EFFORTS TOWARDS THE TOTAL SYNTHESIS OF AMPHIDINOLIDE B

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Submitted to the Graduate Faculty of

Chemistry in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2006

UNIVERSITY OF PITTSBURGH

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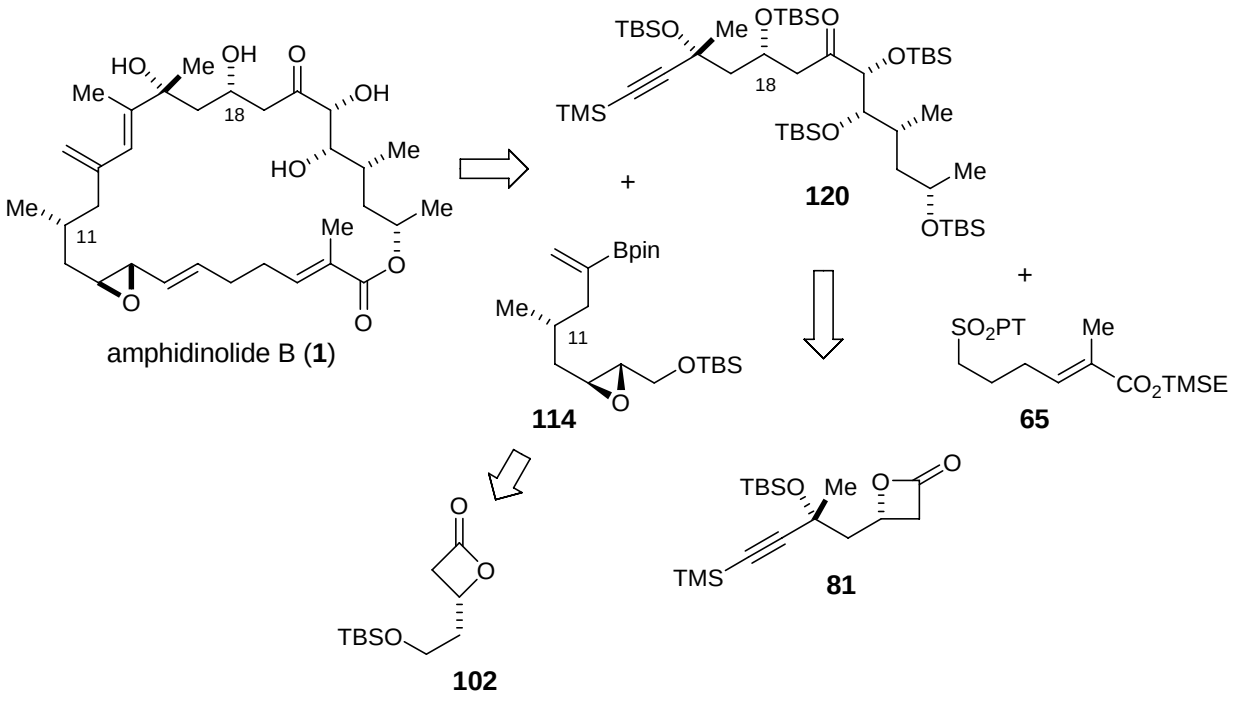
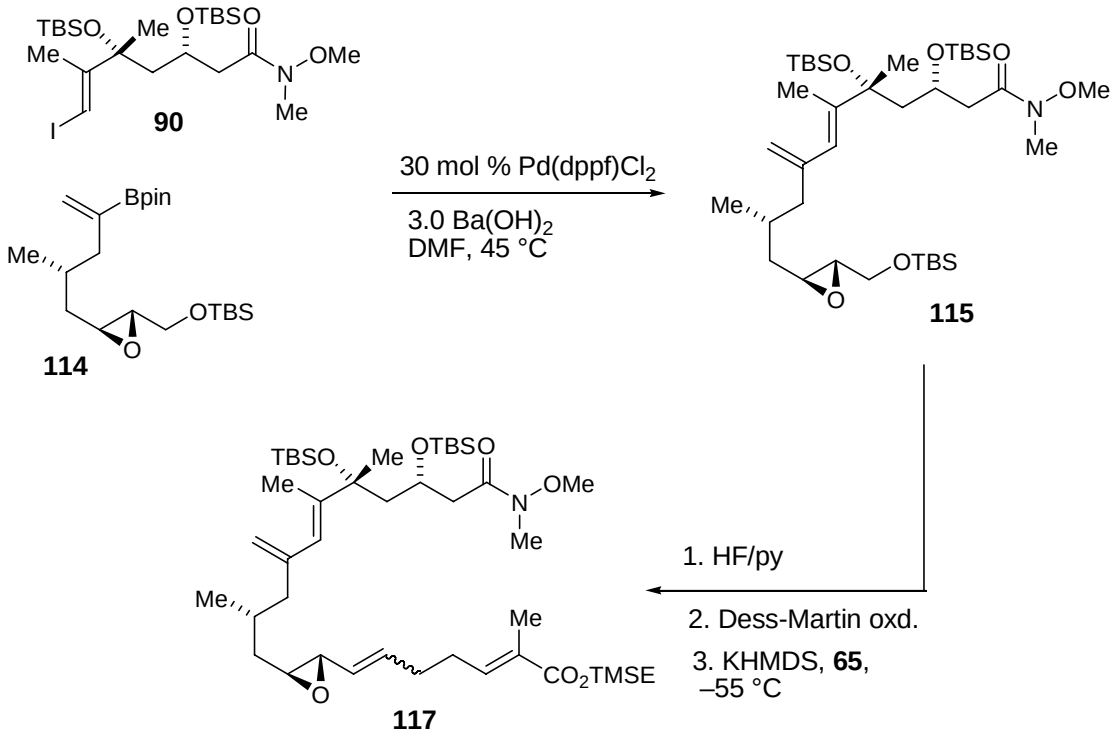
Studies towards the total synthesis of the cytotoxic marine macrolide Amphidinolide B have been disclosed. Catalytic asymmetric AAC methodology has been applied to efficiently generate the C_{11}- and the C_{18}- stereocenters in the requisite fragments **114** and **120** through β-lactones **102** 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_7-C_{20} fragment **115**. Fragment was further homologated and coupled to sulfone **65** to complete a C_1-C_{20} synthon of amphidinolide B.



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LIST OF ABBREVIATIONS

DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
$(DHQ)_2PHAL$	dihydroquinine 1,4-phthalazinediiyl diether
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	diisopropylazodicarboxylate
DMAP	2-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
HMPA	hexamethylphosphoramide
nOe	nuclear Overhauser effect
TBAF	tetrabutylammoniumfluoride
TBSOTf	*tert*-butyldimethylsilyl triflate
TFA	trifluoroacetic acid
TMSCl	trimethylsilylchloride

ACKNOWLEDGEMENTS

I am thankful to God Almighty for giving me the strength to pursue graduate school to obtain an advanced degree.

My thanks are due to my advisor Scott Nelson, for being a great teacher, mentor and giving me the opportunity to work on such an interesting and challenging project. He has offered excellent guidance and support in the project as well as outside; in making his students understand fundamental concepts.

I would like to thank all the members of the Nelson group, past and present, for friendship and good company. In particular, I would like to thank Andrew Kassick, who worked with me on my project, and was a great source of inspiration. Post-doctoral associates Chris Bungard and Cheng Zhu were excellent mentors in my first three years and not only taught me skills, but maintained a lively atmosphere at work. My special thanks are due to Ben Stevens for great moral support in times of trouble and good friendship. I would also like to thank Magda, Andrew, Xiaoqiang, Nessan and Jeremy for nice company at work and during the many group lunches.

I would like to thank Siva, Raghu and Vasu for wonderful friendship and I will always cherish the great times I have had with them. I would also like to thank Dhanalakshmi for being a really good friend and being of great help in my final year.

My parents and my brothers have been extremely supportive in the last five years and I could not have made it through without their inspiration and constant words of advice. I am truly blessed to have them as my family.

I would like to thank my husband Hari, for his constant source of moral support, good advice, for patiently listening to my complaints, especially in the last few months and… just for being there. I consider myself very lucky to be his wife.

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 (**1**) is among the most biologically significant and structurally interesting molecules in this class of macrolides.

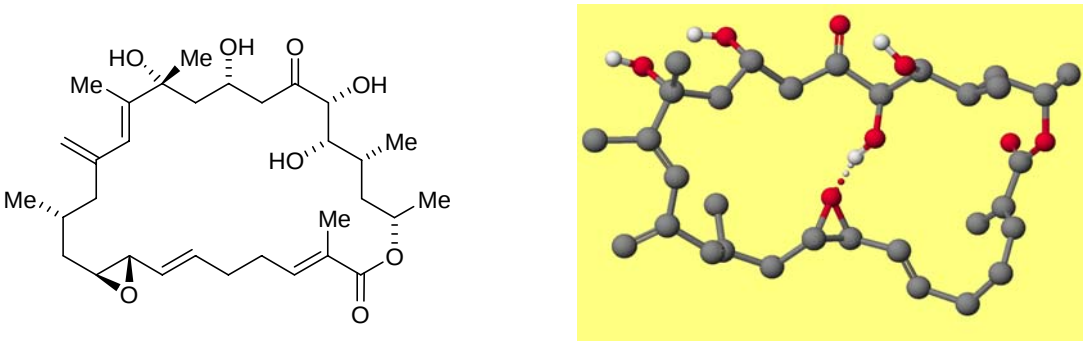
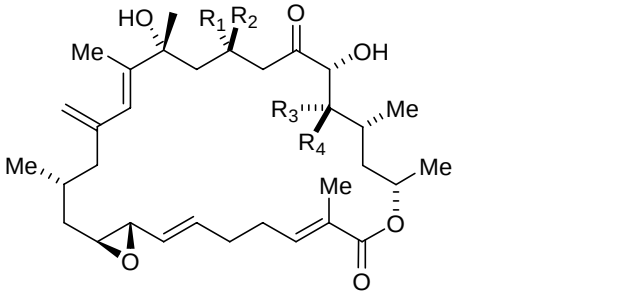


Figure 1. Amphidinolide B (1)

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.



Amphidinolide B_2 (**2**) $R_2 = R_3 = OH$, $R_1 = R_4 = H$
Amphidinolide B_3 (**3**) $R_1 = R_4 = OH$, $R_2 = R_3 = H$

Figure 2. The amphidinolide B congeners

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).[2] 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. [1,4] It displays IC_{50} values of 0.14 ng/mL against the L1210 murine leukemia cell line, 0.12 μg/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_{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 1/600th 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 1. Cytotoxic activities of amphidinolide B and related compounds [1a]

Compounds	IC_{50} [a]/μg mL^{-1} (L1210)[b]	(KB)[c]
amphidinolide B (1)	0.00014	0.0042
amphidinolide D	0.019	0.08
amphidinolide H	0.0004	0.00052
epoxide-opened derivative of 1	0.081	-

[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]

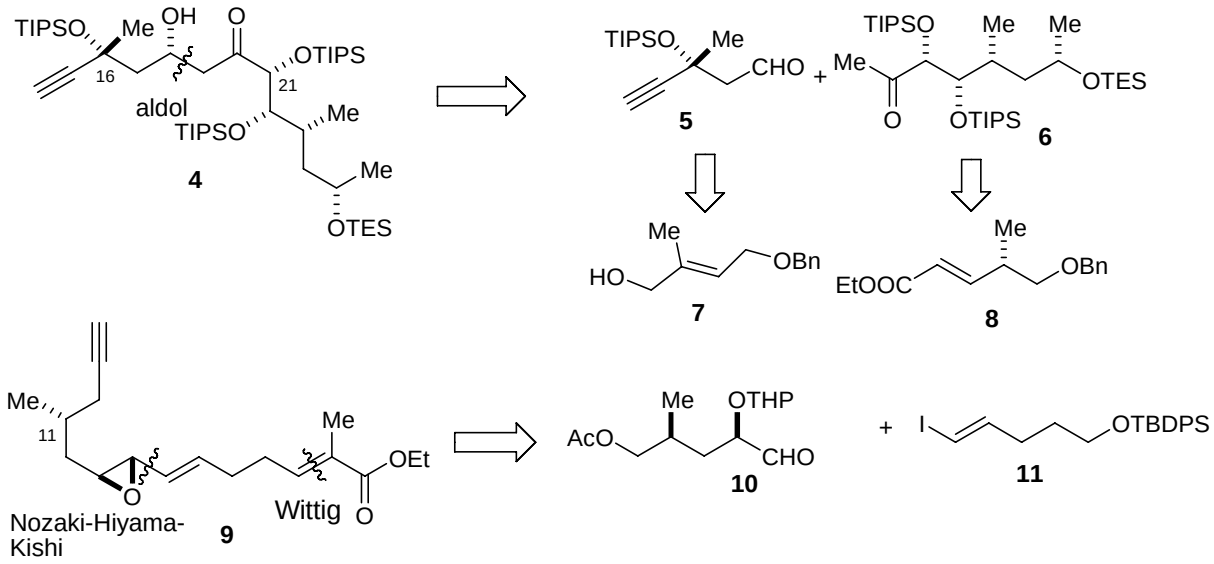


Figure 3. Chakraborty's approach to the synthesis of fragments of amphidinolide B

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_{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_{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_8- and C_9- stereocenters. [8]

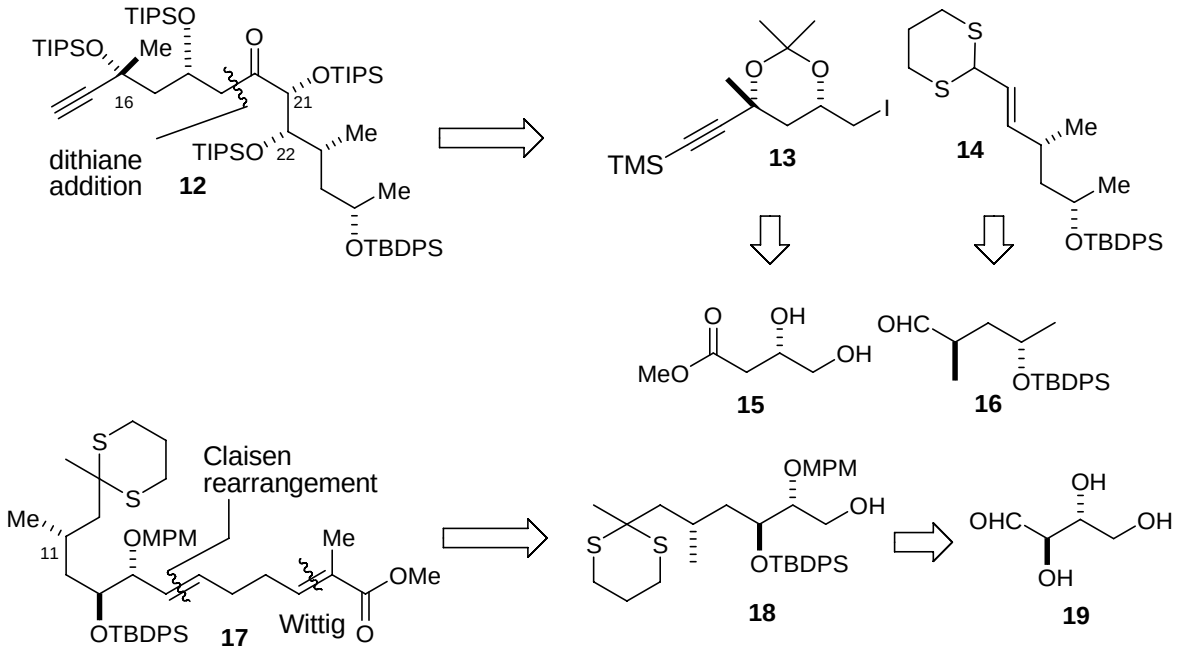


Figure 4. Nishiyama's approach to amphidinolide B fragments

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 C_{16}- stereocenter is generated via a Sharpless epoxidation and subsequent opening with a methylcuprate (Figure 5). [9] The C_{18}- 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 C_{11}- methyl bearing stereocenter is set using Myers' chiral auxiliary. [10] A Sharpless epoxidation reaction on allylic alcohol **27** formed the C_8–C_9 epoxide functionality and subsequent homologation via a Horner-Wadsworth-Emmons reaction completed fragment **26**.

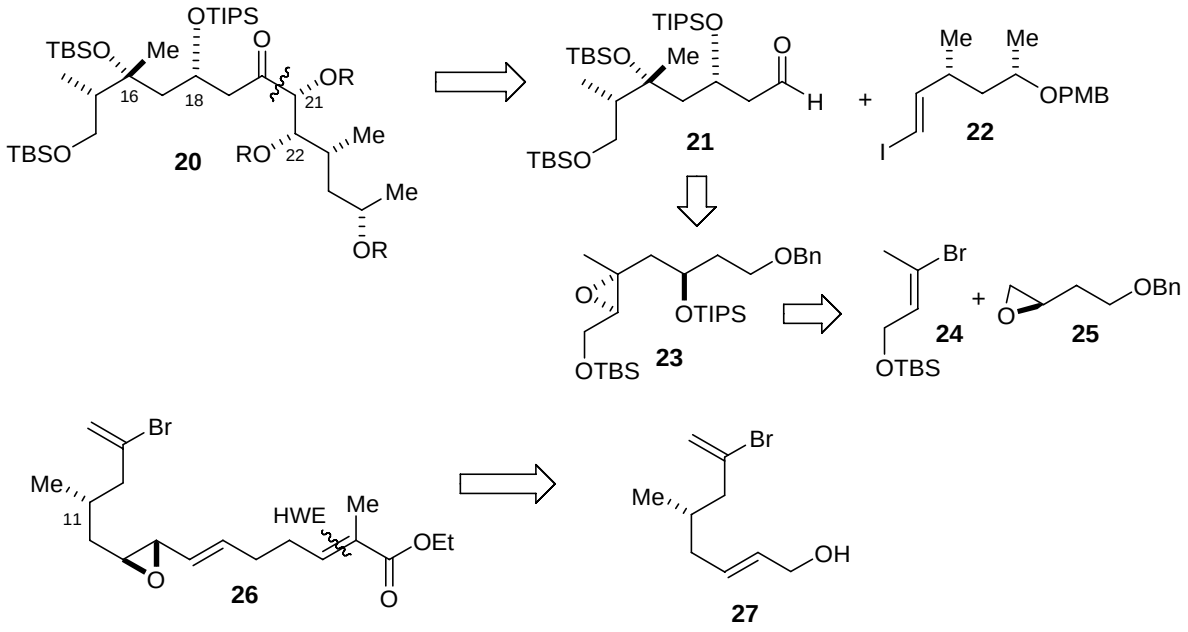


Figure 5. Lee's retrosynthesis of fragments of amphidinolide B

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). [11] 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**. [12] (*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.

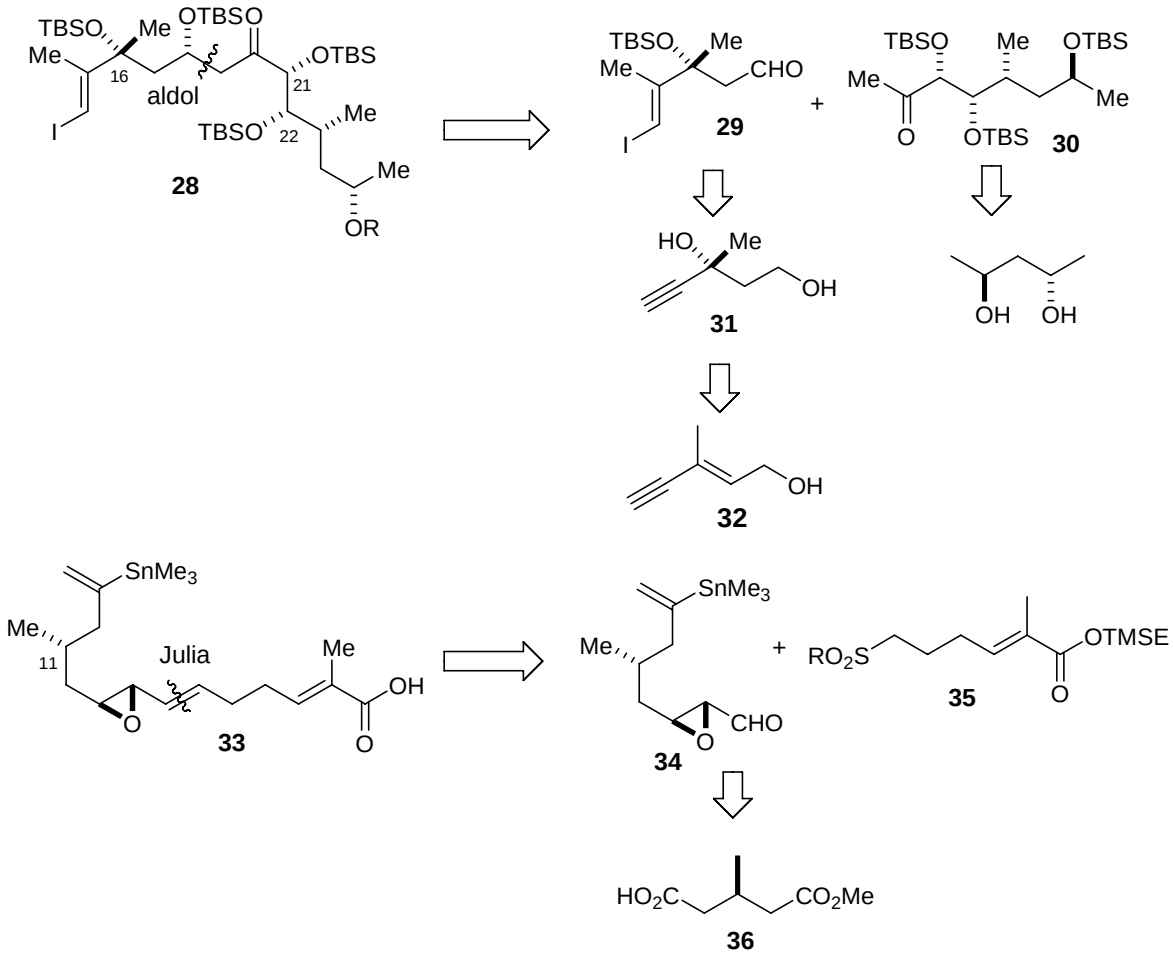


Figure 6. Pattenden's approach to the synthesis of amphidinolide B

Published in 1999, Kobayashi's synthetic approach to the synthesis of the C_{14}–C_{26} fragment **37**, shares common features with Chakraborty's and Pattenden's in that the aldol disconnection is used for the C_{18}–C_{19} bond construction (Figure 7). [13] The C_{16}- tertiary alcohol stereocenter in aldehyde **38** is set using Sharpless' asymmetric dihyroxylation, so also is the syn-diol relationship of the C_{21}–C_{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**.

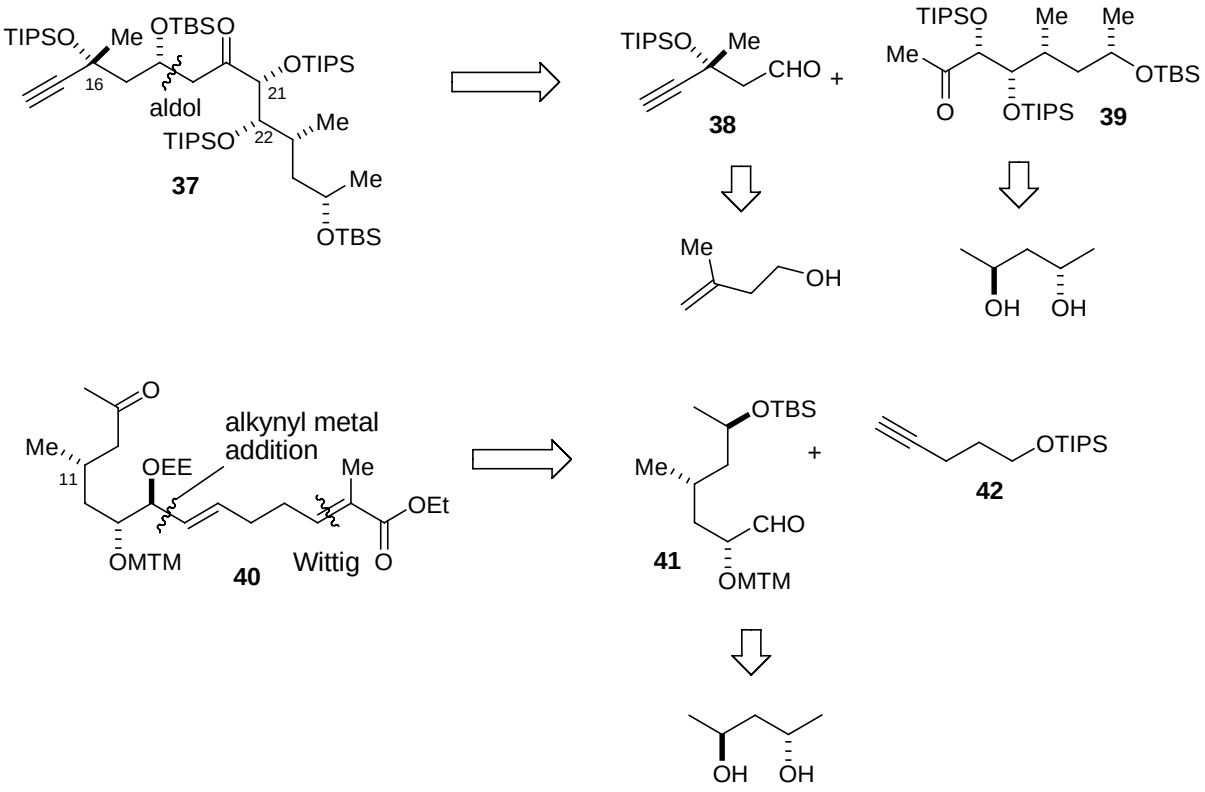


Figure 7. Kobayashi efforts towards the synthesis of amphidinolide B

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**.

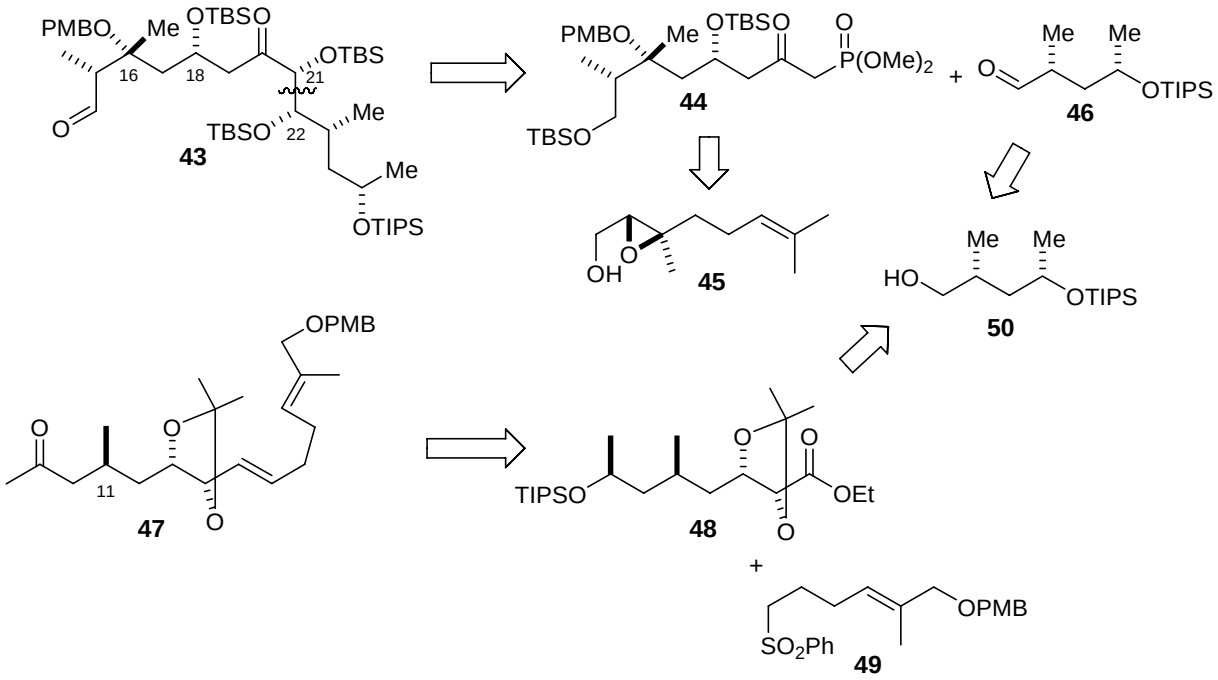


Figure 8. Myles' approach towards the synthesis of amphidinolide B

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.

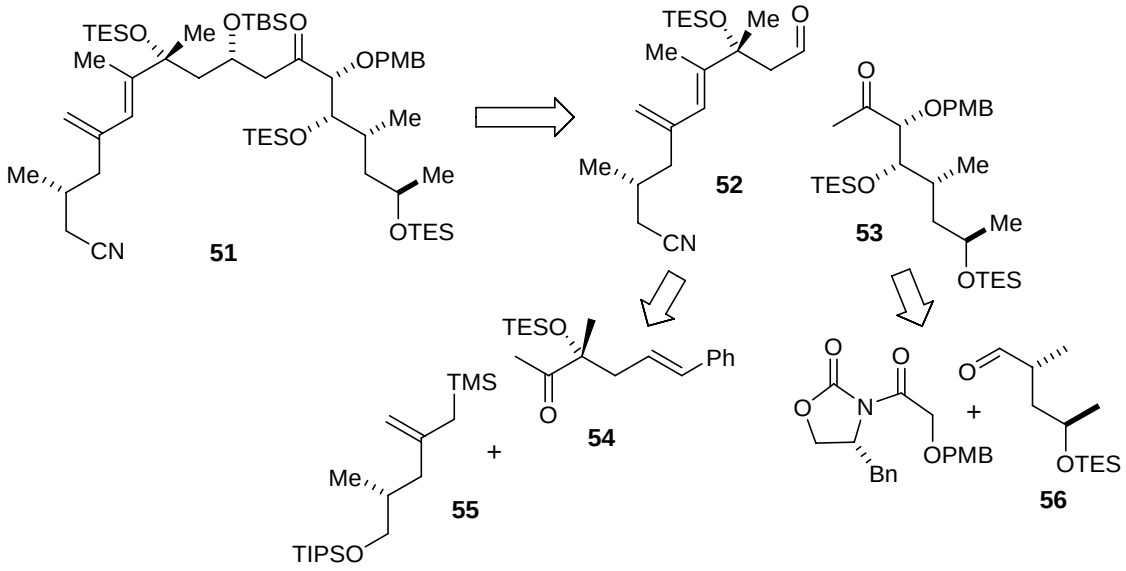


Figure 9. Carter's approach to the C_9-C_{26} fragment of amphidinolide B

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_{16}- 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.

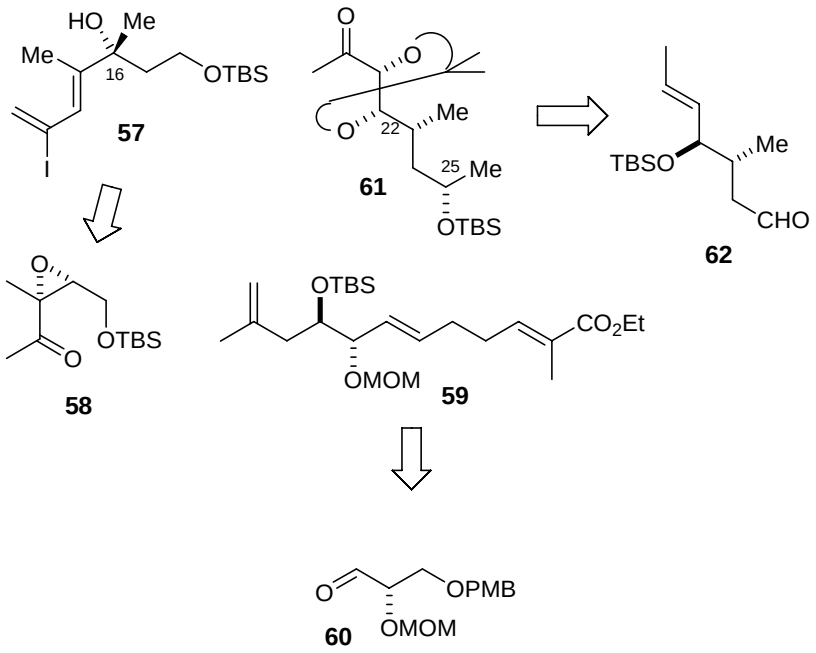
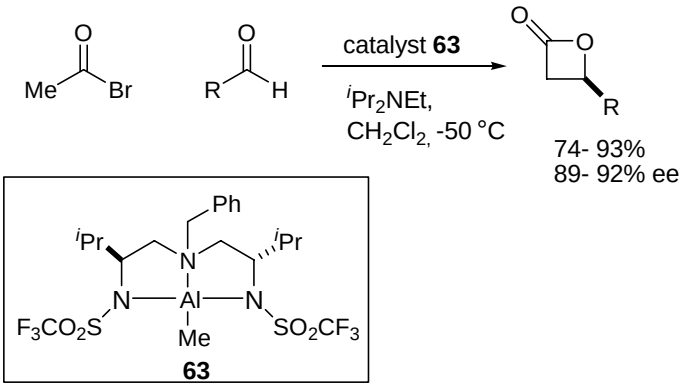


Figure 10: Retrosynthesis of major fragments of amphidinolide B by Crews

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 β-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 β-lactones (Eq 1). These easily prepared β-lactones serve as masked aldol adducts and have been employed as useful synthons in natural product syntheses. [20]



(1)

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 C_4 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.

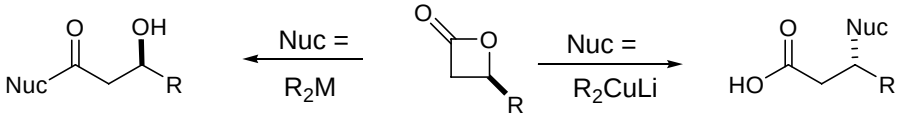


Figure 11: The use of β-lactones as versatile synthons

Amphidinolide B possesses an isolated methyl bearing stereocenter at C_{11} and a hydroxyl- bearing stereocenter at C_{18} 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 C_1–O bond via macrolactonization and the C_6–C_7 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 C_{21}–C_{22} 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**.

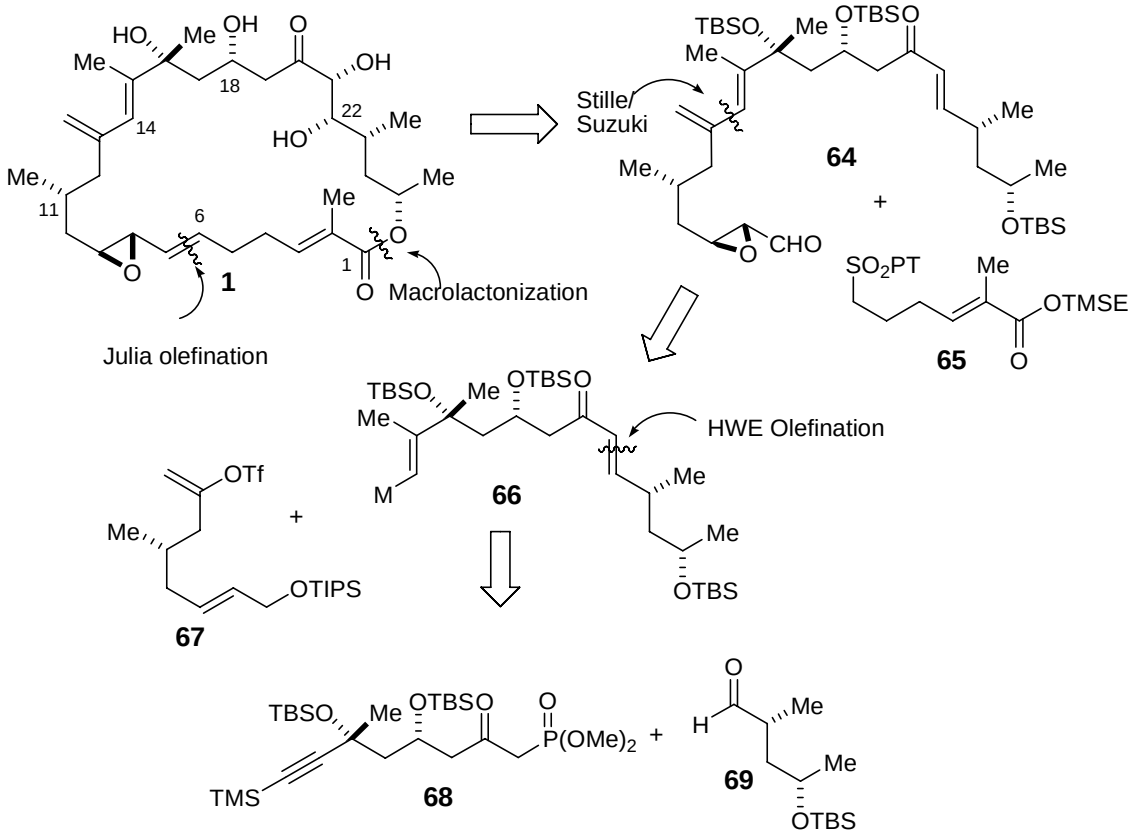


Figure 12: Retrosynthetic analysis of Amphidinolide B

1.4 SYNTHESIS OF THE C_7–C_{13} 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**.

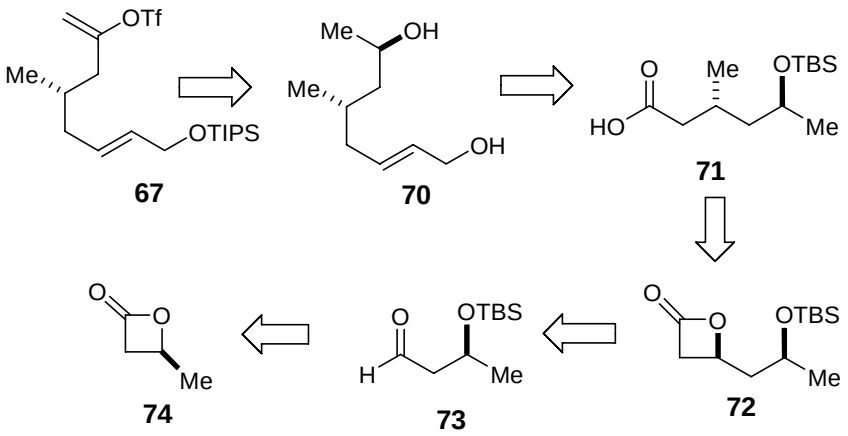


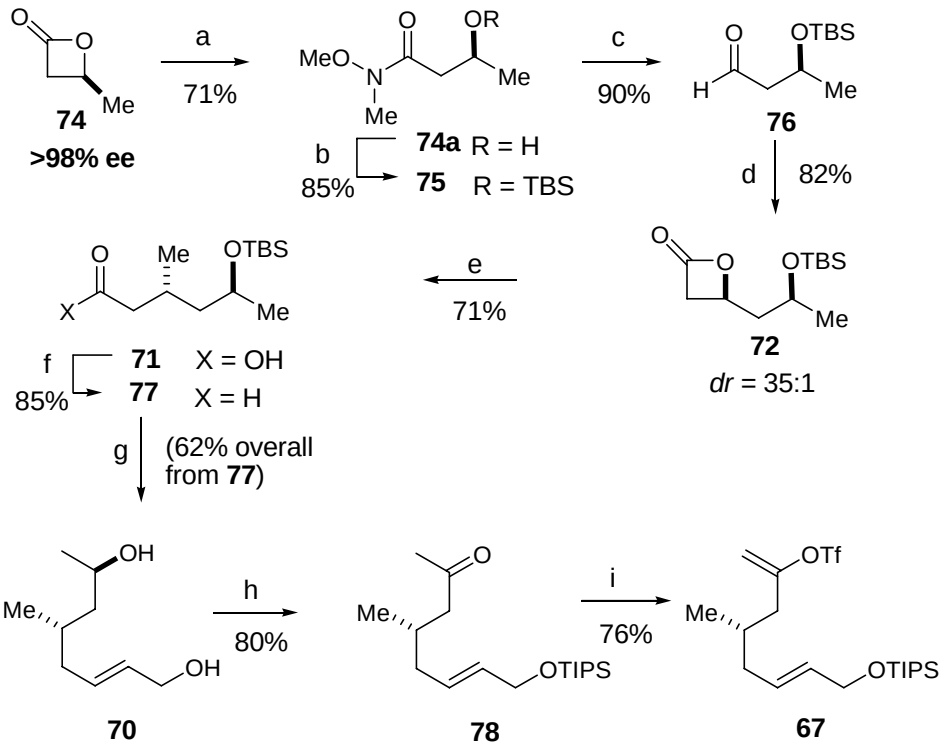
Figure 13: Retrosynthetic analysis of the C_7-C_{13} fragment

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[a]



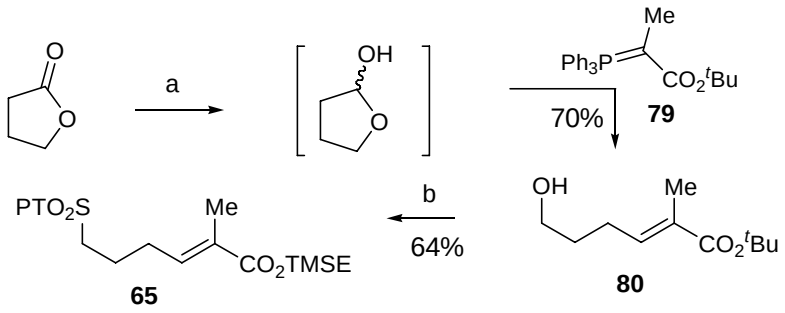
[a]Conditions: (a) MeO(Me)NH•HCl, Me_2AlCl. (b) TBSCl, $^iPr_2NEt$, DMAP. (c) DIBAL-H (d) AcBr, 10mol% **63**, $^iPr_2NEt$, –50 °C. (e) MeMgBr, CuBr•Me_2S. (f) BH_3; then PCC. (g) i. NaH, $(^iPrO)_2P(O)CH_2CO_2Et$; ii. DIBAL-H. (h) i. TIPSCl, im, Et_3N; ii. PCC. (i) KHMDS, $PhNTf_2$, –78 °C, THF.

1.5 SYNTHESIS OF THE C_1–C_6 SULFONE FRAGMENT

The requisite sulfone fragment **65** was synthesized from γ-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

trimethylsilylethyl protecting group by removal of the *tert*-butyl group by TFA and esterification with trimethylsilylethanol to make sulfone **65** (64% for 4 steps).

Scheme 2. Synthesis of C_1–C_6 Subunit[a]



[a]Conditions: (a) $^{i}Bu_2AlH$,CH_2Cl_2; ii. **79**, THF. (b) phenyltetrazolethiol, DIAD, PPh_3, DMF; ii. H_2O_2, $(NH_4)_6Mo_7O_{24}.7H_2O$, 30% H_2O_2 ; iii. TFA, CH_2Cl_2/anisole ; iv. 2-trimethylsilylethanol, DCC, DMAP, CH_2Cl_2.

1.6 SUMMARY

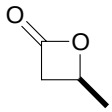
Towards the synthesis of amphidinolide B, an asymmetric synthesis of triflate fragment **67** was achieved by employing the AAC methodology. Sulfone fragment **65** was also made in a short sequence starting from γ-butyrolactone. An efficient synthesis of the C_{14}–C_{26} fragment and formation of the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

EXPERIMENTAL SECTION

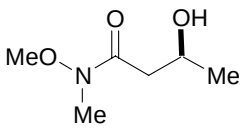
General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100 mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. ^{1}H NMR spectra were recorded on Bruker DPX 301/302 (300 MHz) spectrometers.Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard (C**H**Cl_3: δ 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 δ 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^{TM} –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^{TM} 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.

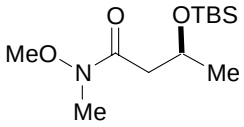


(*S*)-4-Methyl-oxetan-2-one (74) [28]: To a solution of 3.684 g of triamine ligand precursor to catalyst **63** (6.81 mmol) in 100 mL of CH_2Cl_2 was added 3.74 mL of trimethylaluminum (7.49 mmol) (2 M solution in hexanes) and was stirred for 2 h. The solution was cannulated into a solution of 36.0 g of tetraethylammonium bromide in 100 mL of CH_2Cl_2, cooled to –78 °C, and 20.2 mL of diisopropylethylamine (115.6 mmol) was added to it followed by the slow addition of 9.5 mL of acetylbromide (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 °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 °C for 5.0 min, ramp @ 5 °C /min to 100 °C for 10min, ramp @ 5 °C /min to 160 °C for 30 min. T_r 10.94min (*R*) and 11.84 min (*S*) determined enantiomeric excess to be 98.4%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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).



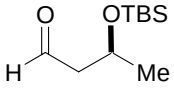
(*S*)-3-Hydroxy-*N*-methoxy-*N*-methyl-butyramide (74a) [28]: To a 0 °C solution of 11.8 g of *N*,*O*-dimethylhydroxylamine hydrochloride (12.0 mmol) in 280 mL of CH_2Cl_2, was added 120 mL of dimethylaluminumchloride (1 M solution in hexanes) (0.12 mmol) and the resulting solution was allowed to stir at ambient temperature for 2 h. To the clear solution was added, a solution of

lactone **74** in 20 mL of CH_2Cl_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_2AlCl). The organic layer was separated, filtered through celite, and the aqueous layer extracted with CH_2Cl_2 (5 x 200 mL). The organics were combined, dried over Na_2SO_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, $CDCl_3$): δ 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).

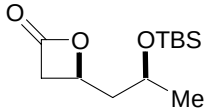


(*S*)-(*tert*-Butyldimethylsilanyloxy)-*N*-methoxy-*N*-methylbutyramide (75): To a 0 °C solution of 3 g of Weinreb amide **74a** (20.5 mmol) in CH_2Cl_2 (41 mL), was added 3.58 mL (20.5 mmol) of diisopropylethylamine, followed by 0.50g (4.1 mmol) of dimethylaminopyridine (DMAP) and 5.26 g (35.0 mmol) of *tert*-butyldimethylchlorosilane. 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_2Cl_2 (5 x 30 mL) and the combined organic layers washed with brine (25 mL) and dried over Na_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 172.2, 66.0, 61.2, 41.6, 31.7, 25.7, 24.0, 18.0, –4.8, –5.0; EI-MS *e/v* 246 (M^+–Me), 204 (M^+–^{t}Bu), 159, 129, 115; HRMS calcd for $C_{11}H_{24}NO_3Si$: 246.1525, found 246.1515.

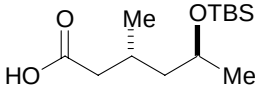


(*3S*)-3-*tert*-Butyldimethylsilanyloxy)butyraldehyde (76): To a –78 °C solution of 0.500 g of Weinreb amide **75** (1.91 mmol) in 10 mL of CH_2Cl_2, was added 2.1 mL (2.1 mmol) of diisobutylaluminumchloride (1.0 M solution in hexanes) slowly. The reaction was stirred for 45 min at –78 °C and quenched with 0.1 M HCl (5 mL). The layers were separated, the organic layer filtered through celite and the aqueous layer washed with CH_2Cl_2 (5 x 20 mL). The combined organics were dried over Na_2SO_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: $[\alpha]_D$ = +16.1 (*c* 1.20, $CHCl_3$); IR (thin film): 3002, 2957, 2930, 1724, 1265, 837, 738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 202.0, 64.5, 53.0, 25.7, 24.1, 18.0, –4.4, –4.9; EI-MS *e/v* 145 (M^+–^{t}Bu), 101 (M^+–^{t}Bu–CH_3CHO), 75; HRMS calcd for $C_6H_{12}O_2Si$: 145.0685, found 145.0681.



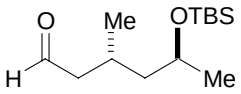
(*4S,2′S*)-4-[2-(*tert*-Butyldimethylsilanyloxy)propyl]-oxetan-2-one (72): To a solution of 0.164 g of triamine ligand precursor to catalyst **63** (0.30 mmol) in 5.8 mL of CH_2Cl_2 was added 0.166 mL of trimethylaluminum (0.33 mmol) (2 M solution in hexanes) and was stirred for 2 h. The solution was 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_2Cl_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: $[\alpha]_D$ = +8.3 (*c* 0.5, $CHCl_3$); IR (thin film): 2956, 2930, 2887, 2857, 1831, 1124, 836 cm^{-1}; ^1H 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 (ddd, *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^+–^{t}Bu), 145, 115, 101, 88; HRMS calcd for $C_8H_{15}O_3Si$: 187.0790, found 187.0800.



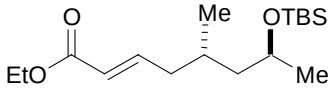
(*3R,5S*)-5-(*tert*-Butyldimethylsilanyloxy)-3-methylhexanoic acid (71): To a –50 °C solution of 0.44 g of CuBr (3.1 mmol) in 20 mL of THF and 5 mL of dimethylsulfide, was added 2.1 mL of methylmagnesiumbromide (6.2 mmol) (3 M solution in ether) slowly to give a yellow suspension. The suspension was 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_4Cl. After separation of the layers, the organic layer was washed with 10 mL of saturated NH_4Cl solution and the aqueous layer extracted with ether (5 x 30 mL).

The combined organics were dried over Na_2SO_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: $[\alpha]_D$ = +23.4 (*c* 0.58, $CHCl_3$); IR (thin film): 3583, 2958, 2929, 2857, 1709, 1462, 1256, 1065, 835 cm^{-1}; ^1H 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_2O), 203 (M^+–^{t}Bu), 185 (M^+–^{t}Bu–H_2O), 159, 143, 129, 111; HRMS calcd for $C_{12}H_{25}O_3Si$: 245.1573, found 245.1565.

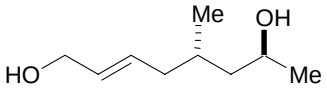


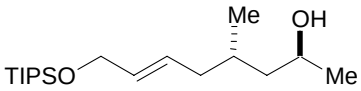
(*3R,5S*)-5-(*tert*-Butyldimethylsilanyloxy)-3-methylhexanal (77): To a solution of 0.868 g of carboxylic acid **77** (3.38 mmol) in 16 mL of THF was added 2.5 mL of a 2.0 M solution of $BH_3.Me_2S$ (5.0 mmol) in 16mL of THF. The solution was refluxed for 2 h, cooled and the solvent evaporated *in vacuo.* The residue was dissolved in 16 mL of CH_2Cl_2, and refluxed with 1.79 g of pyridinium chlorochromate (8.34 mmol) for 3 h. The reaction mixture was cooled, diluted with CH_2Cl_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: $[\alpha]_D$ = + 41.6 (*c* 0.85, $CHCl_3$); IR (thin film): 2957, 2929, 2857, 2710, 1728, 1472, 1255, 1134, 1070, 836 cm^{-1}; ^1H 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,

$CDCl_3$): δ 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/v* 243 (M^+–H), 187 (M^+–^{t}Bu), 159, 145, 115; HRMS calcd for $C_{13}H_{27}O_2Si$: 243.1780, found 243.1783.



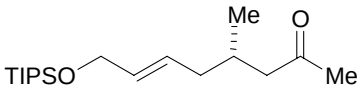
(*5R,7S*)-7-(*tert*-Butyldimethylsilanyloxy)-5-methyl-oct-2-enoic acid ethyl ester (77a): To a 0 °C suspension of 0.15g of NaH (3.95 mmol) in THF (14 mL), was added 0.86 mL of diisopropyl(ethoxycarbonylmethyl) phosphonate (3.59 mmol). This was stirred at 0 °C for 20 min and 0.624 g of aldehyde **77** dissolved in THF (4 mL) was added to it. The reaction mixture was allowed to warm to ambient temperature, and then, 5 mL H_2O 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, $CDCl_3$): δ 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 (ddd, *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, $CDCl_3$): δ 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/v* 257 (M^+–^{t}Bu), 228 (M^+–^{t}Bu–C_2H_4), 211, 159, 149, 115, 109, 95; HRMS calcd for $C_{13}H_{25}O_3Si$: 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 CH_2Cl_2 (10 mL) at ambient temperature, was added 6.4 mL of diisobutylaluminumchloride (6.4 mmol) (1 M in hexanes), and stirred for 2 h. The reaction mixture was quenched with 0.1 M HCl, extracted with CH_2Cl_2 (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: $[\alpha]_D$ = +22.5 (*c* 0.45, $CHCl_3$); IR (thin film): 3334, 963, 2920, 1459, 1376, 1127, 1085, 1003, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 131.0, 130.8, 65.5. 63.1, 45.8, 40.1, 29.5, 24.2, 19.5; EI-MS *e/v* 140 (M^+–H_2O), 122 (M^+–$2H_2O$), 107, 93; HRMS calcd for $C_9H_{16}O$: 140.1201, found 140.1198.

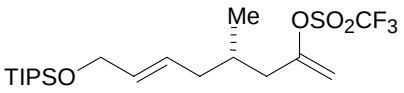
(*4R,2S*)-4-Methyl-8-isopropylsilanyloxy-oct-6-en-2-ol  **(70a):** To a 0 °C solution of 0.230 g of diol **70** (1.46 mmol) in CH_2Cl_2 (10 mL), was added 0.2 mL of triethylamine (1.46 mmol), followed by 0.1 g of imidazole (1.46 mmol) and 0.34 mL (1.46 mmol) of triisopropylchlorosilane. The reaction mixture was stirred for 2 h, and quenched with 5 mL of a saturated solution of $NaHCO_3$. It was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers washed with brine (5 mL) and dried over $MgSO_4$. 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; $[\alpha]_D$ = +8.2 (*c* 1.0, $CHCl_3$); IR (thin film): 3356, 2960, 2943, 1463, 1377, 1104,

1055, 882, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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/v* 271 (M^+–^{i}Pr), 187, 141, 131, 123; HRMS calcd for $C_{15}H_{31}O_2Si$: 271.2093, found 271.2093.

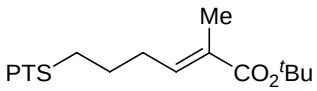
(*4R*)-4-Methyl-8-triisopropylsilanyloxy-oct-6-en-2-one



(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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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/v* 297 (M^+–CH_3), 269 (M^+–^{i}Pr), 239 (M^+–^{i}Pr –2CH_3), 213, 171, 131; HRMS calcd for $C_{15}H_{29}O_2Si$: 269.1936, found 269.1934.

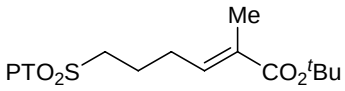


(*3R*)-Trifluoromethanesulfonic acid 3-methyl-1-methylene-7-triisopropylsilanyloxyhept-5-enyl ester (67): To a –78 °C solution of 1.43 mL of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.71 mmol) in THF (8 mL) was added a solution of 0.149 g of ketone **78** in THF (2 mL), dropwise 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 $NaHCO_3$ 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 Na_2SO_4, concentrated and purified by column chromatography over silica gel (0.5% CH_2Cl_2 in hexanes, 2% Et_3N) to afford 0.161 g (76%) of the title compound as a colorless oil; $[\alpha]_D$ = –3.5 (*c* 1.0, $CHCl_3$); IR (thin film): 2943, 2866, 1463, 1419, 1211, 1141, 937, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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), 2.38 (dd, *J* = 15.8, 5.9 Hz, 1H), 2.16–1.83 (m, 4H), 1.14–1.04 (m, 21H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 132.0, 127.2, 118.6 ($J_{C\text{-}F}$ = 318 Hz), 105.4, 63.7, 40.7, 38.7, 30.3, 18.8, 18.0, 12.0; EI-MS *e/v* 401 (M^+–^{i}Pr), 251 (M^+–^{i}Pr–CF_3SO_3H), 209, 157, 131, 121; HRMS calcd for $C_{16}H_{28}O_4F_3$: 401.1429, found 401.1442.



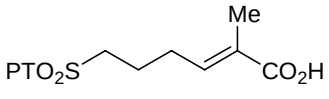
(*E*)-*tert*-Butyl-6-(1-phenyl-1H-tetrazol-5-ylthio)-2-methylhex-2-enoate (80a): To a 0 °C solution of 0.500 g of alcohol **80** (2.5 mmol) and 0.890 g of *N*-phenyltetrazolethiol (5.9 mmol, 2.0 equiv) in 12.5 mL of DMF added 1.314 g of

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 $MgSO_4$ 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, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{18}H_{24}N_4O_2S$: 380.1619, found 380.1603.

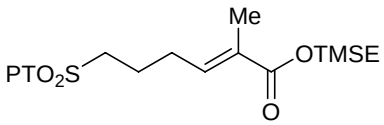


(*E*)-*tert*-Butyl-6-(1-phenyl-1H-tetrazol-5-ylsulfonyl)-2-methylhex-2-enoate (80b): To a solution of 0.660 g of ammonium molybdate (5.32 mmol, 20 mol %) in 2 mL of EtOH added 3.0 mL of a 30% solution of hydrogen peroxide to produce a yellow solution. This was added to a solution of 0.960 g of sulfide **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 $MgSO_4$ 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, $CDCl_3$): 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 $C_{18}H_{24}N_4O_4S$: 392.1518, found 392.1515.



(*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_2Cl_2: 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 *in vacuo* to give a light brown solid which was recrystallized from CH_2Cl_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 $C_{14}H_{16}N_4O_4S$: 336.0892, found 336.0871.



(*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 $MgSO_4$ 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, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{19}H_{28}N_4O_4SiSNa$: 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 unsuccesful. [12] The presence of a trisusbtituted 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**.

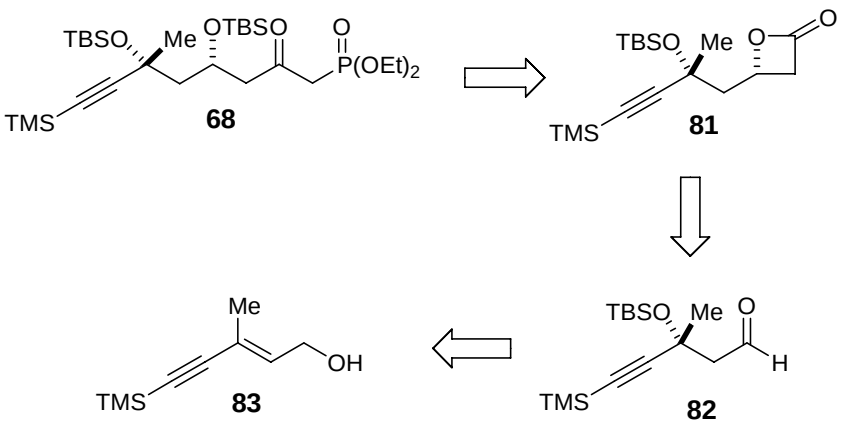
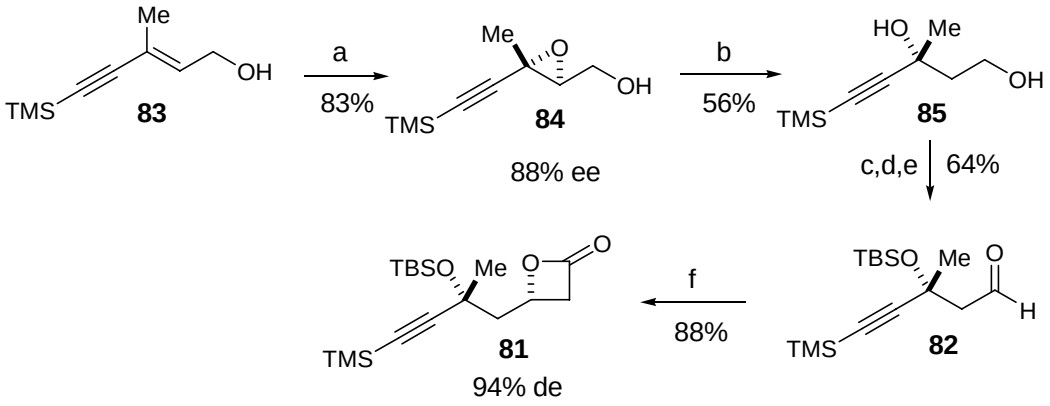


Figure 14: Retrosynthetic analysis of fragment 68

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 C_{16}- and C_{18}- stereocenters[a]

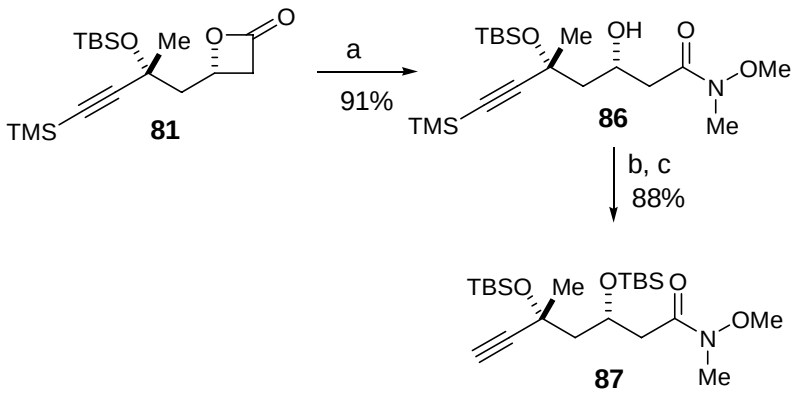


[a]Condtions: (a) 30 mol % $Ti(O^iPr)_4$, (+)-DIPT, ^{t}BuOOH, CH_2Cl_2. (b) $LiAlH_4$, Et_2O, 0 °C. (c) TBSOTf, 2,6-lutidine, 0 C-RT. (d) DDQ, THF-H_2O. (e) Dess-Martin periodinane, CH_2Cl_2. (f) 10 mol % **63**, MeCOBr, $^iPr_2NEt$, –50 °C.

2.3 INSTALLATION OF THE C_{14}–C_{15} 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 C_{14}–C_{15} 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*-butyldimethylsilyl 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 C_{14}–C_{15} bond.

Scheme 4: Synthesis of alkyne substrate for carbometalation studies[a]



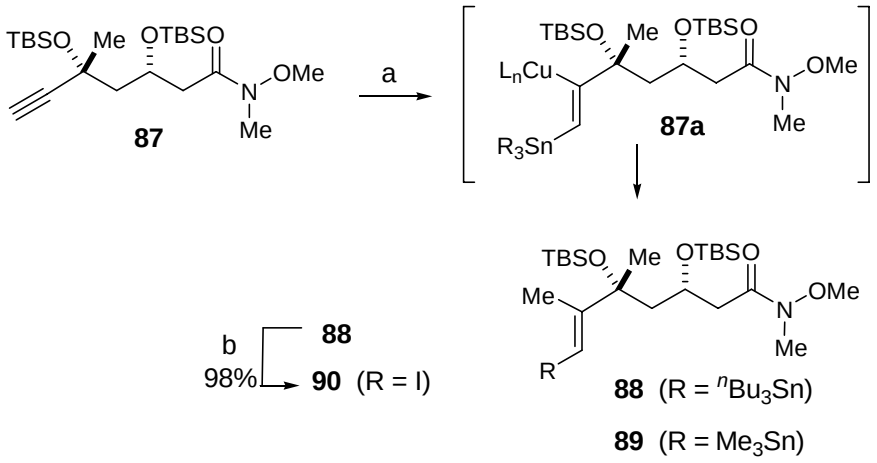
[a]Conditions: (a) MeNH(OMe).HCl, Me_2AlCl. (b)TBSOTf, 2,6-lutidine. (c) KOH, MeOH.

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][33] and alkyne **87** was treated with them at –50 °C (Scheme 5). The intermediate vinyl cuprates **87a** were quenched with excess methyliodide 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[a]



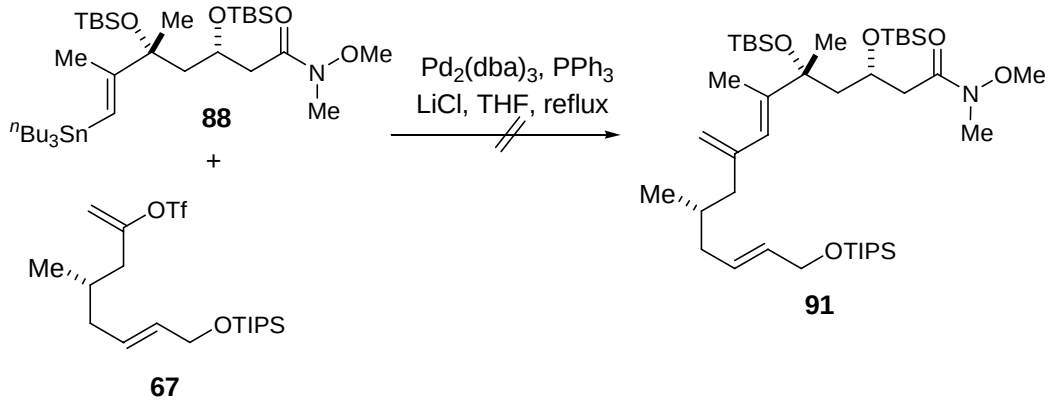
[a]Conditions: (a) i. Cuprate, –50 °C, THF; ii. excess MeI, –50 °C–RT. (b) I_2, CH_2Cl_2.

Cuprate used	yield of **88** or **89**
$(^nBu_3Sn)_2Cu(CN)Li_2$	72%
$(^nBu_3Sn)(Bu)Cu(CN)Li_2$	83%
$(Me_3Sn)_2Cu(CN)Li_2$	41%
$(Me_3Sn)(Bu)Cu(CN)Li_2$	64%

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. [35] However, no desired product was observed (Eq 2) indicating that modified reaction conditions would have to be applied.



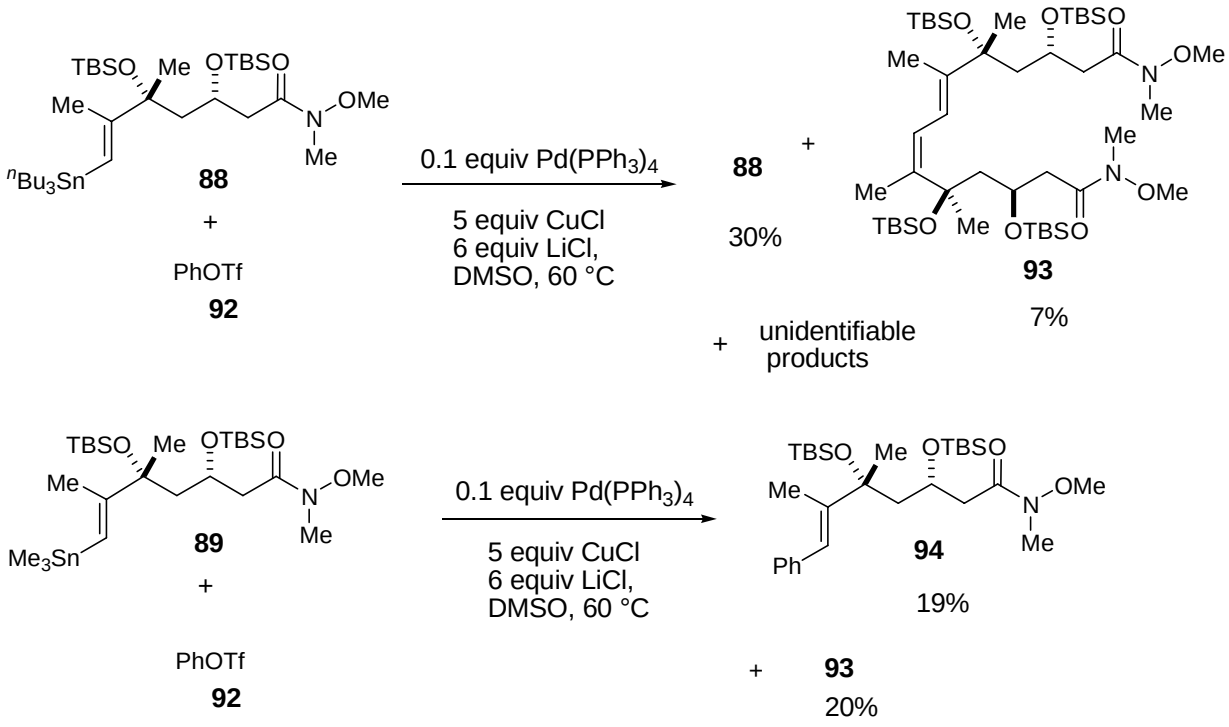
(2)

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

1-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**.

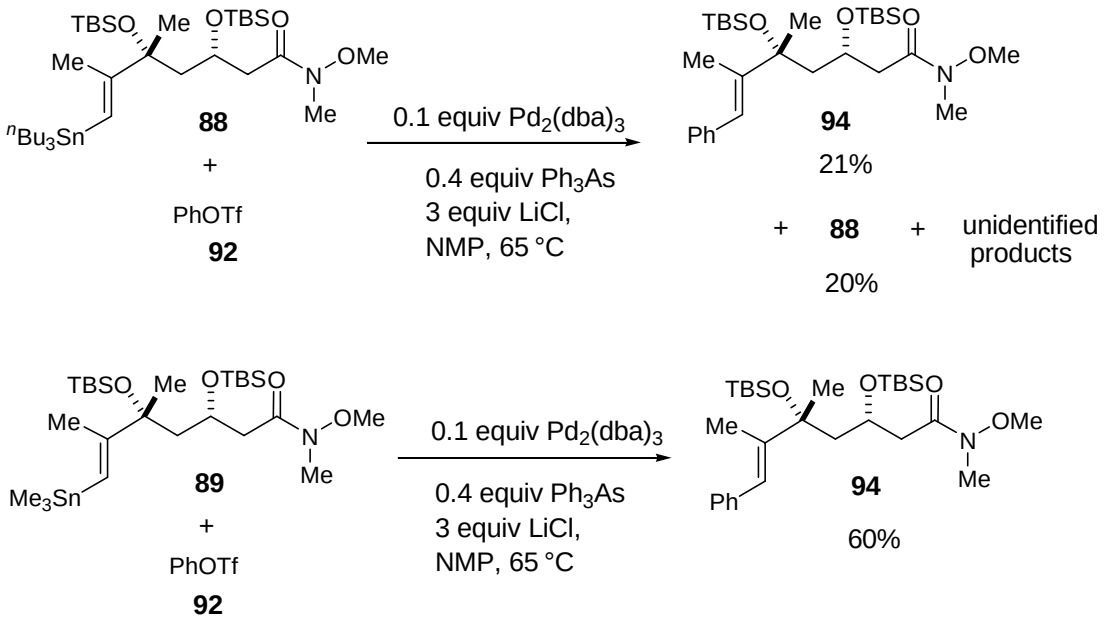
Scheme 6: The Corey-modified Stille trials on model system



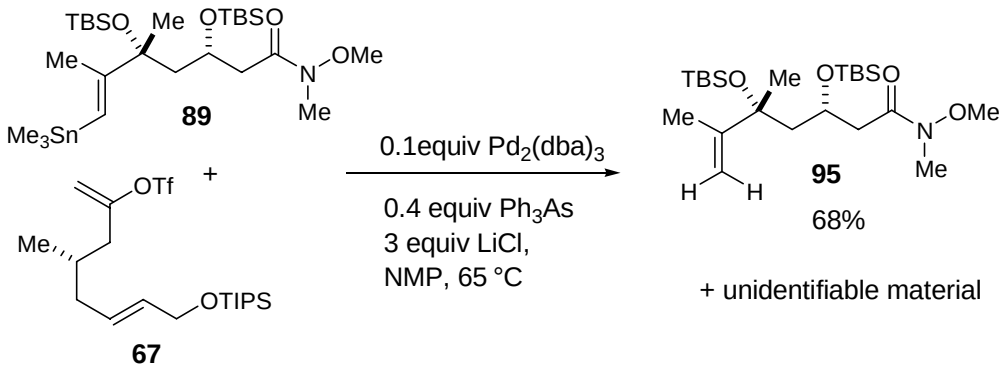
Homocoupling of vinylstannanes in the presence of cuprous chloride has precedent in the literature. [38] Identifying reaction conditions that would retain the reactivity of the stannane and at the same time prevent self-coupling was important for the success of our Stille reaction.

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. [39] When vinylstannane **88** was reacted with model triflate **92** in the presence of 10 mol% $Pd_2(dba)_3$ and 40 mol% Ph_3As 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).



(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

stannane employed	triflate partner	conditions	result
88	PhOTf	$Pd(PPh_3)_4$, CuCl, LiCl, DMSO, 60° C	**88** + dimer 30% 7%
89	PhOTf	$Pd(PPh_3)_4$, CuCl, LiCl, DMSO, 60° C	coupled product + 19% dimer 20%
88	PhOTf	$Pd_2(dba)_3$ Ph_3As, LiCl, NMP, 65° C	coupled + **88** product 20% 21%
89	PhOTf	$Pd_2(dba)_3$ Ph_3As, LiCl, NMP, 65° C	coupled product 60%
89	**67**	$Pd_2(dba)_3$ Ph_3As, LiCl, NMP, 65° C	destannylated product **95** 68%

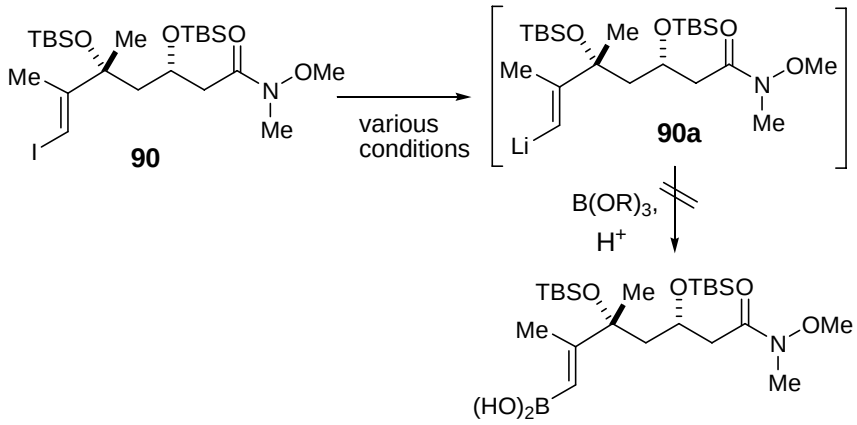
2.5 SUZUKI COUPLING STUDIES

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

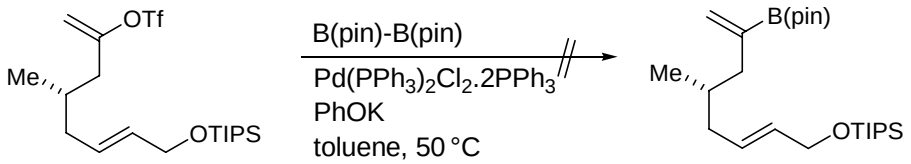


2.5.2 Attempted modification of triflate fragment 67

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.

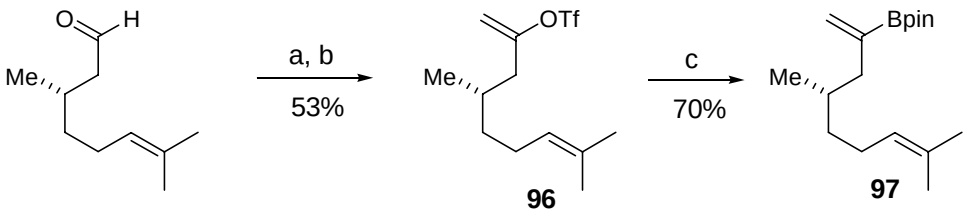


(3)

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.

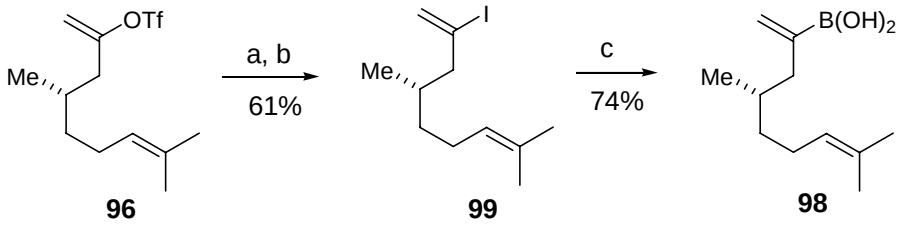
Scheme 9: Synthesis of model boronate ester from S-(-)-citronellal[a]



[a]Conditions: (a) i. MeMgBr, THF; ii. PCC, CH_2Cl_2, reflux. (b) KHMDS, $PhNTf_2$, THF, -78 °C. (c) B(pin)-B(pin), 10 mol % $Pd(PPh_3)_2Cl_2$.$_2PPh_3$, 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).

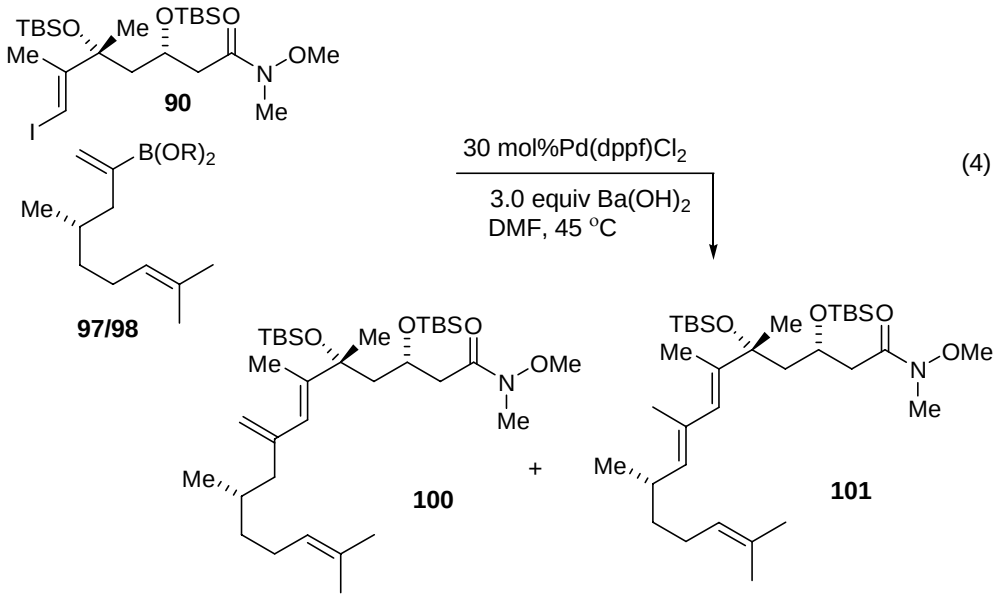
Scheme 10: Synthesis of model boronic acid from S-(-)-citronellal[a]



[a]Conditions: (a) $(Me_3Sn)_2$, 10 mol % $Pd(PPh_3)_4$ LiCl, THF, 60 °C. (b) I_2, CH_2Cl_2. (c) BuLi, $B(OMe)_3$, 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)$PdCl_2$ 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**.



(4)

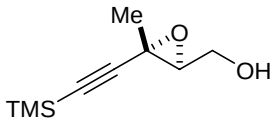
coupling partner (**98/97**)$(OR)_2$ =	base	reaction time (h)	conversion	ratio of dienes (**100 : 101**)
$(OH)_2$	KOH	20	33	100:0
$(OH)_2$	Cs_2CO_3	20	50	0:100
$(OH)_2$	K_3PO_4	20	50	10:90
pin	K_3PO_4	20	100	40:60
pin	Cs_2CO_3	20	100	0:100
pin	$Ba(OH)_2$	3	100	100:0

2.6 SUMMARY

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

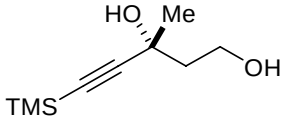
two major fragments of amphidinolide B using the Suzuki coupling strategy were found in a suitable model system.

EXPERIMENTAL SECTION

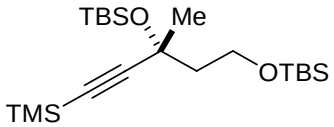


[(*2S,3S*)-3-methyl-3-(2-(trimethylsilyl)ethynyl)oxiran-2-yl]methanol (84): To a –20 °C suspension of 0.62 g of 4Å molecular sieves in 11 mL of CH_2Cl_2 was added a solution of 0.62 g of (+)-DIPT (2.64 mmol, 0.36 equiv) in 3 mL of CH_2Cl_2 followed by 0.65 mL of titanium isopropoxide (2.2 mmol, 0.3 equiv), 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_2Cl_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_2Cl_2 (5 x 30 mL) and the combined organics were dried over Na_2SO_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%: $[\alpha]_D$ = –0.62 (*c* 1.80, $CHCl_3$); IR (thin film): 3431, 2960, 2167, 1642, 1250, 1032, 842 cm^{-1}; ^1H 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, $CDCl_3$): δ 105.1, 87.4, 64.3, 60.5, 51.4, 18.6, –0.2; HRMS calcd for $C_8H_{13}O_2Si$: 169.0685 found 169.0686.

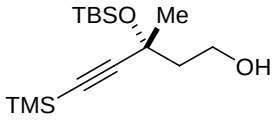


(*R*)-3-methyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (85): To a 0 °C solution of epoxide **84** (4.90 mmol) in 30 mL of ether added 4.9 mL of lithium aluminum hydride (1 M solution in hexanes, 4.90 mmol) dropwise via syringe. Stirred for 15 min at 0 °C and then quenched with 10 mL of 0.2 M aqueous hydrochloric 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_2SO_4. The solvent was evaporated *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, $CDCl_3$): δ 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, $CDCl_3$): δ 108.8, 87.7, 68.8, 60.3, 43.6, 30.5, 0.0; HRMS calcd for $C_8H_{15}O_2Si$: 171.0841 found 171.0840.



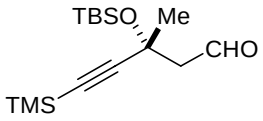
(*R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-3-methyl-1-trimethylsilanylpent-1-yne (85a): To a 0 °C solution of 0.680 g of diol **85** (3.65 mmol) in 18 mL of CH_2Cl_2 added 2.1 mL of 2,6-lutidine (18.33 mmol, 5 equiv.) followed by 2.5 mL of *tert*-butyldimethylsilyl trifluoromethansulfonate (11 mmol, 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_2Cl_2 (5 x 30 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was 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: $[\alpha]_D$ = +5.5 (*c* 1.2, $CHCl_3$); IR (thin film): 2956, 2929, 2886, 2857, 2166, 1472, 1252, 1117, 1093, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{20}H_{43}O_2Si_3$: 399.2571 found 399.2560.

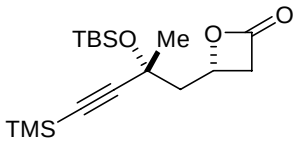


(*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-methyl-5-trimethylsilanylpent-4-yn-1-ol (85b): To a solution of 2.30 g of *tert*-butyldimethylsilyl ether **85a** (5.55 mmol) in a 9:1 solvent mixture of THF: H_2O (20 mL) added 0.12 g of DDQ (0.55 mmol, 10 mol %) at ambient temperature. After 6 h the reaction 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: $[\alpha]_D$ = +20.8 (*c* 1.50, $CHCl_3$); IR (thin film): 3350, 2957, 2930, 2857, 2167, 1472, 1251, 1121, 1041, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 109.4, 89.5, 69.9, 60.2, 46.6, 31.2, 25.7, 17.9,

–0.3, –2.8, –3.2; EI-MS *e/v* 285 (M^+–CH_3), 255, 147, 95; HRMS calcd for $C_{14}H_{32}O_2Si_2$: 285.1706 found 285.1715.

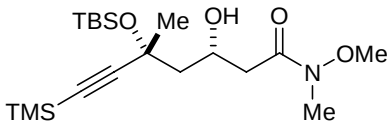


(*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-methyl-5-trimethylsilanylpent-4-ynal (82): To a 0 °C solution of 1.58 g of alcohol **85b** (5.26 mmol) in 25 mL of CH_2Cl_2 added 3.35 g of Dess-Martin periodinane (7.89 mmol, 1.5 equiv). The reaction mixture was allowed to warm to ambient temperature and stirred for 3 h. It was diuted 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: $[\alpha]_D$ = +36 (*c* 1.4, $CHCl_3$); IR (thin film): 2958, 2930, 2857, 1730, 1251, 1115, 1040, 838, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/*v* 283 (M^+–Me), 255 (M^+–CH_3–CO), 241, 147; HRMS calcd for $C_{14}H_{27}O_2Si_2$: 283.1549 found 283.1556.



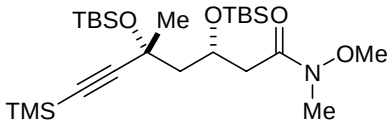
(*4S,2R*)-4-[2-(*tert*-Butyldimethylsilanyloxy)-2-methyl-4-trimethylsilanyl-but3-ynyl]-oxetan-2-one (81): To a solution of 0.036 g of triamine ligand precursor to catalyst **63** (0.067 mmol) in 1.0 mL of CH_2Cl_2 was added 0.04 mL of a 2 M in hexanes solution of trimethylaluminum (0.074 mmol) and was stirred for 2 h. The solution was cooled to –50 °C, and 0.12 mL of $^iPr_2NEt$ (1.14 mmol) was added to it

followed by the slow addition of 0.09 mL of acetylbromide (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 CH_2Cl_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 was purified by flash chromatography on silica (1% EtOAc in hexanes) to afford 0.200 g of lactone **81** (88%) as a colorless oil: $[\alpha]_D$ = +30 (*c* 2.3, $CHCl_3$); IR (thin film): 2957, 2930, 2857, 2169, 1835, 1251, 1165, 1125, 1077, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/v* 325 (M^+–CH_3), 283 (M–CH_3–C_2H_2O), 255, 241, 143, 101; HRMS calcd for $C_{16}H_{29}O_3Si_2$: 325.1655 found 325.1647.



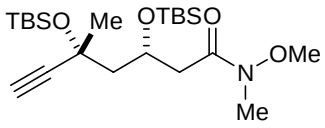
(*3S,5R*)-5-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-5-methyl-7-trimethylsilanylhept-6-ynoic acid methoxymethylamide (86): To a 0 °C solution of 0.202 g of *N,O*-dimethylhydroxylamine hydrochloride (2.06 mmol) in 8 mL of CH_2Cl_2, was added 2 mL of dimethylaluminumchloride (1 M solution in hexanes) (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 CH_2Cl_2, slowly. The resulting pale yellow solution was stirred overnight and quenched with 6 mL of pH 8 phosphate buffer (3 mL/mmol of Me_2AlCl). The organic layer was separated, filtered through celite, dried over Na_2SO_4 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, $CHCl_3$); IR (thin film): 3499, 2957, 2930, 2957, 2167, 1651, 1472, 1251, 1116, 1000, 839, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (dddd, *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, $CDCl_3$): δ 172.7, 109.7, 89.3, 69.2, 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/v* 386 (M^+–Me), 368 (M^+–Me–H_2O), 255, 215; HRMS calcd for $C_{18}H_{36}NO_4Si_2$: 386.2182 found 386.2174.

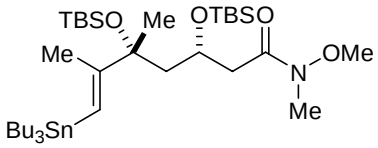


(*3S,5R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-5-methyl-7-trimethylsilanylhept-6-ynoic acid methoxymethylamide (86a): To a 0 °C solution of 0.367 g of alcohol **86** (0.952 mmol) in 10 mL of CH_2Cl_2 was added 0.267 mL of 2,6-lutidine (2.28 mmol) followed by 0.317 mL of TBSOTf (1.373 mmol) and allowed 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_2Cl_2 (3 x 5 mL). The organics were combined, washed with 5 mL of brine, dried over Na_2SO_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 $CHCl_3$); IR (thin film) 2956, 2929, 2856, 2166, 1669, 1472, 1446, 1385, 1251, 1075, 993, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.59 (dddd, *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, $CDCl_3$): δ 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/v* 500 (M^+–Me), 458 (M^+–^{t}Bu), 255, 188, 115, 101; HRMS calcd for $C_7H_{13}OSi$: 500.3047 found 500.3039.

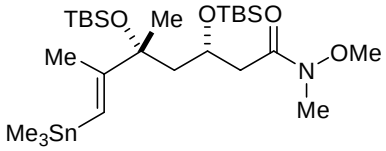


(*3S,5R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-5-methylhept-6-ynoic acid methoxymethylamide (87): To a solution of 1.05 g of trimethylsilylalkyne **86a** (2.04 mmol) in 10 mL of MeOH, was added 0.114 g of KOH (2.04 mmol) and the solution was allowed to stir at ambient temperature for 5 h. The reaction 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: $[\alpha]_D$ = +28.8 (*c* 1.20, $CHCl_3$); IR (thin film): 3308, 3235, 2955, 2930, 2895, 2106, 1665, 1472, 1463, 1252, 1003, 836, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/v* 428 (M^+–Me), 386 (M^+–^{t}Bu), 317, 257, 183, 115; HRMS calcd for $C_{21}H_{42}NO_4Si_2$ 428.2652 found 428.2646.

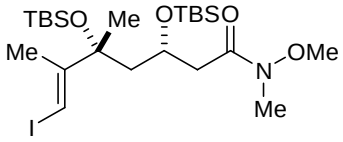


(*3S,5R*)-3,5-Bis(*tert*-butyldimethysilanyloxy)-5,6-dimethyl-7-tributylstannanylhept-6-enoic acid methoxymethylamide (88): To a –60 °C suspension of 0.247 g of CuCN (3.02 mmol) in THF (1.5 mL)was added 1.9 mL of a 1.6 M solution of ^{n}BuLi in hexanes to produce a light

brown solution which was allowed to warm to –30 °C over 30 min. A solution of $^{n}Bu_3SnLi$ was prepared by adding ^{n}BuLi (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 NH_4Cl was added to it, and the aqueous layer was extracted with ether (3 x 20 mL). The organics were combined, dried over Na_2SO_4 concentrated, and the crude product was purified by flash chromatography (1% Et_3N, then 0.2–0.5% EtOAc in hexanes) to afford 0.625 g of the title compound as a pale yellow oil: $[\alpha]_D$ = +17.7 (*c* 1.60, $CHCl_3$); IR (thin film) 2956, 2928, 2855, 1671, 1463, 1384, 1254, 1123, 1084, 835, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (s, J_{Sn-H} = 69.7Hz, 1H), 4.16 (dddd, *J* = 6.6, 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). ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{35}H_{75}NO_4Si_2Sn$ 749.4257 found 749.4294.

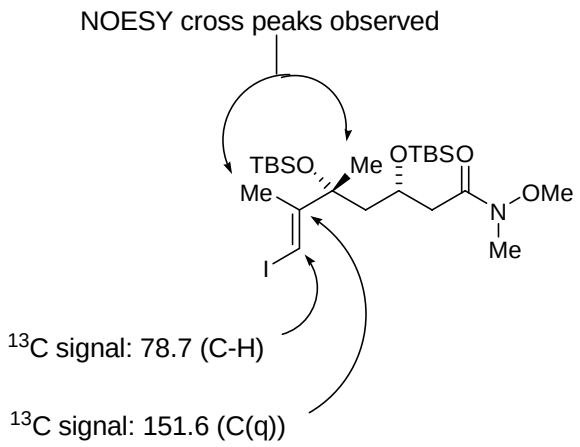


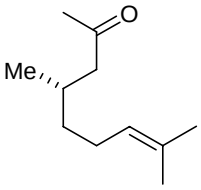
3,5-Bis-(*tert*-butyldimethylsilanyloxy)-5,6-dimethyl-7-trimethylstannanylhept-6-enoic acid methoxymethylamide (89): To a –60 °C suspension of 0.1026 g of CuCN (1.13 mmol) in THF (1.2 ml), was added 0.71 mL of ^{n}BuLi (1.6 M solution in hexanes). The light brown colored solution was stirred and allowed to warm to –30 °C. A solution of Me_3SnLi was prepared by the addition of 0.8 mL of ^{n}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 Me_3SnLi 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 methyliodide (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 NH_4Cl, stirred for 10 min, and the aqueous layer extracted with of ether (3 x 5 mL). The organics were combined, dried over Na_2SO_4, concentrated, and purified by flash chromatography on silica gel (0.2–0.5% EtOAc in hexanes with 5% Et_3N) to afford 0.090 g of stannane **89** (64%) as a bright yellow oil. $[\alpha]_D$ = +15.3 (*c* 1.00, $CHCl_3$); IR (thin film) 2956, 2928, 2856, 1667, 1471, 1462, 1384, 1254, 1003, 834, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (s, $J_{Sn\text{-}H}$ = 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, $J_{Sn\text{-}H}$ = 54.1 Hz, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 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^+–^{t}Bu), 286, 188, 165; HRMS calcd for $C_{25}H_{54}NO_4Si_2Sn$: 608.2586, found 608.2591.



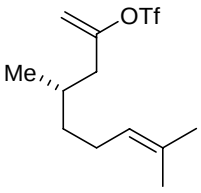
(*3S,5R*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-7-iodo-5,6-dimethylhept-6-enoic acid methoxymethylamide (90): To a solution of 0.021 g of stannane **88** in 5mL of CH_2Cl_2 was added 0.007 g of I_2 in portions. After 10 min, the solvent was evaporated *in vacuo* and the crude product purified by flash chromatography on silica gel (2% EtOAc in hexanes) to yield 0.016 g of iodide **90** (98%) as a pale yellow oil: $[\alpha]_D$ = +8.1 (*c* 0.6, $CHCl_3$); IR (thin film) 2956, 2929, 2856, 1660, 1471, 1386, 1256, 1002, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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^+–^{t}Bu), 188, 165; HRMS calc for $C_{22}H_{45}INO_4Si_2$: 570.1932, found 570.1955.

Proof of regiochemistry using DEPT and nOe studies:



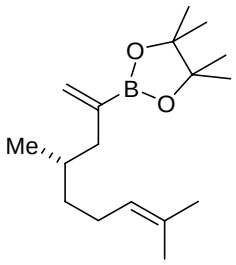


(*S*)-4,8-dimethylnon-7-en-2-one (96a) [39]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (dd, *J* = 4.5, 4.5 Hz, 1H), 2.34 (dd, *J* = 15.7, 5.5 Hz, 1H), 2.13 (dd, *J* = 15.8, 8.1 Hz, 1H), 2.04 (s, 3H), 1.96–1.82 (m, 3H), 1.59 (s, 3H), 1.51 (s, 3H), 1.28–1.07 (m, 2H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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-dimethylnona-1,7-dien-2-yl trifluoromethanesulfonate (96): To a –78 °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 **96a** (2.2 mmol) in THF (3 mL), dropwise. The resulting solution was stirred at –78 °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 °C. Then, 10 mL of a saturated $NaHCO_3$ solution

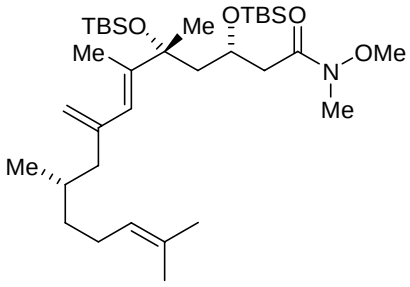
and 20 mL of ether were added to it, the layers were separated, and the aqueous layer washed with ether (5 x 20 mL). The combined organics were dried over Na_2SO_4, concentrated and purified by column chromatography over silica gel (0.5% EtOAc in hexanes, 2% Et_3N) to afford 0.55 g (85%) of the title compound as a colorless oil: $[\alpha]_D$ = –7.2 (*c* 1.4, $CHCl_3$); IR (thin film) 2966, 2919, 1670, 1419, 1249, 1141, 941 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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 (dddd, *J* = 13.9, 8.1, 6.5, 6.5 Hz, 1H), 0.98 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 131.8, 124.0, 118.4 (q, $J_{C\text{-}F}$ = 322 Hz), 105.2, 41.4, 36.3, 29.6, 25.6, 25.2, 19.0, 17.6; HRMS calcd for $C_{12}H_{19}O_3F_3S$: 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_2SO_4, concentrated and the crude product purified by column chromatography over silica gel (1% EtOAc in hexanes, 1% Et_3N) 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, $CDCl_3$): δ 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, $CDCl_3$): δ 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_2O. After separation of the layers, the aqueous layer was extracted with ether (3 x 5 mL). The organics were combined, dried over Na_2SO_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 $Pd(CH_3CN)Cl_2$ (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^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 $C_{34}H_{67}NO_4Si_2$: 609.4608, found 609.4620.

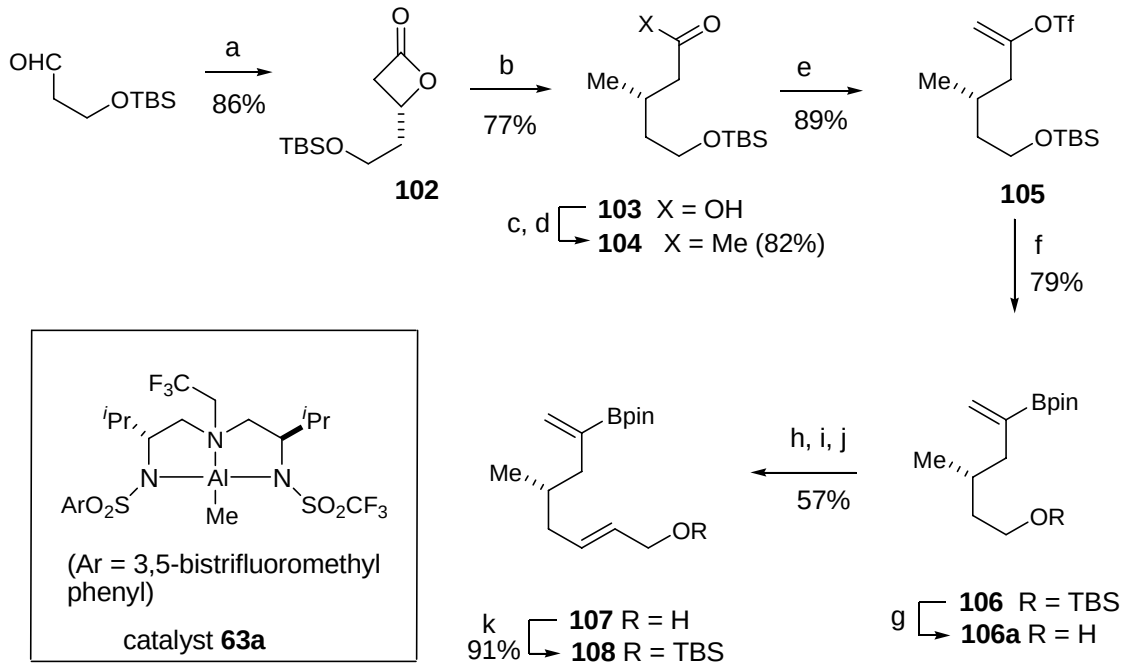
3.0 COMPLETION OF A C_1–C_{20} FRAGMENT AND THE SECOND GENERATION APPROACH

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*-butylsilanyloxy 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 methyllithium 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*-butyldmethylsilyl group proceeded in 91% yield to afford silyl ether **108**.

Scheme 11: Alternate synthesis of the C_7–C_{13} fragment[a]



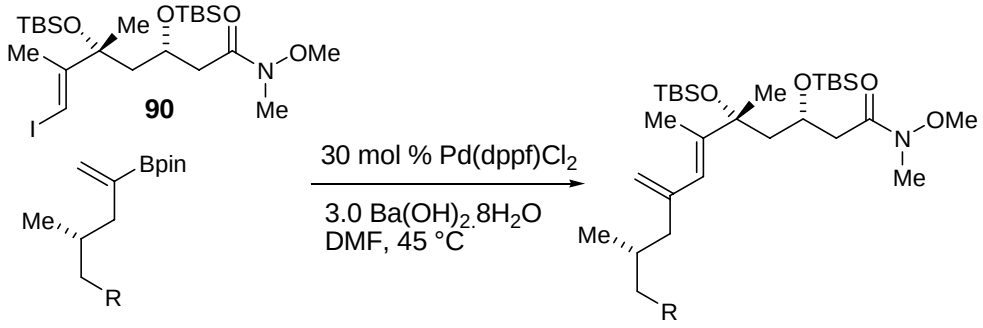
[a]Conditions: (a) 20 mol% catalyst **63a**, $^{i}Pr_2NEt$, –78 °C. (b) MeMgBr, CuBr.DMS. (c) $(OMe)MeNH_2Cl$, EDCI, DMAP. (d) MeLi, THF; (e) KHMDS, $PhNTf_2$, –78 °C - 0 °C. (f) Bpin-Bpin, $Pd(PPh_3)_2Cl_2.2PPh_3$, PhOK, 50 °C. (g) $^{n}Bu_4F$. (h) Dess-Martin/Py. (i) NaH, $(O^{i}Pr)_2P(O)CH_2CO_2Et$. (j) Dibal-H, CH_2Cl_2. (k) TBSCl, imidazole, DMF.

3.2 DIENE FORMATION IN THE REAL SYSTEM

3.2.1 Suzuki coupling studies with the C_7–C_{13} 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 C_{13}–C_{15} diene in the real

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%.



(5)

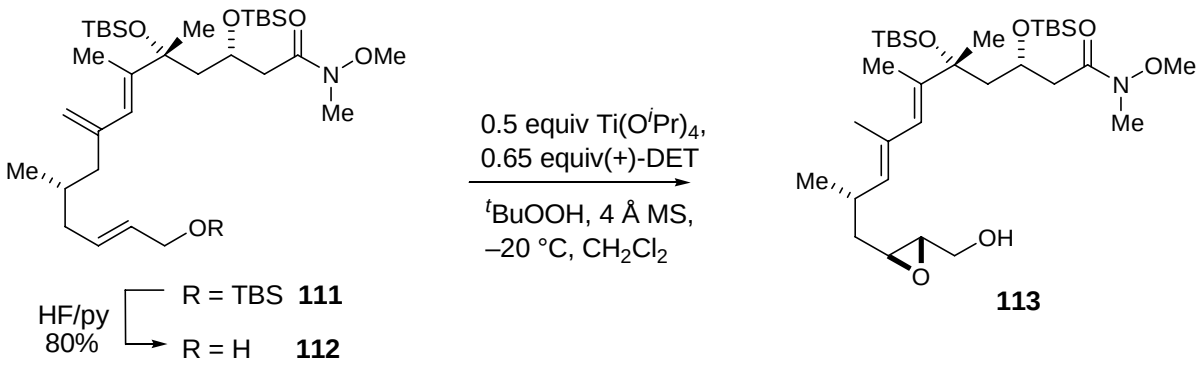
boronate ester (R =)	Isolated yield of diene
CH_2OH (**106a**)	(**109**) 82%
(*E*)-CH=$CHCH_2OH$ (**107**)	(**110**) 39%[a]
(*E*)-CH=$CHCH_2OTBS$ (**108**)	(**111**) 94%

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 C_8–C_9 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 tartarate, 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



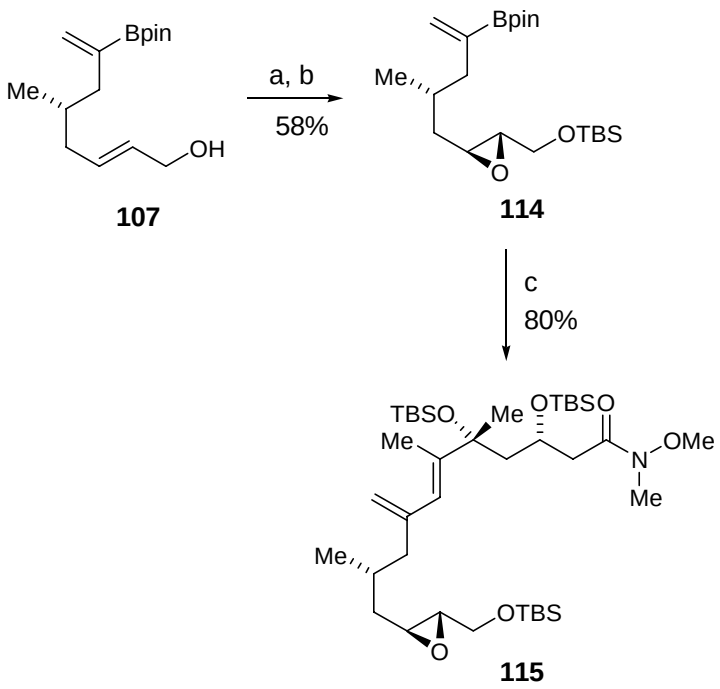
3.2.3 Modification of the epoxide fragment and completion of the C_7–C_{20} fragment

In light of the instability of the C_{13}–C_{15} diene towards Sharpless' epoxidation conditions, we decided to try incorporating the epoxide moiety earlier in the sequence, before the formation

of the C_{13}–C_{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 **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 **114** in an overall yield of 58% (Scheme 13). We were also pleased to find that the Suzuki cross-coupling reaction of boronate ester **114** with iodide **90** under the optimized conditions proceeded smoothly to afford diene **115** in 80% yield without any complications arising from the epoxide.

Scheme 13: Completion of a C_7–C_{20} fragment of amphidinolide B[a]



107 **114** **115**

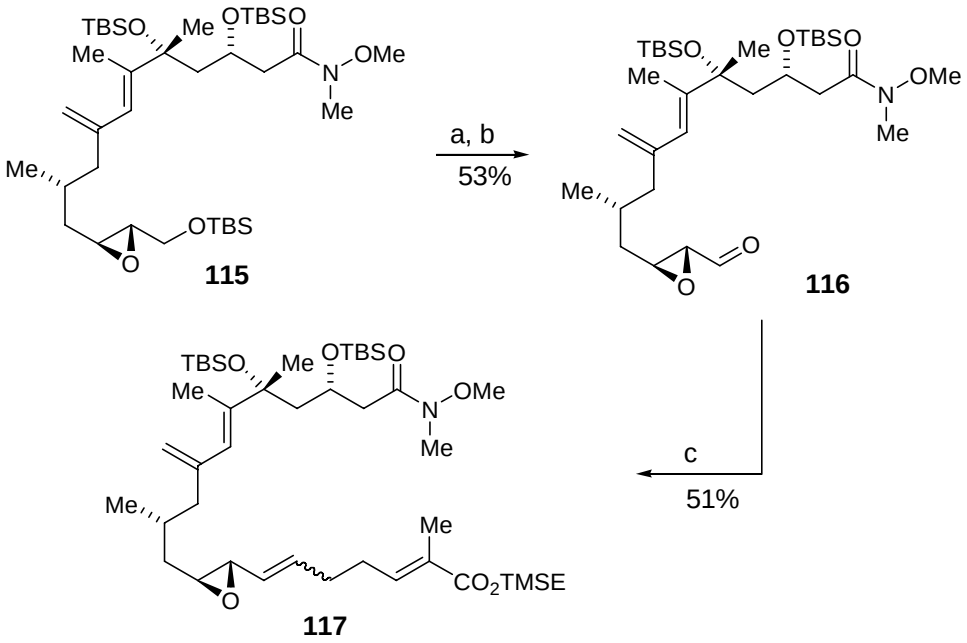
[a]Conditions: (a) 0.5 Ti(O^iPr)$_4$, 0.8 (+)-DET, ^{t}BuOOH. (b) TBSCl, im, DMF. (c) 40 mol % Pd(dppf)Cl_2 ,3.0 Ba$(OH)_2.8H_2O$, **90**, DMF, 45 °C.

3.2.4 Completion of a C_1–C_{20} synthon

Having shown that we could efficiently couple two major fragments **90** and **114** to form a C_7–C_{20} 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; [46] 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_1–C_{20} synthon[a]



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

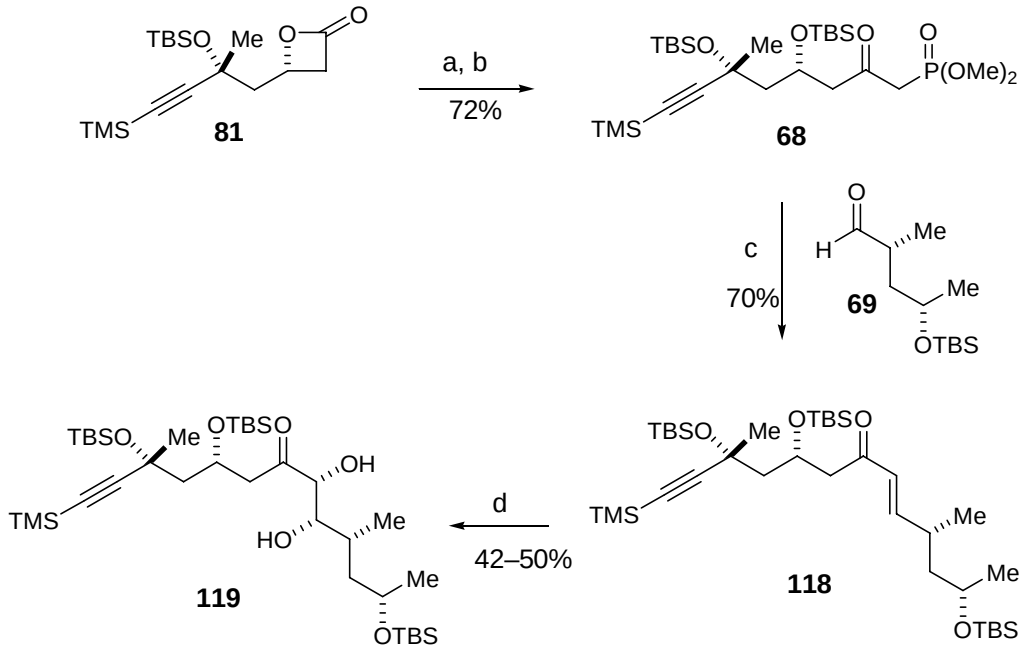
3.3 SHORTCOMINGS OF THE FIRST GENERATION APPROACH

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 β-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 % $K_2OsO_4.2H_2O$, 10 mol % $(DHQ)_2PHAL$, $NaHCO_3$, $MeSO_2NH_2$, $^tBuOH/H_2O$) 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[a]

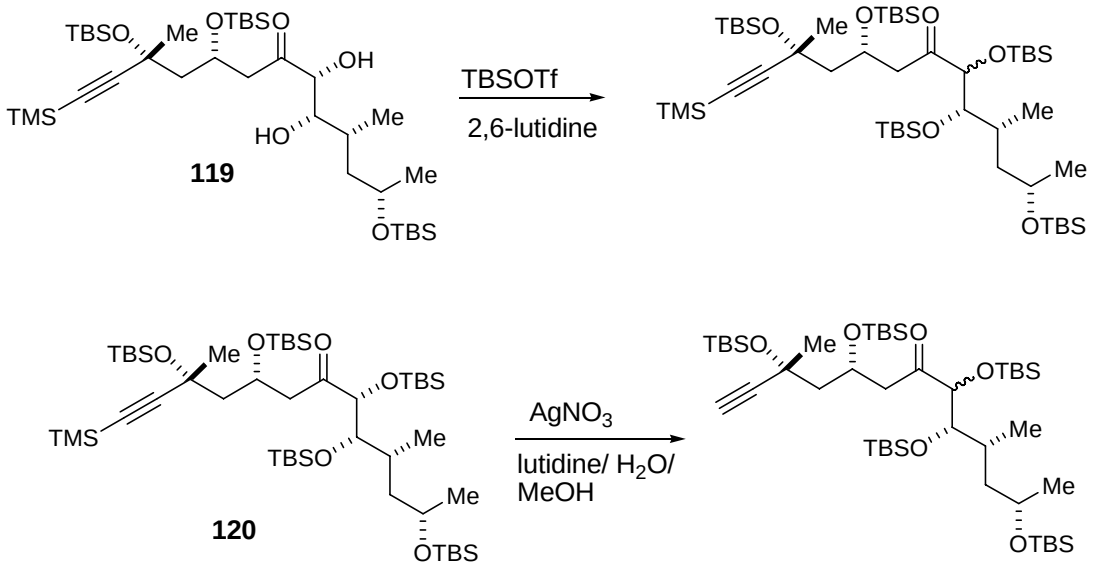


[a]Conditions: (a) $(MeO)_2(P=O)CH_2Li$, THF, –78 °C. (b) TBSCl, imidazole, DMF. (c) LiCl, DIPEA, CH_3CN. (d) AD-mix α, 10 mol % $K_2OsO_4.2H_2O$, 10 mol % $(DHQ)_2PHAL$, $NaHCO_3$, $MeSO_2NH_2$, $^tBuOH/H_2O$.

3.3.2 Sensitivity of the C_{21}- 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 C_{14}–C_{15} 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, CH_2Cl_2, 0 °C) the C_{21}-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 C_{21}- 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.

Scheme 16: Lability of the C_{21} stereocenter



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_{21}- stereocenter under conditions required to deprotect the alkynyl trimethylsilyl group and install the C_{14}–C_{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_{21}–C_{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_{21}–C_{22} bond.

According to our revised retrosynthetic analysis, fragment **121** would be obtained after the first two disconnections across the C_1–O bond and the C_6–C_7 bond via macrolactonization and Julia olefination reactions respectively. Further, disconnection across the C_{13}–C_{14} bond via Suzuki cross-coupling and across the C_{21}–C_{22} bond via a glycolate aldol reaction gave ketone **122**, boronate ester **114** and aldehyde **69**. α-Alkoxy ketone **122** would be formed from Weinreb amide **90** by the addition of an α-alkoxyl methyllithium species to it.

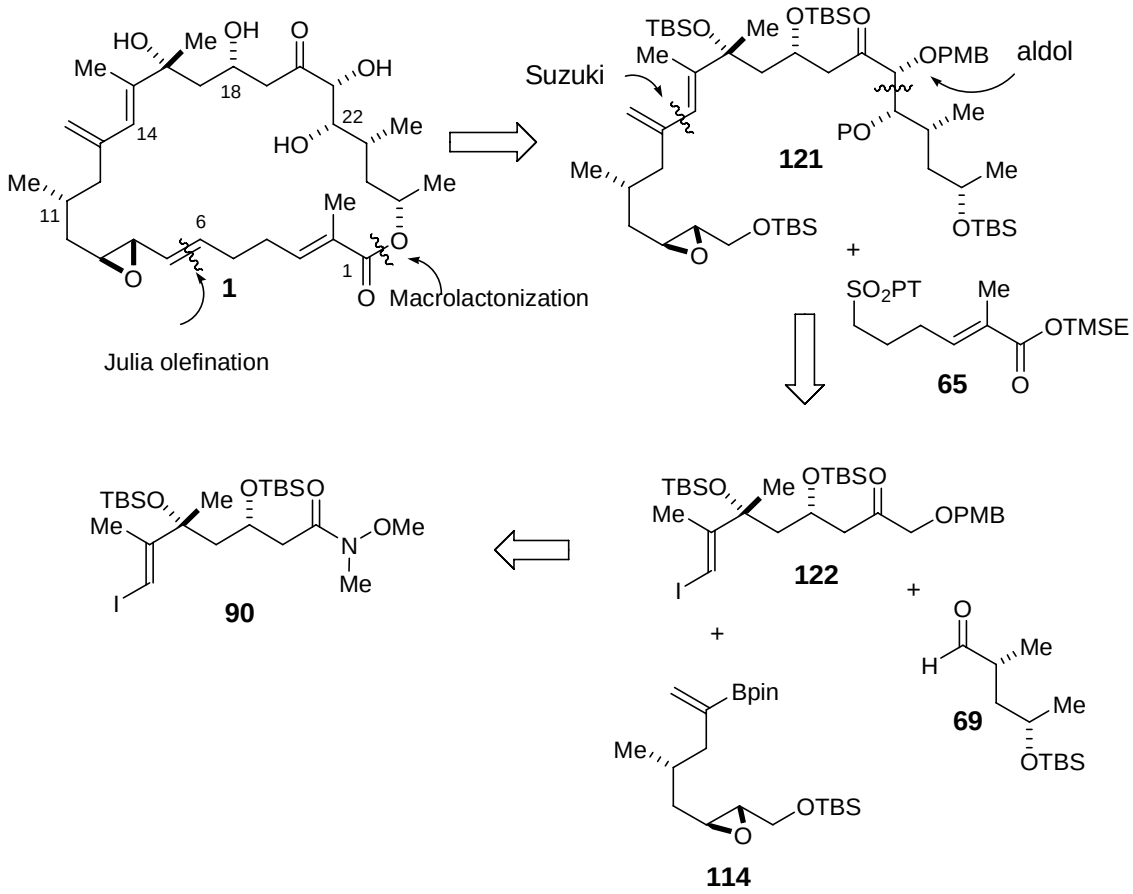
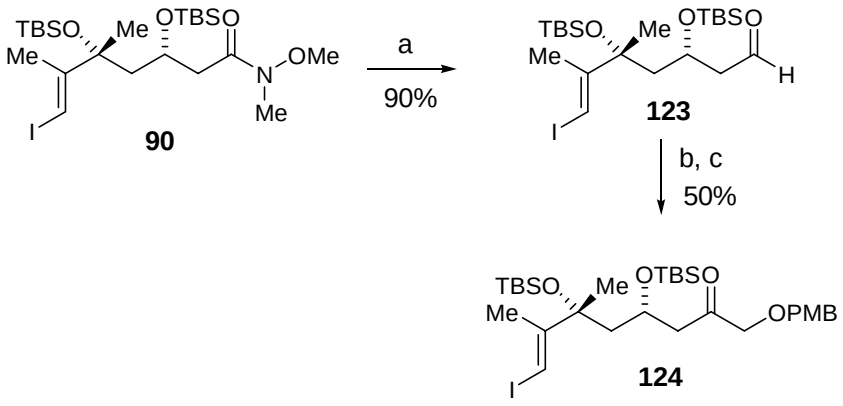


Figure 15: Revised retrosynthetic analysis of Amphidinolide B- the aldol approach

3.4.2 Synthesis of precursors for aldol study

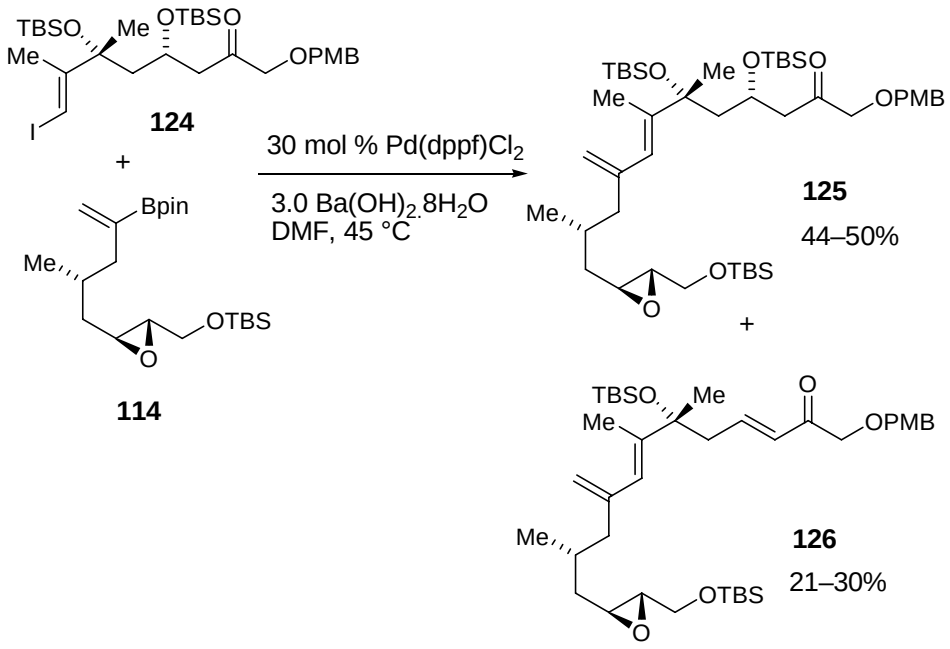
As a two-fold approach to the aldol reaction we decided to prepare enolate precursors arising from iodide **90** as well as diene **115**. Weinreb amide **90** was reduced to aldehyde **123** by diisobutylaluminum hydride in 90% yield (Scheme 17). Subsequently, the lithium anion of paramethoxybenzyloxymethane 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[a]



[a]Conditions: (a) Dibal-H. (b) $PMBOCH_2Li$, THF. (c) Dess-Martin periodinane, CH_2Cl_2.

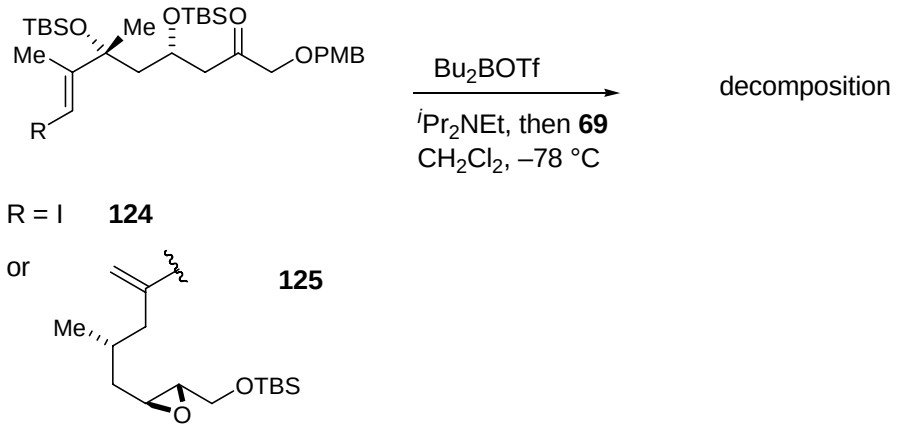
Synthesis of glycolate **125** resulted from the Suzuki cross-coupling of iodide **124** with boronic ester **114** under the previously optimized conditions (Eq 6). Although we were able to isolate diene **125** in 44–50% yields, the presence of the C_{20}- ketone functionality led to elimination of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



(6)

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 CH_2Cl_2 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 CH_2Cl_2 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 C_7–C_8 epoxide.



(7)

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 alkynyl 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 C_{21} carbon through a chelate-Cram transition state. [50]

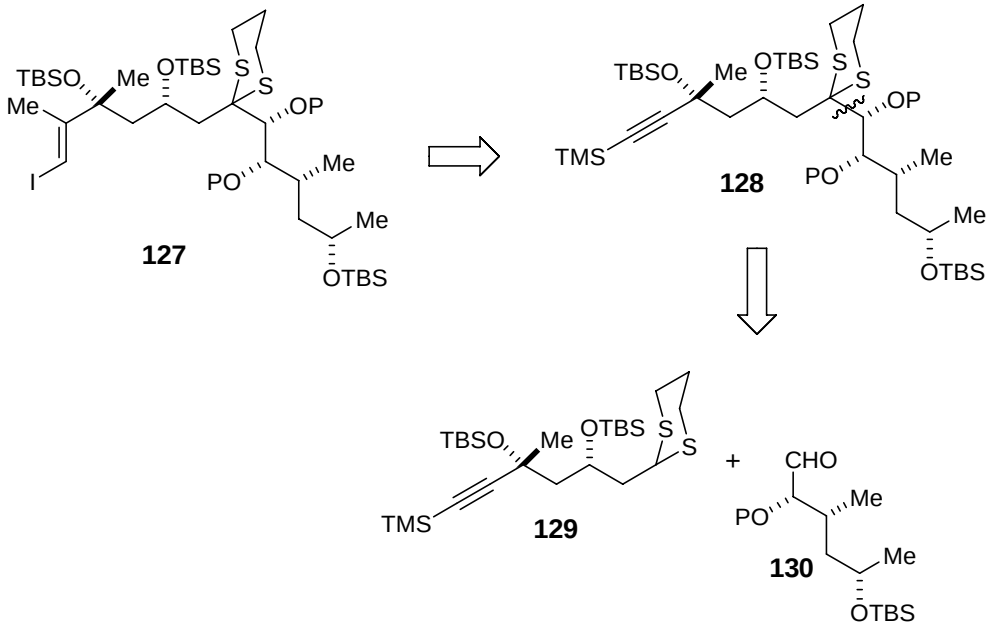


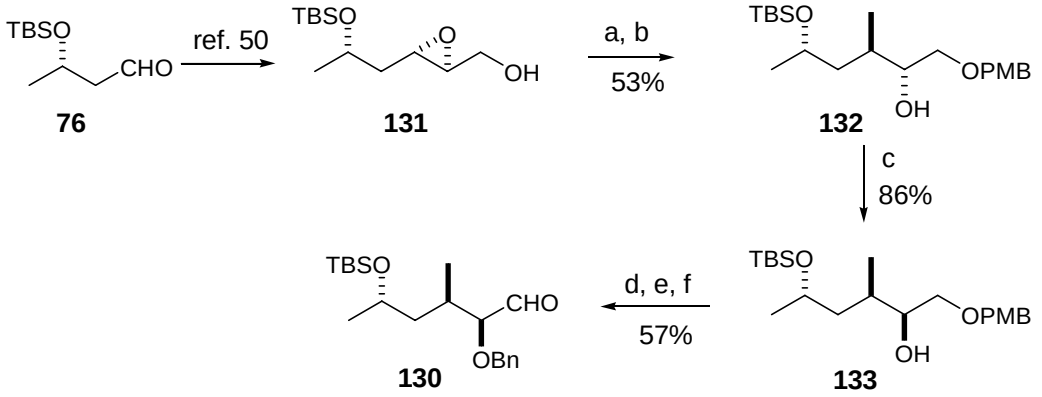
Figure 16: Retrosynthesis of the C_{14}–C_{26} fragment- the dithiane approach

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 C_2- hydroxyl bearing stereocenter was inverted through a Mitsunobu reaction

yielding alcohol **133** in 86% yield. [53] 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.

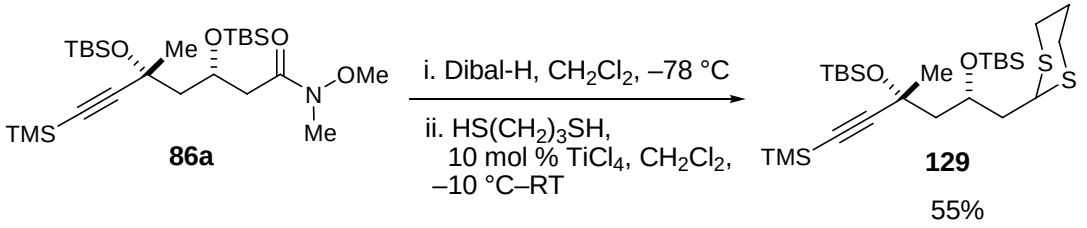
Scheme 18: Synthesis of aldehyde 130 for dithiane trials[a]



76 **131** **132** **133** **130**

[a]Conditions: (a) Me_3Al, hexanes, 0 °C. (b) NaH, PMBCl, $Bu_4N^+I^-$, THF. (c) i. (p-NO_2)C_6H_4COOH, PPh_3, DIAD; ii. 1% NaOH, MeOH. (d) NaH, BnBr, $Bu_4N^+I^-$, THF. (e) DDQ, CH_2Cl_2-pH 7 buffer (9:1). (f) DMSO, $(COCl)_2$, Et_3N, –78 °C.

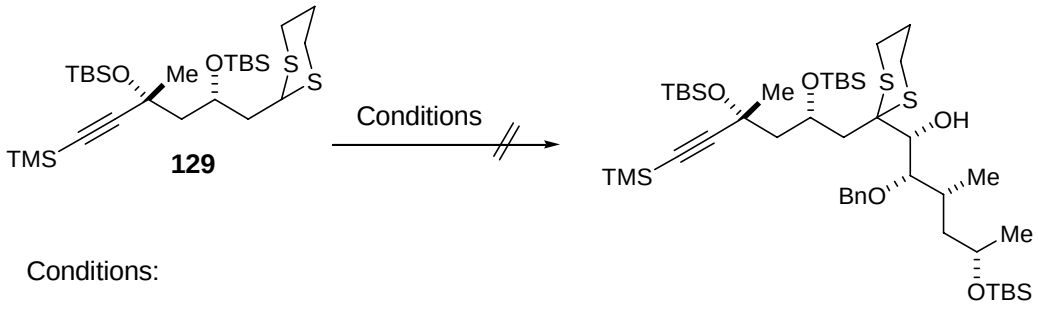
Weinreb amide **86a** was reduced with diisobutylaluminum hydride to the corresponding aldehyde which was then converted to dithiane **129** by treatment with propane 1, 3-dithiol, titanium tetrachloride in CH_2Cl_2 in 55% yield (Eq 8).



86a **129** 55% (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**.



(9)

Conditions:

(a) BuLi, THF, –50 °C, then **130**
(b) ^{t}BuLi, THF, –50 °C – RT, then –50 °C, **130**
(c) BuLi, HMPA, –50 °C, then **130**

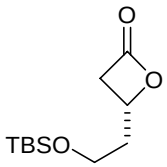
The unsuccessful attempts to add the anion of dithiane **129** into aldehyde **130** prompted us to perform control experiments to trap the anion with other, more reactive electrophiles such as TMSCl. Under a variety of conditions with bases such as butyllithium, *tert*-butyllithium,

potassium bis(trimethylsilyl)amide, experiments to metalate 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

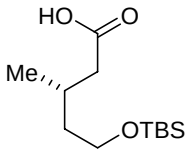
In pursuit of a total synthesis of the cytotoxic macrolide amphidinolide B (**1**), asymmetric AAC reactions have been used to set key stereochemical relationships in major fragments **90** and **114**. An efficient method to couple two major fragments to form the C_{13}–C_{15} trisubstituted diene in **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



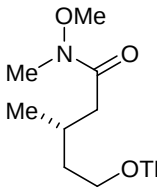
(*R*)-4-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]oxetan-2-one (102) : To a solution of 1.432 g of triamine ligand precursor to catalyst **63a** (2.11 mmol) in 18 mL of CH_2Cl_2 was added 1.27 mL of trimethylaluminum (2.53 mmol) (2 M solution in hexanes) and was stirred

for 2 h. The solution was cooled to –78 °C, and 3.1 mL of $^{i}Pr_2NEt$ (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)-propionaldehyde[42] (10.6 mmol) in 6 mL of CH_2Cl_2. The reaction mixture was stirred overnight at –78 °C, diluted with 3% Et_3N in ether and filtered through a short plug of silica gel using 3% Et_3N 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; $[\alpha]_D$ = +23.2 (*c* 2.20, $CHCl_3$); IR (thin film): 2955, 2929, 2884, 1830, 1472, 1256, 1108, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 69.0, 58.7, 43.1, 37.2, 25.7, 18.1, –5.6; EI-MS *e/v* 173 (M^+–^{t}Bu), 131 (M^+–^{t}Bu–CH_2CO), 101; HRMS calcd for $C_7H_{13}O_4$: 173.0634, found 173.0632.



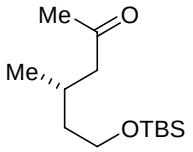
(*S*)-5-(*tert*-Butyldimethylsilanyloxy)-3-methylpentanoic acid (103): To a –50 °C solution of 1.118 g of CuBr (7.79mmol) in 40 mL of THF and 6 mL of dimethylsulfide, was added 5.2 mL of methylmagnesiumbromide (15.6 mmol) (3 M solution in ether) slowly to give a yellow suspension. The suspension was 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 NH_4Cl. After separation of the layers, the organic layer was washed twice with 30 mL of saturated NH_4Cl 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 Na_2SO_4, 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: $[\alpha]_D = -1.5$ (*c* 2.0, $CHCl_3$); IR (thin film): 3582, 2956, 2929, 2857, 1709, 1462, 1256, 1098, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.4, 61.0, 41.5, 39.2, 27.2, 26.0, 19.8, 18.3, –5.4; EI-MS *e/v* 189 (M^+–^{t}Bu), 171 (M^+–^{t}Bu–H_2O), 145 (M^+–^{t}Bu–CO_2), 127, 115; HRMS calcd for $C_8H_{17}O_3Si$: 189.0947, found 189.0952.



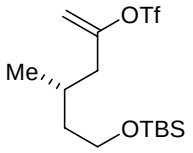
(*S*)-[5-(*tert*-Butyldimethylsilanyloxy)-3-methylpentanoic acid methoxymethylamide (103a): To a solution of 2.05 g (8.29 mmol) of carboxylic acid **103** in 25 mL of CH_2Cl_2 was added 1.21g of *N*,*O*-dimethylhydroxylamine hydrochloride (12.4 mmol), 2.39 g of EDCI (12.4 mmol) and 1.53 g of DMAP (12.4 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 $MgSO_4$ 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}; ^1H 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 $C_{13}H_{28}NO_3Si$: 274.1838, found 229.1839.

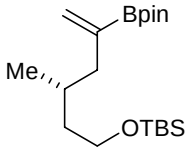


(*S*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methylhexan-2-one (104): To a 0 °C solution of 0.64 g (2.19 mmol) of the above Weinreb amide in 20 mL of THF was added 1.8 mL (2.88 mmol) of a 1.6 M solution of methyllithium in ether. The resulting solution was warmed to ambient temperature and stirred for 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}; ^1H 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),

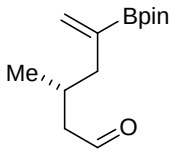
187 (M^+–^{t}Bu), 145 (M^+–^{t}Bu–CH_2CO), 115; HRMS calcd for $C_{12}H_{25}O_2Si$: 229.1624, found 229.1632.



(*S*)-(Trifluoromethanesulfonicacid-[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 $NaHCO_3$ 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 Na_2SO_4, concentrated and purified by column chromatography over silica gel (0.5% EtOAc in hexanes, 2% Et_3N) to afford 2.58 g (89%) of the title compound as a colorless oil; $[\alpha]_D$ = –5.18 (*c* 2.04, $CHCl_3$); IR (thin film): 2957, 2931, 2857, 1669, 1420, 1211, 1141 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 118.5 ($J_{C\text{-}F}$ = 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^+–^{t}Bu), 291, 227; HRMS calcd for $C_{16}H_{28}O_4F_3$: 319.0647, found: 319.0653.

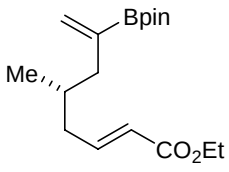


(*S*)-4,4,5,5-Tetramethyl-2-[1-(2-methyl-4-trimethylsilanyloxy-butyl)-vinyl]-[1,3,2]dioxaborolane (106): A mixture of 0.300 g of triflate **105** (0.802 mmol), 0.224 g of bis(pinacolato)diboron (0.882 mmol), 0.056 g of bis(triphenylphosphine)palladium dichloride (0.088 mmol), 0.042 g of triphenylphosphine (0.160 mmol) and 0.154g 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 2mL 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_2SO_4, concentrated and and the crude product purified by column chromatography over silica gel (2% EtOAc in hexanes, 1% Et_3N) to afford 0.225 g (79%) of the title compound as a colorless oil; $[\alpha]_D = -3.39$ (*c* 2.25, $CHCl_3$); IR (thin film): 2977, 2957, 2857, 1614, 1427, 1370, 1308, 1255, 144, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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 (dddd, *J* = 13.1, 7.3, 5.2.5.2 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 ($M^+ - {}^t$Bu), 197, 169, 155; HRMS calcd for $C_{15}H_{30}BO_3Si$: 297.2057, found: 297.2055.



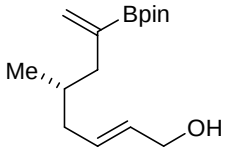
(*R*)-3-Methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-hex-5-enal (106b): To a solution of 0.420 g of boronic ester **106** in THF (12 mL) was added a 1 M solution of tetrabutyl ammonium fluoride in THF at ambient temperature and the reaction mixture was stirred overnight. To this was added 20 mL of ether and 5 mL of $NaHCO_3$ 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 Na_2SO_4, 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 CH_2Cl_2 was added a freshly prepared solution of 1.51 g of Dess-Martin periodinane in 1.7 mL of pyridine and 7mL of CH_2Cl_2. 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%); $[\alpha]_D$ = +6.85 (*c* 1.08, $CHCl_3$); IR (thin film): 2978, 2930, 2716, 1726, 1615, 1370, 1311, 1143, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 131.5, 83.5, 77.2, 50.4, 42.9, 28.1, 24.7, 20.5; HRMS calcd for $C_{13}H_{23}BO_3$: 238.174, found: 238.1741.



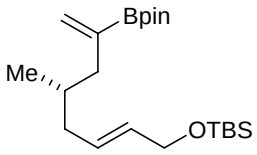
(*S*,*E*)-5-Methyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-octa-2,7-dienoic acid ethyl ester (106c): To a 0 °C suspension of 0.161 g of NaH (4.03 mmol) in THF (0.5 mL), was added 0.85 ml of diisopropyl(ethoxycarbonylmethyl) phosphonate (3.36 mmol). This was stirred at 0 °C for 20 min and a solution 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 H_2O 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: $[\alpha]_D$ = –7.6 (*c* 2.4, $CHCl_3$); IR (thin film) 2978, 2926, 2854, 1722, 1653, 1369, 1310, 1204, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.96 (ddd, *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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{29}BO_4$: 308.2159, found 308.2159.

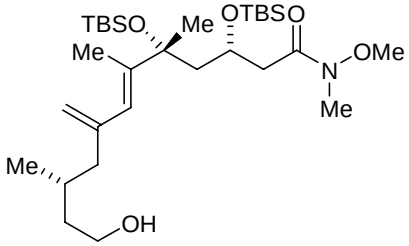


(*S*)-5-Methyl-7-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-octa-2,7-dien-1-ol (107): To a –40 °C solution of 0.445 g of the above ester in 9 mL of CH_2Cl_2 was added 2.7 mL of a 1.6 M solution of diisobutylaluminum hydride in hexanes and the reaction mixture was stirred at that temperature for 30 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 CH_2Cl_2 (3 x 20 mL). The combined organics were dried over Na_2SO_4, 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%): $[\alpha]_D$ = –4.85 (*c* 2.15, $CHCl_3$); IR (thin film): 3377, 2977, 2923, 1614, 1427, 1369, 1308, 1142, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.1, 130.5, 130.2, 83.4, 77.2,

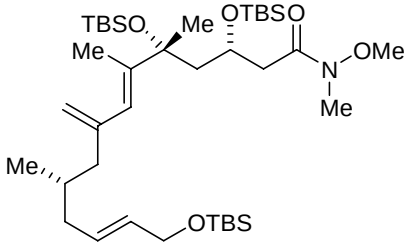
63.8 42.7, 39.4, 32.8, 24.7, 19.4; HRMS calcd for (M^++Na) $C_{15}H_{27}BO_3Na$: 289.1951, found 289.1968.



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 Na_2SO_4, concentrated and 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%): $[\alpha]_D = -3.7$ (*c* 2.0, $CHCl_3$); IR (thin film): 2956, 2928, 2857, 1614, 1462, 1370, 1254, 1144, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{17}H_{32}BO_3Si$: 323.2214, found 323.2202.

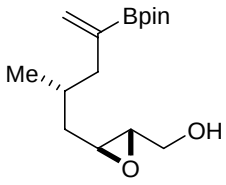


(*E*)-(*3S,5R,10R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-12-hydroxy-5,6,10-trimethyl-8-methylene-dodec-6-enoic acid methoxy-methyl-amide (**109**): General procedure A was followed with 20 mg of iodide **90** (0.03 mmol), 23 mg of boronic ester **106a** (0.09 mmol), 26 mg of $Pd(CH_3CN)_2Cl_2$ (0.01, 30 mol %), 5.7 mg of dppf (0.01 mmol) and 32 mg of $Ba(OH)_2.8H_2O$ (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}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 1H), 5.01 (br s, 1H), 4.82 (br s, 1H), 4.08 (dddd, *J* = 6.3, 6.3, 3.7, 3.7 Hz, 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) $C_{31}H_{61}NO_4Si_2Na$: 594.3986, found 594.4088.



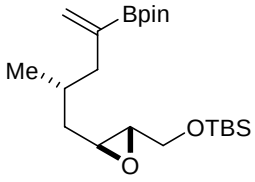
(*6E,12E*)-(*3S,5R,10S*)-3,5,14-Tris-(*tert*-butyldimethylsilanyloxy)-5,6,10-trimethyl-8-methylene-tetradeca-6,12-dienoic acid methoxymethylamide (**111**): General procedure A was followed with 20 mg of iodide **90** (0.03 mmol), 20 mg of boronic ester **108** (0.05 mmol), 26 mg of $Pd(CH_3CN)_2Cl_2$ (0.01, 30 mol %), 5.7 mg of dppf (0.01 mmol) and 32 mg of $Ba(OH)_2.8H_2O$ (0.10 mmol, 3 equiv). Isolated 23

mg of diene **108** (94%) as a colorless oil: $[\alpha]_D$ = –4.9 (*c* 1.2, $CHCl_3$); IR (thin film): 2955, 2928, 2856, 1669, 1462, 1255, 1094, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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.



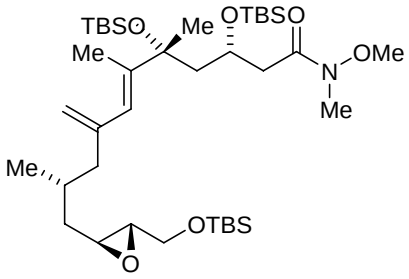
(*2S,3S,5R*)-{3-[2-Methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-enyl]-oxiranyl}-methanol (107a): To a –20 °C suspension of 0.370 g of flame-dried, activated 4 Å molecular sieves in 2 mL of CH_2Cl_2 was added a solution of 0.050 g of (+) diethyl tartarate (0.241 mmol) in 2 mL of CH_2Cl_2 followed by 0.0445 mL of $Ti(O^iPr)_4$ (0.153 mmol) and 0.12 mL of *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 CH_2Cl_2 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 Na_2SO_4, concentrated and 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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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.

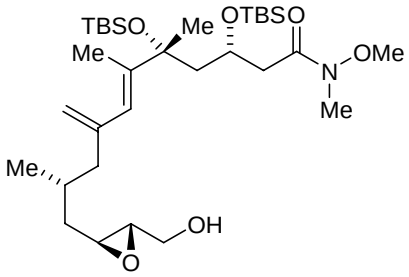


(*2S,3S,5R*)-2-(1-{3-[3-(tert-Butyl-dimethyl-silanyloxymethyl)-oxiranyl]-2-methyl-propyl}-vinyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (114): To a 0 °C solution of 0.045g of epoxy alcohol **107a** (0.159 mmol) in 4 mL of DMF was added 0.033 g of imidazole (0.478 mmol) and 0.072 g of *tert*-butyldimethylsilyl 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_2SO_4, concentrated and 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}; ^1H NMR (300 MHz, $CDCl_3$): δ 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* =

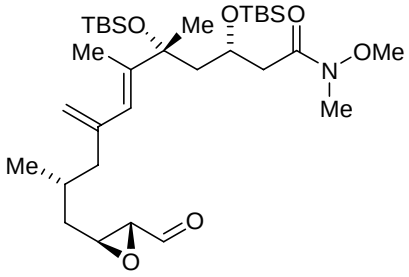
13.2, 6.6 Hz, 1H), 2.04 (dd, J = 12.8, 7.5 Hz, 1H), 1.86 (dddd, *J* = 12.5, 6.3, 6.3, 6.3 Hz, 1H), 1.73–1.65 (m, 2H), 1.26 (s, 12H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.7, 83.3, 63.8, 59.1, 55.2, 43.2, 38.5, 30.6, 25.8, 24.7, 19.4, 18.3, –5.3, –5.4; HRMS calcd for (M^++Na) $C_{21}H_{41}BO_4SiNa$: 419.2765, found 419.2779.



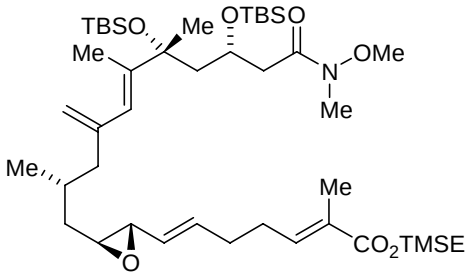
(*3S,5R,10R,12S,13S*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-8-{3-[3-(*tert*-butyldimethylsilanyloxymethyl)-oxiranyl]-2-methyl-propyl}-5,6-dimethyl-nona-6,8-dienoic acid methoxymethylamide (115):General procedure A was followed with 19 mg of iodide **90** (0.032 mmol), 20 mg of boronic ester **114** (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, $CDCl_3$): δ 5.90 (s, 1H), 5.01 (s, 1H), 4.87 (s, 1H), 4.20–4.12 (m, 1H), 3.76 (ddd, *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, $CDCl_3$): δ 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^++Na) $C_{38}H_{77}NO_6Si_3Na$: 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 3.3mL 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 Na_2SO_4. The solvents were evaporated *in vacuo* and the crude product was purified by flash chromatography (2% Et_3N, 10–30% EtOAc in hexanes) to afford 24 mg of the title product (75% yield) as a colorless oil: $[\alpha]_D$ = –27.2 (*c* 1.70, $CHCl_3$); IR (thin film): 3434, 2954, 2928, 2856, 1660, 1462, 1255, 1027, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{32}H_{63}NO_6Si_2Na$: 636.4092, found 636.4092.

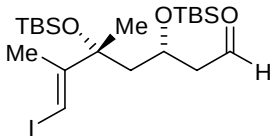


(*E*)-(*3S,5R,10R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-11-((*2S,3R*)-3-formyl-oxiranyl)-5,6,10-trimethyl-8-methylene-undec-6-enoic acid methoxymethylamide (116): Dess-Martin reagent in pyridine was prepared as follows: To a solution of 116 mg of Dess-Martin reagent (0.27 mmol, 12 equiv.) in 0.4 mL of CH_2Cl_2, 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 CH_2Cl_2. 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% Et_3N, then 5–10 % EtOAc in hexanes) to afford 9.8 mg of the title compound as a clear oil (70% yield): $[\alpha]_D$ = +9.6 (*c* 1.0, $CHCl_3$); IR (thin film): 2928, 2855, 1731, 1659, 1462, 1384, 1254, 1001, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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; EI-MS *e/v* 611, 596 (M^+–Me), 554 (M^+–^{t}Bu); HRMS calcd for $C_{28}H_{52}NO_6Si_2$: 554.3333, found 554.3349.

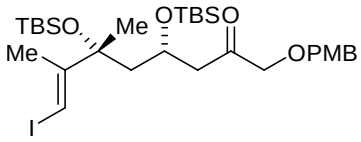


(*E*)-5-{(*2S,3S*)-3-[(*E*)-(*2R,7R,9S*)-7,9-Bis-(*tert*-butyldimethylsilanyloxy)-10-(methoxymethylcarbamoyl)-2,6,7-trimethyl-4-methylene-dec-5-enyl]-oxiranyl}-2-methyl-pent-2-enoic acid 2-trimethylsilanylethyl ester (117): To a –55 °C solution of 51.3 mg of sulfone **65** (0.12 mmol, 8.0 equiv.) in 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 Na_2SO_4. 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: $[\alpha]_D$ = –5.85 (*c* 0.80, $CHCl_3$); IR (thin film): 2954, 2928, 2855, 1709, 1665, 1462, 1252, 1116, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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,

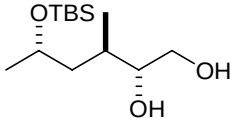
46.0, 39.0, 31.2, 29.7, 29.4, 28.7, 28.1, 26.7, 25.8, 19.6, 18.6, 17.9, 17.3, 15.1, 12.4, –1.5 (2C), –2.0, –4.5, –4.6; HRMS calcd for (M^++Na) $C_{44}H_{83}NO_7Si_3Na$: 844.5375, found 844.5327.



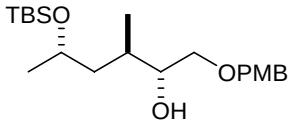
(*E*)-(*3S,5R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-7-iodo-5,6-dimethyl-hept-6-enal (**123**): To a –78 °C solution of 0.160g of Weinreb amide **90** (027 mmol) in 0.6 mL of CH_2Cl_2 added 0.5 mL of diisobutylaluminum hydride (1 M solution in hexanes, 0.54 mmol) dropwise via syringe. The solution 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 CH_2Cl_2 (5 x 10 mL). The combined organics were dried over Na_2SO_4 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: $[\alpha]_D$ = +3.0 (*c* 1.3, $CHCl_3$); IR (thin film): 2955, 2929, 2857, 1727, 1471, 1256, 1124, 1002, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{21}H_{43}O_3Si_2Na$: 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 (paramethoxybenzyoxy)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 NH_4Cl solution. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organics were dried over Na_2SO_4 and the solvents were evaporated *in vacuo*. The crude product was purified by flash chromatography (2–5% EtOAc in hexanes) and was dissolved in CH_2Cl_2 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: $[\alpha]_D$ = +11.5 (*c* 1.90, $CHCl_3$); IR (thin film): 2954, 2929, 2856, 1720, 1612, 1514, 1251, 1093, 1002, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{30}H_{53}IO_5Si_2Na$: 699.2374, found 699.2349.

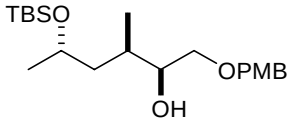


(*2R,3R,5S*)-5-(*tert*-Butyldimethylsilanyloxy)-3-methyl-hexane-1,2-diol (131a): To a 0 °C solution of 400 mg of epoxide **131** (1.6 mmol) in 6 mL of hexanes, added 2.5 mL of Me_3Al (2 M solution in hexanes, 4.9 mmol, 3.0 equiv) dropwise. The resulting solution was warmed to ambient temperature and 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 $MgSO_4$ 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: $[\alpha]_D$ = +28.9 (*c* 1.30, $CHCl_3$); IR (thin film): 3389, 2958, 2929, 2857, 1462, 1255, 1071, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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/v* 231 (M^+–Me–H_2O), 205 (M^+–^{t}Bu), 187, 119, 99; HRMS calcd for $C_{12}H_{27}O_2Si$: 231.1780, found 231.1776.



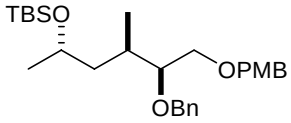
(*2R,3R,5S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(4-methoxy-benzyloxy)-3-methylhexan-2-ol (132): To a 0 °C suspension of 25 mg of NaH (1.0 mmol, 2.0 equiv) in THF (0.5 mL), added a solution of 80 mg of diol **131a** (3.1 mmol) in 1 mL of THF dropwise. The turbid white solution was allowed to warm to 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 $MgSO_4$. 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: $[\alpha]_D$ = +13.8 (*c* 1.30, $CHCl_3$); IR (thin film): 3466, 2956, 2928, 2856, 1613, 1514, 1249, 1078, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{21}H_{38}O_4SiNa$: 405.2437 found 405.2415.



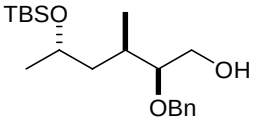
(*2S,3R,5S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(4-methoxy-benzyloxy)-3-methylhexan-2-ol (133): To a solution of 280 mg of alcohol **132** (0.7 mmol) in 7.4 mL of toluene (0.1 M) added 584 mg of triphenylphosphine (2.2 mmol, 3.0 equiv), 371 mg of *p*-nitrobenzoic acid (2.2 mmol, 3.0 equiv) and 0.45 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 $NaHCO_3$ solution. The aqueous layers were extracted with ether (5 x 20 mL) and the combined

organics were dried over $MgSO_4$. After evaporation of the solvents *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 $NaHCO_3$ 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, $CHCl_3$); IR (thin film): 3466, 2957, 2929, 2856, 1613, 1514, 1249, 1074, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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.



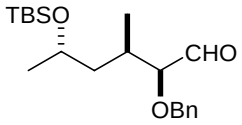
[(*1S,3R,4S*)-4-Benzyloxy-5-(4-methoxybenzyloxy)-1,3-dimethyl-pentyloxy]-*tert*-butyldimethylsilane (133a): To a 0 °C suspension of 118 mg of sodium hydride (2.9 mmol, 4.0 equiv) in 1 mL of THF added a solution of 280 mg of alcohol **133** (0.7 mmol) in 2.7 mL of THF. The resulting solution was allowed 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 $MgSO_4$. 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: $[\alpha]_D$ = +9.9 (*c* 1.6, $CHCl_3$); IR (thin film): 3030, 2956, 2929, 2898, 2855, 1612, 1513, 1301, 1248, 1172, 1074, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{28}H_{44}O_4Si$: 495.2907 found 495.2909.



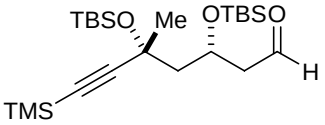
(*2S,3R,5S*)-2-Benzyloxy-5-(*tert*-butyldimethylsilanyloxy)-3-methylhexan-1-ol (133b): To a solution of 55 mg of parамethoxybenzylether **133a** (0.1 mmol) in a 10:1 CH_2Cl_2-H_2O solvent mixture (1.1 mL), was added 26 mg of DDQ (0.1 mmol) at ambient temperature. The mixture was stirred for 1 h and then 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: $[\alpha]_D$ = +49.6 (*c* 1.0, $CHCl_3$); IR (thin film): 3434, 2957, 2929, 2883, 2856, 1496, 1255, 1074, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 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) $C_{20}H_{36}O_3SiNa$: 375.2331 found 375.2332.

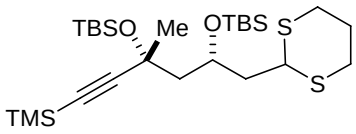


(*2S,3R,5S*)-2-Benzyloxy-5-(*tert*-butyldimethylsilanyloxy)-3-methylhexanal (130): To a –78 ° C solution of 12 μL of oxalyl chloride in 0.4 mL of CH_2Cl_2 added 20 μL of DMSO dropwise. The turbid solution was stirred at –78 °C for 10 min and then a solution of 30 mg of alcohol **133b** in 0.4 mL of CH_2Cl_2 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 Na_2SO_4 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): $[\alpha]_D$ = –15.4 (*c* 0.61, $CHCl_3$); IR (thin film): 2958, 2929, 2856, 1732, 1462, 1255, 1131, 1075, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 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, $CDCl_3$): δ 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) $C_{20}H_{34}O_3Si$: 373.2175 found 373.2179.



(*3S,5R*)-3,5-Bis-(*tert*-butyldimethylsilanyloxy)-5-methyl-7-trimethylsilanyl-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_2Cl_2 added 0.62 mL of diisobutylaliminum 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_2Cl_2 (5 x 10 mL). The combined organics were dried over Na_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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) $C_{23}H_{48}O_3Si_3$: 479.2809, found 479.2811.



2-[(*2S,4R*)-2,4-Bis-(*tert*-butyldimethylsilanyloxy)-4-methyl-6-trimethylsilanyl-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 CH_2Cl_2 was added 13 μL of titanium tetrachloride (1 M solution in CH_2Cl_2, 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 NH_4Cl solution and the layers were separated. The aqueous layer was extracted with ether (3 x 5 mL). The combined organics were dried over $MgSO_4$ 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: $[\alpha]_D$ = +31.7 (*c* 0.606, $CHCl_3$); IR (thin film): 2956, 2929, 2856, 2165, 1472, 1252, 1123, 989, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.30 (dddd, *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 (ddd, *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); ^{13}C NMR (75 MHz, $CDCl_3$): 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 $C_{26}H_{54}O_2Si_3S_2$: 546.2873, found 546.2866.

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