Synthesis of model boronate ester from S-(-)-citronellal

\[
\text{Scheme 9: Synthesis of model boronate ester from S-(-)-citronellal}^a
\]

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{Me} & \quad \text{Me} \\
\text{a, b} & \quad \text{c} \\
\text{Me} & \quad \text{Me} \\
\text{53\%} & \quad \text{70\%} \\
\end{align*}
\]

\(96\) \quad \(97\)

\(^a\text{Conditions: (a) i. MeMgBr, THF; ii. PCC, CH}_2\text{Cl}_2, \text{reflux. (b) KHMDS, PhNTf}_2, \text{THF, -78 °C. (c) B(pin)-B(pin), 10 mol % Pd(PPh}_3)_2\text{Cl}_2\text{PPH}_3, \text{PhOK, toluene, 50 °C.}\)

Since it proved difficult to hydrolyze boronate ester 97 into the corresponding boronic acid in the presence of the isolated double bond in it, [42] we sought to prepare boronic acid 98 from triflate 96. Conversion of triflate 96 to iodide 99 proceeded in two steps through an intermediate trimethylstannane (61%). Transmetalation of iodide 99 with butyllithium, quenching the intermediate vinyllithium with trimethylborate and acidic workup produced boronic acid 98 (Scheme 10).

Scheme 10: Synthesis of model boronic acid from S-(-)-citronellal

\[
\text{Scheme 10: Synthesis of model boronic acid from S-(-)-citronellal}^a
\]

\[
\begin{align*}
\text{OTf} & \quad \text{I} \\
\text{Me} & \quad \text{Me} \\
\text{a, b} & \quad \text{c} \\
\text{Me} & \quad \text{Me} \\
\text{61\%} & \quad \text{74\%} \\
\end{align*}
\]

\(96\) \quad \(99\) \quad \(98\)

\(^a\text{Conditions: (a) (Me}_3\text{Sn})_2, 10 \text{ mol % Pd(PPh}_3)_4\text{LiCl, THF, 60 °C. (b) I}_2, \text{CH}_2\text{Cl}_2. (c) BuLi, B(OMe)_3, \text{THF, -78 °C–RT.}\)
2.5.4 Suzuki trials in the model system

With model boronate fragments 97 and 98 in hand, we investigated their ability to participate in Suzuki reactions with iodide 90 (Eq 4). Under standard Suzuki reaction conditions at 45 °C, employing (dppf)PdCl₂ as the catalyst and DMF as the solvent, it was found that boronic acid 98 was much inferior to boronate ester 97 in terms of conversion to product diene 100. Reaction times and thus integrity of the diene were strongly dependent on the nature of the base additive. Thus, when bases such as potassium hydroxide, cesium carbonate or potassium carbonate were used, prolonged reaction times were observed, and in most cases, isomerized diene 101 was detected. However, reaction of boronate ester 98 when barium hydroxide was used as the base afforded diene 100 in 64% yield as the sole product uncontaminated with isomerized diene 101.
Catalytic asymmetric methodologies were successfully applied to construct the C_{16}- and C_{18}- stereocenters in amphidinolide B. The Stille and Suzuki cross-coupling methods were investigated for the formation of the C_{13}–C_{15} diene. Optimized reaction conditions for connecting
two major fragments of amphidinolide B using the Suzuki coupling strategy were found in a suitable model system.

**EXPERIMENTAL SECTION**

![Chemical Structure](image)

**[(2S,3S)-3-methyl-3-(2-(trimethylsilyl)ethynyl)oxiran-2-yl]methanol (84):** To a –20 °C suspension of 0.62 g of 4Å molecular sieves in 11 mL of CH$_2$Cl$_2$ was added a solution of 0.62 g of (+)-DIPT (2.64 mmol, 0.36 equiv) in 3 mL of CH$_2$Cl$_2$ followed by 0.65 mL of titanium isopropoxide (2.2 mmol, 0.3 equiv), and 2.67 mL of tert-butylhydroperoxide (5.5 M solution in decane, 14.7 mmol, 2.0 equiv). The resulting solution was stirred for 30 min at –20 °C and then a solution of 1.15 g of allylic alcohol 83 (7.35 mmol) in 5 mL of CH$_2$Cl$_2$ was added to it. The reaction mixture was stirred at the same temperature for 5 h and quenched with a freshly prepared solution of 0.57 g of ferrous sulfate and 0.17 g of citric acid in water (10 mL). The organic layer was separated from the aqueous layer and filtered through a short plug of florisil and the filter cake was washed with 20% solution of EtOAc in hexanes. The aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 30 mL) and the combined organics were dried over Na$_2$SO$_4$ and the solvents were evaporated *in vacuo*. The crude product was purified by medium pressure chromatography (10–30% EtOAc in hexanes) to afford 1.04 g of epoxide 84 (83%) as a colorless oil. Mosher ester analysis of the purified epoxide determined the enantiomeric excess to be 88%: [α]$_D$ = –0.62 (c 1.80, CHCl$_3$); IR (thin film): 3431, 2960, 2167, 1642, 1250, 1032, 842 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 3.84 (dd, J = 12.4, 4.4 Hz, 1H), 3.68...
(dd \(J = 12.3, 6.2\) Hz, 1H), 3.37 (dd, \(J = 6.0, 4.6\) Hz, 1H), 2.04 (br s, 1H), 1.53 (s, 3H), 0.16 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 105.1, 87.4, 64.3, 60.5, 51.4, 18.6, −0.2; HRMS calcd for \(\text{C}_8\text{H}_{13}\text{O}_2\text{Si}\): 169.0685 found 169.0686.

\((R)-3\text{-methyl-5-}(\text{trimethylsilyl})\text{pent-4-yn-1,3-diol (85)}\): To a 0 °C solution of epoxide 84 (4.90 mmol) in 30 mL of ether added 4.9 mL of lithium aluminum hydride (1 M solution in hexanes, 4.90 mmol) dropwise via syringe. Stirred for 15 min at 0 °C and then quenched with 10 mL of 0.2 M aqueous hydrochloric acid solution. After the layers were separated, the aqueous layer was extracted with ether (5 x 40 mL). The combined organics were washed with 5 mL of brine and dried over Na\(_2\)SO\(_4\). The solvent was evaporated \textit{in vacuo} and the crude product was purified by medium pressure chromatography (10–35% EtOAc in hexanes to afford 0.510 g of the title compound (56%, 60% brsm) as a colorless oil: [\(\alpha\)]\(_D\) = +24.2 (c 2.10, CHCl\(_3\)); IR (thin film): 3367, 2959, 2165, 1409, 1250, 932 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 4.19 (s, 1H), 4.10–4.03 (m, 1H), 3.87–3.82 (m, 1H), 3.43 (br s, 1H), 1.91 (ddd, \(J = 14.3, 9.3, 4.2\) Hz, 1H), 1.77 (ddd, \(J = 14.4, 4.8, 3.6\) Hz, 1H), 1.47 (s, 3H), 0.12 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 108.8, 87.7, 68.8, 60.3, 43.6, 30.5, 0.0; HRMS calcd for \(\text{C}_8\text{H}_{15}\text{O}_2\text{Si}\): 171.0841 found 171.0840.

\((R)-3,5\text{-Bis-}(\text{tert-butyl}dime\text{thylsilanyloxy})\text{-3-methyl-1-trimethylsilanyl pent-1-yne (85a)}\): To a 0 °C solution of 0.680 g of diol 85 (3.65 mmol) in 18 mL of CH\(_2\)Cl\(_2\) added 2.1 mL of 2,6-lutidine (18.33 mmol, 5 equiv.) followed by 2.5 mL of \textit{tert}-butyldimethylsilyl trifluoromethansulfonate (11 mmol, 3.0 equiv.)
dropwise via syringe. The resulting solution was allowed to warm to ambient temperature and stirred for 3 h. The reaction mixture was then quenched with 10 mL of saturated NaHCO$_3$ solution and 10 mL of brine solution. After separation of layers, the aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 30 mL). The combined organics were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash chromatography (2% EtOAc in hexanes) to yield 1.20 g of the title compound (80% yield) as a colorless oil: $[\alpha]_D^\text{D} = +5.5 \text{ (c 1.2, CHCl}_3)$; IR (thin film): 2956, 2929, 2886, 2857, 2166, 1472, 1252, 1117, 1093, 837 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.90–3.79 (m, 2H), 1.96–1.80 (m, 2H), 1.43 (s, 3H), 0.91 (s, 9H), 0.86 (s, 9H), 0.16 (s, 9H), 0.15 (s, 6H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 109.7, 88.3, 67.9, 60.3, 54.9, 47.5, 31.5, 26.0, 25.7, 18.4, 18.0, –0.2, –2.9, –3.2, –5.2; EI-MS e$^+$/v 399 (M$^+$–CH$_3$), 357 (M$^+$–t-Bu), 329, 255, 189, 147; HRMS calcd for C$_{20}$H$_{43}$O$_2$Si$_3$: 399.2571 found 399.2560.

(R)-3-(tert-Butyldimethylsilanyloxy)-3-methyl-5-trimethylsilanylpent-4-yn-1-ol (85b): To a solution of 2.30 g of tert-butyldimethylsilyl ether 85a (5.55 mmol) in a 9:1 solvent mixture of THF: H$_2$O (20 mL) added 0.12 g of DDQ (0.55 mmol, 10 mol %) at ambient temperature. After 6 h the reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography (1% EtOAc in hexanes) to afford 1.58 g of the title compound (95% yield) as a colorless oil: $[\alpha]_D^\text{D} = +20.8 \text{ (c 1.50, CHCl}_3)$; IR (thin film): 3350, 2957, 2930, 2857, 2167, 1472, 1251, 1121, 1041, 839 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.94 (ddd, $J = 11.3, 5.0, 5.0$ Hz, 1H), 3.84 (ddd, $J = 11.1, 6.0, 6.0$ Hz, 1H), 2.77 (dd, $J = 5.5, 5.5$ Hz, 1H), 1.93–1.88 (m, 2H), 1.49 (s, 3H), 0.87 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.17 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 109.4, 89.5, 69.9, 60.2, 46.6, 31.2, 25.7, 17.9,
(R)-3-(tert-Butyldimethylsilyloxy)-3-methyl-5-trimethylsilanylpent-4-ynal (82): To a 0 °C solution of 1.58 g of alcohol 85b (5.26 mmol) in 25 mL of CH₂Cl₂ added 3.35 g of Dess-Martin periodinane (7.89 mmol, 1.5 equiv). The reaction mixture was allowed to warm to ambient temperature and stirred for 3 h. It was diluted with hexanes and filtered through a short plug of florisil with 5% EtOAc in hexanes. After removal of solvents in vacuo the crude product was purified by flash chromatography (5% EtOAc in hexanes) to obtain 1.32 g of the title compound (84% yield) as a colorless oil: [α]D = +36 (c 1.4, CHCl₃); IR (thin film): 2958, 2930, 2857, 1730, 1251, 1115, 1040, 838, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.88 (t, J = 2.9 Hz, 1H), 2.58 (br d, J = 2.4 Hz, 2H), 1.54 (s, 3H), 0.86 (s, 9H), 0.21 (s, 6H), 0.18 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 201.9, 107.9, 90.4, 66.6, 56.9, 31.3, 25.5, 17.9, −0.4, −2.9, −3.3; EI-MS e/ν 283 (M⁺–Me), 255 (M⁺–CH₃–CO), 241, 147; HRMS calcd for C₁₄H₂₇O₂Si₂: 283.1549 found 283.1556.

(4S,2R)-4-[2-(tert-Butyldimethylsilyloxy)-2-methyl-4-trimethylsilanyl-but3-ynyl]-oxetan-2-one (81): To a solution of 0.036 g of triamine ligand precursor to catalyst 63 (0.067 mmol) in 1.0 mL of CH₂Cl₂ was added 0.04 mL of a 2 M in hexanes solution of trimethylaluminum (0.074 mmol) and was stirred for 2 h. The solution was cooled to −50 °C, and 0.12 mL of iPr₂NEt (1.14 mmol) was added to it.
followed by the slow addition of 0.09 mL of acetyl bromide (1.27 mmol). To the resulting pale yellow solution was added 0.200 g of aldehyde 82 (0.67 mmol) in 1.5 mL of CH₂Cl₂. The reaction mixture was stirred overnight at −50 °C, poured into cold hexanes and filtered through a short plug of silica gel with 30% EtOAc in hexanes. The filtrate was concentrated and the crude product was purified by flash chromatography on silica (1% EtOAc in hexanes) to afford 0.200 g of lactone 81 (88%) as a colorless oil: [α]D = +30 (c 2.3, CHCl₃); IR (thin film): 2957, 2930, 2857, 2169, 1835, 1251, 1165, 1125, 1077, 868 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.83 (dddd, J = 8.8, 5.7, 4.2, 4.2 Hz, 1H), 3.57 (dd, J = 17, 5.7 Hz, 1H), 3.29 (dd, J = 17, 4.2 Hz, 1H), 2.32 (dd, J = 14, 4.2 Hz, 1H), 2.03 (dd, J = 14, 9.0 Hz, 1H), 1.50 (s, 3H), 0.86 (s, 9H), 0.22 (s, 3H), 0.19 (s, 9H), 0.15 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.5, 107.9, 90.3, 69.1, 67.8, 48.9, 44.6, 31.6, 31.5, 25.6, 17.9, −0.3, −3.0, −3.1; EI-MS e/ν 325 (M⁺–CH₃), 283 (M–CH₃–C₂H₂O), 255, 241, 143, 101; HRMS calcd for C₁₆H₂₉O₃Si₂: 325.1655 found 325.1647.

(3S,5R)-5-(tert-Butyldimethylsilanyloxy)-3-hydroxy-5-methyl-7-trimethylsilylhept-6-ynoic acid methoxymethylamide (86): To a 0 °C solution of 0.202 g of N,O-dimethylhydroxylamine hydrochloride (2.06 mmol) in 8 mL of CH₂Cl₂, was added 2 mL of dimethylaluminumchloride (1 M solution in hexanes) (2.06 mmol) and the resulting solution was allowed to stir at ambient temperature for 2 h. To the clear solution was added, 0.350 g of lactone 81 in 2 mL of CH₂Cl₂, slowly. The resulting pale yellow solution was stirred overnight and quenched with 6 mL of pH 8 phosphate buffer (3 mL/mmol of Me₂AlCl). The organic layer was separated, filtered through celite, dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (20% EtOAc/Hex) to afford 0.415 g of the title compound (90%) as a colorless
oil: $[\alpha]_D = +31.4 \ (c \ 22.8, \ \text{CHCl}_3) $; IR (thin film): 3499, 2957, 2930, 2167, 1651, 1472, 1251, 1116, 1000, 839, 777 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.45 (ddddd, $J = 8.6, 5.2, 3.7, 3.7$ Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.67 (dd, $J = 16.0, 7.7$ Hz, 1H), 2.57 (dd, $J = 16.0, 5.0$ Hz, 1H), 1.94 (dd, $J = 14.2, 8.1$ Hz, 1H), 1.85 (dd, $J = 14.1, 3.6$ Hz, 1H), 1.51 (s, 3H), 0.85 (s, 9H), 0.19 (s, 6H), 0.14 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 172.7, 109.7, 89.3, 69.3, 65.2, 65.5, 61.3, 50.7, 39.4, 31.9, 30.5, 25.7, 17.9, −0.4, −2.9, −3.1; EI-MS $e/\nu$ 386 (M$^+$–Me), 368 (M$^+$–Me–H$_2$O), 255, 215; HRMS calcd for C$_{18}$H$_{36}$NO$_4$Si$_2$: 386.2182 found 386.2174.

(3S,5R)-3,5-Bis-(tert-butyldimethylsilyloxy)-5-methyl-7-trimethylsilanylhept-6-ynoic acid methoxymethylamide (86a): To a 0 °C solution of 0.367 g of alcohol 86 (0.952 mmol) in 10 mL of CH$_2$Cl$_2$ was added 0.267 mL of 2,6-lutidine (2.28 mmol) followed by 0.317 mL of TBSOTf (1.373 mmol) and allowed to warm to ambient temperature over 1 h. The reaction mixture was quenched with 5 mL of NaHCO$_3$. After separation of the layers, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The organics were combined, washed with 5 mL of brine, dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by flash chromatography (5% EtOAc in hexanes) to afford 0.450 g of the title compound (95%) as a colorless oil: $[\alpha]_D = +28.9 \ (c \ 2.57 \ \text{CHCl}_3) $; IR (thin film) 2956, 2929, 2856, 2166, 1669, 1472, 1446, 1385, 1251, 1075, 993, 837 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 4.59 (ddddd, $J = 9.0, 9.0, 2.9, 2.9$ Hz, 1H), 3.67 (s,3H), 3.16 (s, 3H), 2.81–2.70 (m, 2H), 1.93 (dd, $J = 13.9, 9.2$ Hz), 1.81 (dd, $J = 13.9, 2.9$ Hz, 1H), 1.46 (s,3H), 0.85 (s, 18H), 0.21 (s, 3H), 0.18 (s, 12H), 0.12 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 172.7, 109.3, 89.3, 77.2, 68.3, 67.8, 61.2, 52.4, 32.5, 25.9, 25.8, 18.0, 17.9, −0.2, −2.8, −3.1, −4.3,
–4.7; EI-MS e/ν 500 (M⁺–Me), 458 (M⁺–t-Bu), 255, 188, 115, 101; HRMS calcd for C7H13OSi: 500.3047 found 500.3039.

(3S,5R)-3,5-Bis(tert-butyldimethylsilyloxy)-5-methylhept-6-ynoic acid methoxymethylamide (87): To a solution of 1.05 g of trimethylsilylalkyne 86a (2.04 mmol) in 10 mL of MeOH, was added 0.114 g of KOH (2.04 mmol) and the solution was allowed to stir at ambient temperature for 5 h. The reaction mixture was concentrated, and the crude product purified by flash chromatography (5–8% EtOAc in hexanes) to yield 0.840 g of the title compound (93%) as a colorless oil: [α]D = +28.8 (c 1.20, CHCl3); IR (thin film): 3308, 3235, 2955, 2930, 2895, 2106, 1665, 1472, 1463, 1252, 1003, 836, 777 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 4.64–4.54 (m, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 2.77 (app. d, J = 5.0 Hz, 2H), 2.51 (s, 1H), 1.97 (dd, J = 14.0, 8.6 Hz, 1H), 1.85 (dd, J = 14.0, 3.3 Hz, 1H), 1.50 (s, 3H), 0.86 (s, 18H), 0.20 (s, 3H), 0.18 (s, 3H), 0.10 (s, 3H), 0..05 (s, 3H); ¹³C NMR (75 MHz, CDCl3): δ 172.6, 87.3, 77.4, 73.0, 67.9, 67.7, 61.2, 52.5, 40.8, 32.4, 25.8, 25.7, 18.0, 17.9, –2.7, –3.1, –4.5, –4.7 ; EI-MS e/ν 428 (M⁺–Me), 386 (M⁺–t-Bu), 317, 257, 183, 115; HRMS calcd for C21H42NO₄Si₂ 428.2652 found 428.2646.

(3S,5R)-3,5-Bis(tert-butyldimethylsilyloxy)-5,6-dimethyl-7-tributylstannanylhept-6-enoic acid methoxymethylamide (88): To a –60 °C suspension of 0.247 g of CuCN (3.02 mmol) in THF (1.5 mL) was added 1.9 mL of a 1.6 M solution of n-BuLi in hexanes to produce a light
brown solution which was allowed to warm to –30 °C over 30 min. A solution of nBu3SnLi was prepared by adding nBuLi (1.6 M solution in hexanes) to a solution of 1.873 g of bis(tributyltin) (3.23 mmol) in 1 mL of THF at –30 °C. This solution was cannulated into the cuprate solution with 3 mL of THF. A dark yellow solution was formed which was stirred at –30 °C for 2 h, cooled to –50 °C, whereupon a solution of 0.445 g of alkyne 87 was added to it via syringe. This was stirred for 10 min and then 1 mL of MeI (excess) was added to it. The solution developed a red color and was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ether, and 10 mL of a saturated solution of NH4Cl was added to it, and the aqueous layer was extracted with ether (3 x 20 mL). The organics were combined, dried over Na2SO4 concentrated, and the crude product was purified by flash chromatography (1% Et3N, then 0.2–0.5% EtOAc in hexanes) to afford 0.625 g of the title compound as a pale yellow oil: [α]D = +17.7 (c 1.60, CHCl3); IR (thin film) 2956, 2928, 2855, 1671, 1463, 1384, 1254, 1123, 1084, 835, 774 cm⁻¹; 1H NMR (300 MHz, CDCl3): δ 5.83 (s, JSn-H = 69.7Hz, 1H), 4.16 (dddd, J = 6.6, 6.6, 6.6 Hz, 1H), 3.65 (s, 3H), 3.14 (s, 3H), 2.80 (app d, J = 4.9 Hz, 2H), 1.86–1.83 (m, 2H), 1.81 (s, 3H), 1.55–1.44 (m, 9H), 1.30 (app sextet, J = 7.29 Hz, 6H), 0.95–0.85 (m, 15H), 0.89 (s, 9H), 0.84 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.01 (s, 3H). 13C NMR (75 MHz, CDCl3): δ 172.4, 157.4, 122.5, 79.0, 67.3, 61.1, 50.2, 40.6, 29.2, 29.1, 28.8, 27.3, 26.7, 25.8, 21.7, 18.5, 18.0, 13.6, 10.0, –1.0, –2.2, –4.2, –4.5 ; HRMS calcd for C35H75NO4Si2Sn 749.4257 found 749.4294. 

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3,5-Bis-(tert-butyldimethylsilyloxy)-5,6-dimethyl-7-trimethylstannylhept-6-enoic acid methoxymethylamide (89): To a –60 °C suspension of 0.1026 g of CuCN (1.13 mmol) in THF (1.2 ml), was added 0.71 mL of "BuLi (1.6 M solution in hexanes). The light brown colored solution was stirred and allowed to warm to –30 °C. A solution of Me₃SnLi was prepared by the addition of 0.8 mL of "BuLi (1.6 M solution in hexanes) to a –30 °C solution of 0.386 g of hexamethylditin (1.18 mmol) in THF (0.3 mL) and stirring the resulting solution for 30 min at –30 °C. The Me₃SnLi thus made was cannulated into the cuprate solution at –30 °C, after which the yellow suspension was maintained at that temperature for 1.5 h. The reaction mixture was cooled to –50 °C, a solution of 0.100 g of alkyne 87 (0.23 mmol) in THF (1.2 mL) was added to it, followed by the addition of 0.3 mL of methyl iodide (4.53 mmol). The solution was allowed to warm to ambient temperature overnight. To the reaction mixture was added 0.2 mL of a saturated solution of NH₄Cl, stirred for 10 min, and the aqueous layer extracted with of ether (3 x 5 mL). The organics were combined, dried over Na₂SO₄, concentrated, and purified by flash chromatography on silica gel (0.2–0.5% EtOAc in hexanes with 5% Et₃N) to afford 0.090 g of stannane 89 (64%) as a bright yellow oil. [α]D = +15.3 (c 1.00, CHCl₃); IR (thin film) 2956, 2928, 2856, 1667, 1471, 1462, 1384, 1254, 1003, 834, 773 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.85 (s, JSn-H = 77.0 Hz, 1H), 4.46–4.38 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.67 (d, J = 4.5 Hz, 2H), 1.96 (dd, J = 14.1, 4.8 Hz, 1H), 1.83 (t, J = 5.0 Hz, 3H), 1.69 (dd, J = 14.1, 3.5 Hz, 1H), 1.45 (s, 3H), 0.90 (s, 9H), 0.84 (s, 9H), 0.15 (s, JSn-H = 54.1 Hz, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.02 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 172.7, 159.3, 122.6, 78.4, 77.0, 67.4, 61.3, 50.2, 40.4, 27.5, 26.3, 26.0, 21.1, 18.7, 18.0, –1.4, –2.5, –4.3, –4.5, –8.9; EI-MS e/v 608 (M⁺–Me), 566 (M⁺–"Bu), 286, 188, 165; HRMS calcd for C₂₅H₅₄NO₄Si₂Sn: 608.2586, found 608.2591.
(3S,5R)-3,5-Bis(tert-butyldimethylsilanyloxy)-7-iodo-5,6-dimethylhept-6-enoic acid methoxymethylamide (90): To a solution of 0.021 g of stannane 88 in 5mL of CH₂Cl₂ was added 0.007 g of I₂ in portions. After 10 min, the solvent was evaporated in vacuo and the crude product purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 0.016 g of iodide 90 (98%) as a pale yellow oil: [α]D = +8.1 (c 0.6, CHCl₃); IR (thin film) 2956, 2929, 2856, 1660, 1471, 1386, 1256, 1002, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.32 (s, 1H), 4.14 (quintet, J = 6.1 Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.65 (dd, J = 14.6, 7.7 Hz, 1H), 2.53 (dd, J = 5.9, 14.6 Hz, 1H), 1.90–1.87 (m, 2H), 1.88 (s, 3H), 1.48 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 172.1, 151.6, 78.8, 78.7, 77.5, 66.7, 61.2, 49.6, 28.6, 26.1, 25.9, 22.1, 18.5, 17.9, −1.5, −2.1, −4.1, −4.3; EI-MS e/v 570 (M⁺–Me), 528 (M⁺–tBu), 188, 165; HRMS calc for C₂₂H₄₅INO₄Si₂: 570.1932, found 570.1955.
Proof of regiochemistry using DEPT and nOe studies:

\[
\begin{array}{c}
\text{NOESY cross peaks observed} \\
\text{\textsuperscript{13}C signal: 78.7 (C-H)} \\
\text{\textsuperscript{13}C signal: 151.6 (C(q))}
\end{array}
\]

\((S)-4,8\text{-dimethylnon-7-en-2-one (96a)}\) \[^{[39]}\]: \(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.00 (dd, J = 4.5, 4.5 Hz, 1H), 2.34 (dd, J = 15.7, 5.5 Hz, 1H), 2.13 (dd, J = 15.8, 8.1 Hz, 1H), 2.04 (s, 3H), 1.96–1.82 (m, 3H), 1.59 (s, 3H), 1.51 (s, 3H), 1.28–1.07 (m, 2H), 0.82 (d, J = 6.6 Hz, 3H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)): \(\delta\) 208.6, 131.1, 124.1, 50.9, 36.7, 30.1, 28.7, 25.5, 25.2, 19.5, 17.4.

\((S)-4,8\text{-dimethylnona-1,7-dien-2-yl trifluoromethanesulfonate (96)}\): To a \(-78^\circ\text{C}\) solution of 5.2 mL of a 0.5 M solution of potassiumbis(trimethylsilyl)amide in toluene (2.6 mmol) in THF (8 mL) was added a solution of 0.36 g of ketone \(96\text{a}\) (2.2 mmol) in THF (3 mL), dropwise. The resulting solution was stirred at \(-78^\circ\text{C}\) for 15 min and then, a solution of 0.85 g (2.4 mmol) of \(N\)-phenyltriflimide in THF (4 mL) was cannulated into the reaction mixture to produce a yellow solution which was then allowed to warm to 0 \(^{\circ}\)C. Then, \(10\) mL of a saturated NaHCO\(_3\) solution
and 20 mL of ether were added to it, the layers were separated, and the aqueous layer washed with ether (5 x 20 mL). The combined organics were dried over Na$_2$SO$_4$, concentrated and purified by column chromatography over silica gel (0.5% EtOAc in hexanes, 2% Et$_3$N) to afford 0.55 g (85%) of the title compound as a colorless oil: $[\alpha]_D = -7.2$ (c 1.4, CHCl$_3$); IR (thin film) 2966, 2919, 1670, 1419, 1141, 941 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.13 (d, $J = 3.4$ Hz, 1H), 5.12–5.06 (m, 1H), 4.92 (d, $J = 15.2$, 6.0 Hz, 1H), 2.37 (dd, $J = 15.2$, 6.0 Hz, 1H); 2.15–1.93 (m, 3H), 1.82–1.75 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.40 (dddd, $J = 13.4$, 9.1, 5.5, 5.5 Hz, 1H), 1.22 (ddddd, $J = 13.9$, 8.1, 6.5, 6.5 Hz, 1H), 0.98 (d, $J = 7.7$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 155.9, 131.8, 124.0, 118.4 (q, $J_{C-F} = 322$ Hz), 105.2, 41.4, 36.3, 29.6, 25.6, 25.2, 19.0, 17.6; HRMS calcd for C$_{12}$H$_{19}$O$_3$F$_3$S: 300.1007, found 300.1011.

4,4,5,5-tetramethyl-2-[(S)-4,8-dimethylnona-1,7-dien-2-yl]-1,3,2-dioxaborolane (97): A mixture of 0.103 g of triflate 96 (0.34 mmol), 0.10 g of bis(pinacolato)diboron (0.37 mmol, 1.1 equiv), 0.056 g of bis(triphenylphosphine)palladium dichloride (0.088 mmol, 10 mol %), 0.042 g of triphenylphosphine (0.160 mmol, 20 mol %) and 0.154 g of potassium phenoxide (1.20 mmol, 1.5 equiv) in 5 mL of toluene (0.2 M) was heated at 50 °C for 3 h. After cooling the reaction mixture to ambient temperature, added 2 mL of water, 20 mL of ether, separated the layers and extracted the aqueous layer with ether (3 x 10 mL). The organics were combined, dried over Na$_2$SO$_4$, concentrated and the crude product purified by column chromatography over silica gel (1% EtOAc in hexanes, 1% Et$_3$N) to afford 0.067 g (70%) of the title compound as a colorless oil: $[\alpha]_D = -6.5$ (c 1.2, CHCl$_3$); IR (thin film): 3061, 2977, 2924, 1614, 1444, 1344, 1307, 1185, 1143, 941 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.79 (d, $J = 3.6$ Hz, 1H), 5.56 (d, $J =$
3.1 Hz, 1H), 5.11 (ddq, J = 4.6, 4.6, 1.2 Hz, 1H), 2.18 (dd, J = 13.0, 6.1 Hz, 1H), 2.04–1.94 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.44–1.33 (m, 2H), 1.26 (s, 12H), 1.14–1.08 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 130.7, 130.0, 125.0, 83.2, 43.2, 36.8, 32.2, 25.7, 25.5, 24.7, 24.6, 19.4, 17.6; HRMS calcd for C\(_{17}\)H\(_{31}\)BO\(_2\): 278.2417, found 278.2423.

General procedure for Suzuki coupling (A): A mixture of of iodide 90, boronic ester, palladium(dppf)dichloride [or palladiumbis(acetonitrile)dichloride and dppf] was evacuated and refilled under nitrogen twice. To this was added DMF and barium hydroxide followed by 2 rapid evacuation and N\(_2\) refilling cycles. The resulting yellow solution was stirred at 45 °C for 30 min, during which time it developed a dark brown color. The reaction mixture was worked up by dilution with ether and the addition of 0.5 mL of H\(_2\)O. After separation of the layers, the aqueous layer was extracted with ether (3 x 5 mL). The organics were combined, dried over Na\(_2\)SO\(_4\), concentrated in vacuo, and the crude product was purified by flash chromatography.

\((E)-(3S,5R,10S)-3,5\)-Bis-(tert-butyldimethylsilanyloxy)-5,6,10,14-tetramethyl-8-methylenepentadeca-6,13-dienoic acid methoxymethylamide (100): General procedure A was followed with 30 mg of iodide 90 (0.04 mmol), 24 mg of boronic acid 97 (0.08 mmol, 1.8 equiv), 3.9 mg of Pd(CH\(_3\)CN)Cl\(_2\) (0.01 mmol, 30 mol %), 8.5 mg of dppf, and 48.5 mg of Ba(OH)\(_2\) (0.15 mmol, 3 equiv). Isolated 18 mg of diene 100 (64%) as a colorless oil: [\(\alpha\)]\(_D\) = –7.5 (c 1.0, CHCl\(_3\)); IR (thin film): 2955, 2928, 1669, 1472, 1255, 1128,
1015, 834 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 5.88 (s, 1H), 5.09 (ddq, \(J= 7.1, 7.1, 1.3\) Hz, 1H), 4.99 (br s, 1H), 4.84 (br s, 1H), 4.17 (dddd, \(J= 8.4, 8.4, 5.9, 5.9\) Hz, 1H), 3.66 (s, 3H), 3.14 (s, 3H), 2.65–2.60 (m, 2H), 2.11 (dd, \(J= 13.6, 6.4\) Hz, 1H), 1.94–1.88 (m, 6H), 1.80 (s, 3H), 1.68 (s, 3H), 1.60 (s 3H), 1.45 (s, 3H), 1.14–1.09 (m, 2H), 0.90 (s, 9H), 0.84 (s, 9H), 0.83 (d, \(J= 6.8\) Hz, 3H), 0.12 (s, 3H), 0.06 (s, 3H), 0.02 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 172.4, 145.2, 141.4, 130.9, 125.7, 125.0, 114.4, 77.8, 77.4, 67.2, 61.2, 50.0, 46.0, 40.5, 37.0, 31.9, 31.0, 28.6, 26.2, 25.9, 25.6, 19.4, 18.5, 17.9, 17.6, 15.0, −1.5, −2.1, −4.5, −4.6; HRMS calcd for C\textsubscript{34}H\textsubscript{67}NO\textsubscript{4}Si\textsubscript{2}: 609.4608, found 609.4620.
3.0 COMPLETION OF A C$_{1}$–C$_{20}$ FRAGMENT AND THE SECOND GENERATION APPROACH

3.1 ALTERNATE SYNTHESIS OF THE C$_{7}$–C$_{13}$ FRAGMENT

From our previous studies, we had learned that conversion of the triflate functionality to a boronic ester in the C$_{7}$–C$_{13}$ fragment of amphidinolide B had to precede the installation of the C$_{7}$–C$_{8}$ double bond. A short alternate synthesis of the C$_{7}$–C$_{13}$ fragment was hence realized starting with an AAC reaction of 2-tert-butyilsilanyloxy propionaldehyde [43] with acetyl bromide in the presence of Al(III) triamine catalyst 63a, [44] delivering β-lactone 102 in 86% yield and 95% ee. [45] β-lactone 102 was subjected to cuprate-mediated ring opening with methylmagnesiumbromide to give carboxylic acid 103 in 77% yield. A two step sequence of conversion to the Weinreb amide with N,O- dimethylhydroxylamine and subsequent reaction with methylthithium formed methyl ketone 104 in 81% overall yield. Functionalization of ketone 104 to a boronate ester was done by conversion to triflate 105 following kinetic enolization and trapping with N-phenyltriflimide (89% yield) and subsequent application of Miyaura’s procedure to form boronic ester 106 in 79% yield from triflate 105. [40] A four step sequence of silyl group deprotection using TBAF, Dess-Martin oxidation to the aldehyde, [31] Horner-Wadsworth-Emmons reaction [23] and Dibal-H mediated reduction to the alcohol afforded allylic alcohol
107 in 57% overall yield. Protection of the primary alcohol 107 with a tert-butyldimethylsilyl group proceeded in 91% yield to afford silyl ether 108.

Scheme 11: Alternate synthesis of the C7–C13 fragment

![Scheme 11: Alternate synthesis of the C7–C13 fragment]

\[ \text{Suzuki coupling studies with the C7–C13 fragment} \]

With boronate esters 106a, 107 and 108 in hand, the optimized Suzuki cross-coupling conditions were applied to evaluate the efficiency of formation of the C13–C15 diene in the real system.
system (Eq 5). Hence, with palladium(dppf) dichloride as the catalyst, barium hydroxide as the base and heating at 45 °C in DMF produced desired dienes 109, 110, and 111 respectively. The reaction showed tolerance to a free hydroxyl group as shown by the reaction with fragment 106a yielding diene 109 in 84% yield. The presence of a primary allylic alcohol in boronate ester 107, however, slowed down the cross-coupling considerably, presumably by coordination to the palladium, resulting in a poor yield of the desired diene 110 of 39%. The corresponding α, β-unsaturated aldehyde formed by oxidation of the allylic alcohol in diene 110 was also isolated in 10% yield. Protection of the free hydroxyl group with a tert-butyldimethylsilyl group, however, solved this problem and diene 111 from boronic ester 108 was obtained in an excellent yield of 94%.

\[
\begin{align*}
\text{boronate ester} & \quad \text{Isolated yield of diene} \\
\text{CH}_2\text{OH (106a)} & \quad (109) \ 82\% \\
\text{(E)-CH=CHCH}_2\text{OH (107)} & \quad (110) \ 39\%^a \\
\text{(E)-CH=CHCH}_2\text{OTBS (108)} & \quad (111) \ 94\%
\end{align*}
\]

\(^a\) 10% of the α, β-unsaturated aldehyde was isolated as a byproduct.
3.2.2 Diene instability under Sharpless’ epoxidation conditions

With diene 111 in hand, we decided to incorporate in it the C₈–C₉ epoxide functionality via the asymmetric Sharpless’ epoxidation reaction. Accordingly, the primary tert-butyldimethylsilyl group was removed using HF/pyridine conditions, and allylic alcohol 112 was obtained in 80% yield. Allylic alcohol 112 was then subjected to Sharpless’ epoxidation conditions [29] with titanium isopropoxide, (+)-diethyl tartrate, and tert-butylhydroperoxide. Although the desired epoxidation reaction took place, the diene in the product underwent isomerization under the reaction conditions and the more stable diene 113 was isolated. Presumably, titanium isopropoxide behaved as a Lewis-acid and facilitated isomerization of the diene to the internal position.

Scheme 12: Sharpless' epoxidation of allylic alcohol 112

3.2.3 Modification of the epoxide fragment and completion of the C₇–C₂₀ fragment

In light of the instability of the C₁₃–C₁₅ diene towards Sharpless’ epoxidation conditions, we decided to try incorporating the epoxide moiety earlier in the sequence, before the formation
of the C\textsubscript{13}–C\textsubscript{14} bond. This would also serve to increase convergence in the sequence of steps. Epoxidation of an allylic alcohol in the presence of a vinyl boronic ester was, however, unprecedented. Another important factor was to check the viability of the Suzuki cross-coupling reaction in the presence of epoxide functionality.

Upon subjecting allylic alcohol \textbf{107} to Sharpless’ epoxidation conditions using (+)-diethyl tartarate ligand, the corresponding epoxide was obtained in which the primary alcohol was protected with a tert-butyldimethylsilyl group to afford silyl ether \textbf{114} in an overall yield of 58\% (Scheme 13). We were also pleased to find that the Suzuki cross-coupling reaction of boronate ester \textbf{114} with iodide \textbf{90} under the optimized conditions proceeded smoothly to afford diene \textbf{115} in 80\% yield without any complications arising from the epoxide.
Scheme 13: Completion of a C<sub>7</sub>–C<sub>20</sub> fragment of amphidinolide B<sup>a</sup>

Having shown that we could efficiently couple two major fragments 90 and 114 to form a C<sub>7</sub>–C<sub>20</sub> synthon which constitutes the “left” portion of amphidinolide B, we wanted to investigate the coupling of this fragment with sulfone fragment 65 via a Julia olefination reaction. The primary silyl group in diene 115 was selectively removed by treatment with pyridine-buffered HF and the free hydroxyl group was oxidized with pyridine-buffered Dess-Martin reagent to yield aldehyde 116 in an overall yield of 53% (Scheme 14). Kocienski-modified Julia olefination conditions were applied; sulfone 65 was deprotonated with potassium
bis(trimethylsilyl)amide at –55 °C in DME and then aldehyde 116 was added to it to afford epoxy alkene 117 in 51% yield as a 2:1 mixture of $E:Z$ isomers.

Scheme 14: Elaboration of 115 to a $C_{14}-C_{20}$ synthon

\[ \text{115} \xrightarrow{a,b} \text{53%} \]

\[ \text{115} \xrightarrow{c} \text{51%} \]

$^a$Conditions: (a) HF/Py, 0 °C. (b) Dess-Martin/Py. (c) KHMDS, 65, DME, –55 °C, then 116.

3.3 SHORTCOMINGS OF THE FIRST GENERATION APPROACH

3.3.1 Completion of the $C_{14}-C_{26}$ fragment

Concurrent with our studies on the formation of the $C_{13}-C_{15}$ diene of amphidinolide B, we undertook studies to form the $C_{14}-C_{26}$ fragment which constitutes the “upper fragment” of 1. Optimized conditions were found to open $\beta$-lactone 81 with the lithium anion of dimethylmethyl
phosphonate to form the corresponding β-ketophosphonate 68 in 90% yield (Scheme 15). [47]
The C_{22–C_{26}} aldehyde fragment 69 was generated according to previously reported literature procedures [11] and then coupled with phosphonate 68 under Roush-Masamune conditions to afford unsaturated ketone 118 in 70% yield, which then served as the precursor for Sharpless’ dihydroxylation to install the C_{21–C_{22}} syn diol unit of amphidinolide B. Dihydroxylation of enone 118 with the Sharpless’ reagent system [48] (AD mix-α, 10 mol % K_{2}OsO_{4}.2H_{2}O, 10 mol % (DHQ)_{2}PHAL, NaHCO_{3}, MeSO_{2}NH_{2}, ‘BuOH/H_{2}O) proceeded in moderate yields (42–50%) to deliver diol 119. This sequence completed the installation of the six requisite stereocenters in the C_{14–C_{26}} fragment of 1.

Scheme 15: Synthesis of the C_{14–C_{26}} fragment

\[ \text{Conditions: (a) (MeO)}_{2}(P=O)CH_{2}Li, \text{THF, } –78^\circ \text{C. (b) TBSCI, imidazole, DMF. (c) LiCl, DIPEA, CH}_{3}\text{CN. (d) AD-mix } \alpha, 10 \text{ mol } \% \text{ K}_{2}\text{OsO}_{4}.2\text{H}_{2}\text{O, 10 mol } \% \text{ (DHQ)}_{2}\text{PHAL, NaHCO}_{3}, \text{MeSO}_{2}\text{NH}_{2}, ‘\text{BuOH/H}_{2}\text{O}.]
3.3.2 Sensitivity of the C₂₁-α-keto stereocenter

Completion of a fully functionalized “upper fragment” of amphidinolide B was predicated on the installation of a trisubstituted alkene moiety in the place of the C₁₄–C₁₅ alkyne in diol 119. Prior to the carbometallation of the alkyne, protection of the diol and deprotection of the alkynyl trimethylsilyl group remained to be accomplished. However, we found that under conditions for protection of the diol (excess TBSOTf, lutidine, CH₂Cl₂, 0 °C) the C₂₁-stereocenter underwent partial or complete racemization (Scheme 16). Moreover, subjecting a single diastereomer of bis-protected compound 120 to alkyne trimethylsilyl deprotection conditions (silver nitrate, lutidine, water, ethanol) also led to epimerization of C₂₁-α-keto stereocenter. Presumably, exposure of the α-keto stereocenter to Lewis-acidic conditions in the presence of an organic base i.e. lutidine facilitated easy epimerization of that stereocenter through soft-enolization and protonation steps.
3.4 THE SECOND GENERATION APPROACH TO AMPHIDINOLIDE B- THE ALDOL STRATEGY

3.4.1 Revised retrosynthesis- homologation through Weinreb amide 90

The lability of the C\textsubscript{21}- stereocenter under conditions required to deprotect the alkynyl trimethylsilyl group and install the C\textsubscript{14}–C\textsubscript{15} trisubstituted alkene led us to explore other routes that would allow the carbometallation reaction to take place prior to the coupling of fragments to complete the top half of 1. As an alternate approach to constructing the top fragment, we considered the formation of the C\textsubscript{21}–C\textsubscript{22} bond via a stereoselective aldol reaction between glycolate 122 and aldehyde 69 (Figure 15). Stereoselectivity would be dictated by a Felkin approach on the α-chiral aldehyde and a Zimmerman-Traxler transition state employing a Z-boron enolate would ensure a syn diol relationship across the C\textsubscript{21}–C\textsubscript{22} bond.
According to our revised retrosynthetic analysis, fragment 121 would be obtained after the first two disconnections across the C₁–O bond and the C₆–C₇ bond via macrolactonization and Julia olefination reactions respectively. Further, disconnection across the C₁₃–C₁₄ bond via Suzuki cross-coupling and across the C₂₁–C₂₂ bond via a glycolate aldol reaction gave ketone 122, boronate ester 114 and aldehyde 69. α-Alkoxyl ketone 122 would be formed from Weinreb amide 90 by the addition of an α-alkoxyl methyllithium species to it.

Figure 15: Revised retrosynthetic analysis of Amphidinolide B- the aldol approach
3.4.2 Synthesis of precursors for aldol study

As a two-fold approach to the aldol reaction we decided to prepare enolate precursors arising from iodide 90 as well as diene 115. Weinreb amide 90 was reduced to aldehyde 123 by diisobutylaluminum hydride in 90% yield (Scheme 17). Subsequently, the lithium anion of paramethoxybenzyloxymethane obtained by the tin-lithium exchange of (paramethoxybenzyoxy)tributylstannane [49] was added to aldehyde 123 and the resulting free alcohol was oxidized to ketone 124 by Dess-Martin periodinane in an overall yield of 56%.

Scheme 17: Synthesis of precursor 124 for aldol study

Synthesis of glycolate 125 resulted from the Suzuki cross-coupling of iodide 124 with boronic ester 114 under the previously optimized conditions (Eq 6). Although we were able to isolate diene 125 in 44–50% yields, the presence of the C\textsubscript{20} ketone functionality led to elimination of the C\textsubscript{18} β-silyloxy group in the product to give 21–30% of undesired enone 126 as a byproduct.

\textsuperscript{a}Conditions: (a) Dibal-H. (b) PMBOCH\textsubscript{2}Li, THF. (c) Dess-Martin periodinane, CH\textsubscript{2}Cl\textsubscript{2}.
3.4.3 Glycolate aldol trials

α-alkoxy ketones 124 and 125 were individually subjected to typical soft-enolization conditions for generating Z-enolates i.e. dibutylboron triflate, Hunig’s base at –78 °C in CH₂Cl₂ and then reacted with aldehyde 69 (Eq 7). Disappointingly, both reactions resulted in decomposition of the starting material glycolates. While the stability of vinyl iodide functionality to boron-based Lewis acids is not well documented in the literature, a sharp color change from colorless to deep red upon addition of dibutylboron triflate to iodide 124 in CH₂Cl₂ led us to believe that complications in the reaction could be arising because of the presence of the vinyl iodide moiety. Decomposition of diene 125 possibly occurred by isomerization of the 1, 1-disubstituted diene to the more stable internal position and/or reactivity of the sensitive C₇–C₈ epoxide.
We did not attempt to test the glycolate aldol coupling strategy in any of the intermediates that precede iodide 124 since we would encounter the problem of epimerization of the C$_{21}$-alkoxide bearing stereocenter while attempting to transform the C$_{14}$–C$_{15}$ alkyne to the trisubstituted alkene functionality.

3.5 THE DITHIANE ROUTE FOR FRAGMENT COUPLING

3.5.1 Alternate coupling strategy to form the C$_{14}$–C$_{26}$ fragment

As an alternate means of forming the complete C$_{14}$–C$_{26}$ fragment we decided to explore the viability of forming the C$_{20}$–C$_{21}$ bond. We envisioned that the fully functionalized top half 127 would result from carbometalation of the alkyne silyl-deprotected form of fragment 128 in which the C$_{20}$-ketone would be protected as a dithiane (Figure 16). Fragment 128 would result from the addition of the anion derived from dithiane 129 into aldehyde 130 followed by protection of the newly formed hydroxyl group. The presence of a chelating alkoxy group in the
α position of the aldehyde would ensure formation of the correct stereochemistry at the C21 carbon through a chelate-Cram transition state. [50]

![Chemical structures](attachment:diagram.png)

*Figure 16: Retrosynthesis of the C14–C26 fragment- the dithiane approach*

### 3.5.2 Synthesis of aldehyde fragment 130 and dithiane 129

Synthesis of the requisite fragment 130 started with aldehyde 76 available through our AAC methodology (Scheme 18). Conversion of aldehyde 76 to epoxy alcohol 131 proceeded in the three steps of Wittig homologation, diisobutylaluminum hydride-mediated reduction and Sharpless’ epoxidation, previously reported in the literature. [51] Epoxide 132 was regioselectively methylated with trimethylaluminum [52] and the primary alcohol in the resulting diol was selectively protected with a paramethoxybenzyl group to afford alcohol 133 in 53% overall yield. The C2– hydroxyl bearing stereocenter was inverted through a Mitsunobu reaction
yielding alcohol 133 in 86% yield. Protection of the 2° alcohol with a benzyl group, selective deprotection of the paramethoxybenzyl group with DDQ was followed by oxidation of the resulting primary alcohol under Swern oxidation conditions to furnish aldehyde 130 in 57% yield over 3 steps.

Scheme 18: Synthesis of aldehyde 130 for dithiane trials

Weinreb amide 86a was reduced with diisobutylaluminum hydride to the corresponding aldehyde which was then converted to dithiane 129 by treatment with propane 1, 3-dithiol, titanium tetrachloride in CH₂Cl₂ in 55% yield (Eq 8).
3.5.3 Dithiane reaction trials

With dithiane 129 and aldehyde 130 in hand, we attempted lithiation of the dithiane and subsequent addition to aldehyde 130 under various conditions (Eq 9). Unfortunately, we were unable to find conditions to metalate dithiane 129. Treatment of excess dithiane 129 with butyllithium at –50 °C in THF and addition of aldehyde 130 led to the recovery of the dithiane and the addition product of butyl anion into aldehyde 130. We then subjected dithiane 129 to metalation with tert-butyllithium in THF at –50 °C and allowed the reaction mixture to warm to ambient temperature to facilitate metalation, and then added aldehyde 130 at –50 °C. This led to the complete recovery of dithiane 129 and decomposition of the aldehyde. Even metalation with butyllithium in the presence of HMPA additive at –50 °C and subsequent addition of aldehyde to the reaction mixture failed to produce any product and resulted in the recovery of dithiane 129 and aldehyde 130.

\[
\text{Conditions:}
\]

(a) BuLi, THF, –50 °C, then 130  
(b) tBuLi, THF, –50 °C – RT, then –50 °C, 130  
(c) BuLi, HMPA, –50 °C, then 130

The unsuccessful attempts to add the anion of dithiane 129 into aldehyde 130 prompted us to perform control experiments to trap the anion with other, more reactive electrophiles such as TMSCl. Under a variety of conditions with bases such as butyllithium, tert-butyllithium,
potassium bis(trimethylsilyl)amide, experiments to metalse dithiane 129 and trap the anion with TMSCl led to the complete recovery of intact 129. At this point, we do not have an explanation for the resistance of dithiane 129 towards metalation; and in order to proceed with our synthesis goals we have decided to abandon this route for the formation of the C_{14} – C_{26} fragment of 1.

3.6 CONCLUSIONS

In pursuit of a total synthesis of the cytotoxic macrolide amphidinolide B (1), asymmetric AAC reactions have been used to set key stereochemical relationships in major fragments 90 and 114. An efficient method to couple two major fragments to form the C_{13} – C_{15} trisubstituted diene in 1 was found and applied in the synthesis of the C_{7} – C_{20} fragment 115. Subsequent homologation was achieved through a Julia olefination reaction to complete a C_{1} – C_{20} synthon, 117. Alternate coupling strategies in forming the C_{21} – C_{22} bond and the C_{20} – C_{21} bond were investigated.

EXPERIMENTAL SECTION

(R)-4-[2-(tert-Butyldimethylsilanyloxy)ethyl]oxetan-2-one (102) : To a solution of 1.432 g of triamine ligand precursor to catalyst 63a (2.11 mmol) in 18 mL of CH_{2}Cl_{2} was added 1.27 mL of trimethylaluminum (2.53 mmol) (2 M solution in hexanes) and was stirred
for 2 h. The solution was cooled to –78 °C, and 3.1 mL of iPr₂NEt (17.9 mmol) was added to it followed by the slow addition of 1.5 mL of acetylbromide (20.1 mmol). To the resulting pale yellow solution was added 2.0 g of 3-(tert-butyl-dimethyl-silanyloxy)-propionaldehyde⁴² (10.6 mmol) in 6 mL of CH₂Cl₂. The reaction mixture was stirred overnight at –78 °C, diluted with 3% Et₃N in ether and filtered through a short plug of silica gel using 3% Et₃N in ether. The filtrate was concentrated in vacuo and the crude product was purified by Kugelrohr distillation (pot temperature: 70–75 °C) at 75 mTorr to afford 2.10 g of the title compound (86%) as a colorless oil. Derivatization with benzylamine followed by the separation of the corresponding enantiomers on HPLC determined the enantiomeric excess to be 95.4%, using racemic sample as standard; [α]D = +23.2 (c 2.20, CHCl₃); IR (thin film): 2955, 2929, 2884, 1830, 1472, 1256, 1108, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.69 (dddd, J = 10.4, 6.1, 4.4, 4.4 Hz, 1H), 3.79–3.74 (m, 2H), 3.55 (dd, J = 16.4, 5.8 Hz, 1H), 3.21 (dd, J = 16.4, 4.3 Hz, 1H), 2.11–1.93 (m, 2 H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 168.3, 69.0, 58.7, 43.1, 37.2, 25.7, 18.1, –5.6; EI-MS e/ν 173 (M⁺–i-Bu), 131 (M⁺–i-Bu–CH₂CO), 101; HRMS calcd for C₇H₁₃O₄: 173.0634, found 173.0632.

(S)-5-(tert-Butyldimethylsilanyloxy)-3-methylpentanoic acid (103): To a –50 °C solution of 1.118 g of CuBr (7.79 mmol) in 40 mL of THF and 6 mL of dimethylsulfide, was added 5.2 mL of methylmagnesiumbromide (15.6 mmol) (3 M solution in ether) slowly to give a yellow suspension. The suspension was allowed to warm to –30 °C and stirred at that temperature for 30 min. The reaction mixture was cooled back to –50 °C, and 1.200 g of the above lactone (5.19 mmol) in 6 mL of THF was added to it, and then
it was maintained at –50 °C for 45 min. Then, 0.9 mL (7.74 mmol) of trimethylsilylchloride was added to it and the reaction mixture was allowed to warm to ambient temperature overnight. It was quenched with 20 mL of a saturated aqueous solution of NH₄Cl. After separation of the layers, the organic layer was washed twice with 30 mL of saturated NH₄Cl solution and once with a saturated solution of EDTA. The combined aqueous layers were extracted with ether (5 x 30 mL). The combined organics were dried over Na₂SO₄, concentrated in vacuo and the crude product was purified by flash chromatography (5% EtOAc in hexanes) to yield 0.993 g of the title compound (77%) as a pale yellow, viscous oil: [α]D = –1.5 (c 2.0, CHCl₃); IR (thin film): 3582, 2956, 2857, 1709, 1462, 1256, 1098, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.75–3.64 (m, 2H), 2.41 (dd, J = 14.2, 5.1 Hz, 1H), 2.25–2.07 (m, 2H), 1.59 (dddd, J = 12.8, 6.8, 6.8, 6.0 Hz, 1H), 0.47 (dddd, J = 13.4, 7.1, 6.3, 6.3 Hz, 1H), 0.99 (d, J = 6.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 179.4, 61.0, 41.5, 39.2, 27.2, 26.0, 19.8, 18.3, –5.4; EI-MS e/ν 189 (M⁺–t-Bu), 171 (M⁺–t-Bu–H₂O), 145 (M⁺–t-Bu–CO₂), 127, 115; HRMS calcd for C₈H₁₇O₃Si: 189.0947, found 189.0952.

(S)-[5-(tert-Butyldimethylsilyloxy)-3-methylpentanoic acid methoxymethylamide (103a): To a solution of 2.05 g (8.29 mmol) of carboxylic acid 103 in 25 mL of CH₂Cl₂ was added 1.21 g of N,O-dimethylhydroxylamine hydrochloride (12.4 mmol), 2.39 g of EDCI (12.4 mmol) and 1.53 g of DMAP (12.4 mmol). The resulting solution was stirred at ambient temperature for 2 h and quenched with 25 mL of brine. After separation of layers, the aqueous layer was extracted with EtOAc (5 x 25mL). The combined organics were dried over MgSO₄ and the solvent evaporated
in vacuo. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to obtain 2.145 g (90%) of the title compound as a colorless oil: $[\alpha]_D = +7.5$ (c 2.3, CHCl$_3$); IR (thin film): 2956, 2857, 1669, 1463, 1411, 1384, 1255, 1095, 836 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 3.67-3.56 (m, 2H), 3.62 (s, 3H), 3.14 (s, 3H), 2.40 (dd, $J = 14.8, 5.6$ Hz, 1H), 2.25 (dd, $J = 14.3, 8.1$ Hz, 1H), 2.18–2.07 (m, 1H), 1.57 (dddd, $J = 13.4, 6.9, 6.9, 6.9$ Hz, 1H), 1.39 (dddd, $J = 13.7, 6.8, 6.8, 6.8$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 174.0, 77.3, 61.3, 61.1, 39.8, 39.2, 26.9, 25.9, 20.0, 18.3, −5.3; EI-MS e/v 274 (M$^+$–Me), 232, 158, 129; HRMS calcd for C$_{13}$H$_{28}$NO$_3$Si: 274.1838, found 229.1839.

(S)-6-(tert-Butyldimethylsilyl oxy)-4-methylhexan-2-one (104): To a 0 °C solution of 0.64 g (2.19 mmol) of the above Weinreb amide in 20 mL of THF was added 1.8 mL (2.88 mmol) of a 1.6 M solution of methyllithium in ether. The resulting solution was warmed to ambient temperature and stirred for 15 min. The reaction was worked up by the addition of 30 mL of ether and 20 mL of water. After separation of the layers, the aqueous layer was extracted with ether (5 x 20 mL). The combined organics were dried over MgSO$_4$ and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography (4% EtOAc in hexanes) to obtain 0.490 g (91%) of the title compound as a colorless oil: $[\alpha]_D = −4.7$ (c 2.1, CHCl$_3$); IR (thin film): 2956, 2927, 1718, 1471, 1255, 1093, 836 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 3.77–3.58 (m, 2H), 2.47 (dd, $J = 15.3, 5.2$ Hz, 1H), 2.28–2.17 (m, 2H), 2.12 (s, 3H), 1.52 (dddd, $J = 12.7, 6.5, 6.5, 6.5$ Hz, 1H), 1.39 (dddd, $J = 13.5, 6.6$ Hz, 1H), 0.92 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 208.8, 60.9, 51.2, 39.5, 30.1, 26.2, 25.9, 19.8, 18.2, −5.4; EI-MS e/v 229 (M$^+$–Me),
(S)-(Trifluoromethanesulfonic acid-4-(tert-butyldimethylsilanyloxy)-2-methylbutyl)-vinyl ester (105): To a –78 °C solution of 18.6 mL of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (9.29 mmol) in THF (10 mL) was added a solution of 1.89 g of ketone 104 (7.74 mmol) in THF (18 mL), dropwise. The resulting solution was stirred at –78 °C for 15 min and then, a solution of 3.87 g (10.8 mmol) of N-phenyltriflimide in THF (20 mL) was cannulated into the reaction mixture to produce a yellow solution which was then allowed to warm to 0 °C. Then, 30 mL of a saturated NaHCO₃ solution and 35 mL of ether were added to it, the layers were separated, and the aqueous layer washed with ether (5 x 30 mL). The combined organics were dried over Na₂SO₄, concentrated and purified by column chromatography over silica gel (0.5% EtOAc in hexanes, 2% Et₃N) to afford 2.58 g (89%) of the title compound as a colorless oil; [α]D = –5.18 (c 2.04, CHCl₃); IR (thin film): 2957, 2931, 2857, 1669, 1420, 1211, 1141 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.14 (d, J = 3.4 Hz, 1H), 4.95 (d, J = 3.4 Hz, 1H), 3.73–3.57 (m, 2H), 2.40 (dd, J = 15.3, 6.2 Hz, 1H), 2.15 (dd, J = 15.2, 7.9 Hz, 1H), 2.01–1.92 (m, 1H), 1.63 (dddd, J = 12.3, 6.8, 5.1, 5.1 Hz, 1H), 1.37 (dddd, J = 11.7, 8.1, 5.8, 5.8 Hz, 1H), 0.97 (d, J = 6.6 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 155.7, 118.5 (J_C-F = 318.2 Hz), 105.3, 60.6, 41.5, 38.9, 26.9, 25.8, 18.9, 18.2, –5.4; EI-MS e/v 319 (M⁺–tBu), 291, 227; HRMS calcd for C₁₆H₂₈O₄F₃: 319.0647, found: 319.0653.
(S)-4,4,5,5-Tetramethyl-2-[1-(2-methyl-4-trimethylsilyloxy-butyl)-vinyl]-[1,3,2]dioxaborolane (106): A mixture of 0.300 g of triflate 105 (0.802 mmol), 0.224 g of bis(pinacolato)diboron (0.882 mmol), 0.056 g of bis(triphenylphosphine)palladium dichloride (0.088 mmol), 0.042 g of triphenylphosphine (0.160 mmol) and 0.154 g of potassium phenoxide (1.20 mmol) in 5 mL of toluene (0.2 M) was heated at 50 °C for 3 h. After cooling the reaction mixture to ambient temperature, added 2 mL of water, 20 mL of ether, separated the layers and extracted the aqueous layer with ether (3 x 10 mL). The organics were combined, dried over Na₂SO₄, concentrated and and the crude product purified by column chromatography over silica gel (2% EtOAc in hexanes, 1% Et₃N) to afford 0.225 g (79%) of the title compound as a colorless oil; [α]D = –3.39 (c 2.25, CHCl₃); IR (thin film): 2977, 2957, 2857, 1614, 1427, 1370, 1308, 1255, 144, 1096 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.80 (d, J = 3.6 Hz, 1H), 5.56 (d, J = 3.3 Hz, 1H), 3.70–3.58 (m, 2H), 2.18 (dd, J = 13.0, 6.0 Hz, 1H), 1.95 (dd, J = 13.0, 7.8 Hz, 1H), 1.80–1.71 (m, 1H), 1.60 (ddd, J = 13.1, 7.3, 5.2 Hz, 1H), 1.33–1.24 (m, 1H), 1.25 (s, 12H), 0.89 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 130.3, 83.2, 77.4, 61.5, 43.3, 39.8, 29.4, 25.9, 24.7, 19.4, 18.3, –5.3; EI-MS e/v 297 (M⁺-Bu), 197, 169, 155; HRMS calcd for C₁₅H₃₀BO₃Si: 297.2057, found: 297.2055.

(R)-3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-hex-5-enal (106b): To a solution of 0.420 g of boronic ester 106 in THF (12 mL) was added a 1 M solution of tetrabutyl ammonium fluoride in THF at ambient temperature and the reaction mixture was stirred overnight. To this was added 20 mL of ether and 5 mL of NaHCO₃ and after separation of the layers, the organic layer was washed with 5 mL of brine and
the aqueous layers were extracted with ether (5 x 20 mL). The combined organics were dried over Na₂SO₄, concentrated and and the crude product taken over to the next step without purification. To a 0 °C solution of the crude alcohol in 5 mL of CH₂Cl₂ was added a freshly prepared solution of 1.51 g of Dess-Martin periodinane in 1.7 mL of pyridine and 7mL of CH₂Cl₂. The reaction mixture was allowed to warm to ambient temperature and stirred for 3 h. It was then diluted with pentane and filtered through a short plug of florisil. The filtrate was concentrated and purified by column chromatography (8% ether in pentane) to afford 0.200 g of the title compound (70%); [α]D = +6.85 (c 1.08, CHCl₃); IR (thin film): 2978, 2930, 2716, 1726, 1615, 1370, 1311, 1143, 861 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.75 (dd, J = 2.1 Hz, 1H), 5.87 (d, J = 3.3 Hz, 1H), 5.61 (s, 1H), 2.42 (ddd, J = 15.7, 4.7, 1.7 Hz, 1H), 2.28–2.23 (m, 1H), 2.19–2.12 (m, 3H), 1.27 (s, 12H), 0.94 (d, J = 6.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 203.3, 131.5, 83.5, 77.2, 50.4, 42.9, 28.1, 24.7, 20.5; HRMS calcd for C₁₃H₂₃BO₃: 238.174, found: 238.1741.

(S,E)-5-Methyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-octa-2,7-dienoic acid ethyl ester (106c): To a 0 °C suspension of 0.161 g of NaH (4.03 mmol) in THF (0.5 mL), was added 0.85 ml of diisopropyl(ethoxycarbonylmethyl) phosphonate (3.36 mmol). This was stirred at 0 °C for 20 min and a solution of aldehyde 106b in THF (2.3 mL) was added to it. The reaction mixture was allowed to warm to ambient temperature, and then, 3 mL H₂O was added to it, the layers were separated and the aqueous layer was washed with EtOAc (3 x 10 mL). The organics were combined and concentrated and the crude material was purified by flash chromatography (4%
EtOAc/Hex) to yield 0.230 g (88%) of the title compound as a yellow oil: [α]D = –7.6 (c 2.4, CHCl3); IR (thin film) 2978, 2926, 2854, 1722, 1653, 1369, 1310, 1204, 1143 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 6.96 (dd, J = 14.8, 7.5, 7.1 Hz, 1H), 5.84 (d, J = 3.5 Hz, 1H), 5.83 (ddd, J = 15.6, 1.4, 1.4 Hz, 1H), 5.58 (d, J = 3.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.29–2.13 (m, 2H), 1.88–1.77 (m, 1H), 1.29 (t, J = 5.2 Hz, 3H), 1.26 (s, 12H), 0.86 (d, J = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl3): δ 166.7, 148.5, 130.9, 122.3, 83.4, 77.4, 60.1, 42.9, 39.2, 32.2, 24.7, 19.4, 14.3; HRMS calcd for C₁₇H₂₉BO₄: 308.2159, found 308.2159.

(S)-5-Methyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-octa-2,7-dien-1-ol (107): To a –40 °C solution of 0.445 g of the above ester in 9 mL of CH₂Cl₂ was added 2.7 mL of a 1.6 M solution of diisobutylaluminum hydride in hexanes and the reaction mixture was stirred at that temperature for 30 min. It was quenched with a saturated solution of Rochelle’s salt and the resulting emulsion was allowed to clear by stirring for 1 h. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organics were dried over Na₂SO₄, concentrated and and the crude product was purified by column chromatography (10–20% EtOAc/ Hex) to afford 0.350 g of allylic alcohol 107 (92%): [α]D = –4.85 (c 2.15, CHCl₃); IR (thin film): 3377, 2977, 2923, 1614, 1427, 1369, 1308, 1142, 970 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.89 (d, J = 3.6 Hz, 1H) 5.68 (ddd, J = 15.4, 5.9, 5.9 Hz, 1H), 5.59 (ddd, J = 15.2, 4.6, 4.6 Hz, 1H), 5.55 (d, J = 2.9 Hz, H), 4.07 (app. d, J = 4.3 Hz, 2H), 2.17 (dd, J = 13.1, 6.2 Hz, 1H), 2.06 (ddd, J = 12.8, 5.4, 5.4 Hz, 1H), 1.94 (dd, J = 13.2, 7.7 Hz, 1H), 1.88–1.77 (m, 1H), 1.75–1.61(m, 1H), 1.66 (s,1H), 1.25 (s, 12H), 0.82 (d, J = 66 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 132.1, 130.5, 130.2, 83.4, 77.2,
2-[(E)-(S)-7-(tert-Butyldimethylsilanyloxy)-3-methyl-1-methylenehept-5-enyl]-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (108): To a 0 °C solution of 0.134 g of allylic alcohol 107 (0.50 mmol) in 4 mL of DMF was added 0.038 g of imidazole (0.55 mmol, 1.1 equiv) and 0.091 g of tert-butyldimethylsilyl chloride (0.60 mmol, 1.2 equiv). The resulting solution was allowed to warm to ambient temperature and stirred for 8 h. It was quenched by the addition of 3 mL of brine and 10 mL of ether. After separation of the layers, the organic layer was washed with 5 mL of brine. The aqueous layers were extracted with ether (3 x 5 mL). The combined organics were dried over Na₂SO₄, concentrated and the crude product purified by flash chromatography (5% EtOAc in hexanes) to afford 0.157 g of silyl ether 108 as a colorless oil (82%); [α]D = −3.7 (c 2.0, CHCl₃); IR (thin film): 2956, 2928, 2857, 1614, 1462, 1370, 1254, 1144, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.81 (d, J = 3.6 Hz, 1H), 5.67–5.47 (m, 3H), 4.13 (dd, J = 5.0, 1.0 Hz, 2H), 2.18 (dd, J = 13.1, 6.2 Hz, 1H), 2.08 (ddd, J = 13.4, 5.8, 5.8 Hz, 1H), 1.96 (dd, J = 13.1, 7.7 Hz, 1H), 1.83 (ddd, J = 14.2, 7.4, 7.4 Hz, 1H), 1.74–1.65 (m, 1H), 1.26 (s, 12H), 0.90 (s, 9H), 0.83 (d, J = 6.5 Hz, 3H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 130.5 (2 C), 130.1, 83.4, 77.5, 64.2, 42.8, 39.4, 33.0, 26.1, 24.8, 19.3, 18.5, −4.9; HRMS calcd for C₁₇H₃₂BO₃Si: 323.2214, found 323.2202.
(E)-(3S,5R,10R)-3,5-Bis-(tert-butyldimethylsilanyloxy)-12-hydroxy-5,6,10-trimethyl-8-methylene-dodec-6-enoic acid methoxy-methyl-amide (109): General procedure A was followed with 20 mg of iodide 90 (0.03 mmol), 23 mg of boronic ester 106a (0.09 mmol), 26 mg of Pd(CH$_3$CN)$_2$Cl$_2$ (0.01, 30 mol %), 5.7 mg of dppf (0.01 mmol) and 32 mg of Ba(OH)$_2$·8H$_2$O (0.10 mmol, 3 equiv). Isolated 16 mg of diene 109 (82%) as a colorless oil: $[\alpha]_D = -41.6$ (c 1.1, CHCl$_3$); IR (thin film): 3443, 2954, 2928, 2856, 1643, 1472, 1386, 1255, 1002, 834 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 5.94 (s, 1H), 5.01 (br s, 1H), 4.82 (br s, 1H), 3.66 (s, 3H), 3.65–3.60 (m, 2H), 3.40 (t, $J = 6.5$ Hz, 1H), 3.14 (s, 3H), 2.72 (d, $J = 5.0$ Hz, 2H), 2.17 (dd, $J = 8.6$, 3.0 Hz, 1H), 1.95 (dd, $J = 10.5$, 3.6 Hz, 1H), 1.94–1.74 (m, 3H) 1.82 (s, 3H), 1.66–1.56 (m, 2H), 1.43 (s, 3H), 0.91 (s, 9H), 0.85 (d, $J = 6.2$ Hz, 3H), 0.83 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), –0.01 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 173.1, 145.4, 141.0, 125.8, 114.9, 78.3, 77.3, 67.7, 61.4, 60.2, 49.2, 47.1, 40.9, 40.3, 31.9, 27.4, 26.4, 26.0, 18.8, 18.7, 15.8, –1.2, –1.7, –4.5, –4.7; HRMS calcd for (M$^+$+Na) C$_{31}$H$_{61}$NO$_4$Si$_2$Na: 594.3986, found 594.4088.

(6E,12E)-(3S,5R,10S)-3,5,14-Tris-(tert-butyldimethylsilanyloxy)-5,6,10-trimethyl-8-methylene-tetradeca-6,12-dienoic acid methoxymethylamide (111): General procedure A was followed with 20 mg of iodide 90 (0.03 mmol), 20 mg of boronic ester 108 (0.05 mmol), 26 mg of Pd(CH$_3$CN)$_2$Cl$_2$ (0.01, 30 mol %), 5.7 mg of dppf (0.01 mmol) and 32 mg of Ba(OH)$_2$·8H$_2$O (0.10 mmol, 3 equiv). Isolated 23
mg of diene 108 (94%) as a colorless oil: \([\alpha]_D = -4.9\) (c 1.2, CHCl₃); IR (thin film): 2955, 2928, 2856, 1669, 1462, 1255, 1094, 835 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta 5.88\) (s, 1H), 5.57–5.53 (m, 2H), 4.99 (s, 1H), 4.84 (s, 1H), 4.12 (d, \(J = 4.5\) Hz, 2H), 3.66 (s, 3H), 3.14 (s, 3H), 2.65–2.63 (m, 2H), 2.14–2.01 (m, 3H), 1.93–1.84 (m, 3H), 1.79 (s, 3H), 1.61 (dddd, \(J = 6.3, 6.3, 6.3, 6.3\) Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.84 (s, 9H), 0.83–0.81 (m, 3H), 0.12 (s, 3H), 0.07 (s, 6H), 0.05 (s, 6H), 0.00 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta 172.5, 145.0, 141.5, 130.6, 129.7, 125.5, 114.6, 77.8, 67.2, 64.1, 61.2, 49.9, 45.5, 40.5, 39.4, 31.9, 31.5, 29.7, 28.6, 26.2, 26.0, 25.9, 18.5, 18.4, 17.9, 15.0, –1.0, –1.4, –2.1, –4.5, –4.6, –5.1; HRMS calcd for (M⁺+Na) \(C_{38}H_{77}NO_5Si_3Na\): 734.5007, found 734.5005.

\((2S,3S,5R)-3-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-enyl]-oxiranyl]-methanol (107a): To a –20 °C suspension of 0.370 g of flame-dried, activated 4 Å molecular sieves in 2 mL of CH₂Cl₂ was added a solution of 0.050 g of (+) diethyl tartarate (0.241 mmol) in 2 mL of CH₂Cl₂ followed by 0.0445 mL of Ti(OiPr)₄ (0.153 mmol) and 0.12 mL of \(\text{tert-butylhydroperoxide}\) (0.602 mmol) dropwise, via syringe. After stirring the resulting white suspension for 30 min, a solution of 0.080 g of allylic alcohol 107 (0.300 mmol) in 3 mL of CH₂Cl₂ was added to it. The reaction mixture was stirred at –20 °C for 16 h and quenched with a freshly prepared solution of 0.040 g of ferrous sulfate and 0.012 g of citric acid in 1 mL of water. After separation of the layers, the organic layer was filtered through a short plug of 1:1 celite/florisil, and the filter cake was washed with EtOAc. The aqueous layer was also extracted with EtOAc (3 x 5 mL). The combined organics were dried over Na₂SO₄, concentrated and the crude product was purified.
by medium pressure liquid chromatography (10–40% EtOAc/ Hex) to afford 0.057 g of epoxide 107a (67%) as a colorless oil : $\alpha_D = -16.3$ ($c$ 2.0, CHCl$_3$); IR (thin film): 3436, 2977, 2950, 1410, 1370, 1309, 1143, 862 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.83 ($d$, $J$ = 3.4 Hz, 1H), 5.58 ($d$, $J$ = 3.1 Hz, 1H), 3.89 ($ddd$, $J$ = 12.5, 5.0, 2.8 Hz, 1H), 3.65 ($ddd$, $J$ = 11.4, 6.8, 4.3 Hz, 1H), 2.99 ($ddd$, $J$ = 5.9, 5.9, 2.3, 1H), 2.91 ($ddd$, $J$ = 4.5, 2.6, 2.6 Hz, 1H), 2.21 ($dd$, $J$ = 13.1, 6.3 Hz, 1H), 2.03 ($dd$, $J$ = 13.0, 7.6 Hz, 1H), 1.80-1.76 ($m$, 2H) 1.69 ($ddd$, $J$ = 11.0, 5.6, 5.6 Hz, 1H), 1.26 ($s$, 12H), 0.92 ($d$, 6.6 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 131.0, 83.4, 77.5, 61.7, 58.8, 54.8, 43.1, 38.4, 30.6, 24.7, 19.6; HRMS calcd for C$_{15}$H$_{27}$BO$_4$: 282.2002, found 282.1986.

$^{2S,3S,5R}$-2-(1-{3-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxiranyl]-2-methyl-propyl}-vinyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (114): To a 0 °C solution of 0.045g of epoxy alcohol 107a (0.159 mmol) in 4 mL of DMF was added 0.033 g of imidazole (0.478 mmol) and 0.072 g of tert-butyldimethylsilyl chloride (0.478 mmol). The resulting solution was allowed to warm to ambient temperature and stirred for 8 h. It was quenched by the addition of 3 mL of brine and 10 mL of ether. After separation of the layers, the organic layer was washed with 5 mL of brine. The aqueous layers were extracted with ether (3 x 5 mL). The combined organics were dried over Na$_2$SO$_4$, concentrated and the crude product purified by flash chromatography (5% EtOAc in hexanes) to afford 0.054 g of silyl ether 114 as a colorless oil (86%): $\alpha_D = -7.46$ ($c$ 0.45, CHCl$_3$); IR (thin film): 2956, 2929, 2857, 1463, 1370, 1311, 1254, 1144, 1110, 837 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.83 ($d$, $J$ = 3.2 Hz, 1H), 5.58 ($br s$, 1H), 3.78 ($ddd$, $J$ = 11.8, 2.3, 2.3 Hz, 1H), 3.67 ($ddd$, $J$ = 12.6, 4.6, 4.6 Hz, 1H), 2.86-2.82 ($m$, 2H), 2.20 ($dd$, $J$ =
13.2, 6.6 Hz, 1H), 2.04 (dd, J = 12.8, 7.5 Hz, 1H), 1.86 (dddd, J = 12.5, 6.3, 6.3, 6.3 Hz, 1H), 1.73–1.65 (m, 2H), 1.26 (s, 12H), 0.92 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 130.7, 83.3, 63.8, 59.1, 55.2, 43.2, 38.5, 30.6, 25.8, 24.7, 19.4, 18.3, –5.3, –5.4; HRMS calcd for \((M^+\text{Na})\) C\(_{51}\)H\(_{41}\)BO\(_4\)Si\(_3\)Na: 419.2765, found 419.2779.

\((3S,5R,10R,12S,13S)-3,5\text{-Bis(\text{tert-butyldimethylsilanyloxy})-8\{-3\text{-[3-(\text{tert-butyldimethylsilanyloxymethyl})-oxiranyl}\}-2\text{-methyl-propyl}\}-5,6\text{-dimethyl-nona-6,8-dienoic acid methoxymethylamide (115)}\):

General procedure A was followed with 19 mg of iodide 90 (0.032 mmol), 20 mg of boronic ester 114 (0.050 mmol), 11 mg of palladium(dppf)dichloride (0.013 mmol, 40 mol %) and 32 mg of barium hydroxide (0.096 mmol). Isolated 20 mg of the title compound as a pale yellow oil (80%): \([\alpha]_D = –7.25\) (c 0.80, CHCl\(_3\)); IR (thin film): 2955, 2928, 2856, 1665, 1472, 1462, 1385, 1254, 835 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.90 (s, 1H), 5.01 (s, 1H), 4.87 (s, 1H), 4.20–4.12 (m, 1H), 3.76 (dddd, J = 11.5, 3.0, 3.0 Hz, 1H), 3.70–3.59 (m, 1H), 3.66 (s, 3H), 3.14 (s, 3H), 2.88–2.80 (m, 2H), 2.66–2.62 (m, 2H), 2.15 (dd, J = 12.9, 6.2 Hz, 1H), 1.98–1.85 (m, 4H), 1.79 (s, 3H), 1.78–1.64 (m, 2H), 1.52 (s, 3H), 0.93–0.90 (m, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.00 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 172.5, 144.6, 141.7, 125.4, 114.8, 77.9, 77.4, 67.3, 63.8, 61.2, 59.1, 55.1, 49.8, 46.0, 40.5, 38.7, 30.3, 28.7, 26.2, 25.9, 19.5, 18.6, 18.3, 17.9, 15.0, –1.5, –2.0, –4.5, –5.3, –5.4; HRMS calcd for \((M^+\text{Na})\) C\(_{38}\)H\(_{77}\)NO\(_6\)Si\(_3\)Na: 750.4956, found 750.4991.
(E)-(3S,5R,10R)-3,5-Bis-(tert-butyldimethylsilanyloxy)-11-((2S,3S)-3-hydroxymethyl-oxiranyl)-5,6,10-trimethyl-8-methylene-undec-6-enoic acid methoxymethylamide (115a):

A 1.2 M solution of pyridine-buffered HF/Py was prepared as follows: To a 0 °C solution of 38 mg of silyl ether 115 (0.05 mmol) in THF (4 mL) added 3.3 mL of the above prepared HF/py solution (3.9 mmol, 80 equiv.) dropwise via syringe. Stirred the reaction mixture for 12 h at 0 °C, then diluted it with 20 mL of ether and added 5 mL of water to it. After separation of layers, extracted the aqueous layer with ether (5 x 5 mL) and dried the combined organics over Na₂SO₄. The solvents were evaporated in vacuo and the crude product was purified by flash chromatography (2% Et₃N, 10–30% EtOAc in hexanes) to afford 24 mg of the title product (75% yield) as a colorless oil: [α]D = −27.2 (c 1.70, CHCl₃); IR (thin film): 3434, 2954, 2928, 2856, 1660, 1462, 1255, 1027, 834 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.95 (s, 1H), 5.04 (s, 1H), 4.84 (s, 1H), 4.07–4.00 (m, 1H), 3.88–3.85 (m, 1H), 3.67 (s, 3H), 3.60 (dd, J = 12.4, 4.6 Hz, 1H), 3.13 (s, 3H), 2.94–2.90 (m, 2H), 2.76–2.61 (m, 2H), 2.23 (dd, J = 12.8, 3.8 Hz, 1H), 2.02–1.80 (m, 4H), 1.82 (s, 3H), 1.82–1.80 (m, 2H), 1.43 (s, 3H), 0.93 (s, 9H), 0.92–0.89 (m, 3H), 0.82 (s, 9H), 0.15 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 172.8, 144.6, 141.3, 125.0, 114.8, 78.1, 77.4, 67.4, 62.4, 61.3, 58.8, 55.7, 49.6, 46.5, 40.4, 39.4, 31.9, 29.3, 26.3, 25.8, 19.3, 18.7, 17.9, 15.4, −1.3, −1.7, −4.5, −4.8; HRMS calcd for (M⁺+Na) C₃₂H₆₃NO₆Si₂Na: 636.4092, found 636.4092.
(E)-(3S,5R,10R)-3,5-Bis-(tert-butyldimethylsilanyloxy)-11-((2S,3R)-3-formyl-oxiranyl)-5,6,10-trimethyl-8-methylene-undec-6-enoic acid methoxymethylamide (116): Dess-Martin reagent in pyridine was prepared as follows: To a solution of 116 mg of Dess-Martin reagent (0.27 mmol, 12 equiv.) in 0.4 mL of CH₂Cl₂, added 0.13 mL of pyridine (72 equiv). The resulting solution was stirred at ambient temperature for 2 minutes and the supernatant liquid was added via syringe into a 0 °C solution of 14 mg of alcohol 115a (0.022 mmol) in 0.2 mL of CH₂Cl₂. The resulting solution was allowed to warm to ambient temperature and stirred for 1.5 h. It was diluted with hexanes, filtered through a short plug of florisil, with 10% EtOAc in hexanes. After concentration in vacuo the crude product was purified by column chromatography (5% Et₃N, then 5–10 % EtOAc in hexanes) to afford 9.8 mg of the title compound as a clear oil (70% yield): [α]D = +9.6 (c 1.0, CHCl₃); IR (thin film): 2928, 2855, 1731, 1659, 1462, 1384, 1254, 1001, 834 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.99 (d, J = 6.2 Hz, 1H), 5.92 (s, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 4.18–4.05 (m, 1H), 3.66 (s, 3H), 3.33 (dd, J = 5.8, 5.8 Hz, 1H), 3.13 (s, 3H), 3.12–3.08 (m, 1H), 2.69–2.65 (m, 2H), 2.19 (dd, J = 12.7, 5.3 Hz, 1H), 2.05–1.90 (m, 3H), 1.80 (s, 3H), 1.71–1.65 (m, 2H), 1.48 (s, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 0.83 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), −0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 198.5, 172.5, 144.3, 141.9, 125.3, 115.1, 78.0, 77.2, 67.4, 61.2, 59.6, 55.7, 49.6, 45.9, 40.5, 38.3, 31.9, 29.7, 26.2, 25.8, 19.5, 18.6, 17.9, 15.2, −1.4, −1.9, −4.5, −4.6; El-MS e/ν 611, 596 (M⁺–Me), 554 (M⁺–¹Bu); HRMS calcd for C₂₈H₅₂NO₆Si₂: 554.3333, found 554.3349.
(E)-5-{(2S,3S)-3-{[(E)-(2R,7R,9S)-7,9-Bis-(tert-butyldimethylsilyloxy)-10-methylene-dec-5-enyl]-oxiranyl}-2-methyl-pent-2-enyl}acid 2-trimethylsilaneylethyl ester (117): To a −55 °C solution of 51.3 mg of sulfone 65 (0.12 mmol, 8.0 equiv.) in DME (0.21 mL) added 0.26 mL of a 0.5 M solution of potassium bistrimethylsilylamide in toluene (0.13 mmol, 8.7 equiv.). The resulting pale yellow solution was stirred for 30 min and then a solution of 9 mg of aldehyde 116 (0.015 mmol) in 0.17 mL of DME was added to it to make the overall concentration 0.3 M w.r.t. sulfone 65. The solution was stirred at −55 °C for 2 h and warmed to ambient temperature over 2 h. The reaction mixture was quenched by the addition of 1 mL of brine and 5 mL of ether. After separation of layers, the aqueous layer was extracted with ether (3 x 5 mL) and the combined organics were dried over Na₂SO₄. The solvents were evaporated in vacuo and the crude product was purified by flash chromatography (1% Et₃N, then 5% EtOAc in hexanes) to afford 6 mg of the title compound (51% yield), a colorless oil, as a 2:1 mixture of E:Z isomers: [α]D = −5.85 (c 0.80, CHCl₃); IR (thin film): 2954, 2928, 2855, 1709, 1665, 1462, 1252, 1116, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.73 (dd, J = 5.6, 5.6 Hz, 1H), 5.90 (s, 1H), 5.91–5.87 (m, 1H), 5.23 (dd, J = 15.5, 8.1 Hz, 1H), 5.00 (s, 1H), 4.87 (s, 1H), 4.24 (dd, J = 8.2, 8.2 Hz, 2H), 4.21–4.13 (m, 1H), 3.66 (s, 3H), 3.14 (s, 3H), 3.02 (dd, J = 7.9, 2.9 Hz, 1H), 2.86–2.82 (m, 1H), 2.66–2.63 (m, 2H), 2.28–2.13 (m, 5H), 1.96–1.88 (m, 3H), 1.83 (br s, 3H), 1.80 (s, 3H), 1.70–1.65 (m, 2H), 1.45 (s, 3H), 1.04 (dd, J = 8.4, 8.4 Hz, 2H), 0.92 (d, J = 6.1 Hz, 3H), 0.91 (s, 9H), 0.84 (s, 9H), 0.13 (s, 3H), 0.07 (s, 6H), 0.05 (s, 9H), 0.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 168.2 (2C), 144.5, 141.7, 141.0, 140.4, 134.7, 128.6, 125.4, 114.9, 78.3, 77.2, 67.3, 62.7, 61.2, 59.0, 49.8,
(E)-(3S,5R)-3,5-Bis-(tert-butyldimethylsilanyloxy)-7-iodo-5,6-dimethyl-hept-6-enal (123): To a –78 °C solution of 0.160 g of Weinreb amide 90 (027 mmol) in 0.6 mL of CH₂Cl₂ added 0.5 mL of diisobutylaluminum hydride (1 M solution in hexanes, 0.54 mmol) dropwise via syringe. The solution was stirred at –78 °C for 10 min and then quenched with 10 mL of 0.2 M solution of HCl. The resulting turbid solution was allowed to stir for 1 h during which time it separated into clear layers. The layers were separated and the organic layer was filtered through a 1:1 mixture of celite: florisil. The aqueous layers were extracted with CH₂Cl₂ (5 x 10 mL). The combined organics were dried over Na₂SO₄ and the solvents were removed in vacuo. The crude product was purified by falsh chromatography (2% EtOAc in hexanes) to afford 0.129 g of aldehyde 123 (90%) as a clear oil: [α]D = +3.0 (c 1.3, CHCl₃); IR (thin film): 2955, 2929, 2857, 1727, 1471, 1256, 1124, 1002, 836 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 9.77 (dd, J = 3.1, 1.8 Hz, 1H), 6.36 (s, 1H), 4.12 (dddd, J = 11.8, 6.3, 4.6, 4.6 Hz, 1H), 2.75 (ddd, J = 15.9, 4.4, 1.8 Hz, 1H), 2.46 (ddd, J = 15.9, 6.3, 3.2 Hz, 1H), 1.97 (dd, J = 14.4, 4.8 Hz, 1H), 1.87 (s, 3H), 1.83 (dd, J = 14.4, 7.4 Hz, 1H), 1.45 (s, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H);¹³C NMR (75 MHz, CDCl₃): δ 202.0, 151.0, 79.0, 78.7, 65.3, 52.0, 49.3, 28.7, 26.1, 25.8, 22.2, 18.5, 17.9, –1.6, –2.2, –4.2, –4.4; HRMS calcd for (M⁺+Na) C₂₁H₄₃O₃Si₂Na: 549.1693, found 549.1643.
(E)-(4S,6R)-4,6-Bis-(tert-butyldimethylsilanyloxy)-8-iodo-1-(4-methoxybenzyloxy)-6,7-dimethyl-oct-7-en-2-one (124): To a –78 °C solution of 70 mg of (paramethoxybenzyloxy)tributylstannane (0.16 mmol, 1.5 equiv) in 0.4 mL of THF, was added 80 μL of BuLi (1.6 M solution in hexanes, 0.13 mmol, 1.2 equiv) and the solution was stirred for 20 min. To this was added a solution of 56 mg of aldehyde 123 (0.1 mmol) in 0.35 mL of THF. The reaction mixture was stirred at –78 °C for 15 min and quenched with saturated NH₄Cl solution. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organics were dried over Na₂SO₄ and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (2–5% EtOAc in hexanes) and was dissolved in CH₂Cl₂ at 0 °C, to which 78 mg of Dess-Martin periodinane was added. The resulting solution was stirred for 3 h at ambient temperature, diluted with hexanes and filtered through a plug of florisil with 2% EtOAc in hexanes. The solvents were evaporated and the crude product purified by flash chromatography (2% EtOAc in hexanes) to afford 36 mg of the title compound (50%) as a colorless oil: [α]D = +11.5 (c 1.90, CHCl₃); IR (thin film): 2954, 2929, 2856, 1720, 1612, 1514, 1251, 1093, 1002, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.33–7.26 (m, 2H), 6.88 (d, J = 8.7, 2H), 6.31 (s, 1H), 4.52 (s, 2H), 4.14–4.09 (m, 1H), 3.98 (s, 2H), 3.82 (s, 3H), 2.64 (dd, J = 15.7, 4.5 Hz, 1H), 2.54 (dd, J = 15.6, 7.3 Hz, 1H), 1.86 (s, 3H), 1.83–1.79 (m, 2H), 1.44 (s, 3H), 0.88 (s, 9H), 0.83 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 206.6, 159.5, 151.4, 129.6, 129.4, 113.9, 78.8, 78.7, 75.5, 72.9, 65.8, 55.3, 49.5, 47.7, 28.5, 26.1, 25.9, 22.1, 18.5, 17.9, –1.6, –2.3, –4.3, –4.5; HRMS calcd for (M⁺+Na) C₃₀H₅₃IO₅Si₂Na: 699.2374, found 699.2349.
(2R,3R,5S)-5-(tert-Butyldimethylsilyloxy)-3-methyl-hexane-1,2-diol (131a): To a 0 °C solution of 400 mg of epoxide 131 (1.6 mmol) in 6 mL of hexanes, added 2.5 mL of Me₃Al (2 M solution in hexanes, 4.9 mmol, 3.0 equiv) dropwise. The resulting solution was warmed to ambient temperature and stirred for 1h. It was diluted with 4mL of water, 4 mL of 0.2 M aqueous HCl solution and 10 mL of ether. The turbid white suspension was allowed to clear by stirring and then the layers were separated and the aqueous layer was extracted with ether (5 x 10 mL). The combined organics were dried over MgSO₄ and concentrated. The crude product was purified by flash column chromatography (10–25% EtOAc in hexanes) to afford 350 mg of the title compound (83% yield) as a colorless oil: [α]D = +28.9 (c 1.30, CHCl₃); IR (thin film): 3389, 2958, 2929, 2857, 1462, 1255, 1071, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.90–3.85 (m, 1H), 3.64 (dd, J = 10.6, 2.4 Hz, 1H), 3.51–3.37 (m, 2H), 3.17 (br s, 1H), 1.79–1.62 (m, 2H), 1.22–1.17 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 0.90 (d, J = 4.6 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 76.7, 67.3, 65.0, 42.9, 32.9, 26.1, 24.8, 18.1, 17.0, −4.0, −4.5; EI-MS e/ν 231 (M⁺–Me–H₂O), 205 (M⁺–tBu), 187, 119, 99; HRMS calcd for C₁₂H₂₇O₂Si: 231.1780, found 231.1776.

(2R,3R,5S)-5-(tert-Butyldimethylsilyloxy)-1-(4-methoxy-benzylxy)-3-methylhexan-2-ol (132): To a 0 °C suspension of 25 mg of NaH (1.0 mmol, 2.0 equiv) in THF (0.5 mL), added a solution of 80 mg of diol 131a (3.1 mmol) in 1 mL of THF dropwise. The turbid white solution was allowed to warm to ambient temperature over 1h. Then, 57 mg of tetrabutylammonium bromide (1.5 mmol, 0.5 equiv) was
added followed by 60 mg of paramethoxybenzylbromide (3.7 mmol, 1.2 equiv) as a neat liquid. The resulting solution was stirred at ambient temperature for 24 h. The reaction mixture was diluted with 15 mL of ether and 5 mL of water. The layers were separated; the aqueous layer was extracted with ether (5 x 10 mL) and the combined organics were dried over MgSO₄. After evaporation of the solvent in vacuo the crude product was purified by flash chromatography (5–10 % EtOAc in hexanes) to afford 75 mg of the title compound (64% yield) as a colorless oil: [α]D = +13.8 (c 1.30, CHCl₃); IR (thin film): 3466, 2956, 2928, 2856, 1613, 1514, 1249, 1078, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.27 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.49 (s, 2H), 3.94–3.84 (m, 1H), 3.81 (s, 3H), 3.62 (ddd, J = 8.3, 5.6, 2.6 Hz, 1H), 3.51 (dd, J = 9.4, 2.9 Hz, 1H), 3.44–3.38 (m, 1H), 1.88–1.79 (m, 1H), 2.51 (s, 1H), 1.66 (ddd, J = 13.2, 9.3, 3.3 Hz, 1H), 1.15 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 130.1, 129.3, 113.8, 74.7, 73.0, 72.4, 66.3, 55.2, 42.2, 32.2, 25.9, 24.6, 18.0, 16.0, –4.1, –4.8; HRMS calcd for (M⁺+Na) C₂₁H₃₈O₄SiNa : 405.2437 found 405.2415.

(2S,3R,5S)-5-(tert-Butyldimethylsilanyloxy)-1-(4-methoxybenzylacyloxy)-3-methylhexan-2-ol (133): To a solution of 280 mg of alcohol 132 (0.7 mmol) in 7.4 mL of toluene (0.1 M) added 584 mg of triphenylphosphine (2.2 mmol, 3.0 equiv), 371 mg of p-nitrobenzoic acid (2.2 mmol, 3.0 equiv) and 0.45 mL of diisopropylazadicarboxylate (2.2 mmol, 3.0 equiv). The resulting solution was allowed to stir at ambient temperature for 1 h, following which it was diluted with 20 mL of ether and 10 mL of brine solution was added to it. The organic layer was separated and washed with saturated NaHCO₃ solution. The aqueous layers were extracted with ether (5 x 20 mL) and the combined
organics were dried over MgSO₄. After evaporation of the solvents \textit{in vacuo}, the crude product was purified by flash chromatography to give 380 mg of the benzoate ester that was saponified by the addition of 10 mL of a 1% solution of NaOH in MeOH. After stirring for 2 h, the solution was concentrated. To gave a white solid that was dissolved in ether (10 mL) and saturated NaHCO₃ solution (5 mL). After separation of layers, the aqueous layer was extracted with ether (5 x 20 mL). The crude product obtained after evaporation of the solvent was purified by flash chromatography (3–5% EtOAc in hexanes) to afford 241 mg of the title compound (86% overall yield) as a colorless oil: [\(\alpha\)]D = +20 (c 1.1, CHCl₃); IR (thin film): 3466, 2957, 2929, 2856, 1613, 1514, 1249, 1074, 835 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 7.29 (d, \(J = 8.5\) Hz, 2H), 6.90 (d, \(J = 8.5\) Hz, 2H), 4.50 (s, 2H), 3.96–3.88 (m, 1H), 3.82 (s, 3H), 3.68 (ddd, \(J = 8.1, 4.1, 3.3\) Hz, 1H), 3.53 (dd, \(J = 9.4, 3.3\) Hz, 1H), 3.41 (dd, \(J = 8.9, 8.9\) Hz, 1H), 2.47 (br s, 1H), 1.82–1.78 (m, 1H), 1.55 (ddd, \(J = 8.4, 4.3, 3.9\) Hz, 1H), 1.28–1.18 (m, 1H), 1.15 (d, \(J = 6.0\) Hz, 3H), 0.93 (d, \(J = 6.8\) Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); \(^1^3\)C NMR (75 MHz, CDCl₃): \(\delta\) 159.1, 130.0, 129.3, 113.7, 73.9, 72.9, 72.8, 66.1, 55.1, 43.5, 31.9, 25.8, 24.6, 17.9, 14.1, –4.1, –4.8; HRMS calcd for (M\(^{+}\)+Na) \(C_{21}H_{38}O_4Si\): 405.2437 found 405.2415.

\[\text{[(IS,3R,4S)-4-Benzylxoy-5-(4-methoxybenzxyloxy)-1,3-dimethylpentyloxy]-tert-butyldimethylsilane (133a)}\]: To a 0 °C suspension of 118 mg of sodium hydride (2.9 mmol, 4.0 equiv) in 1 mL of THF added a solution of 280 mg of alcohol 133 (0.7 mmol) in 2.7 mL of THF. The resulting solution was allowed to warm to ambient temperature stirred for 30 min. Then, 136 mg of tetrabutylammonium bromide (1.5 mmol, 0.5 equiv) was added followed by 0.35 mL of benzylbromide (2.9 mmol, 4.0 equiv) as a
neat liquid. The resulting solution was stirred at ambient temperature overnight. The reaction mixture was diluted with 15 mL of ether and 5 mL of water. The layers were separated, and the organic layer was washed with 5 mL of brine solution. The aqueous layer was then extracted with ether (5 x 10 mL) and the combined organics were dried over MgSO₄. After evaporation of the solvent in vacuo the crude product was purified by flash chromatography (2% EtOAc in hexanes) to afford 310 mg of the title compound (90% yield) as a colorless oil: [α]₀ = +9.9 (c 1.6, CHCl₃); IR (thin film): 3030, 2956, 2929, 2898, 2855, 1612, 1513, 1301, 1248, 1172, 1074, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.36–7.22 (m, 7H), 6.84 (ddd, J = 8.7, 2.5, 2.5 Hz, 2H), 4.70 (d, J = 11.8 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.47–4.45 (m, 2H), 3.91–3.85 (m, 1H), 3.79 (s, 3H), 3.57–3.55 (m, 1H), 3.49–3.45 (m, 1H), 2.00 (ddd, J = 10.2, 7.0, 3.6 Hz, 1H), 1.59 (ddd, J = 13.2, 9.2, 3.5 Hz, 1H), 1.20 (ddd, J = 13.4, 9.9, 3.3 Hz, 1H), 1.12 (d, J = 6.0 Hz, 3H), 1.08–1.03 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 159.2, 139.4, 130.7, 129.3, 128.6, 128.3, 127.9, 127.7, 127.4, 113.9, 82.7, 73.1, 72.7, 71.8, 66.3, 55.4, 43.5, 31.4, 26.1, 24.9, 18.2, 14.6, −3.9, −4.6; HRMS calcd for (M⁺+Na) C₂₈H₄₄O₄Si: 495.2907 found 495.2909.

**(2S,3R,5S)-2-Benzylxy-5-(tert-butyldimethylsilanyloxy)-3-methylhexan-1-ol (133b):** To a solution of 55 mg of paramethoxybenzylether 133a (0.1 mmol) in a 10:1 CH₂Cl₂–H₂O solvent mixture (1.1 mL), was added 26 mg of DDQ (0.1 mmol) at ambient temperature. The mixture was stirred for 1 h and then the solvents were evaporated in vacuo and the crude product was purified by flash chromatography (5–20% EtOAc in hexanes) to afford 31 mg of the title compound (75% yield)
as a colorless oil: [α]D = +49.6 (c 1.0, CHCl3); IR (thin film): 3434, 2957, 2929, 2883, 2856, 1496, 1255, 1074, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 7.37–7.27 (m, 5H), 4.70 (d, J = 11.3 Hz, 1H), 4.49 (d, J = 11.3 Hz, 1H), 3.94–3.87 (m, 2H), 3.69–3.59 (m, 2H), 3.43 (ddd, J = 8.3, 7.5, 4.2 Hz, 1H), 2.22–2.12 (m, 1H), 1.96 (br s, 1H), 1.70 (ddd, J = 12.9, 9.7, 2.7 Hz, 1H), 1.16 (d, J = 6.0 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.90 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (75 MHz, CDCl3): δ 138.5, 128.4, 127.8, 127.7, 84.1, 71.8, 66.0, 62.2, 41.8, 29.7, 25.9, 24.8, 18.0, 15.3, –4.1, –4.8; HRMS calcd for (M⁺+Na) C₂₀H₃₆O₃SiNa : 375.2331 found 375.2332.

**(2S,3R,5S)-2-Benzylloxy-5-(tert-butyldimethylsilanyloxy)-3-methylhexanal (130):** To a –78 °C solution of 12 μL of oxalyl chloride in 0.4 mL of CH₂Cl₂ added 20 μL of DMSO dropwise. The turbid solution was stirred at –78 °C for 10 min and then a solution of 30 mg of alcohol 133b in 0.4 mL of CH₂Cl₂ was added and the resulting solution was stirred at –78 °C for 30 min following which 70 μL of DIPEA was added. After stirring at –78 °C for 10 min it was warmed to ambient temperature over 30 min. The reaction was worked up by the addition of 2 mL of ether and 3 mL of saturated ammonium chloride solution. After separation of layers, the aqueous layer was extracted with ether (3 x 5 mL). The combined organics were dried over Na₂SO₄ and evaporated in vacuo. The crude product was purified by column chromatography (5% EtOAc in hexanes) on Iatrobeads to isolate 26 mg of the title compound (84% yield): [α]D = –15.4 (c 0.61, CHCl3); IR (thin film): 2958, 2929, 2856, 1732, 1462, 1255, 1131, 1075, 835 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 9.67 (d, J = 2.2 Hz, 1H), 7.37–7.33 (m, 5H), 4.70 (d, J = 11.7 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 3.89 (ddq, J = 9.3, 2.6, 2.6 Hz, 1H), 3.62 (dd, J = 4.6, 2.6 Hz, 1H), 2.30–2.20 (m, 1H), 1.57 (ddd, J = 13.5,
9.4, 4.1 Hz, 1H), 1.30 (ddd, \( J = 13.4, 9.9, 3.3 \) Hz, 1H), 1.14 (d, \( J = 6.0 \) Hz, 3H), 0.97 (d, \( J = 6.9 \) Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\( \text{3} \)): \( \delta \) 204.2, 137.6, 128.4, 128.2, 127.9, 87.6, 72.7, 65.9, 42.8, 31.2, 25.9, 24.6, 18.0, 14.2, –4.1, –4.8; HRMS calcd for (M\(^{+}\)+Na) C\(_{20}\)H\(_{34}\)O\(_3\)Si: 373.2175 found 373.2179.

(3\( S \),5\( R \))-3,5-Bis-(tert-butyldimethylsilyloxy)-5-methyl-7-trimethylsilyl-hept-6-ynal (86b): To a –78 °C solution of 0.160 g of Weinreb amide 86a (0.31 mmol) in 0.7 mL of CH\(_2\)Cl\(_2\) added 0.62 mL of diisobutylalimimum hydride (1 M solution in hexanes, 0.62 mmol) dropwise via syringe. The solution was stirred at –78 °C for 10 min and then quenched with 10 mL of 0.2 M solution of HCl. The resulting turbid solution was allowed to stir for 1 h during which time it separated into clear layers. The layers were separated and the organic layer was filtered through a 1:1 mixture of celite: florisil. The aqueous layers were extracted with CH\(_2\)Cl\(_2\) (5 x 10 mL). The combined organics were dried over Na\(_2\)SO\(_4\) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (2% EtOAc in hexanes) to afford 0.124 g of aldehyde 86b (88%) as a clear oil: \([\alpha]_D = +8.3 \) (c 1.0, CHCl\(_3\)); IR (thin film): 2956, 2930, 2857, 2710, 2166, 1729, 1472, 1252, 1114, 838 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 9.81 (dd, \( J = 3.2, 2.1 \) Hz, 1H), 4.58 (dddd, \( J = 10.3, 7.6, 5.9, 3.0 \) Hz, 1H), 2.87 (ddd, \( J = 15.9, 2.6, 1.8 \) Hz, 1H), 2.58 (ddd, \( J = 10.9, 7.6, 3.2 \) Hz, 1H), 1.98 (dd, \( J = 14.0, 9.4 \) Hz, 1H), 1.81 (dd, \( J = 13.8, 2.6 \) Hz, 1H), 1.46 (s, 3H), 0.86 (s, 9H), 0.84 (s, 9H), 0.21 (s, 3H), 0.18 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 202.8, 108.9, 89.7, 68.4, 66.6, 52.1, 32.5, 25.7 (2C), 17.9, 17.8, –0.3, –2.9, –3.1, –4.1, –4.7; HRMS calcd for (M\(^{+}\)+Na) C\(_{23}\)H\(_{48}\)O\(_3\)Si\(_3\): 479.2809, found 479.2811.
2-[(2S,4R)-2,4-Bis-(tert-butyldimethylsilanyloxy)-4-methyl-6-trimethylsilyl-hex-5-ynyl]-[1,3]dithiane (129): To a −10 °C solution of 60 mg of aldehyde 86b (0.130 mmol) and 17 mg of 1, 3-propanedithiol (0.16 mmol, 1.2 equiv) in 1 mL of CH₂Cl₂ was added 13 μL of titanium tetrachloride (1 M solution in CH₂Cl₂, 0.013 mmol, 0.1 equiv). The resulting solution was allowed to warm to ambient temperature and stirred for 1 h. It was then quenched with saturated NH₄Cl solution and the layers were separated. The aqueous layer was extracted with ether (3 x 5 mL). The combined organics were dried over MgSO₄ and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography (1% EtOAc in hexanes) to afford 44 mg of dithiane 129 (61%) as a clear oil: [α]_D = +31.7 (c 0.606, CHCl₃); IR (thin film): 2956, 2929, 2856, 2165, 1472, 1252, 1123, 989, 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.30 (ddddd, J = 12.1, 8.1, 6.5, 3.8 Hz, 1H), 4.17 (dd, J = 11.2, 3.3 Hz, 1H), 2.95–2.69 (m, 4H), 2.32 (dd, J = 14.1, 11.3, 2.7 Hz, 1H), 2.14–2.04 (m, 1H), 1.95–1.67 (m, 4H), 1.43 (s, 3H), 0.90 (s, 9H), 0.87 (s, 9H), 0.23 (s, 3H), 0.21 (s, 3H), 0.19 (s, 9H), 0.15 (s, 3H), 0.12 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 109.1, 89.4, 77.2, 68.0, 67.1, 52.6, 44.8, 43.7, 32.5, 30.9, 30.1, 25.9, 25.8, 18.0, 17.9, −0.2, −2.7, −2.8, −4.0, −4.5; HRMS calcd for C₂₆H₅₄O₂Si₃S₂: 546.2873, found 546.2866.
BIBLIOGRAPHY


[25] This is an alternative route to the known sulfone fragment 65, previously made by Pattenden and co-workers. See ref. 11.

[26] This step was performed by Dr. Andrew J. Kassick. See Andrew J. Kassick, Ph.D. thesis, University of Pittsburgh, 2004.


[28] Compounds 74 and 74a were not fully characterized since they are known compounds.


[42] Treatment of boronic ester 97 with mineral acids led to hydrolysis of the trisubstituted double bond.


[45] Enantiomeric excess was determined by opening the lactone with benzylamine and HPLC analysis of the corresponding amide.


