This is to certify that the

dissertation entitled

THE TOTAL SYNTHESIS OF THE ASSIGNED STRUCTURE OF
AMPHIDINOLIDE A

presented by

Lamont R. Terrell

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

Major professor

Date August 17, 2001

THE TOTAL SYNTHESIS OF THE ASSIGNED STRUCTURE OF AMPHIDINOLIDE A

By

Lamont R. Terrell

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2001

ABSTRACT

THE TOTAL SYNTHESIS OF THE ASSIGNED STRUCTURE OF AMPHIDINOLIDE A

By

Lamont R. Terrell

We initiated a synthetic venture aimed at the construction of the anti-leukemic macrocycle amphidinolide A (**1**). A synthetic target of considerable interest, amphidinolide A has marked biological activity and several striking structural features, including the contrast of lipophilic and hydrophilic moieties as well as the presence of both conjugated and non-conjugated dienes. Issues guiding our retrosynthetic plan, included the formation of multiple stereocenters early in the synthesis, the development and evaluation of new synthetic methods, and maintaining a flexible approach to the target molecule. Indeed, the successful construction of the subunits in our first generation retro-analysis allowed for the investigation of multiple coupling strategies and provided valuable information as to which coupling sequence was employed in our final approach to the total synthesis of amphidinolide A.

ACKNOWLEDGMENTS

I would like to express my deep appreciation to Professor Robert E. Maleczka, Jr. for his guidance and encouragement throughout the course of my Ph.D. studies. I could not have asked for a better advisor. I would also like to thank Professors Greg Baker, Babak Bohran, Paul Mantica and Paul McCracken for serving on my guidance committee. I wish to thank Professors William Reusch, Mike Rathke and Peter Wagner for the helpful discussions throughout my Ph.D. studies. I am very grateful to the NMR staff, Le Long Dinh and Kermit Johnson, for without their support my work would be impossible.

On a personal note, I must thank my parents, Thelma and Larry, for encouraging me throughout my life. Without your support, all of my achievements and successes would not have been possible. This one is for you. Upon my arrival at MSU, I only had one family but upon my departure I have been blessed with a lovely wife, Susan, and son,Tyrus. You both are the love of my life. I will be forever grateful for you'll acceptance and understanding of the long hours that I spent in the lab. I will make it up.

Thanks to all my colleagues in Professor Maleczka's group for their friendship and help, especially Joseph Ward and Feng Geng, who have worked so hard to finish the total synthesis of amphidinolide A.

I would like to thank all my basketball buddies from Tuesday mornings and Friday afternoons. It was fun. If you'll practice a little harder, maybe one day you will win.

TABLE OF CONTENTS

CHAPTER 1

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
$AgNO_3$	silver nitrate
aq	aqueous
CH_2Cl_2	dichloromethane
CI	chemical ionization
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
eq	equation
FAB	fast atom bombardment
hr	hour

HMPA	hexamethyl phosphoramide
HRMS	high resolution mass spectrometry
HWE	Horners-Wadsworth-Emmons reaction
IMES-H_2	4,5-dihydro-1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	*m*-chloroperbenzoic acid
mL	milliliter
mmol	millimole
MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	p-methoxybenzyl
RCM	ring closing metathesis
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
PTSA	*p*-toluenesulfonic acid

Introduction and Prior Work:

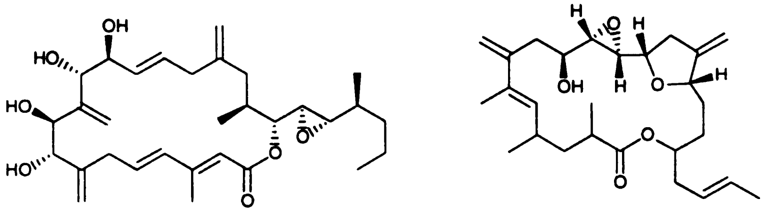
Marine microalgae are of considerable interest as new promising sources of bioactive substances. The amphidinolides (A-V),[1] isolated by Kobayashi from the marine dinoflagellate *Amphidinium sp*, represent a novel and significant class of natural products which originate from such algae. The amphidinolides have marked biological properties especially activity against L1210 marine leukemia cells and human epidermoid carcinoma KB cells in vitro as summarized in Table

Table 1 – Cytotoxicity Data of Various Amphidinolides

Amphidinolide	lactone ring size	Cytotoxicity (IC_{50}, µg/ml) L1210	KB
A	20	2.0	5.7
J	15	2.7	3.9
K	19	1.65	2.9
P	15	1.6	5.8
N	26	0.00005	0.0006

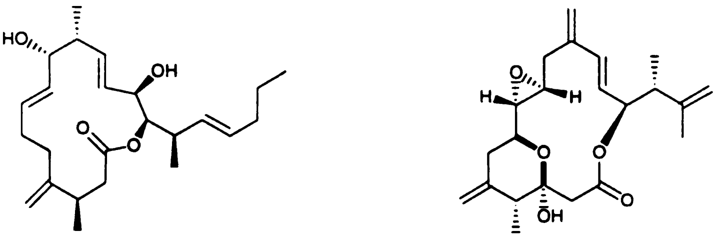
1. Amphidinolide A (**1**), Scheme 1, isolated in 1986 was the first polyolefinic macrolide of this unique series of compounds to be identified.[2] Since 1986 there have been over twenty-two of these unique macrolides isolated with the complete stereochemistry of only a few elucidated. The absolute stereochemistry[3] of amphidinolide A was elucidated in 1991 by one- and two-dimensional NMR; however, to date the proposed stereochemistry has not been verified by X-ray crystallography. In addition to its impressive anti-cancer activity, the 20-membered lactone (**1**), has several striking structural features, including the

Scheme 1. Several Amphidinolides



Amphidinolide A (1)

Amphidinolide K



Amphidinolide J

amphidinolide P

presence of lipophilic and hydrophilic moieties as well as the presence of exocyclic olefins and both conjugated and non-conjugated dienes. Because of these structural and biological features amphidinolide A is a current target for total synthesis.[4] To date no total synthesis of amphidinolide A has been reported. Amphidinolides J, K, and P have been synthesized by Williams.[5]

Although Mother Nature supplies us with millions of molecules, the quantity isolated is often only minute (< 1 mg). For detail biological studies, which are needed for understanding the mode of action of the target compound, the minute quantities isolated are not sufficient. Since the natural source is often not the most efficient means of obtaining the target molecules, synthetic efforts are needed. The total synthesis of natural products also allows for structure-activity relationship (SAR) studies. Often new synthetic methodology is developed or expanded to assist in the synthetic quest. In our approach to amphidinolide A (Figure 1), we were interested in the development or application

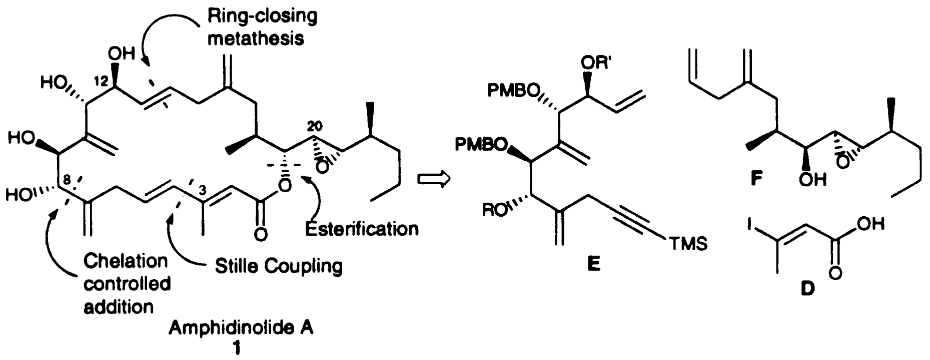


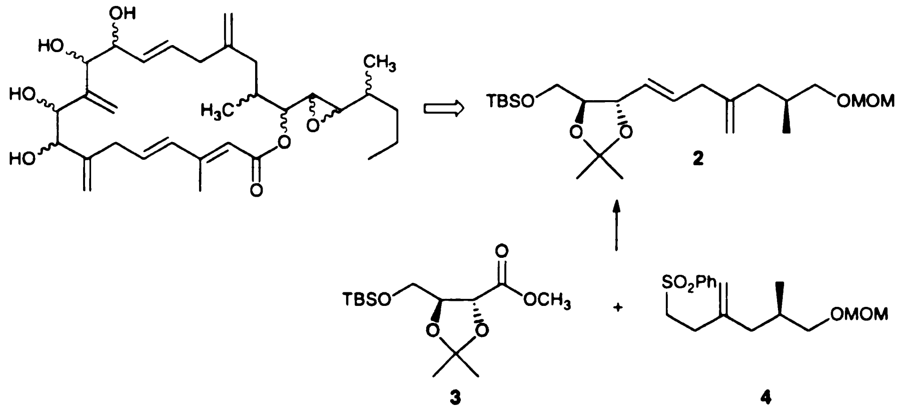
Figure 1. Retrosynthetic Analysis of Amphidinolide A

of organometallic reactions. Essential in the design of this synthesis was the generation and reaction of vinyl organometallics.

For the synthesis of vinyl tins, it was proposed that palladium-mediated hydrostannylations be investigated.[6] Two aims of such a study would be to determine what effect the presence of the non-conjugated olefin would have on the hydrostannylations and (b) could such a palladium-catalyzed reaction be developed into a single pot stannylation-Stille coupling? Besides adding expediency to the synthesis, a one-pot sequence could minimize side reactions such a protiodestannylation which often occurs upon workup and isolation of vinylstannanes. Besides using the total synthesis of amphidinolide A to developed new methodology, we were also interested in the application of recently developed novel chemical transformations. In particular, ruthenium based macrocyclizations were investigated in our second and third generation approach to the natural product. The first ruthenium-based macrocyclization to be investigated was the ring-closing metathesis (RCM) reaction, which has developed into a powerful synthetic tool with the advent of well-defined carbene catalysts by Grubbs.[7] In our third generation approach, an intramolecular variant of an Alder-ene type cross-coupling[8] was investigated.

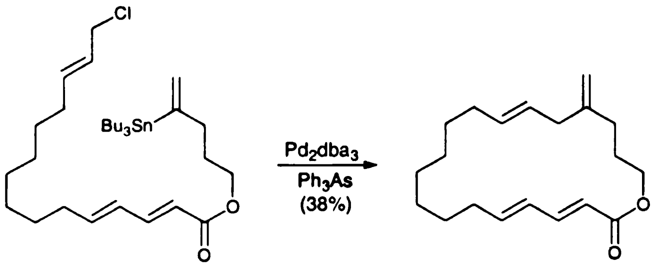
To date only two other groups in addition to ours have reported synthetic efforts towards amphidinolide A. The first was Williard in 1989.[9] Williard's work was prior to the stereochemical elucidation and therefore in his approach (Scheme 2) to the $C_{10} - C_{19}$ fragment **2**, methodology was developed to prepare all possible stereoisomers of **2** in order to make an unambiguous assignment of the stereochemistry. From his reaction sequences, the other stereoisomers could be readily available by changing chirality of the starting materials. The optically pure ester **3** is readily available as either enantiomer from (+)- or (-)-tartaric acid. Sulfone **4** is prepared from commercially available S-(+)-methyl-3-hydroxy-2-methylpropinate, whose enantiomer is also commercially available. More recently, Williard presented a poster at the 221st ACS National Meeting in San Diego detailing his current synthetic approach to amphidinolide A.[10]

Scheme 2. Williard's Approach



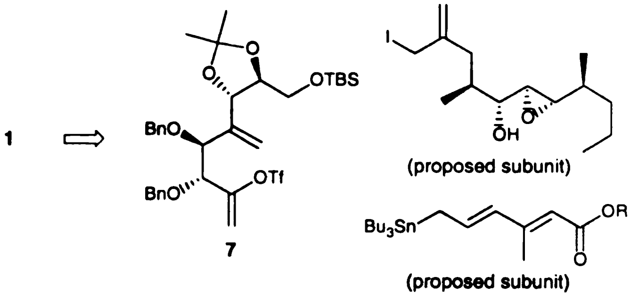
The second group to take on the task of synthesizing amphidinolide A was Pattenden.[11] In 1994, Pattenden published his first of two reports on amphidinolide A. In his first report (Scheme 3) a model study was undertaken to investigate the feasibility of a cross-coupling macrocyclization as a key step in the construction of (**1**). In particular, the chemical transformation investigated was a palladium mediated intramolecular coupling of an alkenyl stannane and an allylic halide. The methodology proved moderately successfully when applied to the model amphidinolide A system **5**. The desired macrocycle **6** was obtained in a 38% yield along with the Z-isomer (6%) and the allylic isomer (2%). Pattenden outlined his actual synthetic approach (Scheme 4) toward the natural product, in a second publication. The underlying theme of the retro-analysis is the application of the above-mentioned $sp^2 - sp^3$ coupling methodology. In these studies he prepared the properly functionalized $C_7 - C_{13}$ ene-tetra-ol unit **7**. This subunit was prepared from a known readily available derivative of D-glucose in 13 linear steps with an overall yield of 2%.

Scheme 3. Pattenden's Model Study



5 **6**

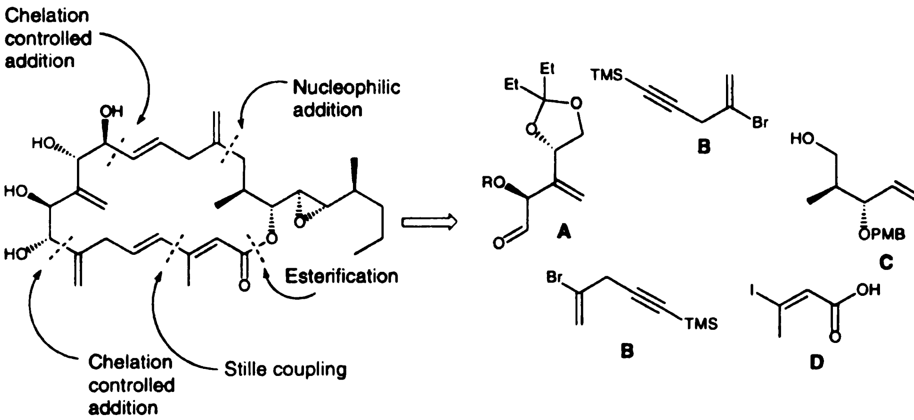
Scheme 4. Pattenden's Retro-analysis



Chapter 1. 1st Generation Approach – Synthesis of Fragments

Our initial retrosynthetic breakdown of amphidinolide A (Scheme 5) afforded four fragments **A** – **D** and illustrated the main synthetic challenges of this molecule. Several issues guided our retrosynthetic plan. These included the formation of multiple stereocenters early in the synthesis, the development and evaluation of new synthetic methods, and maintaining a flexible approach to the target molecule. Furthermore, the successful construction of subunits **A** – **D** would allow us to simultaneously investigate multiple coupling strategies, providing valuable information as to which coupling sequence should be employed in our final elaboration of amphidinolide A. The overall synthesis was envisioned to involve the independent couplings of common precursor **B** to molecules **A** and **C**, followed by the coupling of the resultant products. Compound **D** was expected to be added last via a Stille coupling[12] followed by macrolactonization to close the ring.

Scheme 5. Amphidinolide A Retrosynthetic Analysis



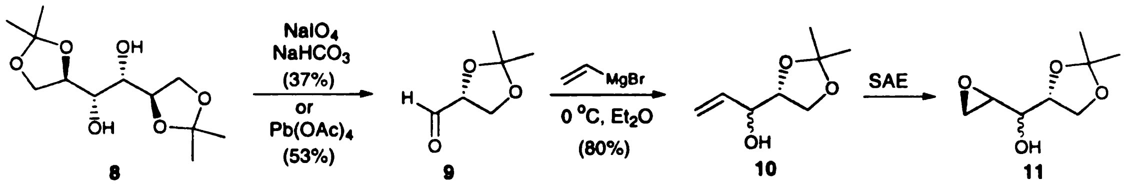
A. Synthesis of Fragment A

In our retro-synthetic analysis of fragment **A**, the 1,2-epoxy-3-ol **11** is a key advanced intermediate and thus several routes towards its synthesis were investigated. In all cases, the starting chiral source was D-mannitol.

1. D-Glyceraldehyde Acetonide Approach

D-glyceraldehyde acetonide is readily available via the oxidative cleavage of the bisisopropylidene acetal of mannitol.[13] The success of the oxidative cleavage in our hands depended on reagent choice. Following a procedure, which called for sodium periodate as the oxidant (Scheme 6) the desired aldehyde **9** was isolated in low yields (~37%). Although the setback was early in the synthesis, alternative oxidants were probed. With the use of lead (IV) tetraacetate as the oxidant, glyceraldehyde acetonide **9** was obtained in a moderately good yield (53%). Addition of vinyl magnesium bromide to the isolated aldehyde was not stereoselective. As a result, secondary allylic alcohol **10** was isolated as a mixture of diastereomers in 80% yield. The diastereomeric mixture was not problematic strategically since this stereocenter would be lost in the ensuing oxidation and olefination. With isolation of allylic alcohol **10**, the target 1,2-epoxy-3-ol **11** was only a Sharpless asymmetric epoxidation away. This one step proved to be quite challenging. In an effort to make the purification and identification of the epoxy alcohol easier, the epoxidation was run under

Scheme 6. Synthesis of 1,2-epoxy-3-ol (**11**)

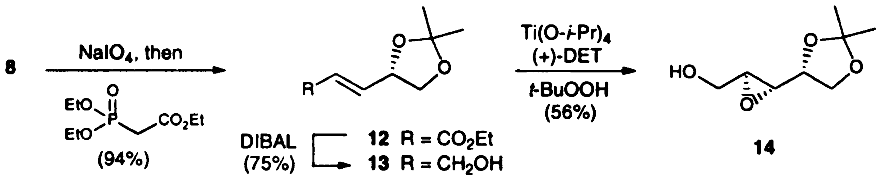


kinetic resolution conditions with (-)-DIPT as the chiral ligand. Unfortunately, epoxy alcohol **11** was isolated in very low yields (~5%). Attempted optimization of the reaction i.e. distillation of reagents, addition of molecular sieves, stoichiometric reagents, or increased reaction temperature, proved fruitless. Furthermore, upon purification of the reaction mixture, very little starting allylic alcohol was recovered. These results were quite baffling since the epoxidation of the enantiomer of **10** under kinetic resolution conditions is reported to occur in a 56% yield.[14] One possible explanation for this phenomenon is that the tartrate-allylic alcohol complex is an unfavorable mismatch case and thus unproductive complexes are formed. Although the yield was not synthetically useful, the isolation of epoxy alcohol **11** was beneficial since spectroscopic data were obtained.

2. Triol Approach

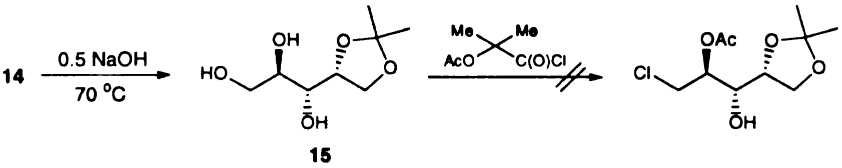
Since the above route to epoxy alcohol **11** was not preparatively viable, an indirect route to **A** through known triol **15**[15] was also investigated. The synthesis of triol **15** (Scheme 7) began with the oxidative cleavage of **8**.[16] The newly

Scheme 7. Synthesis of 2,3-epoxy-1-ol (**14**)



generated aldehyde **9** was then subjected to an *in situ* Horners-Emmons olefination to give allylic ester **12**. DIBAL reduction of the ester provided allylic alcohol **13** in 85% yield over three steps. Sharpless asymmetric epoxidation of **13** gave 2,3-epoxy-1-ol **14** in a 56% yield with complete stereocontrol as judged by ^{1}H NMR. Although the epoxide opening of **14** with aqueous NaOH is a known procedure, in our hands the procedure was nonreproducible (Scheme 8). We believed that the solubility of triol **15** in water was the major reason. In efforts to optimize the reaction, a biphasic system (*t*-BuOH / water) with a phase transfer catalyst (*n*-Bu$_4$NI) was employed, but to no avail. However, with a notion that triol **15** was formed but the isolation was problematic, the subsequent reaction with the Moffatt reagent to form the 1,2-epoxy-3-ol precursor was carried out on crude material. Unfortunately, upon purification of the reaction, the desired product was not isolated.

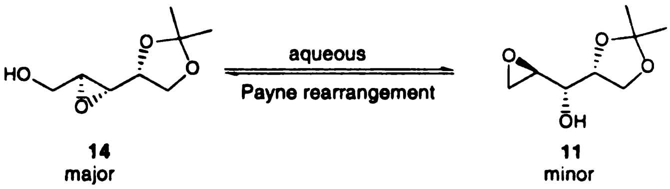
Scheme 8. Attempted Moffatt Epoxidation



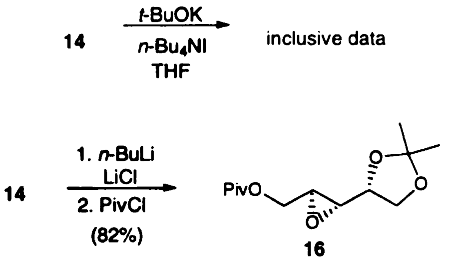
3. Payne Rearrangement Approach

It was found in the literature that non-aqueous Payne rearrangement[17] of epoxy alcohols often gives complementary results to the aqueous reaction.[18] In the aqueous case, epoxy alcohol **14** is the major isomer (>99%) after equilibration with alcohol **11** (Scheme 9). Unfortunately, in our case the minor isomer was the desired compound, and therefore non-aqueous conditions were investigated (Scheme 10). Simply quenching the equilibrating alcohols (*t*-BuOK, *n*-Bu$_4$NI) with water or TMSCl gave inconclusive results after isolation and purification of products. Therefore,

Scheme 9. Model Payne Rearrangement



quenching with other electrophiles was looked at. The use of pivalolyl chloride as the trapping electrophile proved to be the most successful in terms of identification of isolated products. Contrary to precedent, the "presumed" equilibration of epoxy alcohols **11** and **14** under non-aqueous conditions gave identical results as the aqueous Payne rearrangement.

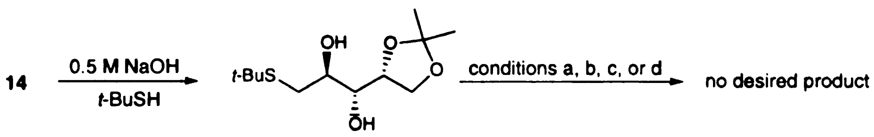


Scheme 10. Non-aqueous Payne Rearrangement

Although the direct isolation of the 1,2-epoxy-3-ol **11** via the Payne rearrangement is not possible, Sharpless has developed a procedure which utilizes the Payne rearrangement to obtain the minor epoxide.[19] In an extensive study, he showed that exposure of 2,3-epoxy-1-ols to the equilibrating conditions of the Payne rearrangement can result in selective opening of the terminal epoxide upon the addition of *t*-butylthiol. It was found that the product distribution is affected by several factors including sodium hydroxide concentration, reaction temperature, and the rate of thiol addition. Upon exposure of **14** (Scheme 11) to the equilibrating conditions (0.5 M NaOH, 70 °C) and slow addition (~ 45 minutes) of *t*-butyl thiol, the expected diol **17** was isolated in good yields (75%). To obtain the desired 1,2-epoxy-3-ol (**11**), **17** must be selectively S-methylated (Me_3OBF_4) which is then followed by intramolecular displacement of methyl *t*-butyl sulfide by the *in situ* generated (NaH) neighboring oxygen anion. This sequence of reactions is worthy of additional comment. Due to the acid lability of the acetonide, a proton scavenger was needed during the methylation step.

Upon substituting 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 2,4,6-trimethylpyridine for 2,6-di-*tert*-butylpyridine, the material isolated after the addition of Me$_3$OBF$_4$ and NaH was either recovered starting material or unidentifiable mixtures presumably from acetal hydrolysis. When the reaction was repeated in the presence of the reportedly preferred 2,6-di-*tert*-butylpyridine, the desired epoxy alcohol was still not isolated. It is believed that the epoxy alcohol was decomposing during silica gel chromatography because TLC analysis suggested that a reaction was occurring. Based on the assumption that the epoxy alcohol **11** was unstable on silica gel, the crude "presumed" epoxy alcohol was subjected to a pivalolyl protection. Unfortunately, the desired protected epoxy alcohol was not isolated after purification. To alleviate the potential instability of 1,2-epoxy-3-ol (**11**), the acid labile isopropylidene protecting group was replaced with the more stable isopentylidene analog.^{20}

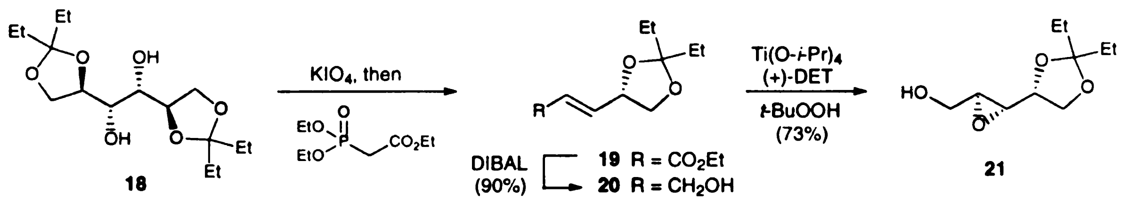
Scheme 11. Intramolecular Sulfide Displacement Investigation



17

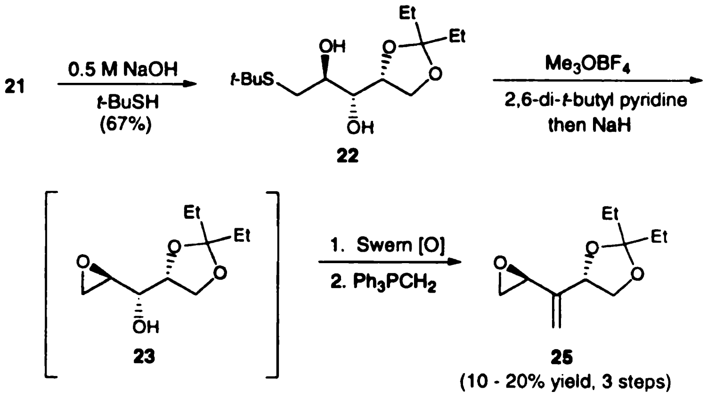
conditions: (a) DBU, Me$_3$OBF$_4$, NaH
(b) 2,4,6-trimethylpyridine, Me$_3$OBF$_4$, NaH
(c) 2,6-di-*tert*-butylpyridine, Me$_3$OBF$_4$, NaH
(d) (1) 2,6-di-*tert*-butylpyridine, Me$_3$OBF$_4$, NaH; (2) PivCl, pyridine

Scheme 12. Synthesis of 2.3-epoxy-1-ol (**21**)



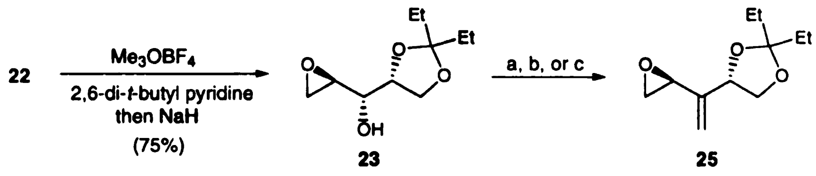
This synthesis began with the bisisopentylidene of D-mannitol via an approach which largely paralleled the above procedures for the preparation of the isopropylidene analog. As illustrated in Scheme 12, bisisopentylidene **18** was oxidatively cleaved by KIO_4 and then subjected to an *in situ* Wittig olefination. DIBAL reduction of the resultant ester **19** provided allylic alcohol **20** in 85% yield over three steps. Asymmetric epoxidation of **20** gave 2,3-epoxy-1-ol **21** with complete stereocontrol. With the isolation of the isopentylidene variant of the 2,3-epoxy-1-ol, the previously problematic three step procedure aimed at obtaining the 1,2-epoxy-1-ol via the 2,3-epoxy-1-ol was investigated. Subjection of epoxy alcohol **21** (Scheme 13) to the Payne rearrangement conditions and slow addition of *t*-butyl thiol resulted in isolation of diol sulfide **22** in a 67% yield. Due to problems in isolating the isopropylidene 1,2-epoxy-3-ol analog, purification of the isopentylidene epoxide was not attempted until after oxidation and Wittig olefination. As such, diol sulfide **22** was selectively

Scheme 13. Payne Rearrangement and *In Situ* Opening



S-methylated with Me_3OBF_4 in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine and after TLC analysis indicated complete consumption of the sulfide NaH was added to generate the alkoxide for the intramolecular displacement. The assumed crude 1,2-epoxy-3-ol **23** was subjected to a Swern oxidation[21] to give the apparent ketone **24**, which was in turn subjected to Wittig olefination. These successive reactions did indeed give the desired allylic epoxide **25** (~10% overall yield) after purification by flash chromatography on basic alumina. After substantial experimentation, the overall yield of the three tandem reactions was increased to only ~20%. Unfortunately, a low yield at this stage of the synthesis was not acceptable, and therefore each individual step was investigated. As illustrated in Scheme 14, optimization of the S-methylation / intramolecular displacement procedure with diol sulfide **22** gave the 1,2-epoxy-3-ol (**23**) in reproducible yields of 75%. Obviously, the above results suggest that one or both of the latter reactions in the three reaction sequence was the reason for the overall low yield. Therefore, the tandem oxidation/Wittig olefination procedure was investigated. When investigating the tandem reaction, a Swern, Dess-Martin,[22] or Doering-Parikh[23] oxidation followed by subsequent Wittig olefination gave allylic epoxide **25** in 41%, 29%, and 25% yields, respectively. Since the oxidation/olefination tandem protocol is well established, and the above results are fairly consistent,

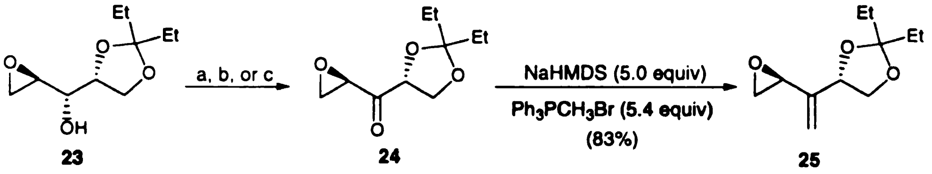
Scheme 14. Isolation of 1,2-epoxy-3-ol (**23**)



Conditions: (a) (i)Swern, (ii) Ph_3PCH_2; 41% yield, 2 steps
(b) (i) Dess-Martin, (ii) Ph_3PCH_2; 29% yield, 2 steps
(c) (i) Doering-Parikh, (ii) Ph_3PCH_2; 25% yield, 2 steps

the olefination reaction was likely the low yielding step. This indeed turned out to be the case (Scheme 15) as the Doering-Parikh oxidation gave ketone **24** in an 80% yield. In our earlier Wittig olefination procedure, *n*-BuLi (1.1 equivalents) was the base used to form the ylide of methyltriphenylphosphonium bromide (1.1 equivalents). In our optimized procedure it was found that NaHMDS (5 equivalents) and excess methyltriphenylphosphonium bromide (5.4 equivalents) gave the desired allylic epoxide **25** in excellent yields (83%). As a note, we also believe that the addition of the ylide to the carbonyl is a fast step, but the breakdown of the 4-membered ring intermediate is slow because the starting material is consumed within minutes. Yet, only upon extended reaction times (~3 hours) was exo-olefin **25** isolated in high yields. With the establishment of high yielding and reproducible procedures for the synthesis of these advanced intermediates, the synthesis of fragment **A** was carried forward.

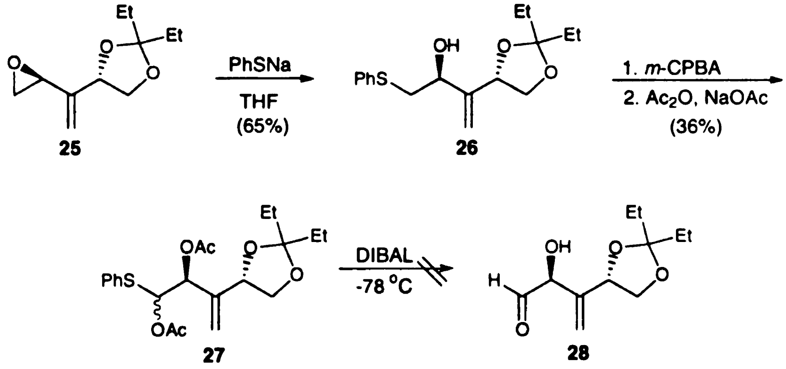
Scheme 15. Optimization of the Oxidatin and Wittig Olefination



Oxidation: (a) Doering-Parikh, 80% yield
(b) Dess-Marin periodanane, 24% yield
(c) TPAP, NMO, 0% yield

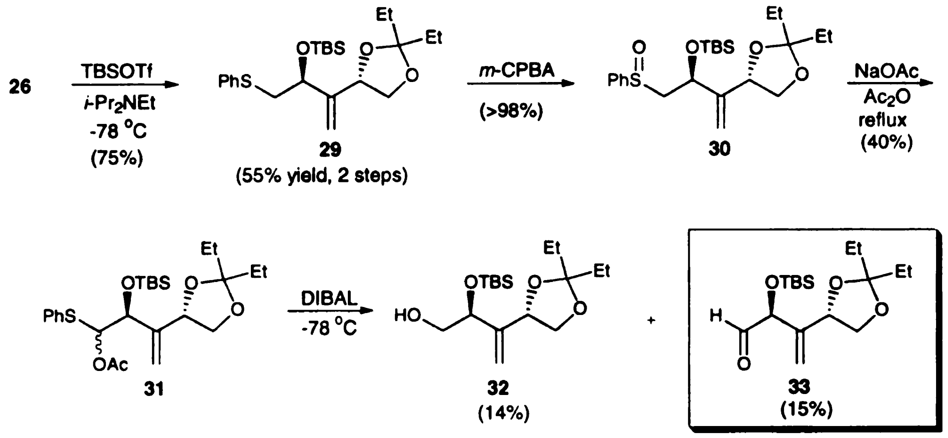
As illustrated in Scheme 16, epoxide **25** was opened regioselectively with sodium benzenethiolate to give phenyl sulfide **26** in 65% yield. In preparation for a Pummerer rearrangement, oxidation of sulfide **26** with *m*-CPBA gave the corresponding sulfoxide which was immediately rearranged (Ac_2O, NaOAc, reflux).[24] This allowed for isolation of acetoxy sulfide **27** in 36% yield as a mixture of diastereomers. Acetoxy sulfide **27** is a masked aldehyde and upon reduction of the esters with DIBAL the aldehyde would be expected to be liberated without epimerization of the α-stereocenter. In contrast, subjection of the acetoxy sulfides to DIBAL reduction did not give the desired aldehyde, but instead a product that probably is derived from a 5-endo cyclization of the highly reactive dianion intermediate.

Scheme 16. Preparation of α-acetoxy sulfide **27**



To circumvent this highly reactive dianion intermediate (Scheme 17) the alcohol of phenyl sulfide **26** was protected as a silyl ether prior to oxidation and subsequent Pummerer rearrangement. It was found that the protection of alcohol **26** to give silyl ether **29** in 75% yield had to be carried out at –78 °C with TBSOTf in order to avoid a side reaction that occurred if the protection was carried out at room temperature and/or with bulkier silyl protective groups, i.e. BPS. Interestingly, at room temperature, a TBSOTf / *i*-Pr_2NEt solution could be used as a quench after the epoxide opening of **25** to give the desired silyl ether **29** (55%) along with unprotected alcohol **26** (36%) and recovered starting epoxide (9%) with no indication of side reactions. Exposure of sulfide **29** to *m*-CPBA gave sulfoxide **30** in near quantitative yield. The crude sulfoxide was subjected to the Pummerer rearrangement (Ac_2O, NaOAc, reflux) to give a

Scheme 17. Isolation of Fragment **A**

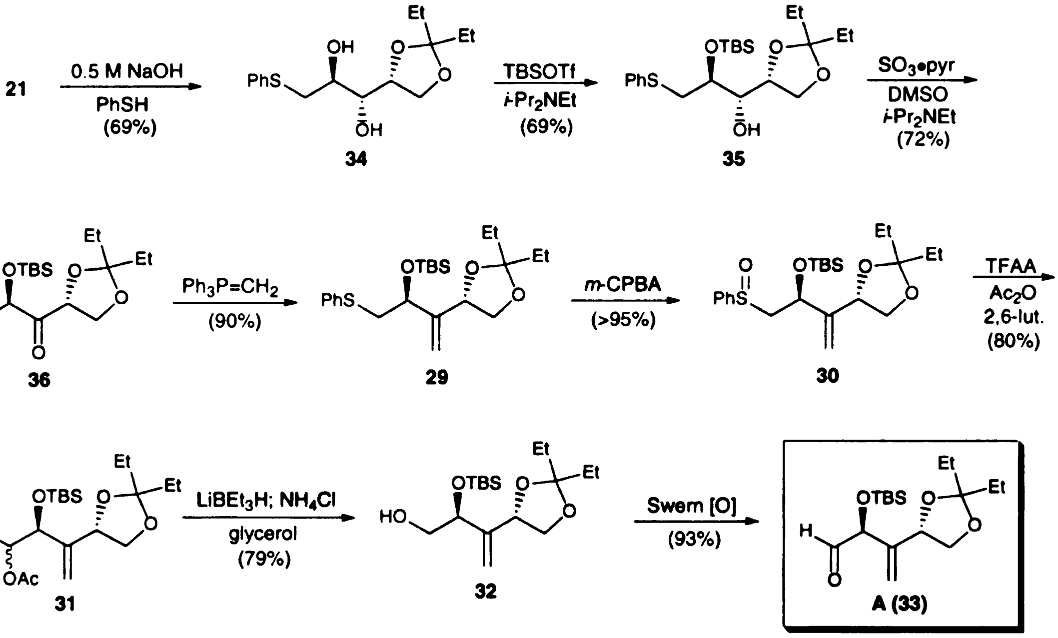


diastereomeric mixture of acetoxy sulfide **31** in a 40% yield. DIBAL reduction of acetoxy sulfide **31** led to the target aldehyde **33** (15%) along with the corresponding fully reduced product, alcohol **32** (14%).

4. Improved Synthesis

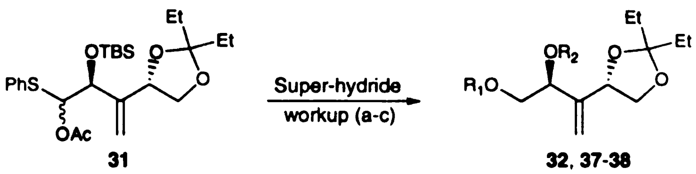
In efforts to streamline the synthesis of fragment **A**, we decided to open the equilibrating epoxy alcohols of the Payne rearrangement with thiophenol instead of *t*-butylthiol. This would directly set up the molecule for the ensuing Pummerer rearrangement. In practice (Scheme 18) this tactic provided sulfide **34** in a 69% yield. However, this synthetic approach can only be useful if the newly formed diol is selectively mono protected. Somewhat surprisingly, the C-2 hydroxyl could be mono protected with TBSOTf to give TBS ether **35**[25] in 69% yield along with disilylated material (10%) and unreacted diol (17%). A Doering-Parikh oxidation gave ketone **36** and subsequent reaction with $Ph_3P{=}CH_2$ (NaHMDS, Ph_3PCH_3Br) efficiently installed the exo olefin of **29**. After the quantitative oxidation of sulfide **29** with *m*-CPBA the Pummerer rearrangement of sulfoxide **30** was investigated. Instead of the harsh conditions of refluxing acetic anhydride, a milder procedure utilizing a mixture of trifluoroacetic anhydride[26] and acetic anhydride in the presence of 2,6-lutidine at room temperature gave the desired diastereomeric mixture of acetoxy sulfide **31** in 80% yield. Unmasking of the aldehyde was accomplished in 70% yield by a lithium triethylborohydride (Super-Hydride®) reduction giving alcohol **32**. Subsequent Swern oxidation provided target aldehyde **33**.

Scheme 18. Streamline Synthesis of Fragment **A**



It is worth noting that during the initial experiments on the Super-Hydride® reduction of **31** (Scheme 19) aqueous NH_4Cl workup led solely to the isolation of an unhydrolyzed organoborane species (**37**) as indicated by a green flame test.[27] Given the resiliency of the organoborane to mildly acidic conditions, we

Scheme 19. Super-Hydride Workup



(a) aqueous NH_4Cl; **37** [R_1=BR_2, R_2=TBS (95% crude yield)]
(b) aqueous NaOH; **32** [R_1=H, R_2=TBS (49%) + **38** [R_1=TBS, R_2=H (25%)]
(c) aqueous NH_4Cl, then glycerol; **32** [R_1=H, R_2=TBS (75%)]

attempted a basic workup. While treatment with aqueous NaOH did bring about complete removal of the boron, it also resulted in partial migration of the TBS group to the primary alcohol **38**. In the end, we found that a combined NH_4Cl/glycerol[28] workup afforded high yields of alcohol **32** without migration of the silyl ether.

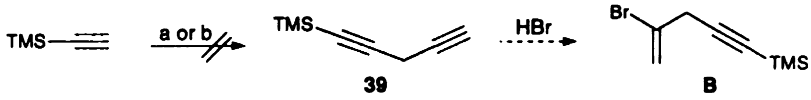
This revised synthesis of fragment **A** involves a total of 11 steps from readily available bisisopentylidene **12** with an overall yield of 12%. Besides eliminating 2 steps, the revised synthesis eliminates the need to isolate the labile 1,2-epoxy-3-ol (**23**).

B. Synthesis of Fragment B

We anticipated the need for multigram quantities of subunit **B** as it is a common building block for both the upper and lower hemispheres of amphidinolide A. Somewhat surprisingly, this relatively simple molecule had yet to be described in the literature. With hindsight this should have suggested a nontrivial synthesis.

However, our earlier synthetic endeavors began with straightforward approaches (Scheme 20). The starting trimethylsilylacetylene, although commercially available, was easily prepared from ethynyl magnesium bromide and trimethylsilylchloride. However, due to an almost impossible distillation from THF, the target compound was used as a THF solution. With the isolation of

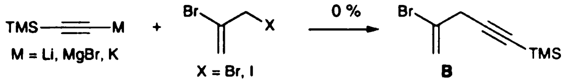
Scheme 20. Attempts Toward Known Diyne 39



conditions: (a) (i) ethynylmagnesium bromide (ii)CuCl (iii) propargyl bromide
(b) (i) *n*-BuLi (ii) CuCN (iii) propargyl bromide

trimethylsilylacetylene secured, the reaction to obtain diyne **39** was investigated. Unfortunately, diyne **39** was not isolated via the adapted literature procedure,[29] as well as, several variations. With the failure of the copper mediated Grignard displacement, a direct cuprate displacement was also investigated but with no success. Simultaneously, efforts were directed toward the displacement of both 2,3-dibromo- or 2-bromo-3-iodopropene by either the lithium, sodium, or potassium TMS-acetylides (Scheme 21). However, neither changing the metal nor varying the reaction conditions gave fragment **B**.

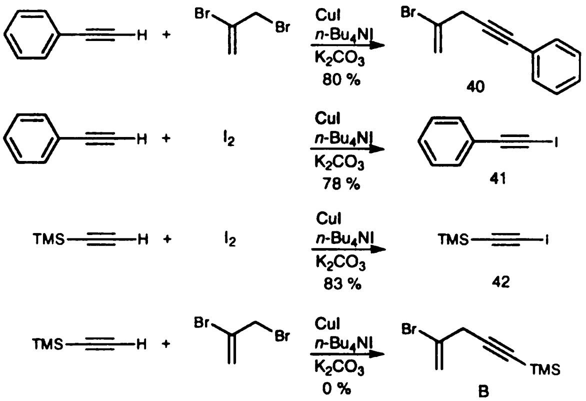
Scheme 21. Unsuccessful TMS-acetylide Displacement



Our next attempt at the synthesis of subunit **B** involved the addition of trimethylsilylacetylene to 2,3-dibromopropene under phase transfer conditions (Scheme 22).[30] Disappointingly, these two reactants, which individually were efficiently employed in similar reactions, failed to couple.

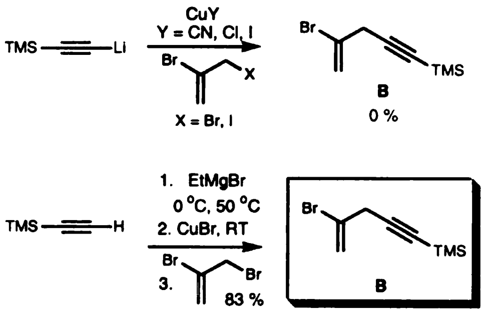
Research efforts then returned to the use of trimethylsilylacetylide metal salt displacements of 2,3-dihalopropene but the metal salts were now converted to cuprate species as seen in Scheme 23. With the use of

Scheme 22. Phase Transfer Conditions Toward Subunit **B**



CuCN, CuCl, and CuI as the copper source the formation of a cuprate species was not in question since copper salts are insoluble in THF while cuprates gave a homogeneous solution. The presumed cuprate species were unreactive toward 2,3-dihalopropene from –78 °C to 25 °C. Finally, after considerable experimentation, we discovered copper assisted Grignard conditions which ultimately provided gram quantities of **B** in 83% - 95% yield. For formation of the Grignard species of trimethylsilylacetylene heating (~55 °C) was found to be crucial. The reaction was then allowed to cool to room temperature after which CuBr was added. The reaction mixture was then heated to 50 °C, followed by the dropwise addition (~3 hours) of 2,3-dibromopropene. This sequence finally resulted in the formation of subunit **B**.

Scheme 23. Synthesis of Fragment B



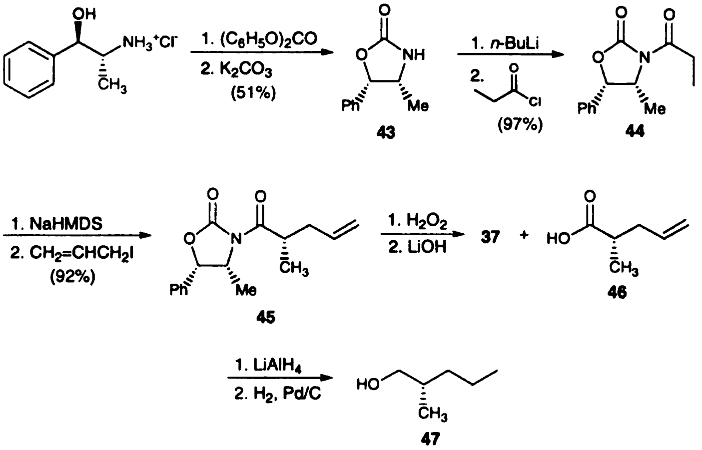
Initially, we thought that the success of the reaction was due to the copper (I) source instead of the reaction procedure. However, it was found that either CuCN or CuI could be substituted for CuBr with no lost in reactivity or yield. This indicated that temperature modulation was key. Finally, the stability of fragment **B** proved to be a non-issue, as after several months of storage, **B** showed no signs of decomposition by ^{1}H NMR.

C. Synthetic Studies Toward Fragment C

Prior to our synthesis of fragment **C**, (S)-2-methylpentan-1-ol **47**[31] was known. However, as we planned to employ an Evans aldol reaction to generate what would ultimately become the C-18 and C-19 asymmetric centers of amphidinolide A, it was decided that an iterative chiral auxiliary based approach to all of the stereogenic carbons in **C** would make for the most efficient synthesis of that fragment.

The synthesis of fragment **C** (Scheme 24) began with the preparation of the Evans' oxazolidinone chiral auxiliary **44**. Upon exposure and heating of the commercially available (1S,2R)-norephedrine HCl salt to K_2CO_3 and diphenyl carbonate, the desired oxazolidinone **43** was isolated in a 51% yield. The oxazolidinone was acylated by deprotonation with *n*-BuLi and subsequent addition of propionoyl chloride gave the desired chiral auxiliary **44** in an excellent yield (97%). With the isolation of the chiral auxiliary, several asymmetric alkylations were investigated. Initially, alkylations were attempted with the

Scheme 24. Synthetic Approach to Fragment **C**

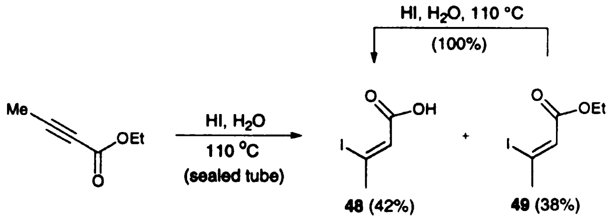


relatively unactivated electrophile, propyl chloride. These failed.[32] Therefore, the chiral auxiliary was alkylated with allyl bromide or iodide, to afford **45** in a crude yield of 92%. The chiral auxiliary was oxidatively cleaved with H_2O_2 and LiOH to give recovered oxazolidinone **43** and acid **46**, which was immediately reduced with $LiAlH_4$ and subsequently hydrogenated to give (S)-2-methylpentan-1-ol **47**. The above series of reactions were run once, and therefore the yields are not optimized.[33]

D. Synthesis of Fragment D

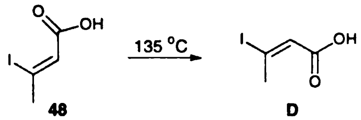
The known β-iodo acid **D** is readily available from ethyl 2-butynoate as illustrated in Schemes 25 and 26.[34] The alkyne was added to a sealed tube containing hydriodic acid (48% aqueous) and heated to 110 °C. After 12 hours, the reaction was allowed to cool to room temperature at which time the crystalline carboxylic acid **48** which had precipitated from solution was filtered off, and the remaining filtrate which contained unhydrolyzed ester **49** (38%) was subjected to reaction conditions where the ester hydrolysis was nearly quantitative. This recycling protocol afforded β-iodo acid **48** in an 80% combined overall yield. In terms of throughput, this process turned out to be more efficient than running the reaction to completion in a single pass.

Scheme 25. Synthesis of Fragment **D** (I)



As reported, isomerization of the double bond was achieved with heating at 135 °C. In our hands, the isomerization of (Z)-β-iodo acid **48** to the desired (E)-β-iodo

Scheme 26.
Isomerization of Acids



48 **D**

E/Z (3:1)

acid **D** was high yielding but only afforded a 3:1 E/Z ratio. The ratio consistently remained 3:1 even with prolonged heating or addition of aqueous HI. Fortunately, the isomers could be separated by careful flash chromatography on silica gel.

Although the experimental procedure for obtaining β-iodo acids was straightforward, the "*cis-trans*" nomenclature assignment in the Le Noble communication is confusing and resulted in an early misinterpretation[35] as to which β-iodo acid, i.e. **48** or **D**, was initially obtained. This was not clarified until late into our synthetic venture. Therefore, all of our earlier work with the β-iodo acid was with the undesired (Z)-isomer. Our synthetic efforts toward the naturally occurring amphidinolide A (**1**), and its $C_2 - C_3$ Z-isomer analog will be presented.

Chapter 2. Coupling and Elaboration of 1st Generation Subunits

The successful construction of subunits **A-D** allowed us to simultaneously investigate multiple coupling strategies and in turn provided valuable information as to which coupling sequence would be employed in our final elaboration of amphidinolide A.

A. Coupling of Fragments A and B

A chelation controlled addition of an organometallic derived from **B** to **A** was planned for the union of **A** and **B**. Organometals examined included organolithium, organomagnesium, and organozinc species. In our studies, the Grignard reaction proved to be the most successful. TBS-protected subunit **A** can not undergo chelation controlled addition; although the desired *threo*-diol could be obtained from Grignards if the addition occurs under the Felkin-Ahn model (Figure 2) with the vinyl appendage acting as the large group. As such, aldehyde **33** (**A**) was investigated in our early studies.

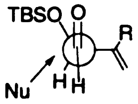
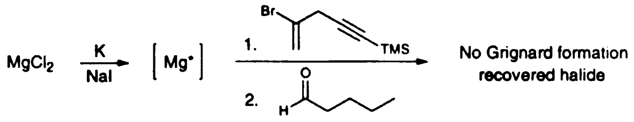


Figure 2. Felkin-Ahn Model

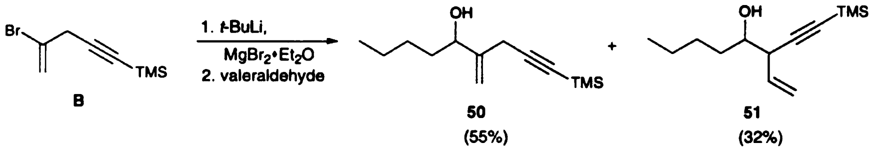
Prior to an investigation of the stereoselectivity of the nucleophilic addition, a reliable protocol for the formation of a metallated **B** species need to be established. As such, the formation of the Grignard reagent of fragment **B** was investigated. The vinyl bromide was unreactive toward several types of magnesium turnings as

Scheme 27. Attempted Grignard Formation



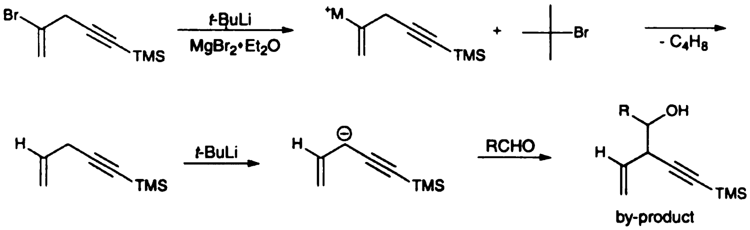
apparent by the recovered halide. Therefore a more reactive form of magnesium was examined (Scheme 27). Rieke developed conditions to form a highly reactive Mg° species through the reduction of magnesium salts.[36] Several attempts to generate the organomagnesium under these conditions were tried. The reduction of $MgCl_2$ with potassium metal showed characteristics traditional for Rieke conditions; however, upon isolation of the reaction mixture the Grignard formation was clearly incomplete (<1%) since vinyl bromide **B** was recovered. The reaction was futile even with the addition of NaI, an additive that is known to accelerate the formation of Grignard reagents from sluggish substrates such as alkyl fluorides.

Scheme 28. Coupling of Fragment **B** and Valeraldehyde



Although the lack of reactivity of fragment **B** under Grignard-forming conditions was discouraging, efforts at forming a metallated species continued. After considerable experimentation a transmetallation protocol was discovered to give the Grignard (Scheme 28). First, vinyl bromide **B** was converted to the lithium derivative by a halogen-metal exchange (*t*-BuLi, -78 °C). Once formed, the lithium derivative was converted into the magnesium species by transmetallation

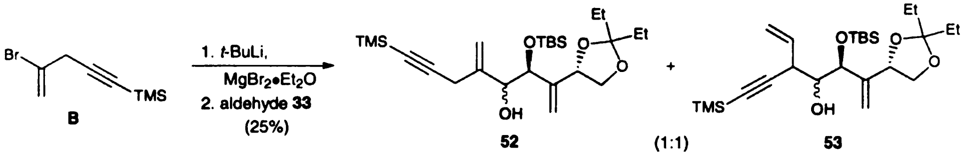
Scheme 29. Mechanism of By-product Formation



with $MgBr_2•Et_2O$. Upon addition of valeraldehyde, two products were isolated in an excellent yield, the desired alcohol **50** (55%) and a by-product alcohol **51** (32%). The by-product (Scheme 29) comes about because the metallated vinyl species acts as a base and deprotonates the *t*-butyl bromide generated in the reaction mixture. The newly formed alkene is then deprotonated at the acidic allylic carbon by excess *t*-BuLi and the resultant anion adds to the aldehyde giving by-product **51**.

Although the above procedure was not optimized and gave a considerable amount of a by-product, the coupling protocol was tested with the amphidinolide A subunits. In practice the coupling of fragments **A** and **B** (Scheme 30) was not as clean as the model reaction. Furthermore, upon purification of the reaction mixture two separable diastereomers (1:1) were isolated indicating that there was no significant steric bias in this system. Besides not being stereoselective, the reaction also produced the undesired allylic addition product, as was seen in the model study. Several modifications to the reaction procedure were investigated to increase the stereoselectivity of the addition, and to eliminate or suppress the side reaction. To suppress the side reaction, the rate of addition of *t*-BuLi was increased and the order of addition of *t*-BuLi and vinyl bromide **B** was reversed. The latter proved to be the most successful. With the reverse addition of reagents, the transmetallation reagent ($MgBr_2•Et_2O$) had to be changed due to

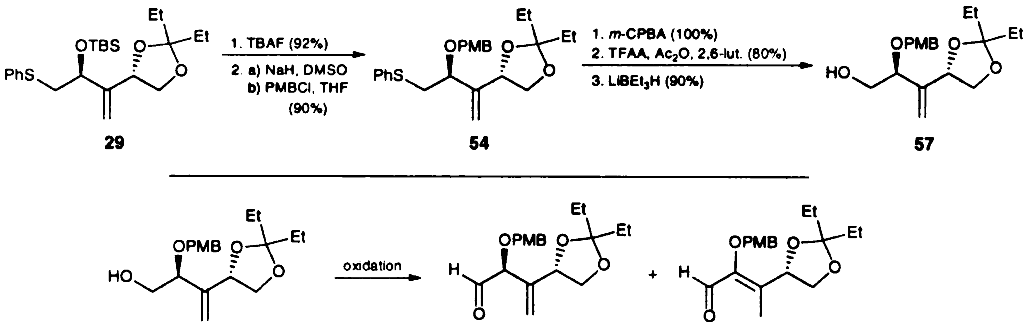
Scheme 30. Coupling of Fragment **B** and Aldehyde **33** (A)



several complications i.e. poor solubility and the addition of a solid. The new reagent of choice for the transmetallation was a toluene solution of dimethylzinc ($ZnMe_2$).[37] Secondly, given the poor stereoselectivity of the coupling with the TBS-ether derivative of aldehyde **A**, a more desirable chelating ether was needed. The PMB derivative of fragment **A** was chosen.

The PMB ether derivative of fragment **A** is readily available (Scheme 31) with slight modifications of our original synthesis of aldehyde **33**. Deprotection of TBS-ether **29** with TBAF (90%), followed by protection of the free hydroxyl as the PMB-ether (NaH, PMBCl, DMSO/THF) (85%) gave protected alcohol **54**. Analogous to the TBS series, oxidation of the sulfide to the sulfoxide **55** with *m*-CPBA (100%), followed by subjection of the crude mixture to a Pummerer rearrangement (TFAA, Ac_2O, 2,6-lutidine) (80%) and reduction of the

Scheme 31. Synthesis of the PMB Derivative of Fragment **A**



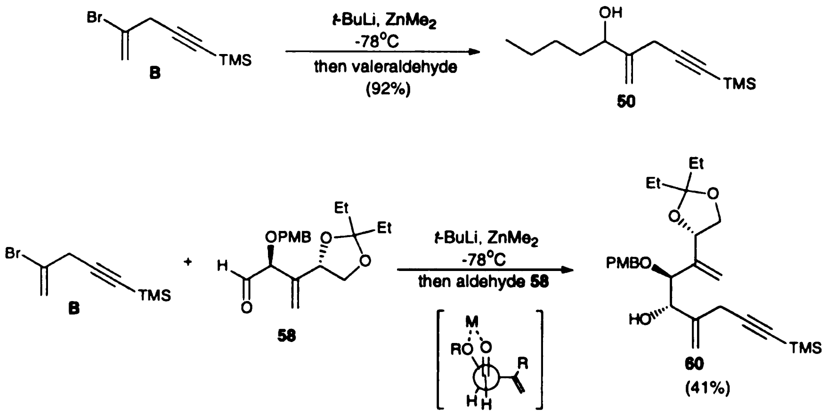
	58	**59**
Swern (small scale)	76%	-
Swern (large scale)	17%	52%
Doering-Parikh	-	83%
Dess-Martin	90%	-

diastereomeric α-acetoxy sulfide **56** mixture with $LiBEt_3H$ (90%) gave alcohol **57** the precursor to aldehyde **A**. Unlike the TBS series, the oxidation of the aldehyde precursor under Swern and Doering-Parikh oxidation was problematic.

Oxidation of alcohol **57** to aldehyde **58** was successful under Swern conditions on a small scale; however, upon scale-up enal **59** was seen as a minor product (Scheme 31). Moreover, after column chromatography on silica gel, enal **59** was the major isolated product. With the Doering-Parikh oxidation enal **59** was the only product as indicated by TLC and ^{1}H NMR of the crude mixture. Fortunately, internalization of the olefin was suppressed under Dess-Martin conditions, giving the desired aldehyde **58** in excellent yields (>90%).[38] With the appropriate aldehyde in hand, the addition of a metal species of fragment **B** to aldehyde **58** under chelation conditions was investigated.

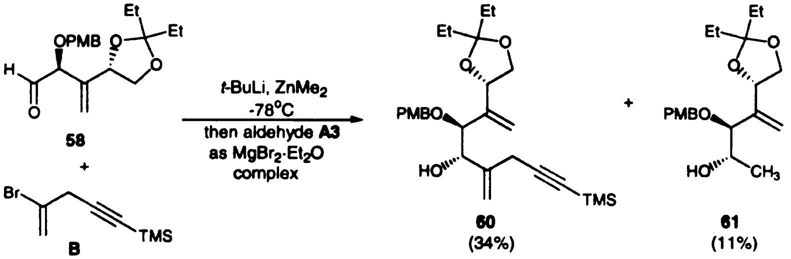
Before coupling **B** with the PMB-variant of fragment **A**, a new experimental procedure was sought which would suppress the above mentioned side reactions. A new experimental procedure, which consisted of the addition of vinyl bromide **B** to the *t*-BuLi solution and $ZnMe_2$ as the transmetallating reagent, was successful. In our model study (Scheme 32) the desired alcohol **50** was isolated in excellent yields (92%) with none of the earlier by-product. More

Scheme 32. Diastereoselective Coupling of Fragment **B** and Aldehyde **58**



importantly, with the amphidinolide A subunits, aldehyde **58** and zincate **B** this experimental procedure was stereoselective with only the desired diastereomer **60** being isolated albeit in modest yields (41%). One explanation for the low yield, as compared with the model study, is that aldehyde **58** is unstable in the presence of zinc Lewis acids. Therefore, $MgBr_2•Et_2O$ was again studied as the chelating metal. It was found that magnesium bromide etherate is not soluble in Et_2O alone but often dissolved in Et_2O/benzene solutions. The successful coupling procedure was repeated using $MgBr_2•Et_2O$ in an Et_2O/benzene solution (9:1) for the zinc Lewis acid. In this coupling procedure the crude TLC was promising, although the precomplexed aldehyde solidified upon cooling the reaction mixture. Indeed the desired addition product was isolated as a single diastereomer but in a lower yield (20%). Although the yield was low, the reaction was promising since $MgBr_2•Et_2O$ could be used in the stereoselective chelation controlled addition. Efforts to improve the yield via a mixed metal reaction were conducted as illustrated in Scheme 33. Prechelating aldehyde **58** with $MgBr_2•Et_2O$ and using the zincate derivative of **B** as the nucleophile afforded alcohol **60** (34% yield) and a diastereomerically pure by-product (11% yield) alcohol **61**. The by-product was the result of the transfer of methyl instead of

Scheme 33. Optimization of Chelation Addition



fr

s

in

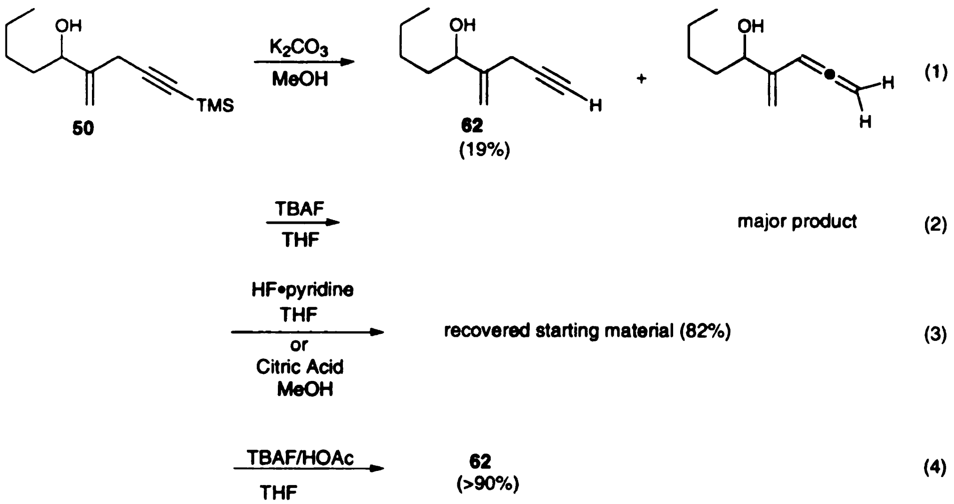
s

fragment **B** onto aldehyde **58**. It should be noted that the above observation is surprising, since it has been shown that the methyl group has the least aptitude in transferring from a zincate species.[37] Furthermore, if two groups have the same aptitude in transferring then the larger of the two will typically transfer to relieve steric congestion. With the formation of by-product **61** under the zincate nucleophilic addition conditions, optimization of the coupling reaction using only magnesium was attempted. A stock solution [1.0 M Et_2O/PhH (3:1)] of $MgBr_2 \bullet Et_2O$ was prepared, which facilitates the addition of the magnesium salt. Secondly, CH_2Cl_2 was added to the aldehyde solution to increase solubility. Finally the flash column was deactivated with Et_3N (1%) to prevent any acid promoted decomposition. With the above changes yields of 50 – 60% for the coupling were obtained.

B. Hydrostannylation of Skipped Enyne and Subsequent Cross-Coupling

With the successful stereoselective synthesis of the **AB** fragment, the hydrostannylation of skipped enynes was investigated. This would be important for the planned Stille cross-coupling to form the $C_3 - C_4$ bond. We were particularly interested in the regiochemistry of such hydrostannylation because with conjugated enynes it is known that the regiochemical outcomes are different under palladium and free radical mediated reactions i.e. the internal isomer predominates under palladium conditions and the E-isomer under free radical conditions. In the preparation of the enyne substrates (Scheme 34), the trimethylsilyl moiety of the protected alkynes had to be removed. In earlier attempts, this deprotection was incomplete and low yielding under K_2CO_3/MeOH conditions but quantitative under basic fluoride (TBAF) conditions. Unfortunately, the deprotection did not scale-up well. When the deprotection was run on a 0.5 mmol scale or greater, the TBAF solution proved too basic leading to the formation of the allene product (eq. 2 , Scheme 34). Allene formation could be

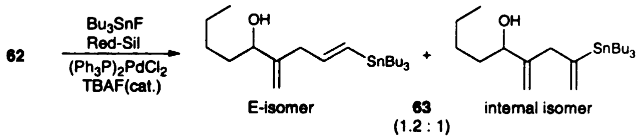
Scheme 34. Investigation into the Deprotection of TMS-alkynes



minimized if the reaction was carried out at 0 °C, albeit with low to moderate yields of the desired alcohol. Since deprotection under basic conditions was unsuccessful, acidic conditions were tried. First a citric acid/MeOH protocol was used. Although the citric acid / MeOH protocol is known to cleave silyloxy ethers, the procedure gave none of the desired product. Only starting material (eq. 3, Scheme 34) was recovered. Even with more traditional acidic conditions (HF•pyridine/THF), deprotection did not occur. Fortunately, it was found that an acetic acid buffered TBAF solution[39] could be used (eq. 4, Scheme 34) for **50** and similar substrates (>90% yield).

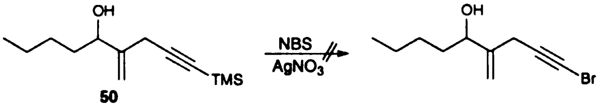
We then began to explore the hydrostannylation reaction of skipped enynes. No reaction under free radical condtions was observed. We postulate that the lack of stannane formation could result from the formation of a stabilized radical at the doubly allylic methylene position. Hydrostannylation of skipped enyne **62** (Scheme 35), under palladium catalysis was nonregioselectivity (1.2:1 E- to internal isomer).

Scheme 35. Pd-Mediated Hydrostannylation



Therefore, attempts were made to convert skipped enyne **50** to the 1-bromo-alkyne derivative which under palladium catalysis are known to give predominately the E-isomer.[40] When TMS-alkyne **50** was subjected to the

Scheme 36. Attmpted Bromo-alkyne Synthesis

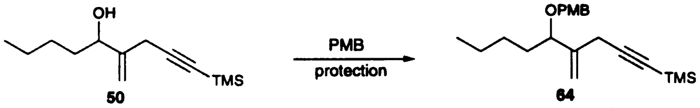


bromo-silicon exchange reaction (Scheme 36) several products were formed none of which was the desired compound.

If the Stille reaction is to be the last bond connection in the total synthesis of amphidinolide A, the poor regioselectivity in the palladium mediated hydrostannylation would mean that half of our material would be lost. Therefore, other hydrometallation reactions were investigated i.e. hydrozirconation and hydroboration. Both of these metallated species can be used directly or derivatized for cross-coupling.

Hydrozirconation of TMS-alkynes is known to occur with the desired regioselectivity.[41] In terms of diene construction, the newly formed zirconocene could be used directly or converted to the vinyl stannane species for the cross coupling reaction. In our hydrozirconation investigation, we found that the alcohol of skipped enyne **50** had to be protected. The protective group of choice was the PMB group. As illustrated in Scheme 37, the protection was unsuccessful under basic conditions (NaH, PMBCl) leading only to formation of several by-products. Fortunately, protection under acidic conditions (PMB-trichloroacetimidate, catalytic acid) gave moderate yields of the PMB ether after optimization. Although literature recommends the use of triiflic acid (0.3

Scheme 37. PMB Protection of Model Skipped Enyne



50

64

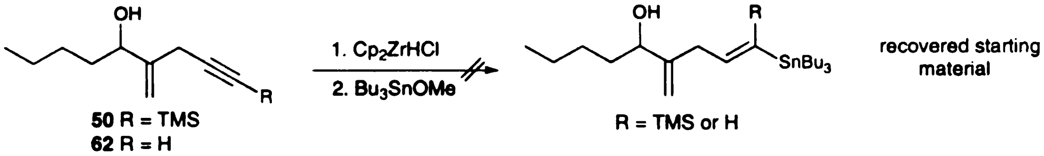
(12 - 55%)[a]

[a] Conditions A: p-$CH_3OPhCH_2OC(NH)CCl_3$, TfOH (0.3 mol%), Et_2O, 42 hours, (12%)
Conditions B: p-$CH_3OPhCH_2OC(NH)CCl_3$, TfOH (0.3 mol%)/CSA,cyclohexane/CH_2Cl_2, 44 hours, (55%)
Conditions C: p-$CH_3OPhCH_2OC(NH)CCl_3$, CSA (10 mol%), cyclohexane/CH_2Cl_2, 24 hours, (45%)
Conditions D: p-$CH_3OPhCH_2OC(NH)CCl_3$, CSA (10 mol%), cyclohexane/CH_2Cl_2, 40°C, 12 hours, (51%)
Conditions E: NaH, PMBCl, 3 hours, several by-products, no desired protection

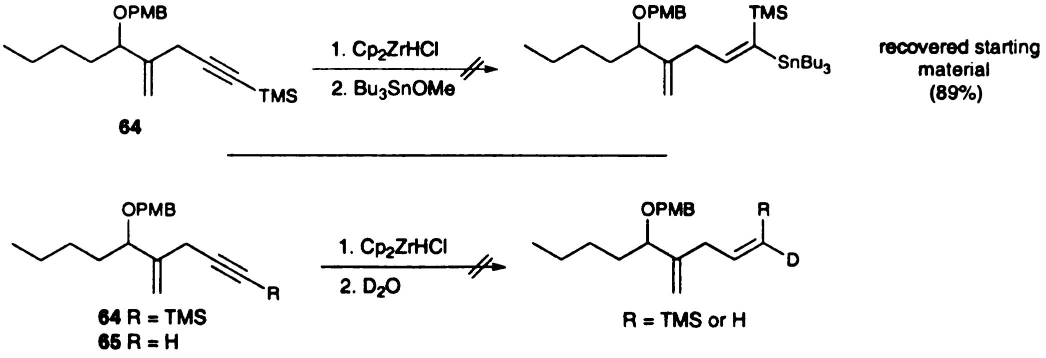
mol%) as the acid catalyst, in our system it was found that CSA gave better yields and in shorter reaction times.

Attempts at the hydrozirconation of skipped enyne **50** included a subsequent *in situ* transmetallation[42] to the vinyl stannane (Scheme 38). Isolation of the vinyl stannane and subsequent protiodesilylation would allow us to verify the success of the reaction by spectroscopic comparison with an authentic sample formed by hydrostannylation/protiodestannylation of the parent alkyne. Unfortunately, attempts at this sequence failed and only starting material was recovered. Therefore, the TMS moiety was removed, and the hydrozirconation reaction was repeated with skipped enyne **62**. Unfortunately, the results were the same as before. It is known that acidic protons can be incompatible with such reaction conditions.[41b] Thus, the alcohol hydrogen could be contributing to the reaction's failure. Therefore, the PMB-protected alcohol

Scheme 38. Attempted Hydrozirconation of TMS-alkynes (I)



Scheme 39. Attempted Hydrozirconation of TMS-alkynes (II)

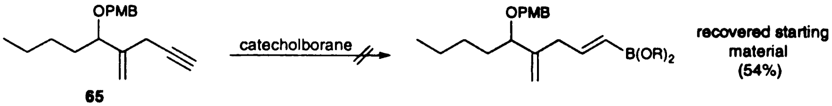


series was investigated (Scheme 39).

When the reaction was repeated with skipped enyne **64**, the same results were obtained, recovered starting material (89%). With this failure we began to consider if the doubly activated methylene hydrogens were again problematic. To explore this, the hydrozirconation reaction was repeated with both skipped enynes **64** and **65** and quenched D_2O. Deuterium incorporation at either the doubly activated methylene position of **64** or at the acetylenic position of **65**, would suggest an incompatibility between skipped enyne and the relatively basic Swartz reagent. Experimentally several products were isolated; however, none of them was the result of a simple deprotonation then deuteration.

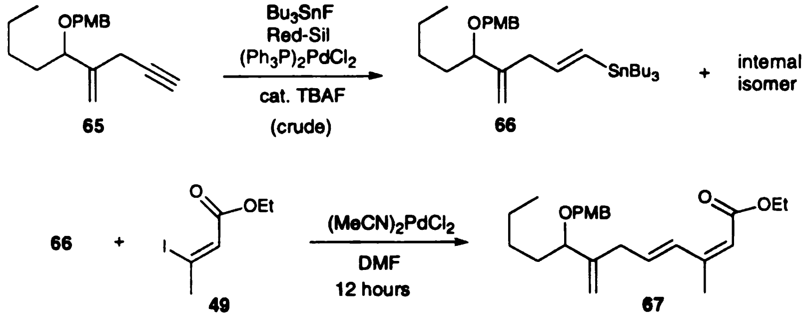
With the lack of success with the hydrozirconation reaction, skipped enyne **65** was subjected to hydroboration conditions with catecholborane (Scheme 40). The hydroboration of **65** was unsuccessful affording only recovered starting enyne (54%). Since neither the hydrozirconation nor the hydroboration of skipped enynes could be realized, the palladium mediated hydrostannylation protocol was reinvestigated in efforts to improve the regioselectivity.

Scheme 40. Attempted Hydroboration of Skipped Enyne **65**



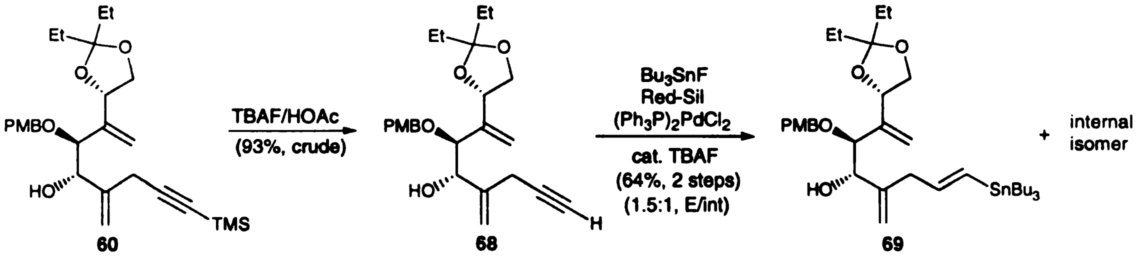
Although the palladium mediated procedure was inefficient, it was used in preparing the E-vinyl stannane, that was needed for the $C_3 - C_4$ bond cross coupling investigations. Our initial cross coupling investigation began with model vinyl stannane **66** as a mixture of regioisomers. The inseparable mixture of regioisomers was used in a subsequent Stille reaction since precedant suggests that E-vinyl stannanes react preferably over internal stannanes in cross coupling reactions. This proved true in our case (Scheme 41). This successful albeit low yielding Stille reaction between vinyl stannane **66** and β-iodo ester **49** was "proof of principle" for the proposed mode of diene construction.

Scheme 41. Stille Cross-coupling of Model System



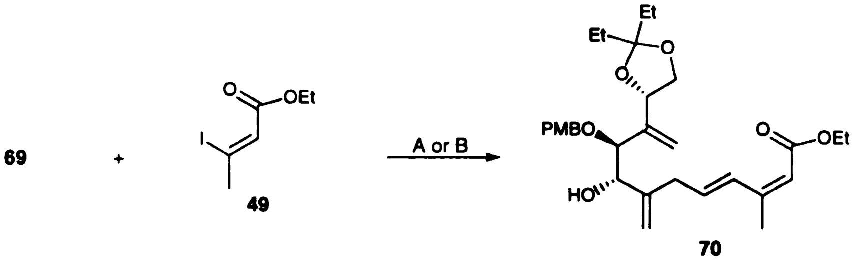
In a total synthesis, a model study is only beneficial if the "real" system parallels the model system in reactivity and compatibility. In our early model investigations, the trimethylsilyl moiety of the skipped enynes had to be deprotected with an acetic acid buffered TBAF solution to prevent the presumed methylene deprotonation. Accordingly, skipped enyne **60** was deprotected with the TBAF/HOAc protocol (> 98% yield, crude) to give terminal enyne **68** (Scheme 42). Bu_3SnH was introduced across the triple bond of alkyne **68** under the palladium protocol utilizing our anhydrous *in situ* method (Bu_3SnF, TBAF, Red-

Scheme 42. Pd-mediated Hydrostannylation of Enyne 68



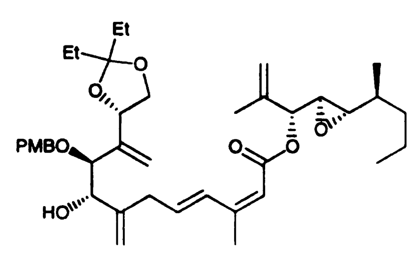
Sil) of Bu_3SnH generation (vide infra) to give a separable mixture of regioisomers. With E-vinyl stannane **69** in hand the "real" cross-coupling question could be addressed (Scheme 43). With the sluggishness of the Stille reaction utilizing $(CH_3CN)_2PdCl_2$ as the palladium catalyst in our model study, a more reactive catalyst system was sought. The catalyst system of choice was the combination of Pd_2dba_3 and $AsPh_3$ in NMP. The Stille reaction between vinyl stannane **69** and vinyl iodide **49** using the above conditions gave the desired diene **70**, fragment **ABD**, in 50% yield. Although the Stille reaction gave a moderate yield, heat (50 °C) and long reaction times were needed (16 hours).

Scheme 43. Synthesis of Fragment ABD



Conditions A: Pd_2dba_3, $AsPh_3$, NMP, 50 °C, 16 hours, 50% yield.
Conditions B: CuTc, NMP, room temp., 30 min, 56% yield.

Liebeskind[43] has developed a copper mediated cross coupling protocol, which substitutes stoichiometric quantities of the inexpensive and air stable copper (I) thiophene-2-carboxylate (CuTc) for the Pd(0) catalyst. The Liebeskind procedure is often carried out at ambient temperatures but can occur at 0 °C and dramatically shorter reactions times are often possible i.e only minutes instead of hours. In our system (Scheme 43), the cross coupling reaction between vinyl stannane **69** and vinyl iodide **49** with CuTc as the "catalyst" was indeed quicker (30 minutes, room temperature) and slightly better yielding (56%). To test the scope of the cross-coupling reactions a more elaborate vinyl iodide ester was investigated, and it was found to be similar in all regards to the previous cases under both the Stille and Liebskind protocols (Figure 3).

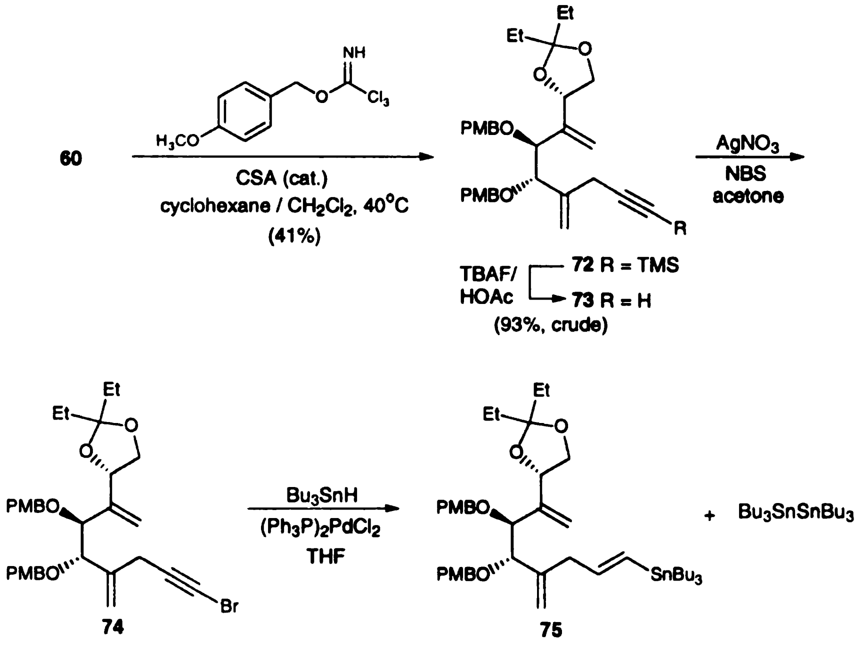


71

Figure 3. Diene **ABCD**

Although the hydrostannylation/Stille reaction sequence was successful, the regioselectivity of the hydrostannylation of skipped enynes still needed improvement. In particular, we wanted to reinvestigate the formation of 1-bromo-alkynes, and the subsequent palladium mediated hydrostannylation. In our earlier model investigation we found it necessary to protect the alcohol of the enyne as a PMB ether in order to prevent side reactions during certain hydrometallation reactions. As such (Scheme 44), the reinvestigation into the formation of the 1-bromo-alkyne series began with the protection of alcohol **60** as PMB ether **72** under the optimized acidic conditions. The TMS moiety of the protected skipped enyne **72** was deprotected under standard TBAF/HOAc

Scheme 44. PMB Protection of Fragment **AB**

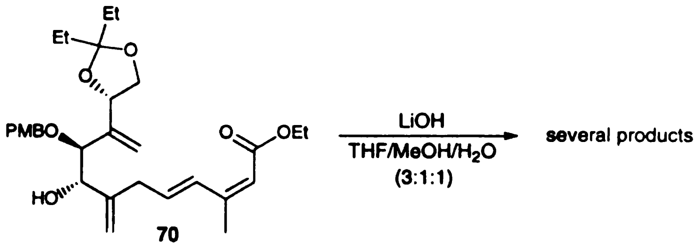


conditions to give the desired alkyne **73** (93% yield, crude). Upon exposure to $AgNO_3$ and NBS in acetone 1-bromo-alkyne **74** was isolated (90% yield, crude). Instead of using our *in situ* method for the generation of Bu_3SnH, stock Bu_3SnH was initially used for the hydrostannylation reaction. This proved problematic as the Bu_3SnH was added too fast, resulting in the Pd(0) mediated formation of hexabutyltin dimer. Purification and product ratio determination was difficult since the reaction was run on a very small scale (37 mg, 0.062 mmol). However, while the hydrostannylation reaction was not synthetically useful, it was again "proof of principle" that the bromo-silicon exchange is a viable reaction. This would pave the way for future experiments (see page 56).

C. Hydrolysis of Advanced Intermediates

In our retrosynthetic analysis, we envisioned a Yamaguchi macrolactonization as a potential method for forming the 20-membered macrocycle. For this macrolactonization to be realized, the ethyl ester of advanced intermediate **70** would have to be hydrolyzed. The hydrolysis of ethyl ester **70** would serve two purposes. First, it would properly fuctionalize the **ABD** fragment for potential esterification with a **BC** fragment. Secondly, we hoped that the carboxylic acid would be a crystalline product and that an X-ray structure could be obtained. The X-ray structure would allow us to unambiguously assign the stereochemistry at C_8, which was established during

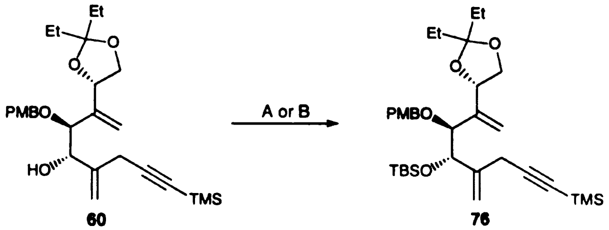
Scheme 45. Hydrolysis of ABD Ester **70**



the earlier chelation coupling. Unfortunately, all attempts at the above mentioned hydrolysis (LiOH, THF/MeOH/H_2O) were unsuccessful (Scheme 45). Although TLC analysis suggested the ester was hydrolyzed, the parent acid was not isolated. This result is significant since it suggested that for a successful approach to the natural product either the ester bond linkage between fragments **C** and **D** must be formed before the $C_3 - C_4$ bond formation or the current $C_3 - C_4$ bond cross-coupling connection must occur with the parent β-iodo acid instead of the ethyl ester. In regards to the latter approach, all attempts at a Stille cross-coupling between vinyl stannane **85** and β-iodo acid **42** were unsuccessful. Therefore, in our revised retrosynthetic analysis of amphidinolide A, the former approach was pursued.

In earlier investigations, the alcohol of advanced intermediate **60** could only be protected as the PMB ether under acidic conditions (PMB trichloroacetimidate, catalytic CSA). The yield of the reaction was poor to moderate, and often contaminated with residual imidate and/or the corresponding amide. All efforts to optimize the protection, such as using cyclohexane freshly distilled from CaH_2 and recrystallized CSA were not overly beneficial. The reaction was slightly cleaner, but the yield was still only moderate (50%) at best. The decision to protect the alcohol as a PMB ether was chosen simply because at the end

Scheme 46. TBS Protection of Fragment **AB**

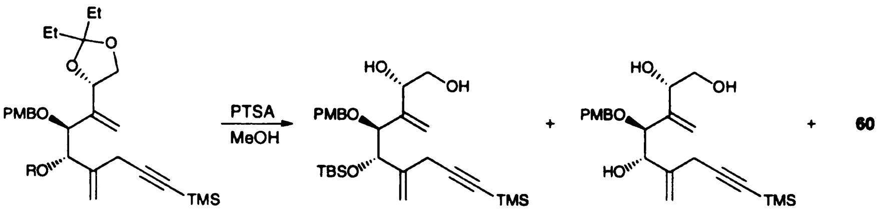


Conditions A: TBSOTf, *i*-Pr_2NEt, 0% yield.
Conditions B: TBSOTf, 2,6-lut., 95% yield.

game an exhaustive DDQ deprotection could be used to obtain the desired tetrol. However given the difficulties above, a different protection strategy was investigated. The alcohol was protected as a silyl ether (Scheme 46). Interestingly, the protection of alcohol **60** with TBSOTf and *i*-Pr_2NEt as the base yielded none of the desired product. Instead, addition of a saturated aqueous solution of NH_4Cl turned the reaction solution black and a solid formed after the addition of Et_2O. With no apparent explanation for this phenomenon, the reaction was repeated with 2,6-lutidine instead of *i*-Pr_2NEt, giving advanced intermediate **76**. The yield of this protection consistently ranged from 90% to quantitative.

With a high yielding protocol for the protection of the advanced **AB** subunit, attention was directed toward derivatizing the hydrophilic segment. After hydrolysis of the isopentylidene acetal, we planned to protect the newly formed diol as the *p*-methoxybenzylidene acetal. A selective reductive opening of the acetal would liberate the parent diol with the secondary alcohol protected as a PMB ether. Upon oxidation of the primary alcohol, the second chelation

Scheme 47. Acetal Hydrolysis of Fragment **AB** Derivatives

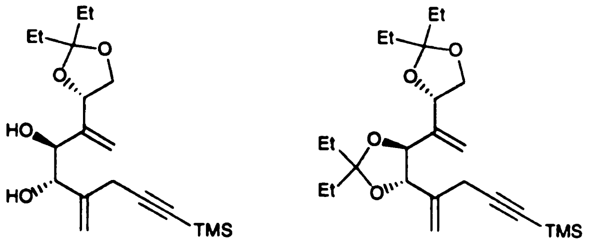


77 **78**

		77	78	60
(1) **72** R = PMB		-	-	-
(2) **76** R = TBS		6%	23%	17%
(3) **60** R = H		-	49%	17%
(4) **76** R = TBS	CSA, CH_2Cl_2/MeOH	-	46%	25%

see experimental section for detail procedures.

controlled vinyl addition could be investigated. As such (Scheme 47), *p*-toluenesulfonic acid monohydrate (PTSA)[44] was initially studied as the acid catalyst for acetal hydrolysis of several **AB** fragment derivatives. First isopentylidene **72** (eq. 1, Scheme 47) was hydrolyzed at room temperature over 14 hours. Although the desired product was not isolated, the reaction was very informative, since it suggested that the hydrolysis was slow. Indeed, slow hydrolysis of the isopentylidene acetal was further demostrated when acetal **76** was hydrolyzed (eq. 2, Scheme 47). Deprotection of the TBS-silyl ether was competitive with hydrolysis of the acetal as indicated by the products isolated: desired diol **77** (6% yield), triol **78** (23% yield) via loss of TBS moiety, and alcohol **60** (17%) via loss of TBS moiety only. Since TBS-silyl ether **76** was very labile under the acidic conditions, hydrolysis of the parent isopentylidene acetal was investigated (eq. 3, Scheme 47). When the hydrolysis of isopentylidene acetal **60** was tested on a small scale, it was found that heat was needed to drive the reaction to completion. Hydrolysis of isopentylidene acetal **60** on a preparative scale afforded several products: desired triol **78** (49% yield), recovered acetal **60** (17%) and two minor products as indicated in Figure 4. In efforts to increase the yield and selectivity, alternative reaction conditions were studied. The acid catalyst was changed from PTSA to CSA, and the solvent system from MeOH to a MeOH/CH_2Cl_2 solution. In addition, all reactions employing CSA



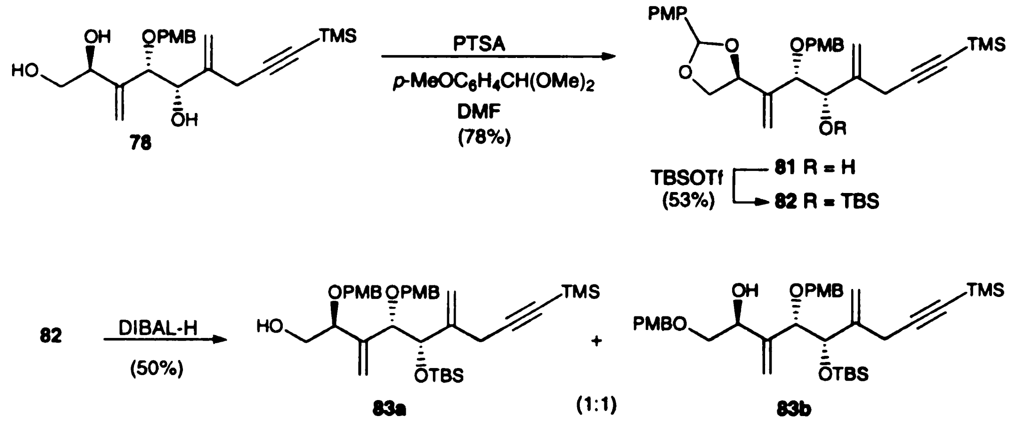
79 **80**

Figure 4. Acetal Hydrolysis By-products

were run at ~ 40 °C. Hydrolysis of acetal **76** (eq. 4, Scheme 47) with the above conditions afforded triol **78** (46%) and alcohol **60** (25%) via loss of TBS moiety. The products formed under these conditions (no diol) show that the TBS-silyl ether is more labile to protic acidic conditions than the acetal. Other methods for the removal of acetals, which are more compatible with TBS-silyl ethers were investigated at a later time (see page 44).

Continuing with the functionalization of the advanced **AB** fragment (Scheme 48), triol **78** was protected with the dimethyl acetal of *p*-anisaldehyde to give a diastereomeric mixture of *p*-methoxybenzylidene acetal **81** (78% yield). In turn, the secondary alcohol was protected with TBSOTf (53% yield) to give silyl ether **82**, which is the substrate needed for investigation of the reductive opening of the benzylidene acetal. Towards this end, benzylidene acetal **82** was subjected to DIBAL-H conditions, which are known to give the desired regioselectivity. Unfortunately, the reaction yielded a regiochemical mixture of mono-protected alcohols **83a/83b** (50% yield), as well as, a polar by-product that suggests the loss of a TBS moiety. Reductive opening of benzylidene acetals are also directed by heteroatoms,[45] in particular oxygen. Therefore, in our case

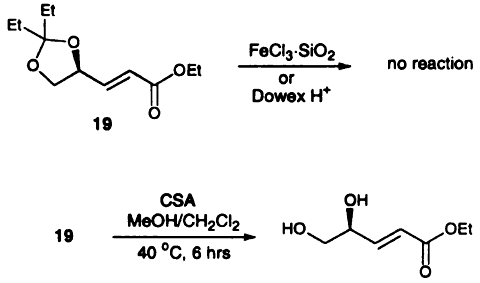
Scheme 48. Functionalization of AB triol **78**



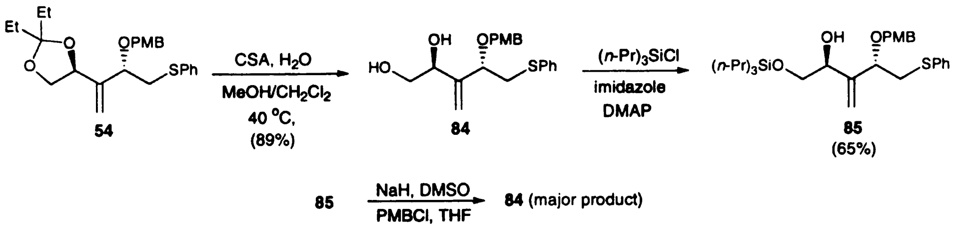
the PMB ether of **82** could serve as a chelating site for DIBAL-H and thus direct the undesired ring opening of the acetal as well as assisting in the deprotection of the TBS-silyl ether.

With the apparent lack of selectivity in the reductive ring opening of benzylidene acetal **82** and poor chemoselectivity in the hydrolysis of the isopentylidene acetal of advanced **AB** intermediates, we decided the hydrolysis of the isopentylidene acetal would have to occur earlier in the synthesis. Hence, a quick investigation into the acetal hydrolysis of earlier intermediates was undertaken. Borrowing from our earlier results, conditions that are reported compatible with TBS-silyl ethers were explored initially, but to no avail. One such reagent was ferric chloride supported on silica gel,[46] which is easily prepared from $FeCl_3•6H_2O$ and silica gel. When isopentylidene acetal **19** (Scheme 49) was subjected to the $FeCl_3•SiO_2$ reagent in $CHCl_3$, no reaction occurred even after prolonged stirring (~15 hours) at room temperature. Obviously, the reaction conditions were too mild. Subjecting acetal **19** to stronger conditions such as Dowex H^+ resin also resulted in recovered starting material. Since TBS-silyl compatible hydrolysis conditions were not successful, acetal **19** was subjected to CSA conditions in a solution of $MeOH/CH_2Cl_2$. These conditions afforded the hydrolysis product within six hours. Furthermore, application of the above

Scheme 49. Hydrolysis of Early Intermediates



Scheme 50. Hydrolysis of Acetal **54** to give Diol **84**



conditions to a synthetically useful intermediate was also successful (Scheme 50). The hydrolysis of isopentylidene **54** afforded the desired diol **84** (64%), along with recovered starting material (9%) and a small amount of a triol presumably via deprotection of the PMB ether. When the reaction was carried out with a small amount of water, the completion time was shortened, and the yield of desired diol **84** increased to 80%. The selective protection of diol **84** would give an appropriate functionalized "semi-symmetrical" molecule (Figure 5) and would increase our flexibility in the total synthesis of amphidinolide A. Toward this end (Scheme 50), the primary alcohol of diol **84** was selectivity protected to afford the tripropylsilyl ether **85** (65%) along with the diprotected derivative **86** (22%). Unfortunately, all attempts at protecting the secondary alcohol as a PMB ether were unsuccessful. The major product of the attempts was parent diol **84**, indicating hydrolysis of the tripropylsilyl ether under the protection conditions. In later investigations, a successful protection protocol was realized when the initial protection was as the triisopropyl silyl ether (see page 48).

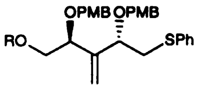
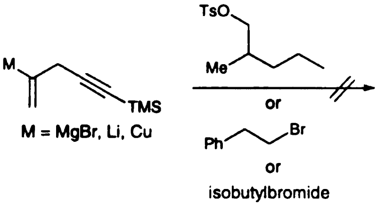


Figure 5. Semi-symmetrical Intermediate

In addition to the couplings previously discussed, one other attempted coupling gave valuable information for the design of our new approach. In studies by Joe Ward and myself, it was determined that a metallated fragment **B** derivative could not serve as a nucleophilic source in the displacement of halides and/or tosylates (Scheme 51). Therefore, a displacement coupling between fragments **B** and **C** to form the $C_{16} - C_{17}$ bond would not be possible. In summary, although the first generation approach did not lead to the total synthesis of amphidinolide A, much valuable information was gained that assisted in the design of our second and third generation approaches to the natural product.

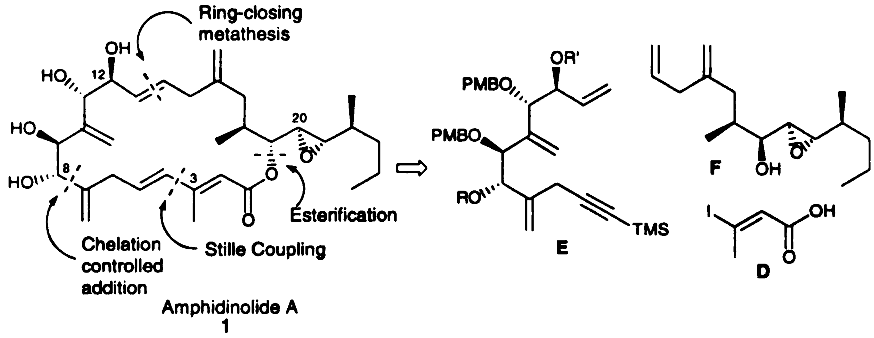
Scheme 51. Attempted Fragment **B** Displacement



Chapter 3. 2nd Generation Approach – Application of RCM

The successful construction of the subunits in our first generation approach allowed for the investigation of multiple coupling strategies and provided valuable information as to which coupling sequence would be employed in our second-generation approach. Our second retrosynthetic breakdown of amphidinolide A (Scheme 52) affords three fragments **D** – **F**. Key steps for the final elaboration included a Stille cross-coupling, chelation controlled addition, indium allylation, Mitsunobu esterification, and ring-closing metathesis (RCM). Application of the RCM reaction is the underlying theme of our second generation approach. The RCM reaction is a powerful synthetic tool for the construction of carbon-carbon double bonds. Moreover, with the advent of well-defined metal ruthenium centered carbene catalysts developed by Grubbs, the RCM reaction has served as a key step in the total synthesis of several natural products. With regards to the total synthesis of amphidinolide A, several questions concerning chemo- and stereoselectivity of the RCM must be addressed. In terms of chemoselectivity, there exists the potential for the metathesis to occur at several different olefins, which poses two questions: Could

Scheme 52. 2nd Generation Retrosynthetic Analysis

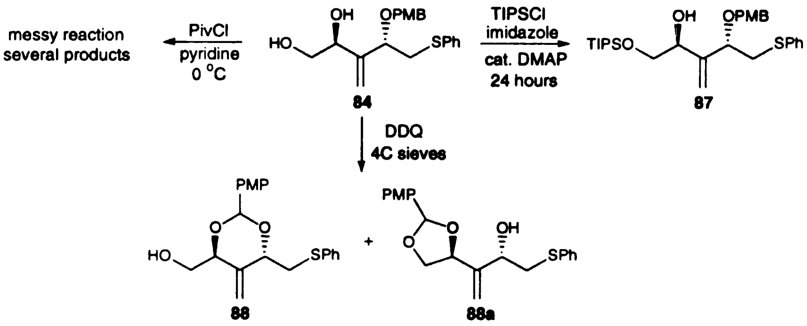


we limit metathesis to the two mono-substituted olefins? Secondly, can we minimize dimerization and favor versus ring closure? In terms of stereoselectivity, could we control the geometry of the newly formed olefin? The above questions and others that emerged in our investigations were answered through the total synthesis of several analogs of amphidinolide A.

A. Synthesis of "Z"-amphidinolide A

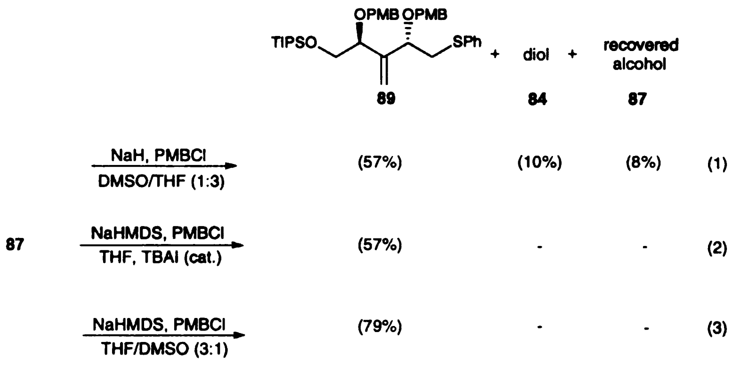
The transition from our first to second generation approach was relatively easy due to flexibility in our initial design. An RCM precursor corresponding to the left hemisphere of amphidinolide is readily prepared from isopentylidene acetal **54**, an intermediate in our original synthesis of fragment A. The synthesis of RCM precursor **E** (Scheme 53) began with hydrolysis (CSA, MeOH/CH_2Cl_2, 40 °C) of the acetal **54** to give diol **84**. At this stage, two approaches were investigated to differentiate the two alcohols: (1) selective protection of the primary alcohol as either an alkyl ester or silyl ether and (2) selective protection of the secondary alcohol via PMB acetal formation with the neighboring PMB ether. When diol **84** was subjected to the DDQ oxidative conditions in the absence of water,[47] the desired *p*-methoxyphenyl 1,3-dioxane **88** was formed but

Scheme 53. Selective Protective Group Functionalization of Diol **84**



the corresponding *p*-methoxyphenyl 1,3-dioxolane **88a** was also formed presumably via migration of the acetal moiety. Without the ability to control the regioselectivity during the acetal formation, efforts were directed toward the selective protection of the primary alcohol. Attempted protection of the primary alcohol with pivaloyl chloride gave several unindentifable products.[48] Reaction of diol **84** with TIPSCl, imidazole and catalytic DMAP gave the desired mono-protected diol **87** in excellent yields (91%). With an efficient protocol to differentiate the primary alcohol, protection of the remaining secondary alcohol was studied (Scheme 54). The TIPS-silyl ether was chosen for the 1° alcohol due to its known resistance to basic hydrolysis. However, under standard basic conditions (eq. 1, Scheme 54) (NaH, DMSO/THF) for PMB-ether formation, the TIPS-silyl ether in alcohol **87** was partially hydrolyzed. The desired fully protected triol **89** was isolated in moderate yields (57%) along with recovered

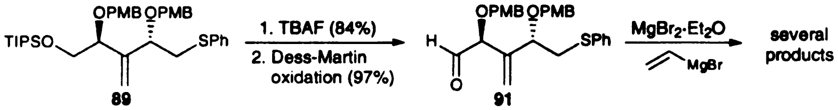
Scheme 54. PMB Protective Investigation of 2° alcohol **87**



alcohol **87** (8%) and the deprotected diol derivative **84** (10%). When the reaction was repeated in the absence of DMSO and with NaHMDS as the base (eq. 2, Scheme 54), the reaction was sluggish. However, the reaction went to completion upon the addition of catalytic TBAI and heating albeit in a modest yield (57%). The optimized reaction protocol (eq. 3, Scheme 54) consists of deprotonating the alcohol with NaHMDS and subsequent addition of DMSO and PMBCl to give the fully protected triol **89** in excellent yields (79%).

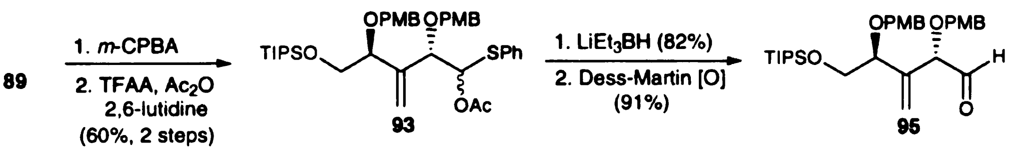
Intermediate **89** is a pseudo-symmetrical molecule in the sense that both ends are masked aldehyde equivalents and with routine transformations either end can participate in the chelation controlled nucleophilic addition reactions (Scheme 55). Initially, the TIPS-silyl ether was deprotected with TBAF (84%) to give alcohol **90**. Oxidation of alcohol **90** with Dess-Martin periodinane in the presence of pyridine gave aldehyde **91** in excellent yields (97%). Unfortunately, aldehyde **91** proved to be incompatible with the chelation controlled nucleophilic addition. Upon addition of $MgBr_2 \bullet Et_2O$ to the aldehyde, the reaction solution turned black. Analysis of the crude material by ^1H NMR showed no indication of the desired product. The sulfide, which is only six atoms away from the aldehyde and thus capable of intramolecular nucleophilic addition,[49] is possibly causing the poor reaction.

Scheme 55. Vinyl Magnesium Bromide Addition (I)



To overcome this, the phenyl sulfide was converted into the corresponding aldehyde (Scheme 56). Oxidation of sulfide **89** with *m*-CPBA and subsequent Pummerer rearrangement (TFAA, Ac_2O, 2,6-lutidine) of crude sulfoxide **92** gave α-acetoxy sulfide **93** (65% yield, 2 steps). Reduction of α-acetoxy sulfide **93** with

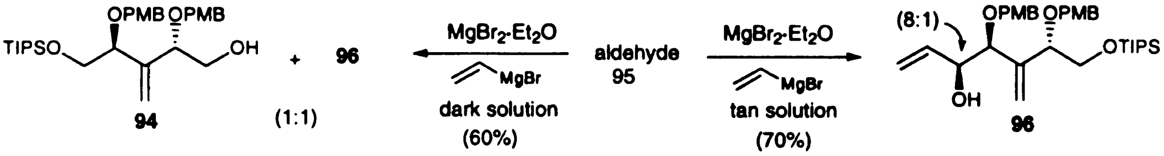
Scheme 56. Conversion of Phenyl Sulfide **89** to Aldehyde **95**



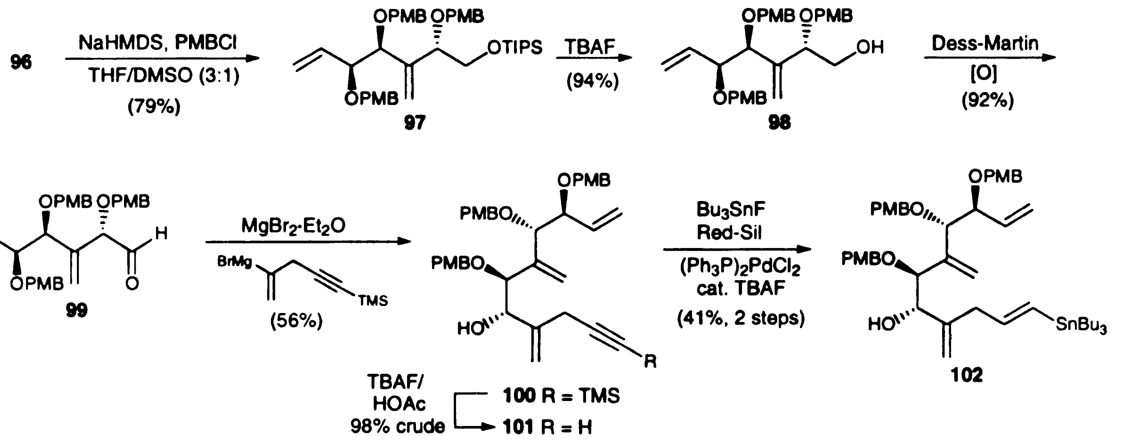
Super-hydride® gave alcohol **94** (82%), and with subsequent oxidation under Dess-Martin conditions, aldehyde **95** was isolated (91%).

With the isolation of aldehyde **95**, the first of two chelation-controlled additions was investigated. Addition of vinyl magnesium bromide to aldehyde **95** (Scheme 57) was inconsistent. Depending on the Grignard source, a substantial amount of alcohol **94**, presumably via 1 electron reduction, was isolated. Indeed the Grignard solution proved to be the cause of this phenomenon, because with careful observation it was found that the dark black commercial solutions of vinyl magnesium bromide gave considerable reduced product while the clear tan transparent commercial solutions gave desired alcohol **96** diastereoselectively (8:1) in average yields of 70%. The TIPS-silyl ether of **97** was deprotected with TBAF (94%) to give alcohol **98** (Scheme 58), which was oxidized with Dess-Martin periodinane (92%) to give aldehyde **99**. The addition of the Grignard of fragment **B** under chelation conditions occurred with poor diastereoselectivity (1:1). Unfortunately, alcohol **100** was isolated as a diastereomeric mixture due to poor separation via flash chromatography. After deprotection (TBAF/HOAc, 98% yield, crude) of the TMS-acetylene to give terminal alkyne **101**, application of our

Scheme 57. Vinyl Magnesium Bromide Addition (II)

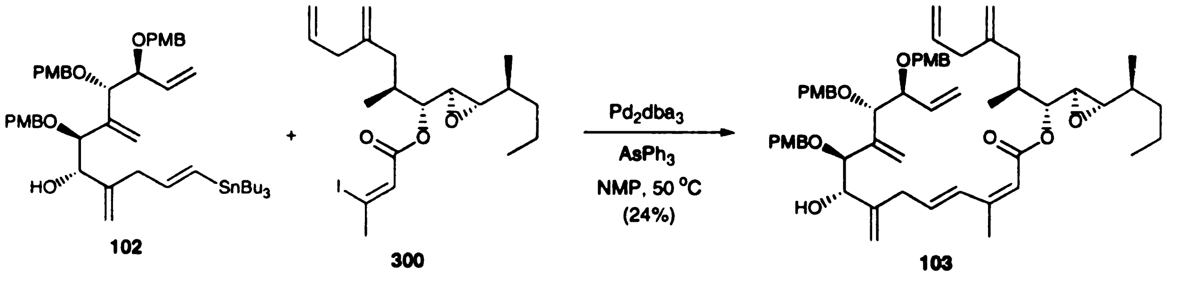


Scheme 58. Preparation of E-vinyl stannane **102**



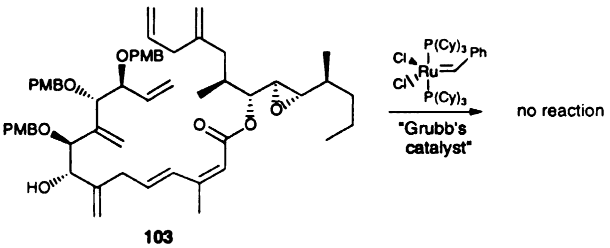
novel siloxane reduction of organotin halides and subsequent *in situ* hydrostannylation methodology gave RCM precursor vinyl stannane **102** as a regio-mixture (41% yield over 2 steps, E / internal 1.2:1). The left and right RCM precursors, vinyl stannane **102** and (Z)-vinyl iodide **300**,[50] were connected via a Stille cross-coupling reaction to give diene **103** (Scheme 59). Although the vinyl stannane employed in the Stille reaction was a mixture of E- and internal stannanes, only the E-isomer reacted. With the isolation of diene **103**, the ring-closing metathesis reaction was investigated (Scheme 60). The reaction was attempted under dilute conditions to minimize dimerization. Initially, a room temperature benzene solution of diene **103** was allowed to stir for 24 hours in the presence of the first generation Grubb's catalyst, $(Cy_3P)_2Cl_2Ru{=}Ph$. As indicated

Scheme 59. Cross-coupling of vinyl stannane **102** and (Z)-vinyl iodide **300**

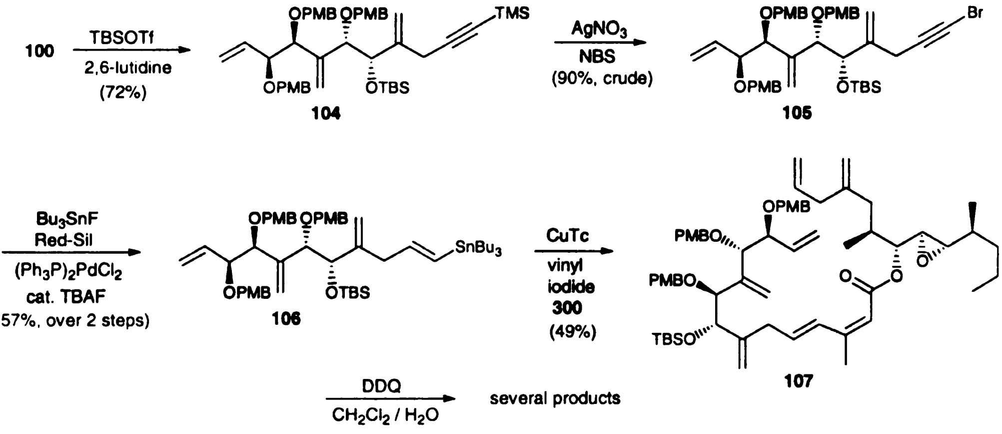


by ^{1}H NMR, no apparent reaction occurred. The reaction was repeated several times in benzene-(d_6) with and without heating (60 °C) but to no avail. There was no reaction even after 2 days of heating. One potential problem for the lack of reactivity is that the catalyst is rendered inactive through coordination to one of several hetero-atoms in diene **103**. It has been shown that the addition of Ti(*i*-PrO)$_4$ can break up inactive chelates and thus facilitate ring-closing metathesis. However, the addition of Ti(*i*-PrO)$_4$ was not beneficial in our RCM reaction. Another potential reason for the lack of reactivity is sterics. Hoye has shown that allylic alcohols increase the rate of reactivity of RCM reactions in comparison to the corresponding allylic alkoxy ether. Thus, an RCM precursor with a deprotected allylic alcohol was needed. Synthesis of such a precursor began with intermediate **100** (Scheme 61). After protecting the alcohol as

Scheme 60. Attempted RCM (I)

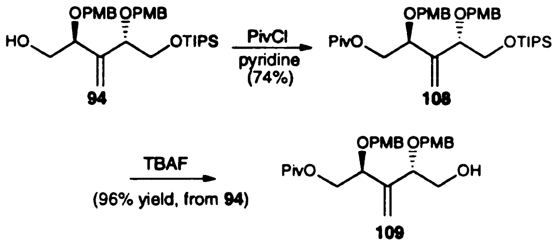


Scheme 61. Preparation of RCM acyclic diene **107**



TBS-ether **104**, it was noticed that the substrate was clearly a mixture of diastereomers. Although the substrate was a mixture, the material was carried forward. Trimethylsilyl-alkyne **104** was converted to 1-bromo-alkyne **105** upon exposure to $AgNO_3$ and NBS (90%, crude). Once again, application of our novel siloxane reduction of organotin halides and subsequent *in situ* hydrostannylation methodology gave E-vinyl stannane **106** in a 57% yield over 2 steps. Instead of using a Stille protocol for the cross-coupling reaction, the Liebeskind copper (I) thiophene-2-carboxylate (CuTc) methodology was utilized. The copper mediated cross-coupling between stannane **106** and (Z)-vinyl iodide **300**[50] gave the RCM diene **107** in a moderate yield (49%). As stated earlier, the more favorable unprotected allylic oxygen moiety was needed to test our sterics hypothesis and probe Hoye's acceleration observation. Thus, we attempted to deprotect the PMB-ethers. While exposure of diene **107** to the DDQ oxidation protocol lead to removal of the PMB moieties, as evident by the R_f change, none of the several products isolated were the desired triol. With the need for an allylic alcohol in the RCM substrate and the lack of success in deprotecting acyclic diene **107**, the synthesis of the left half of the RCM substrate clearly required a different protection strategy.

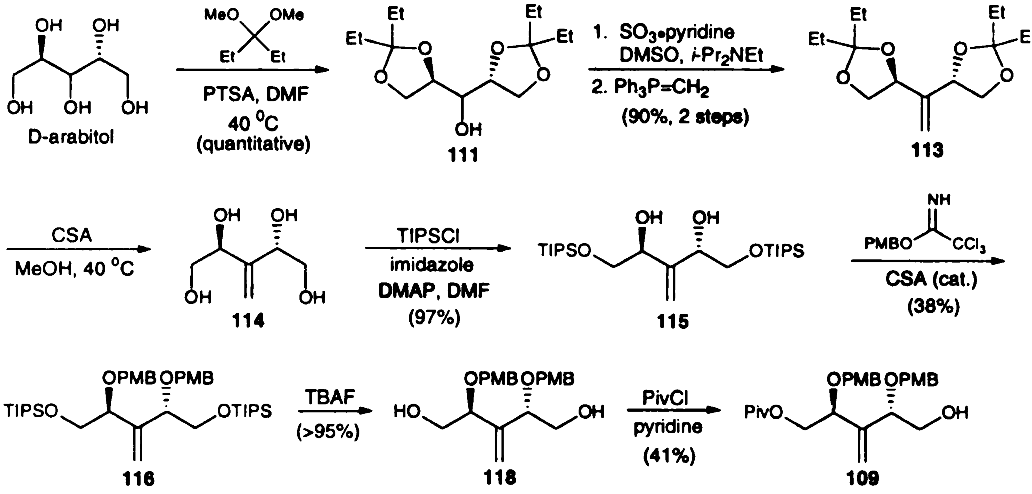
Scheme 62. Preparation of Alcohol **109**



Toward this end, the synthesis of the new RCM diene began with alcohol **94** (Scheme 62). Since a TBS-silyl ether is needed later in our synthetic pathway, protective group manipulation of the primary alcohols was examined. Protection of the free alcohol with pivaloyl chloride gave fully protected tetra-ol **108** in a 74% yield. Subsequent deprotection of the TIPS-silyl ether with TBAF gave alcohol **109**. In this sequence of reactions, it was found that subjection of the crude pivaloyl ester to the TBAF deprotection conditions gave the desired alcohol in better yields (96% yield over 2 steps).

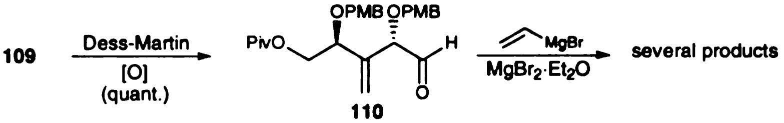
At this stage of our synthetic venture, it was apparent that multi-gram quantities of advanced intermediates would be needed. Thus a shorter high yielding route to intermediate **109** was sought. As illustrated in Scheme 63, D-arabitol was chosen as the starting chiral sugar and through desymmerization via protective group manipulation, gram quantities of alcohol **109** were prepared.

Scheme 63. Preparation of Alcohol **109** via D-arabitol



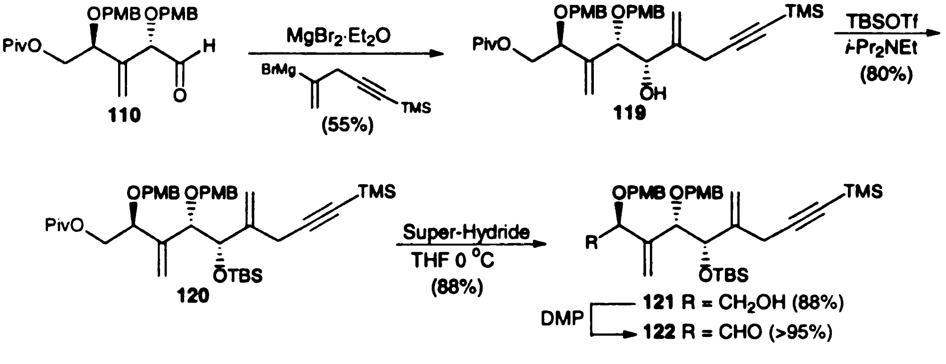
D-arabitol was protected as bisisopentylidene acetal **111** in high yields. Oxidation of the 2° alcohol with SO_3•pyridine and DMSO gave ketone **112** in 68% yield. Wittig olefination with $Ph_3P=CH_2$ installed the olefin in near quantitative yields affording acetal **113**. Hydrolysis of the acetal with CSA in MeOH provided tetra-ol **114** quantitatively, which was then selectively disilylated at the primary alcohols with TIPSCl to give diprotected tetrol **115** (77% yield) along with the mono-protected derivative (20%). Both secondary alcohols were protected as the PMB-ether under acidic conditions to give fully protected tetrol **116** (38% yield) and the mono-protected PMB derivative **117** (37%). The removal of the TIPS-silyl ethers with TBAF provided the corresponding diol **118**. Selective mono-protection of the diol with pivaloyl chloride provided the target alcohol **109** in 41% yield along with di-pivaloyl derivative (24%). Although some of the yields for the desired compounds are at best moderate, most side products formed were easily converted to the target alcohol **109**.

Scheme 64. Vinyl Magnesium Bromide Addition (III)



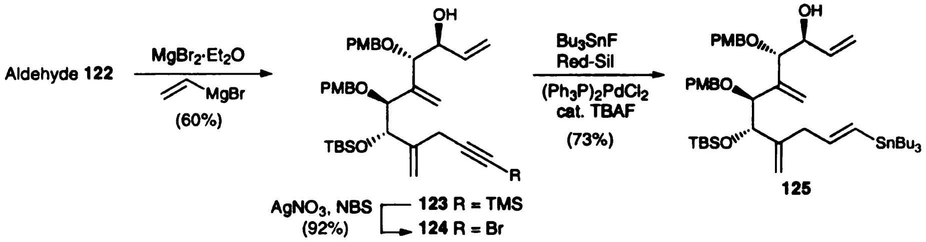
Returning to the synthesis of the amphidinolide A analog (Scheme 64), the oxidation of alcohol **109** with Dess-Martin periodinane in the presence of pyridine was uneventful and gave aldehyde **110** in a 98% yield. Aldehyde **110**, like similar aldehydes in our earlier approach, is pseudo-symmetrical and therefore

Scheme 65. Preparation of Aldehyde **122**



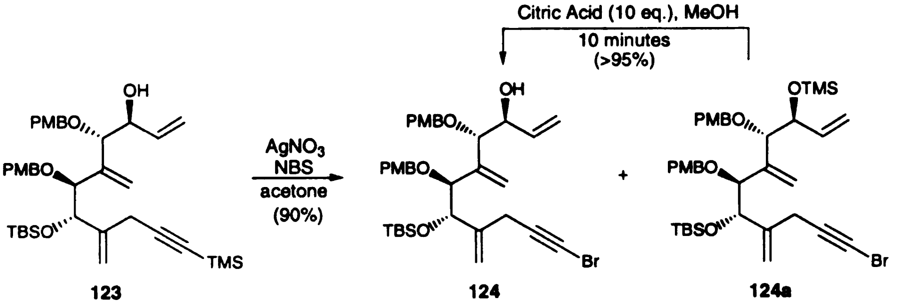
the addition of vinyl magnesium bromide or the Grignard of fragment **B** could be reversed. The addition of the latter proved to be the most rewarding. With the addition of vinyl magnesium bromide, several products were isolated and none of which were the desired alcohol. Addition of fragment **B** under chelation condition gave only one diastereomer of alcohol **119** in a 55% yield (Scheme 65). The resultant alcohol was protected as a TBS-silyl ether **120** (TBSOTf, *i*-Pr_2NEt, 80% yield). With the successful protection of the secondary alcohol, the Piv protected 1° alcohol was deprotected with Super-hydride® (88% yield) to give alcohol **121**.

Scheme 66. Preparation of (E)-vinyl Stannane **125**



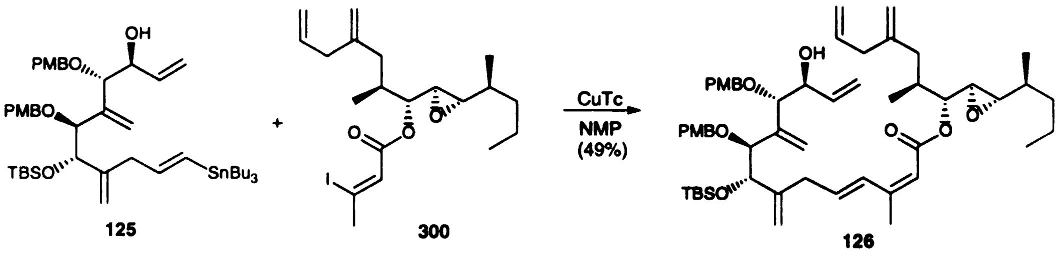
Oxidation of the alcohol with Dess-Martin periodinane gave aldehyde **122** (98% yield). With the isolation of aldehyde **122**, the second chelation controlled nucleophilic addition was carried out. Contrary to the earlier vinyl magnesium bromide addition, the coupling (Scheme 66) of the aldehyde and vinyl Grignard gave the desired alcohol **123** with good diastereoselectivity (7:1) (60% yield). In preparation for the hydrostannylation reaction, the trimethylsilyl alkyne was converted to 1-bromo-alkyne **124** (92% yield). The preparation of 1-bromo-alkyne warrants a brief comment. During the formation of 1-bromo-alkyne **124** (Scheme 67) a C-12 silylated by-product (**124a**) was often formed in 25% - 50% yield. Fortunately, exposure of TMS-silyl ether **124a** to citric acid in MeOH

Scheme 67. Recycling of 1-bromo-alkyne by-product



allowed for the selective deprotection of the TMS-ether in the presence of the TBS-ether to give the desired alcohol **124** in excellent yields (>95%). The 1-bromo-alkyne was hydrostannylated to give the (E)-vinyl stannane **125** in excellent yields (73%) (Scheme 66). If the crude 1-bromo-alkyne was used in the subsequent hydrostannylation reaction, the vinyl stannane was isolated in an average yield of 50% over the 2 steps. As illustrated in Scheme 68, (E)-vinyl

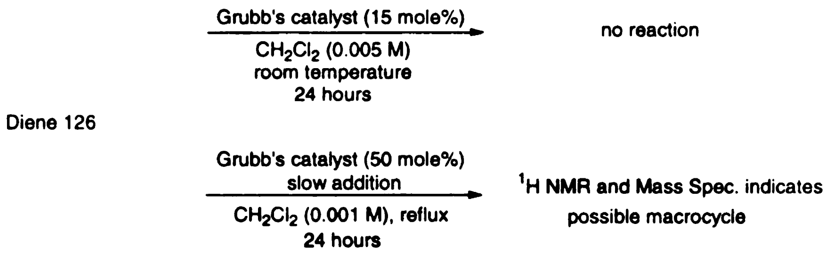
Scheme 68. Cross-coupling of Vinyl Stannane **125** and (Z)-vinyl Iodide **300**



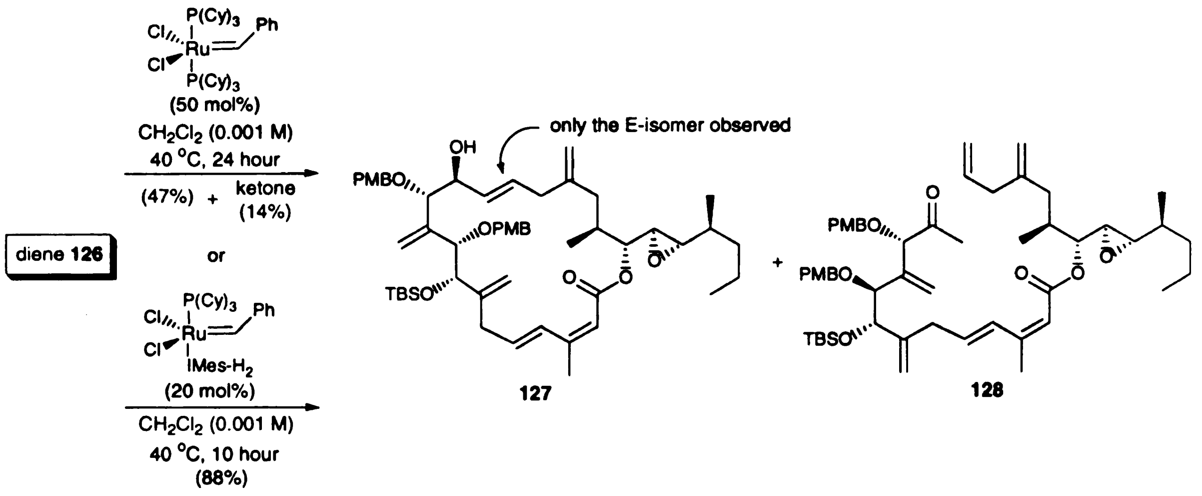
stannane **125** was coupled with the RCM substrate right half, (Z)-vinyl iodide **300**,[50] via the Liebeskind cross-coupling protocol to give diene **126** in 60% yield. With the isolation of a sterically less demanding RCM diene substrate, our hypothesis about the steric demands in the RCM reaction was tested.

When a solution of diene **126** (Scheme 69) in CH_2Cl_2 (0.005 M) at room temperature was combined with 15 mol% of Grubb's catalyst added dropwise (~ 22 minutes), no reaction was detected by ^{1}H NMR after 24 hours. When the reaction was repeated with 50 mol% of the catalyst and a diene concentration of 0.001 M in refluxing CH_2Cl_2, reaction finally occurred. Two identifiable products were isolated, one of which had the correct molecular ion peak as indicated by high resolution mass spectrometry and the appropriate ^{1}H NMR signals. The ^{1}H NMR spectrum of the second isolated compound was not clean and the mass spectrum did not correspond to the starting diene, desired macrocycle, or dimer. The mass balance of the two isolated products (1:1 ratio) accounted for 67% of the correct mass balance. After extensive experimentation, a reaction procedure was established (Scheme 70), which consisted of the dropwise addition (~4 – 6 hours) of Grubbs' catalyst (50 mol %) to a refluxing CH_2Cl_2 (0.001 M) solution of diene **126** and continuation of stirring for a total of 24 hours. This procedure resulted in the isolation of the desired macrocycle **127** in a 47% yield along with a by-product in a 14% yield. The by-product was not the dimer as initially thought but truncated ketone **128**. Besides the presence of ketone **128**, the reaction was highly chemoselective with respect to which olefins participated in the metathesis. Only the mono-substituted olefins reacted with no sign of

Scheme 69. Attempted RCM of Diene **126**



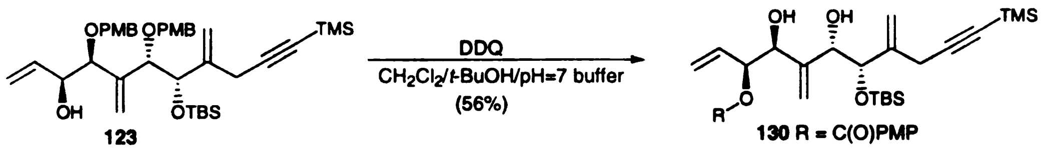
Scheme 70. Preparation of (Z)-macrocycle **127** via RCM



dimerization. Moreover, only the E-olefin was formed. In retrospect, formation of ketone **128** is not surprising given Hoye's observations on the use of allylic alcohols in RCM reactions. He found that if the rate of RCM was not fast, then this truncating pathway competed with cyclization. This competing pathway was eliminated with the use of the more active second generation Grubb's catalyst. With the use of the N-heterocyclic carbene catalyst (Scheme 70) not only was the desired macrocycle isolated in a higher yield (88%) but the amount of catalyst (20 mol%) and time for the cyclization (10 hours) was substantially reduced.

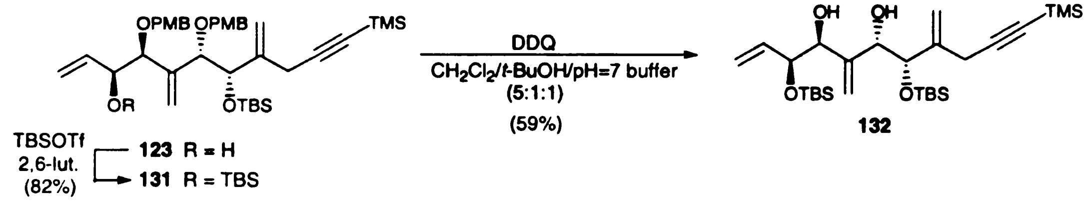
At this point in our synthetic venture, all that was needed to complete the synthesis of the Z-isomer analog of amphidinolide A was removal of the protective groups. Given the poor results of our earlier deprotection efforts, a model system was investigated in order to find optimal conditions for the

Scheme 71. PMB Deprotection Investigation (I)



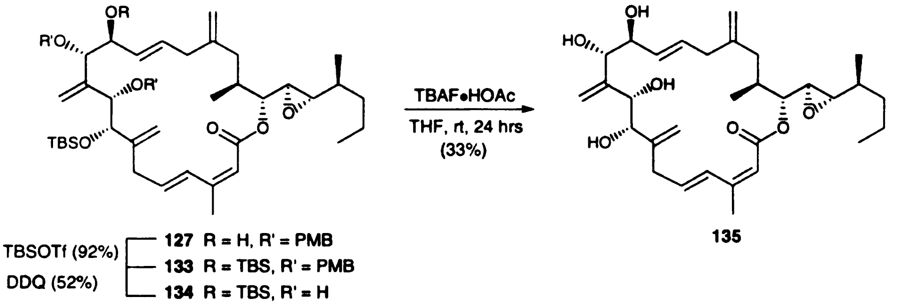
deprotection of the PMB-ethers. As such (Scheme 71), exposure of PMB-ether **123** to DDQ in a CH_2Cl_2 / *t*-BuOH / pH=7 phosphate buffer solution (5:1:1) gave the undesired *p*-methoxyphenyl ester **130** as a regioisomer mixture. Ester formation proceeds through the intramolecular capture of a benzyl carbocation by the neighboring alcohol and subsequent opening of the newly formed benzylidene acetal by DDQ oxidation and hydrolysis. To alleviate this problem, alcohol **123** was protected as a TBS-silyl ether **131** (82% yield) as outlined in Scheme 72. Although the deprotection of **131** was initially quite frustrating, it was a helpful learning experience. In that, even successful results do not always occur as expected. Careful observation is always needed. For instance, we thought that the removal of the PMB residues would lead to a more polar product. However, deprotection of the PMB ethers gave a diol with an R_f very close to that of the parent compound. This led me to initially believe that no reaction had occurred. However upon more careful analysis, we learned that the deprotection was a success, allowing isolation of the desired diol **132** in 59% yield. This successful protection-deprotection strategy was applied to the macrocycle analog as illustrated in Scheme 73.

Scheme 72. PMB Deprotection Investigation (II)



Protection of Z-macrocycle **127** as TBS-silyl ether **133** was substantially slower (12 hours) than the acyclic model system, but the yield remained consistently high (>90 %) as long as the reaction was cooled (0 °C) during the initial addition of 2,6-lutidine and TBSOTf. With the isolation of **133**, the all important PMB deprotection step was investigated. Similar to the model system, the yield of diol **134** was only moderate (52%), and relatively small differences in R_f were observed. The final step in the total synthesis of the fully deprotected Z-analog of amphidinolide A was the removal of the TBS-silyl ethers. This was accomplished with an acetic acid buffered TBAF solution in THF, giving Z-amphidinolide analog **135** in 33% yield.

Scheme 73. Synthesis of the (Z)-amphidinolide A analog



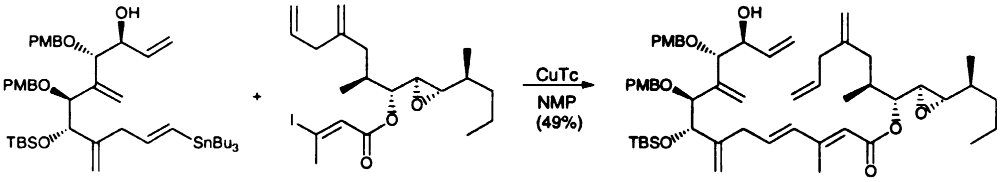
127 R = H, R' = PMB
133 R = TBS, R' = PMB
134 R = TBS, R' = H

135

B. Total Synthesis of the Assigned Structure of Amphidinolide A

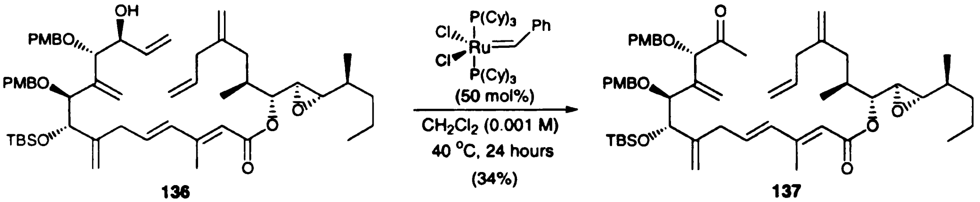
The divergent point toward the synthesis of amphidinolide A began with the cross coupling of vinyl stannane **125** with (E)-vinyl iodide **301**[50] (Scheme 74). Liebeskind cross coupling protocol between vinyl stannane **125** and (E)-vinyl iodide **301**[50] provided diene **136** in a moderate 49% yield. Attempts to increase the cross-coupling yield were to no avail. Interestingly and in contrast to the Z-analog, reaction with the (E)-vinyl iodide was very slow at 0 °C and thus had to be carried out at room temperature. Equally, interesting is our use of excess vinyl iodide (2 – 4 equivalents). Liebeskind has shown that the CuTC reagent is efficient in promoting the homo-coupling of vinyl iodides.[51] In our system the presence of the homo-coupled product is not evident until the vinyl stannane is completely consumed.

Scheme 74. Cross-coupling of Vinyl Stannane **125** and (E)-vinyl Iodide **301**



Following the preparation and isolation of diene **136**, the all-important RCM reaction was investigated (Scheme 75). Initially, the first generation Grubbs' catalyst was used with the optimized conditions from the Z-analog sequence. Unlike the Z-isomer, diene **136** under the RCM conditions only afforded truncated ketone **137** and recovered starting diene. With a notion that the conformational predisposition of the starting diene may affect the rate of ring closure, the reaction was repeated in refluxing benzene with hopes that the

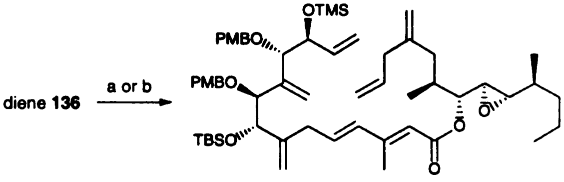
Scheme 75. RCM of Diene **136** to Give Truncated Ketone



increased temperature and change in solvent may influence and/or change the conformation of the diene and thus promote the cyclization. Unfortunately, the change in solvent had no affect on the RCM reactions as the ^{1}H NMR of crude reaction mixture showed only the ketone and starting diene. The change in olefin geometry between the Z- and E-acyclic dienes could essentially have two effects: (1) moving the end olefins farther apart (2) affording a new conformation which allows for internal chelates. Both of these outcomes would disfavor cyclization of the E-isomer. With hopes that the second hypothesis was operative, the reaction was repeated with the addition of Ti(*i*-PrO)$_4$ to hopefully break up any chelates and promote cyclization. Unfortunately, ^{1}H NMR of the crude residue was identical to all previous cases; only ketone and starting diene.

Besides by the addition of additives, formation of the truncated ketone could possibly be suppressed by protecting the allylic alcohol. Such a protection could also provide insight into the exact timing of the 1,3-hydrogen shift and reductive elimination in Hoye's mechanism for ketone formation.

Scheme 76. TMS protection of RCM diene

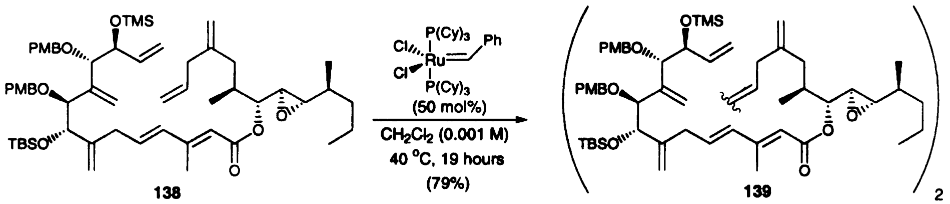


138

conditions: (a) TMSOTf, 2,6-lutidine; (70% yield)
(b) AcCl, pyridine; (0% yield)

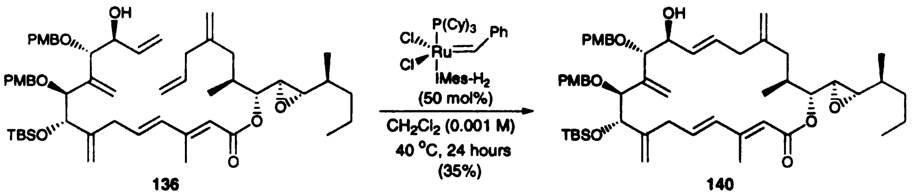
The protective group must be relatively small in order to avoid steric problems; therefore, the alcohol was protected as the TMS-silyl ether as illustrated in Scheme 76. Unfortunately, exposure of diene **138** to the RCM conditions (Scheme 77) only resulted in dimerization as evident by both ^{1}H NMR and HRMS. Presumably the newly introduced steric demands prohibited metathesis from occurring at the olefin nearest the allylic oxygen. Instead the mono-substituted olefin of the skipped diene reacted in an intermolecular manner with itself. This result further substantiates Hoye's theory concerning the acceleration of the RCM reaction with the use of allylic alcohols.[51] Clearly, the initial metathesis does not occur at the olefin nearest the allylic oxygen moiety with the use of the less Lewis basic and sterically more crowded silyl ether.

Scheme 77. Dimerization of Diene **138** via RCM



Still aiming to exploit the rate acceleration of the RCM reaction by allylic oxygen functionality, protection of the allylic alcohol with a more Lewis basic (and better coordinating) protecting groups (i.e. aceto) were attempted. Unfortunately,

Scheme 78. RCM of Diene **136** to give (E)-macrocycle **140**



all efforts at installing the acetate group failed. With the lack of success with the first generation Grubbs' catalyst in the RCM of both diene **136** and **138**, the more reactive second generation catalyst was explored. RCM with the second generation N-heterocyclic carbene catalyst afforded macrocycle **140** in only 35% yield along with several unidentifiable products (Scheme 78).[53] Several modifications to the reaction procedure were investigated in attempts to increase the yield of macrocyclization. As part of these efforts, the reaction medium was changed to refluxing benzene. Unfortunately, the elevated temperature did not have a substantial effect on the yield of the reaction or the products produced. Hoveyda has developed a modified second generation catalyst, where the cyclohexyl phosphine ligand is replaced with the tethered isopropyl styrene moiety (Figure 6).[54] With his catalyst the reactivity is retained and the initial metathesis has even been initiated at room temperature. More importantly, his catalyst is inherently more stable, presumbly due to the styrene ether tether. This enhanced stability should theoretically allow one to maintain good reactivity with less catalyst since decomposition is minimized. Decreased catalyst loads should also give a cleaner reaction i.e. less ruthenium decomposition products and hopefully facilitate identification of the by-products. Our initial RCM investigation with Hoveyda's catalyst began by repeating the optimized procedure for the second generation Grubb's catalyst. Unfortunately, reaction in either CH_2Cl_2 or benzene still gave several products in low yield. The reaction was repeated at room

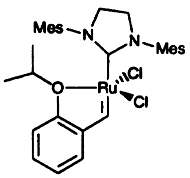
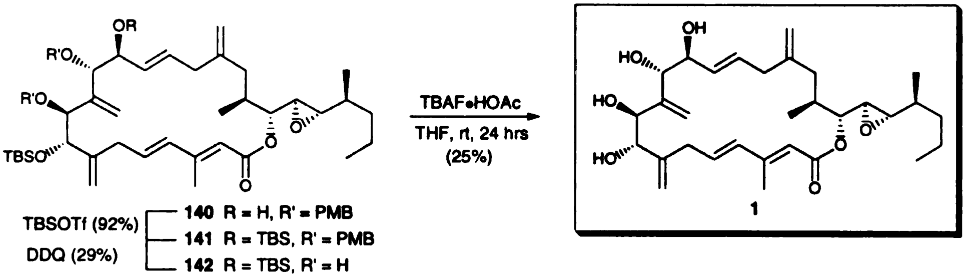


Figure 6. Hoveyda's Catalyst

temperature with hopes that the lower temperature would disfavor the unproductive pathways. Unfortunately, at room temperature the initial metathesis was very sluggish, and decomposition of the starting diene was evident after 2 days. Although the more reactive N-heterocyclic carbene catalysts allowed for some cyclization with diene **136**, exposure of TMS-protected diene **138** resulted only in dimerization, suggesting that the steric demands were overriding the enhanced reactivity of the catalyst.

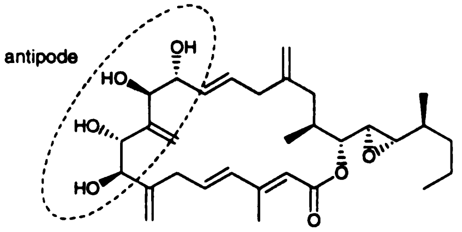
The difference in reactivity between the E- and Z-dienes is very significant for understanding the mechanism of the RCM reaction and how subtle changes can affect both the reactivity and selectivity of the reaction. Currently, there is a debate in the literature as to the extent that the predisposition of the starting diene conformation influences the efficiency of ring-closure.[55] The results in our study clearly show that the conformation of the starting diene does indeed matter. Despite our inability to improve the RCM, the protocol could provide us sufficient material needed to complete the synthesis.

Scheme 79. Synthesis of the Proposed Structure of Amphidinolide A



Thus application of the earlier protection-deprotection strategy was studied. As illustrated in Scheme 79, the alcohol of macrocycle **140** was protected with TBSOTf in the presence of 2,6-lutidine to give the fully protected macrocycle **141**. DDQ oxidative deprotection led to the isolation of diol **142** albeit in low yield (29%). The TBS-silyl ethers were deprotected with a TBAF•HOAc solution to give **1**, the proposed structure of amphidinolide A.

Disappointingly ^{1}H NMR data of the synthesized material do not completely correlate to Kobayashi's ^{1}H NMR data on the natural product. The structural assignment of our compound would appear sound since all chemical transformations used are all well established, but more importantly the assigned structures of all intermediates were fully supported spectroscopically. In some cases, advanced one- and two-dimensional NMR techniques were used to absolutely secure the assigned structures.



166

Figure 7. Possible Structure of Amphidinolide A (or its enantiomer)

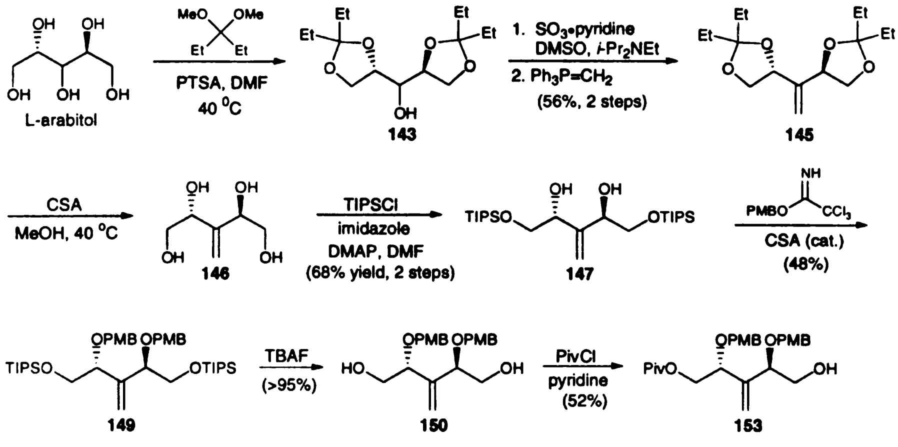
Careful examination of Kobayashi's data, revealed no direct correlation between the relative chirality of the left and right halves of the molecule. Therefore, if the relative stereochemistry *within each half* is correct, one of the halves of the natural product could actually be the antipode of Kobayashi's assigned structure.

Toward this end, the total synthesis of epimer **166** (Figure 7) was carried out. If Kobayashi's relative stereochemistry for each half is correct but how the correlation is incorrect, then epimer **166** would be the natural product or its enantiomer.

C. Total synthesis of an Epimer of Amphidinolide A via L-arabitol

Compound **166** was targeted since the antipode of the left hemisphere is easily accessed by simply changing the starting chiral sugar. As illustrated in Scheme 80, L-arabitol was protected as bisisopentylidene acetal **143** in high yields albeit as a regio-mixture. The ratio of the acetals greatly depended on controlling the reaction temperature. Oxidation of alcohol **143** with SO_3•pyridine and DMSO gave ketone **144** in 68% yield, which was readily separated from the aldehydic by-product.[56] Wittig olefination with $Ph_3P=CH_2$ installed the exo-olefin in excellent yields to give bisisopentylidene acetal **145**. Hydrolysis of the acetal with CSA in MeOH provided tetra-ol **146** quantitatively, which was selectively disilylated at the primary alcohols with TIPSCl to give diprotected tetra-ol **147** (68% yield, 2 steps) along with the mono-protected derivative **148** (22% yield, 2 steps). Both secondary alcohols were protected as the PMB-ether under acidic conditions to give fully protected tetra-ol **149** (48% yield). Removal of the TIPS-silyl ethers with TBAF provided the corresponding diol **150**. Selective mono-

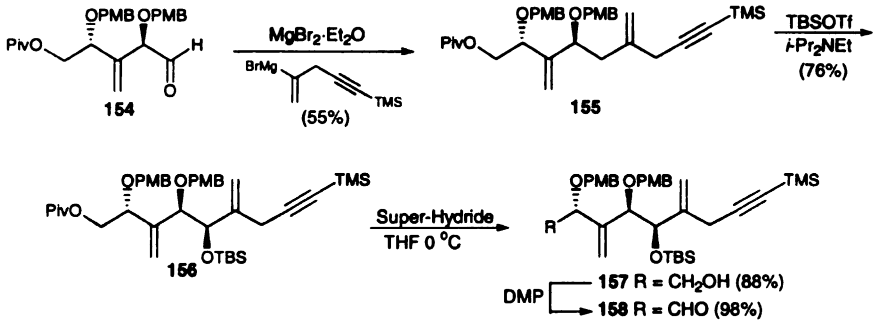
Scheme 80. Preparation of RCM substrate via L-arabitol (I)



protection of the diol with pivaloyl chloride provided the target alcohol **153** (52% yield).

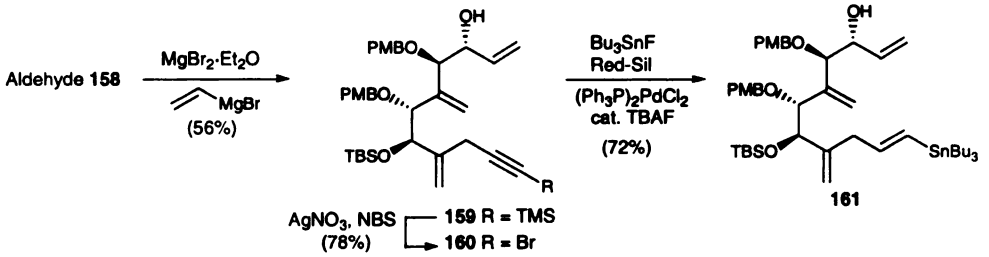
The previously prepared mono-protected TIPS tetra-ol (**148**) is readily converted to the target alcohol through a similar but modified protection strategy. The remaining primary alcohol is selectively protected as the pivaloyl ester (81% yield) to give diprotected tetra-ol **151**, where the primary alcohols are differentiated. Protection of the two remaining secondary alcohols as the PMB-ethers (PMB-trichloroacetimidate, CSA, 81% yield) provided fully protected tetra-ol **152**, which upon deprotection of the TIPS-silyl ether with TBAF (75% yield) provided target alcohol **153**. With the above sequence of reactions, gram quantities of alcohol **153** can be prepared. Dess-Martin oxidation of alcohol **153** in the presence of pyridine gave aldehyde **154** (>98% yield) which was set up for the first of two chelation controlled additions. Addition of the Grignard of fragment **B** (Scheme 81) occurred with complete diastereoselectively giving alcohol **155**. The resultant alcohol was protected as a TBS-silyl ether (**156**) (TBSOTf, i-Pr_2NEt, 76% yield). Primary alcohol **157** was liberated after Super-Hydride® reduction of the ester (THF, 0 °C, 91% yield). Oxidation of the alcohol

Scheme 81. Preparation of RCM substrate via L-arabitol (II)



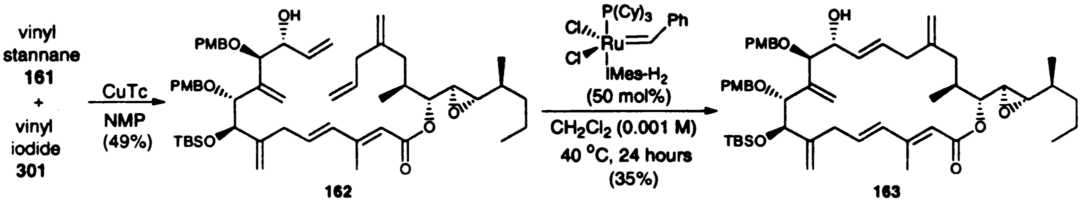
with the Dess-Martin periodinane in the presence of pyridine gave aldehyde **158** (98% yield) setting the stage for the second chelation controlled addition. Similar to the D-arabitol series, the addition of vinyl magnesium bromide (Scheme 82) occurred with only good diastereoselectivity (8:1 ratio) and in modest yields (56% yield). In preparation for the hydrostannylation reaction, TMS-alkyne **159** was converted to 1-bromo-alkyne **160** upon exposure to NBS and catalytic $AgNO_3$ (78% yield). The hydrostannylation of **160** utilizing our *in situ* Bu_3SnH protocol afforded (E)-vinyl stannane **161** in a 72% yield. As illustrated in Scheme 83, the copper mediated cross-coupling between vinyl stannane **161** and (E)-vinyl iodide **301**[50] provided RCM diene **162** in 63% yield.

Scheme 82. Preparation of RCM substrate via L-arabitol (III)



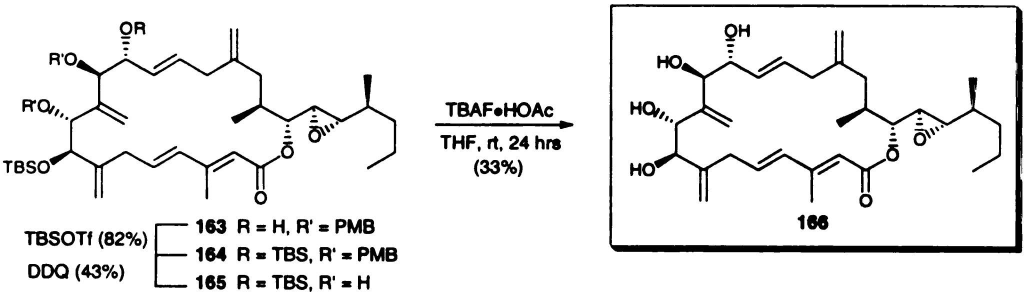
When diene **162** (Scheme 83) was subjected to our optimized RCM conditions, the desired macrocycle **163** was isolated in only 27% yield along with an unidentifiable by-product. To complete the total synthesis of amphidinolide A

Scheme 83. Preparation of Diene **162** and Subsequent RCM



isomer **166**, the protection-deprotection strategy was again utilized. As such (Scheme 84), the alcohol of macrocycle **163** was protected as TBS-silyl ether **164** (82% yield). DDQ oxidative deprotection led to the isolation of diol **165** albeit in poor yields (43%). After removal of the TBS-silyl ethers with a TBAF•HOAc solution, isomer **166** was isolated. Unfortunately, there were still inconsistencies between the ^{1}H NMRs of our synthetic material and the natural product. This result combined with our previous result suggest that the relative stereochemical assignments maybe in error.

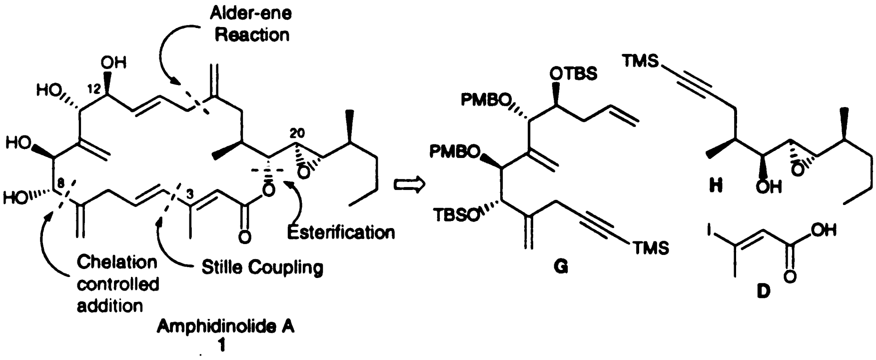
Scheme 84. Synthesis of **166**, an Isomer of Amphidinolide A



Chapter 4. 3rd Generation Approach – Application of Alder-ene Reaction

As with the second generation approach, the flexibility of our original retrosynthetic design allowed us to simultaneously explore a third generation approach to the natural product. Our third retrosynthetic breakdown of amphidinolide A affords three fragments **D**, **G**, and **H**. The planned syntheses of these fragments paralleled the syntheses of the 2nd generation subunits. The major difference between the second and third generation approaches is how the top $C_{12} - C_{16}$ skipped diene moiety will be installed. In this approach, we envisaged Trost's recently developed ruthenium mediated Alder-ene reaction, as the key step. This reaction could occur either intramolecularly (cycloisomerization) or intermolecularly (cross-coupling). We intended to investigate both approaches.

Scheme 85. 3rd Generation Retrosynthetic Analysis



In preparation for the Alder-ene reaction, the known ruthenium catalyst was prepared as outlined in Scheme 86. The catalyst was obtained as a yellow solid in an overall yield of 49% from $RuCl_3$.

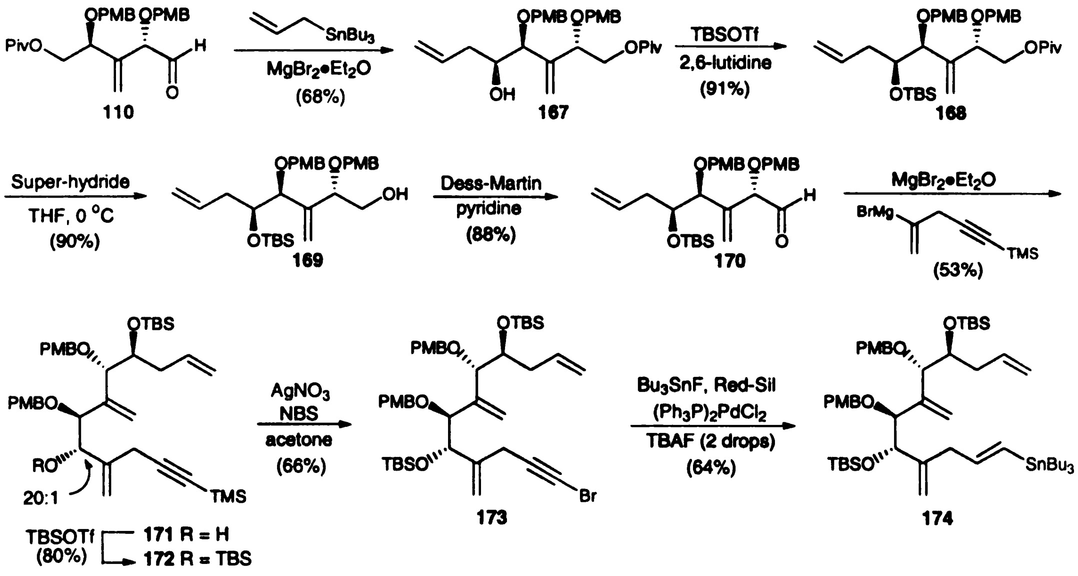
Scheme 86. Preparation of the Alder-ene Ruthenium Catalyst

$$RuCl_3 \xrightarrow{\text{1,3-cyclohexadiene}} [(\pi\text{-}C_6H_6)RuCl_2]_2 \xrightarrow{Tl(C_5H_5)} [CpRu(\pi\text{-}C_6H_6)]Cl \xrightarrow{NH_4PF_6}$$

$$[CpRu(\pi\text{-}C_6H_6)]PF_6 \xrightarrow{h\nu} \boxed{[CpRu(CH_3CN)_3]PF_6}$$

Synthesis of fragment **G** began with aldehyde **110** (Scheme 87). Chelation controlled allylation of aldehyde **110** with tributylallylstannane gave alcohol **167** with excellent diastereoselectivity (>99:1) and moderate yields (68%). The newly generated alcohol was protected with TBSOTf to give TBS-silyl ether **168** in excellent yields (91%). Alcohol **169** was liberated upon exposure of the pivaloyl ester to a Super-Hydride® reduction (THF, 0 °C, 90% yield). Oxidation of the alcohol with the Dess-Martin periodinane in the presence of pyridine provided aldehyde **170** (88% yield). Addition of the Grignard of

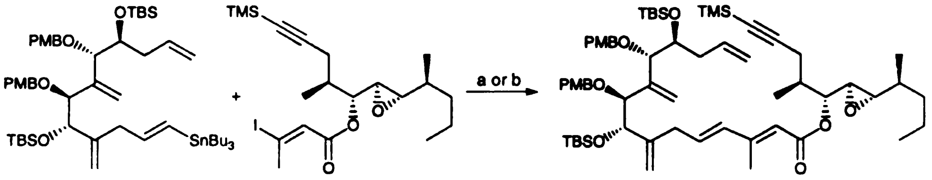
Scheme 87. Preparation of Alder-ene Vinyl Stannane **174**



fragment **B** to aldehyde **170** under chelation control occurred with excellent diastereoselectivity to give alcohol **171**. After protection of the resultant alcohol as a TBS-silyl ether (**172**) (TBSOTf, 2,6-lutidine, 80% yield), it was noticed that the product existed as a 20:1 mixture of diastereomers, presumably at C-8.

As before preparation for the upcoming hydrostannylation (Scheme 87), began by conversion of the TMS-alkyne to a 1-bromo alkyne (**173**) (66% yield). The prerequisite for the subsequent cross-coupling reaction, (E)-vinyl stannane (**174**), was generated with our *in situ* Bu_3SnH hydrostannylation protocol (64% yield). Oddly enough, the cross coupling between vinyl stannane **174** and (E)-vinyl iodide **302**[50] proved quite challenging (Scheme 88). Leibeskind's protocol, which consistently gave yields in the range of 50 – 60% with similar substrates, only afforded an unidentifiable by-product in low yield (<10%).

Scheme 88. Cross-coupling of Vinyl Stannane **174** and (E)-vinyl Iodide **302**



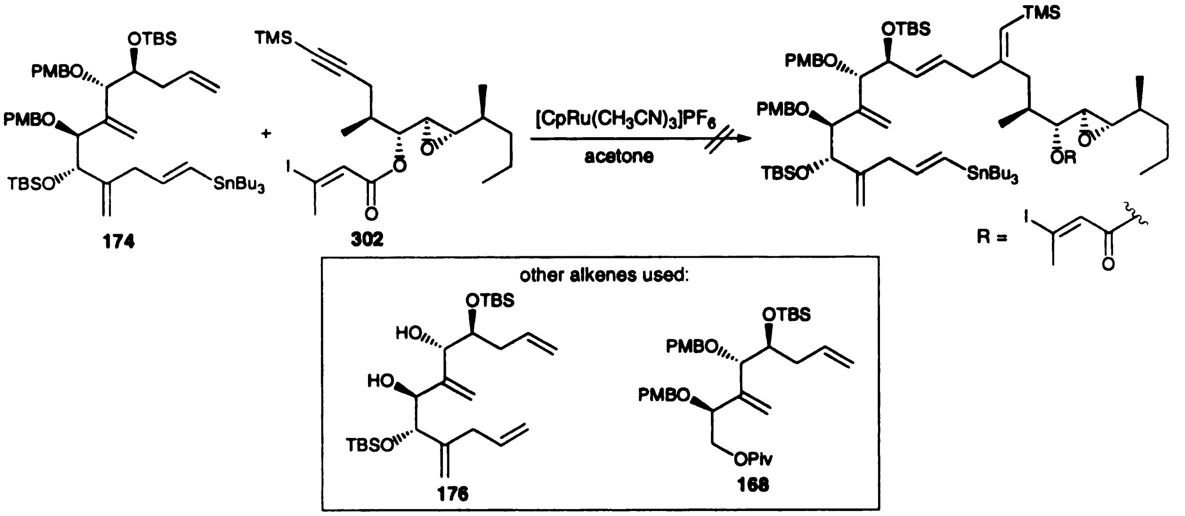
174 **302** **175**

conditions: (a) CuTC, NMP; (0% yield)
(b) Pd_2dba_3, Ph_3As, NMP, 50 °C; (30% yield)

Although diene **175** could be prepared via a Stille protocol, the yield (30%) was considerably lower than previous Stille reactions with similar substrates.

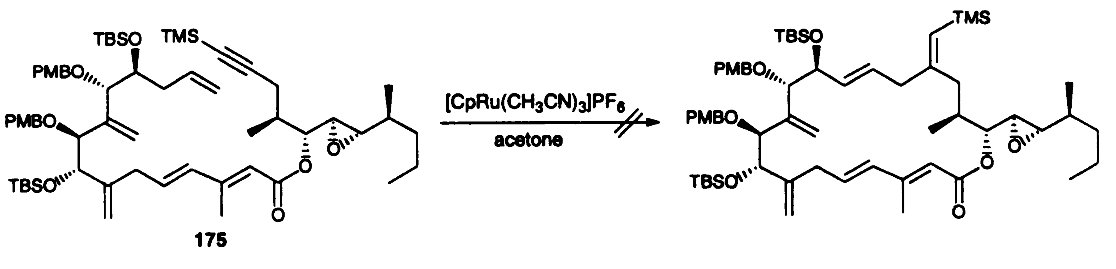
With the synthesis and isolation of the intramolecular Alder-ene substrate, and the collection of several substrates for the intermolecular version, the ruthenium mediated reaction was investigated. After extensive experimentation with model compounds a procedure was established that gave a small amount of

Scheme 89. Ruthenium Mediatated Alder-ene Cross-coupling Investigation



the desired product (~22% yield).[57] As illustrated in Scheme 89, application of our model conditions to the intermolecular coupling of the amphidinolide A substrates did not provide any of the desired products. As indicated by TLC analysis, the reactions proceeded with very little consumption (<5%) of starting substrates. The lack of reactivity with alkenes **168** and **174** could potentially be explained through the coordination of the substrates via the PMB-ethers to the catalyst. The coordination of aromatic residues to the CpRu$^+$ fragment has been shown to inhibit the activity of such catalysts. To eliminate the possibility of such binding, a substrate where the PMB moieties were removed was investigated. Unfortunately the vinyl stannane did not survive a DDQ deprotection of PMB-

Scheme 90. Ruthenium Mediatated Alder-ene Cycloisomerization Investigation



ether **174**. Furthermore, exposure of alkene **176** to the ruthenium Alder-ene reaction also gave little or no reaction as indicated by TLC. The intramolecular investigations (Scheme 90) did not fair much better. Exposure of substrate **175** to the reaction conditions only resulted in recovered starting material. In all cases, prolonged stirring (24 hours) and/or increased catalyst loads did not affect the outcome of the reaction. Given these difficulties the Alder-ene approach was abandoned.

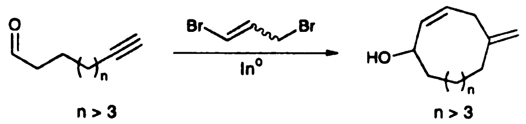
Chapter 5. Indium Mediated Reactions

Quite often a total synthesis project is accompanied with a synthetic methodology study. More importantly, the development of synthetic methods is often one of the reason for the synthetic venture itself. As such, the structure of amphidinolide A served as the basis for an alternative vinyl indium organometallic chelation controlled addition and would serve as a means of constructing the C_8 and C_{12} bonds of our retro-analysis stereoselectively. In addition, the structure of amphidinolide A served as a scaffold for the invention of an indium mediated macrocyclization.

A. Investigation of an Indium Mediated Macrocyclization

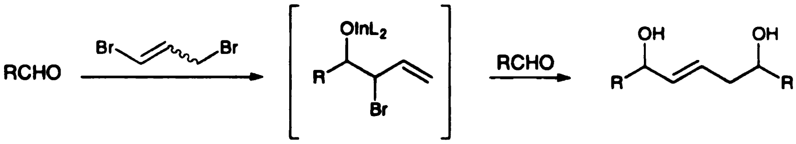
Recently, there has been increased interest in the use of organoindium[58] reagents for selective organic syntheses. Although the use of indium in organic synthesis has grown tremendously over the last several years, the scope of indium mediated reactions remains relatively limited. To our knowledge there is not yet an indium mediated cyclization protocol to form medium and/or large ring systems via a tandem di-allyl indium addition as that illustrated in Scheme 91. Allyl halides in the presence of indium metal will add to both aldehydes[59] and alkynes.[60] These results led us to investigate a tandem di-allyl indium addition to a substrate bearing an aldehyde and terminal alkyne. Formation of a medium-to-large ring system via this method could serve as a model study for the construction of amphidindolide A.

Scheme 91. Indium Mediated Cyclization



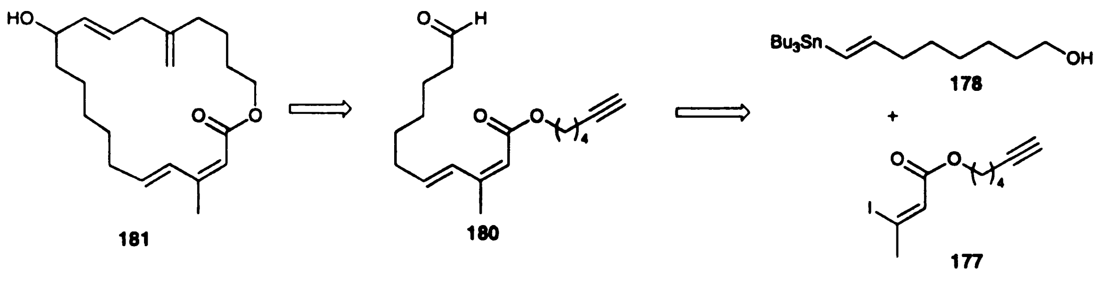
The generation of allylic diindium species is both alkyl halide and solvent dependent.[61] It has been shown that some di-haloalkenes react as if a geminal dianion was the reactive intermediate. In our case, the generation of such a dianion species would be detrimental since both nucleophilic additions would occur at the same allylic carbon resulting in a ring system with an undesired exo-olefin. To get addition at the C-1 and C-3 positions the desired cyclization must proceed in a stepwise fashion as illustrated in Scheme 92. Toward this end, a model study was investigated to probe such reactions.

Scheme 92. Proposed Stepwise Indium Diallylation



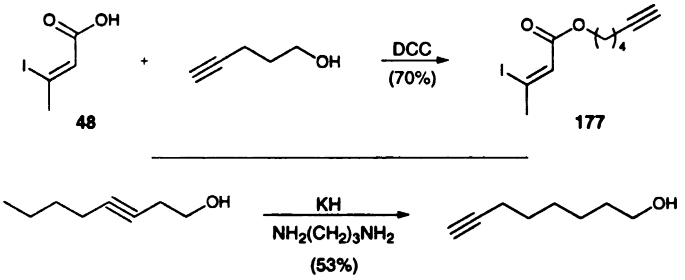
A retrosynthetic analysis (Scheme 93) of the model 20-membered lactone **181** gave rise to two fragments, vinyl iodide **177** and vinyl stannane **178**. These two fragments would be joined via a Stille coupling and formation of the corresponding diene. Oxidation of the primary alcohol should give the acyclic substrate **180**, which is a prerequisite for the indium mediated cyclization investigation.

Scheme 93. Retrosynthetic Analysis of Model Macrocycle

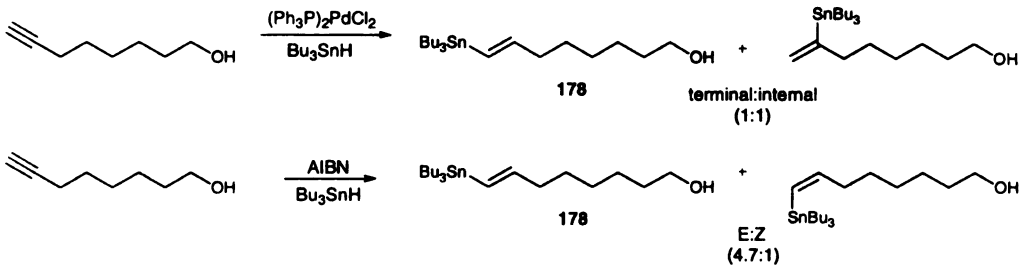


Vinyl iodide **177** was readily prepared by a DCC mediated esterification of the (Z)-β-iodo acid **48** and 5-hexyn-1-ol (Scheme 94) in a 70% yield. For the synthesis of the second Stille component a Zipper reaction[62] of 3-octyn-1-ol gave the required terminal alkyne in a modest yield of 55%. Due to difficulties with the employment of potassium hydride, including foaming during the formation of potassium 3-aminopropylamide (KAPA), an alternative Zipper procedure using sodium hydride[63] was investigated. The NaH protocol was not as successful as the KH procedure as incomplete reaction with the former resulted in an inseparable mixture of terminal and internal alkynes.

Scheme 94. Synthesis of Model Vinyl Iodide **177**



Scheme 95. Synthesis of Model Vinyl Stannane **178**

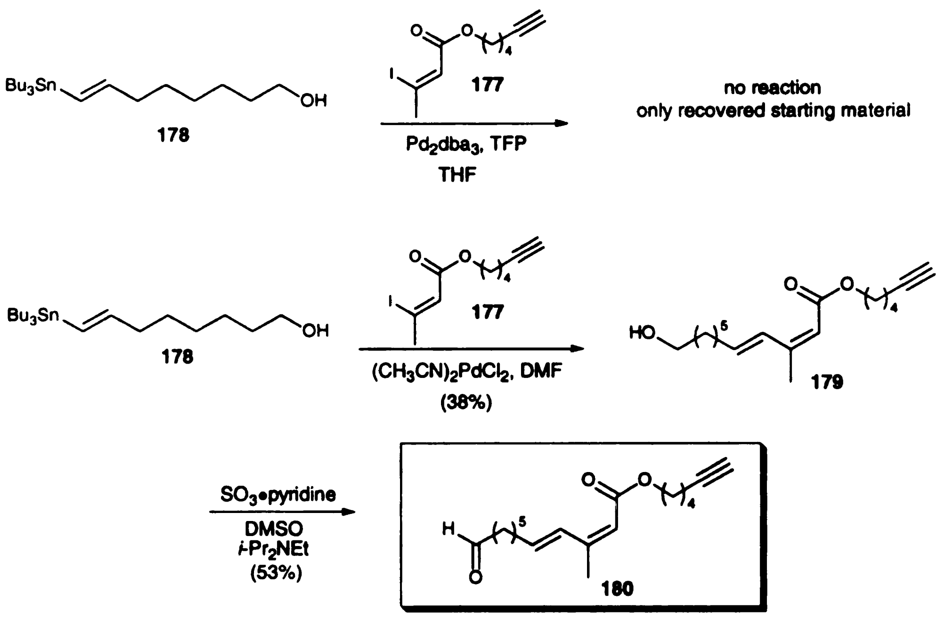


With the isolation of 7-octyn-1-ol via the Zipper reaction, the desired vinyl stannane **178** was generated (Scheme 95). With the palladium mediated protocol, both the internal and terminal vinyl stannanes were isolated in a 1:1

ratio. Fortunately, free radical hydrostannylation, only afforded the terminal vinyl stannane **178** with an E:Z ratio of 4.7:1.

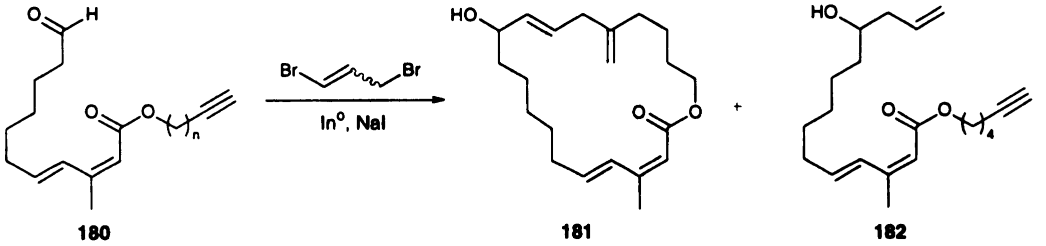
With both subtargets for the model macrolactone in hand, their union was investigated (Scheme 96). Diene **179** was prepared by a Stille protocol in low yield. In reaction optimization experiments, it was found that the cross-coupling required reaction over 18 hours at room temperature. With regards to the palladium catalyst, it was found that the bis(acetonitrile)palladium (II) dichloride catalyst was superior in the coupling reaction. Ironically, with tris(dibenzlideneacetone)dipalladium (Pd_2dba) and tri-2-furylphosphine (TFP) as the catalyst system, only recovered starting material was isolated after 30 hours in refluxing THF. In any event, after subjecting the primary alcohol to the Doering-Parikh oxidation and obtaining aldehyde **180**, the indium-mediated cyclization was ready to be investigated.

Scheme 96. Cross-coupling of Vinyl Stannane **177** and (Z)-vinyl Iodide **178**



After examining the literature for allyl indium addition conditions to aldehydes and alkynes, our initial protocol for the cyclization reaction consisted of the following conditions[64] (Scheme 97): THF as the solvent, indium powder as the indium source, and NaI for an *in situ* Finkelstein reaction. The reaction was stirred at room temperature for 6.5 hours until judged complete by TLC. After purification of the crude material by flash chromatography, two compounds were isolated. From ^{1}H and ^{13}C NMR both compounds were not of acceptable purity; therefore, further purification was attempted by preparatory HPLC. The amount of material recovered after preparatory HPLC was insufficient for complete spectroscopic identification. However, from the initial NMR data structures **181** and **182** are proposed. Compound **181** is the desired macrocycle, while alcohol **182** is proposed to be the result of an allylation of the aldehyde followed by protio-debromination. All efforts to optimize the reaction were unsuccessful, and therefore this approach to amphidinolide A was also abandoned.

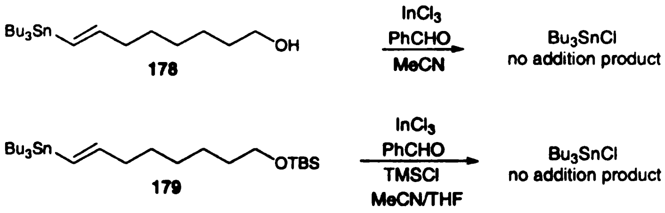
Scheme 97. Indium Mediated Cyclization



B. Generation of Vinyl Indanes and Subsequent Addition

In conjuction with the chelation controlled formation of the C_7-C_8 and C_{12}-C_{13} bonds, the generation and subsequent reaction of vinyl indium nucleophiles were investigated. Recent reports on the chelation-controlled additions of allylindanes to carbonyls suggested that indium or ligated indium species may be useful in the chelation-controlled addition of vinyl species to carbonyls. Moreover, the generation of allyl and alkynyl indane species have been reported by several groups under varying conditions. Initially, we believed that the tin to indium transmetallation[65] protocol would better serve our purpose. In preparation for the transmetallation reaction, several vinyl stannanes were prepared via the hydrostannylation of the parent alkyne.

Scheme 98. Tin - Indium Transmetallation



Vinyl stannane **178** was the initial stannane investigated. The progress of the reaction was monitored by the disappearance of starting material by TLC analysis. After 20 minutes of stirring at room temperature, stannane **178** was completely consumed and the distinguishable Bu_3SnCl TLC streak appeared. Unfortunately, direct spectroscopic identification of organoindanes is not yet possible. Therefore, the presumed formation of the vinylindane is based solely on the apparent formation of Bu_3SnCl. After the addition of benzaldehyde, the reaction was allowed to stir at room temperature for an additional 60 minutes. Unfortunately, by ^1H NMR the crude residue showed no signs of an addition product but rather destannylated alkene. Due to the acidic nature of hydroxy protons, an internal quenching process may be operative. Therefore, the protected silyl ether **179** was used in future reactions. Although the preferred solvent for the transmetallation is acetonitrile, protected alcohol **179** was insoluble in acetonitrile, and therefore, a solvent mixture of acetonitrile and THF (3:1) was utilized. Also, the reaction was run under Barbier-type conditions, where the electrophile was present during formation of the organometallic. After stirring for one hour at room temperature, GC-MS analysis showed three peaks that corresponded to the mass of benzaldehyde, Bu_3SnCl, and destannylated alkene. The reaction was allowed to proceed at room temperature for a total of 4 hours, after which it was heated at 55 °C for 15 hours. The GC-MS analysis after heating was identical to the one after the initial hour. The reaction was quenched by the addition of trimethylsilyl chloride (TMSCl) with two goals in mind: (a) TMSCl could activate the carbonyl for nucleophilic addition and/or (b) the presumed vinyl anion would be trapped with TMSCl thus providing evidence of vinyl indium formation. GC-MS analysis after the addition of TMSCl no longer showed the peak corresponding to the destannylated alkene. In addition to the disappearance of the destannylated alkene peak two additional peaks appeared. Unfortunately, these peaks exhibited no readily recognizable molecular ion. The crude residue was purified by flash chromatography but the isolated products were unidentifiable by ^1H NMR. The reaction was not a complete failure since it suggested that TMSCl or another Lewis acid could indeed initiate vinylindane formation. With that knowledge, the reaction was repeated with two equivalents of indium (III) chloride under the notion that the first equivalent would transmetallate with tin generating the vinyl indium species, and the second would serve to activate the carbonyl for nucleophilic addition. Unfortunately, the GC-

MS analysis was identical to the previous reactions initially showing three peaks corresponding to the aldehyde, Bu_3SnCl, and the destannylated alkene.

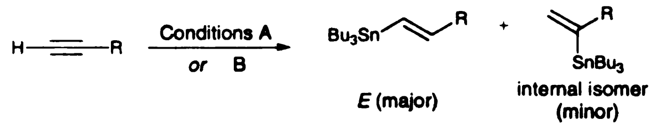
Collectively the results suggest that transmetallation from tin to indium is operative due to formation of Bu_3SnCl. Secondly, all the above reactions were stoichiometric in $InCl_3$, and the formation of Bu_3SnCl was complete (100%) within 30 minutes. Therefore, although the reactions were a failure in effecting a nucleophilic addition, they suggested that a "vinyl indane" species was present but internally quenched. Under the following conditions: catalytic in indium, rigorously dried and distilled THF as the solvent, and no TMSCl, GC analysis after 1 hour and 16 hours were identical and showed the presence of Bu_3SnCl and destannylated alkene. More importantly, the starting vinyl stannane **179** was present, thus verifying the hypothesis of an internal quench by "wet" solvent or adventitious protons. Moreover, after the addition of TMSCl, which is known[65a,b] to be needed for nucleophic additions with catalytic indium, the GC trace was again identical to all the previous cases where the reaction failed. These results are significant because they infer that the presumed "vinyl indane" species are stable over substantial periods of time but are not nucleophilic enough to add to carbonyl electrophiles.

Chapter 6. *In Situ* Generated Bu_3SnH and Subsequent Hydrostannylation

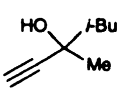
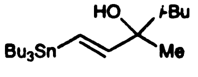
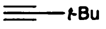
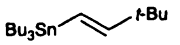
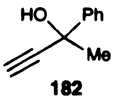
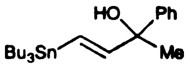
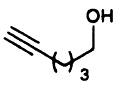
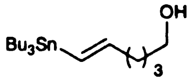
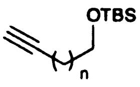
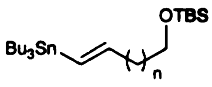
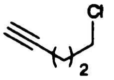
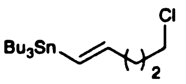
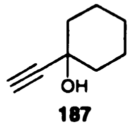
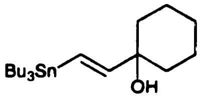
In concert with our total synthesis, amphidinolide A has served as a scaffold for the invention of new synthetic methodology. The genesis of these studies lies in the $C_3 - C_4$ diene disconnection of our retrosynthetic analysis. The overall goal of our methods project was to develop a one-pot hydrostannylation /Stille reaction catalytic in both palladium and tin. Traditionally, the vinyl stannane is generated by either a palladium mediated or free radical hydrostannylation of the parent alkyne with Bu_3SnH. Although the use of Bu_3SnH in organic synthesis is widespread, there are several drawbacks with its direct use i.e. its cost and toxicity. While investigating different aspects of this project, I have focused on gaining a fuller understanding of applying siloxane reductions of tin halides for the generation of tin hydrides and subsequent *in situ* hydrostannylation of alkynes.

Drawing on our experience with one-pot hydrostannylation/Stille couplings,[66] we first focused on palladium-mediated hydrostannylations. We were initially disappointed when the reactions of several 1-alkynes with Bu_3SnCl, aqueous KF, and PMHS in THF proved inconsistent. Although the anticipated vinyltins were produced, yields and purity levels were usually low. However, after some experimentation, we found that using Et_2O as the solvent and including a catalytic amount tetrabutylammoniun fluoride (TBAF) or iodide (TBAI)[67] in the reaction, the expected vinylstannanes were formed in good yields and with standard regiochemical outcomes (Scheme 99; conditions A[68]). Importantly, potentially reactive groups such as alkyl halides or silyl ethers[69]

Scheme 99. In Situ Bu_3SnH and Subsequent Hydrostannylation (I)



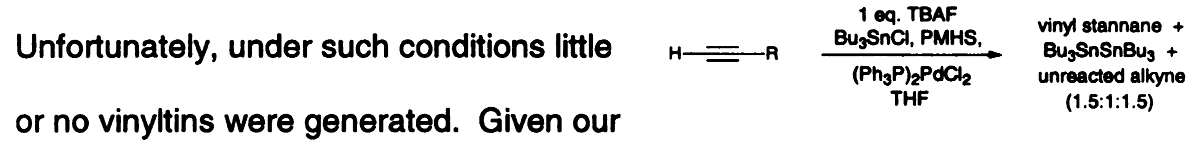
Conditions A:	Conditions B:
Bu_3SnCl, PMHS, aq. KF, cat. Bu_4NF (or Bu_4NI), cat. $(Ph_3P)_2PdCl_2$, Et_2O	Bu_3SnF, PMHS, cat. Bu_4NF cat. $(Ph_3P)_2PdCl_2$, Et_2O

alkyne	product	yields Conditions A	 Conditions B
 **180**		66% E/int. (24:1) **188a/188b**	67% E/int. (21:1) **188a/188b**
 **181**		59% E/int. (>99:1) **189a/189b**	67% E/int. (>99:1) **189a/189b**
 **182**		86% E/int. (12:1) **190a/190b**	68% E/int. (>99:1) **190a/190b**
 **183**		72% E/int. (1.4:1) **191a/191b**	77% E/int. (1.4:1) **191a/191b**
 **184** (n=2) **185** (n=3)		51% (n=2) E/int. (1:1) **192a/192b**	53% (n=3) E/int. (1.3:1) **193a/193b**
 **186**		84% E/int. (1.4:1) **194a/194b**	78% E/int. (1.4:1) **194a/194b**
 **187**		62% E/int. (17:1) **195a/195b**	70% E/int. (>99:1) **195a/195b**

remained intact throughout the reaction sequence. Furthermore, we observed no evidence of palladium-mediated hydrosilylation by the PMHS. Although the hydrostannylations with $Bu_3SnCl/PMHS/KF_{(aq.)}$ proved similar in many regards to those carried out with pre-made Bu_3SnH, there were several significant differences. For example, palladium-catalyzed hydrostannylations using Bu_3SnH directly are often complicated by the palladium-promoted conversion of Bu_3SnH into $Bu_3SnSnBu_3$.[70] Under the $Bu_3SnCl/PHMS/KF_{(aq.)}$ conditions, the vinylstannanes are accompanied by little if any hexabutylditin byproduct. Presumably, the rates of tin hydride formation and hydrostannylation are such that the relative concentration of tin hydride is always low, thereby minimizing dimer formation. This phenomena can be of particular practical advantage when vinyltins are desired in quantities that dissuade their distillation and when they are also sufficiently nonpolar so as to make the chromatographic separation from the ditin difficult.

In terms of solvent, an obvious difference between our method and traditional hydrostannylations is the inclusion of water in the reaction. Although the advantages of running organic reactions in water have been well documented,[71] we also recognized that a more anhydrous variant of our protocol would have its own advantages. Toward this aim, we examined the potential of KF or CsF in anhydrous ether to serve as sources of fluoride for our reaction. Unfortunately, under such conditions little or no vinyltins were generated. Given our observation that the biphasic reactions were facilitated by the presence of catalytic amounts of TBAF, we decided to explore its use in stoichiometric quantities. Employing 1 equivalent of TBAF did result in complete and rapid generation of Bu_3SnH; however, the subsequent hydrostannylation did not go to

Scheme 100. In Situ Bu_3SnH Stoichiometric TBAF

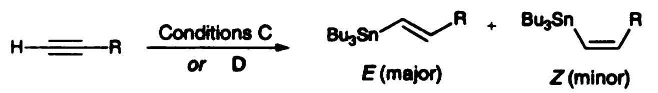


completion, as the reaction afforded a 1:1 ratio of vinylstannane and unreacted alkyne, along with a 50% yield of hexabutylditin (Scheme 100). This result was not entirely unexpected as tetrabutylammonium salts are known to greatly activate the Sn-H bond, leading to hydrogen gas evolution and ditin formation.[72] The presence of $Bu_3SnSnBu_3$ and product were evidence that TBAF could serve to activate PMHS[73] and thus generate Bu_3SnH; however, it was also clear that we would have to minimize the TBAF concentration if we wished for the tin hydride to be available for hydrostannylation versus dimer formation. However, treatment of terminal alkynes with Bu_3SnCl, PMHS, and catalytic TBAF in the absence of KF also failed to provide any vinylstannane. Presumably the TBAF is reacting with the Bu_3SnCl to form Bu_3SnF and thereby not allowing for the activation of the PMHS.[74] Assuming this were the case, we rationalized that by using pre-made Bu_3SnF as the starting material the reaction could be made catalytic with respect to the TBAF, because a fluoride anion would be generated upon the PMHS-mediated conversion of Bu_3SnF into Bu_3SnH. Indeed, this proved to be the case. As indicated in Scheme 99 (conditions B), the catalytic TBAF/PMHS/Bu_3SnF combination gave the desired hydrostannylation products in good yields and with no $Bu_3SnSnBu_3$ formation. Interestingly, the addition of aqueous KF to THF or Et_2O mixtures of Bu_3SnF and PMHS results in the formation of only trace amounts of stannane.

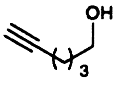
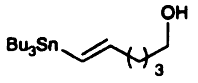
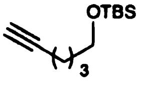
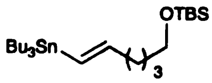
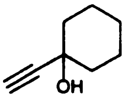
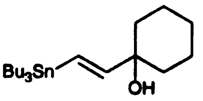
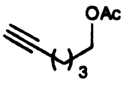
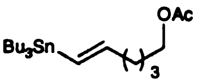
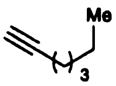
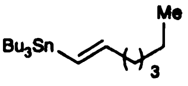
Having applied the Bu_3SnX/PMHS/F^- method of generating Bu_3SnH to *in situ* hydrostannylations via palladium catalysis, we next decided to investigate the performance of the method in the free radical hydrostannylations. We believed the most significant difference between the palladium-mediated and free radical reactions would be the elevated temperatures under which the free radical hydrostannylations are usually conducted. Specifically, we were concerned that in refluxing benzene or toluene our fluoride source would react with the product stannanes, diminishing the overall yield and/or effectively quenching the reaction prematurely.[75]

These concerns proved to be unfounded. As illustrated in Scheme 101, both the catalytic TBAF/PMHS/Bu_3SnF method and the KF/PMHS/Bu_3SnCl

Scheme 101. In Situ Bu_3SnH and Subsequent Hydrostannylation (II)



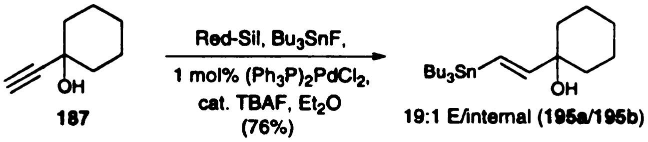
Conditions C:	Conditions D:
Bu_3SnCl, PMHS, aq. KF, AIBN, PhH or PhMe, Δ	Bu_3SnF, PMHS, cat. Bu_4NF, AIBN, PhH or PhMe, Δ

alkyne	product	yields Conditions C	 Conditions D
 **183**		62% E/Z (3:1) **191a/191b**	91% E/Z (3:1) **191a/191b**
 **185**		60% E/Z (4:1) **193a/193b**	51% E/Z (4:1) **193a/193b**
 **187**		58% E/Z (19:1) **195a/195b**	63% E/Z (77:1) **195a/195b**
 **196**		56% E/Z (4:1) **198a/198b**	69% E/Z (4:1) **198a/198b**
 **197**		50% E/Z (4:1) **199a/199b**	53% E/Z (4:1) **199a/199b**

performed quite well under free radical reactions. Again the chemical yields and regioselectivities[76] observed in these reactions paralleled those found with the use of commercial tributyltin hydride. Unlike the palladium-catalyzed reactions, the employment of KF/PMHS/Bu_3SnCl under the free radical conditions did not require the inclusion of catalytic TBAF or TBAI. Presumably, the elevated temperatures of the free radical process allow the initial reaction between the KF, Bu_3SnCl, and the PMHS to take place at the water/benzene (or toluene) interface. The free radical reactions were similar to the palladium protocols in many regards, including the compatibility of silyl ethers with the procedure.

At this point, we needed to address the PMHS-related phenomena, which occasionally complicates the workup of these reactions. Our standard workup usually involves a NaOH treatment, evaporation, and chromatographic purification. With base-sensitive substrates such as the acetate in Scheme 101, the caustic workup needs to be omitted to avoid partial saponification of the ester. In such cases, the NaOH wash can be eliminated from the workup, but when omitted an almost "plastic" substance will occasionally solidify upon evaporation of the reaction solvent. This material is quite insoluble, and significant amounts of product are usually trapped within the polymer. To avoid this periodic annoyance, we sought a low cost PMHS substitute that could be easily removed from the reaction mixture in an efficient and simple way. Surface-immobilized silyl hydrides on silica such as those

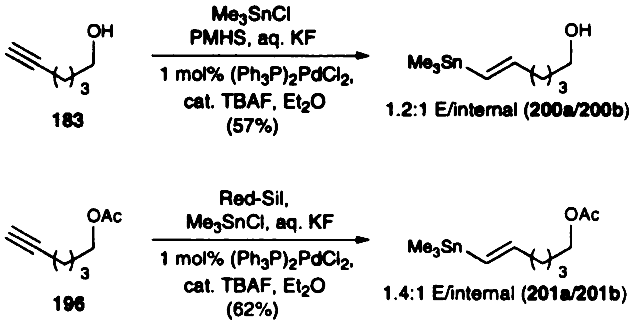
Scheme 102. In Situ Bu_3SnH via Red-Sil



popularized by Fry et al.[77] were viewed as excellent candidates for such a PMHS substitute. Reducing silica or "Red-Sil" is relatively simple to make[77a] and when applied to palladium-mediated reductions[77b] can be easily removed by filtration of the reaction mixture. In our reactions, Red-Sil performed admirably (Scheme 102), although a 4-fold excess of silane was required. Importantly, the reactions are very clean, and simple filtration of the reaction mixture through a short pad of silica gel completely removed the silane, which did not contain any detectable amounts of vinylstannane, and simultaneously removed the other reaction salts. Again, no $Bu_3SnSnBu_3$ byproduct was observed.

We have also investigated the application of our new method to the *in situ* generation and reaction of other tin hydrides, especially trimethyltin hydride. The very high toxicity of trimethyltin hydride coupled with its volatility (59 °C at 760 mmHg)[78] makes this reagent quite dangerous to handle. Ideally, this reagent is best prepared *in situ*, allowing its use without isolation. However, because of the absence of any commercially available trimethyltin oxides, the synthesis of trimethyltin hydride has traditionally relied on the reaction of strong hydride donors with trimethyltin chloride.[78a] Given the substrate tolerance exhibited by our method, we believed the Me_3SnCl/siloxane/fluoride combination would represent the best way to perform reactions with trimethyltin hydride.[79] Indeed, trimethylvinylstannanes were

Scheme 103. In Situ Me_3SnH



efficiently prepared via palladium-mediated hydrostannylations with trimethyltin hydride generated from the reaction of Me_3SnCl, KF (aq) and either PMHS or Red-Sil (Scheme 103).

In summary, either Bu_3SnCl/PMHS/KF (aq) or the combination of tributyltin fluoride, PMHS, and catalytic quantities of tetrabutylammonium fluoride (TBAF) can serve as in situ sources of tributyltin hydride for both free radical and palladium-catalyzed hydrostannylation reactions. Furthermore, other trialkyltin halides such as trimethyltin chloride, as well as alternative reductants such as Red-Sil appear to be amenable to the method.

Conclusion:

The convergent approach to amphidinolide A allowed for the construction of synthetically versatile building blocks. The synthesis of these building blocks and the flexibility in our design allowed for the simultaneous investigation of multiple coupling strategies, which gave valuable information as to which coupling sequence was used in our final approach to amphidinolide A. Our final approach allowed for the ready synthesis of amphidinolide A and unnatural analogs in 35 steps from articles of commerce with the longest linear sequence being 23 steps from L-(-)-ephedrine. The synthesis of amphidinolide A and unnatural analogs allowed for the instructional applications of organo-tin, indium, copper, palladium and ruthenium mediated reactions.

In addition, the *in situ* Bu_3SnH methodology study, which had its genesis at the $C_3 - C_4$ bond of our retro-analysis of, laid the ground work for the realization of a Stille reaction catalytic in both palladium and tin.

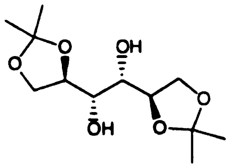
Experimental Section

Materials and Methods:

All air or moisture sensitive reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere unless otherwise noted. All commercial reagents were used without purification. All solvents were reagent grade. Diethyl ether and THF were freshly distilled from sodium/benzophenone under nitrogen. Benzene, toluene, DMSO, diisopropylethylamine and cyclohexane were freshly distilled from calcium hydride under nitrogen. Except as otherwise noted, all reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates or capillary GC with a fused silica column. Flash chromatography was performed with silica gel 60 Å (particle size 230-400 mesh ASTM). High performance liquid chromatography (HPLC) was performed with Ranin component analytical/ semiprep system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Gemini-300, VXR 500 or INOVA 600 spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ ($\delta = 7.24$ ppm for ^{1}H NMR or $\delta = 77.0$ ppm for ^{13}C NMR). Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) data were obtained at either the Michigan State University Mass Spectrometry Service Center or at the Mass Spectrometry Laboratory of the

University of South Carolina, Department of Chemistry & Biochemistry. GC/MS were performed with a fused silica column (30 m by 0.25 mm i.d.).

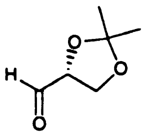
Preparation of bisisopropylidene acetal (8):



8

A 1-L, three-necked flask equipped with an overhead stirrer, heating mantle and condenser with drying tube was charged with D-mannitol (100 g, 0.549 mol), freshly distilled 1,2-dimethoxyethane (240 mL), and 2,2-dimethoxypropane (160 mL, 1.3 mol). The reaction mixture was stirred and stannous chloride (0.1 g) was added. The remaining neck was capped with a septum, and the stirred slurry was heated to reflux. Reflux was maintained until the mixture became clear (30 – 50 minutes) and was continued for 30 minutes after clarity was attained. The heating mantle was removed, and the solution was cooled below the reflux temperature and followed by the addition of pyridine (0.2 mL). After the solution was cooled to room temperature, it was transferred to a tared flask and concentrated on a rotary evaporator, beginning at room temperature and increasing the water bath to 100 °C. The semi-solid, which was white in color, was cooled to room temperature, and the residual solvent was removed with the vacuum pump to give 163 g of a white solid. According to the literature,[13] the purity of the product is ~ 55%.

Preparation of D-glyceraldehyde (9):



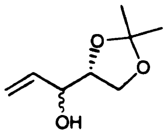
9

To a slurry of the bisisopropylidene of D-mannitol (36.0 g, 75.6 mmol, 55% purity) in CH_2Cl_2 (360 mL) and a saturated aqueous $NaHCO_3$ solution (20 mL) was added $NaIO_4$ (20 g, 93 mmol) portionwise (~ 2-3 minutes). After stirring for 2 hours at room temperature, $MgSO_4$ (20 g) was added and stirred for an additional 10 minutes. The reaction mixture was then vacuum filtered, and the filtrate concentrated to give a thick yellow oil. The crude residue was purified by distillation (54 °C @ 15 mm Hg) to give 7.25 g (37%) of D-glyceraldehyde acetonide **9** as a clear oil. For ^1H NMR data see below.

$Pb(OAc)_4$ procedure:

To a cold (0 °C) solution of the bisisopropylidene of D-mannitol (36.0 g, 75.6 mmol, 55% purity) in EtOAc (260 mL) was added $Pb(OAc)_4$ (52 g, 120 mmol) portionwise. The reaction mixture was warmed to room temperature and stirred for an additional 2.5 hours. The reaction mixture was filtered, and the filtrate was concentrated to give a clear syrup. Carbon tetrachloride (30 mL) was added to the residue and then evaporated under reduced pressure. This procedure was repeated three more times. The resulting residue was purified by distillation (40 °C, 3.6 mm Hg) to give 10.3 g (53%) of D-glyceraldehyde acetonide **9** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 9.70$ (d, $J = 1.9$ Hz, 1H), 4.37 (ddd, $J = 7.4, 4.9, 1.9$ Hz, 1H), 4.15 (ABq, $J = 8.8, 7.4$ Hz, 1H), 4.08 (ABq, $J = 8.8, 4.9$ Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H). The spectroscopic data was in complete agreement with the literature.[13]

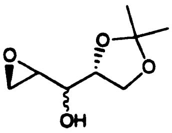
Preparation of Allylic Alcohol (10):



10

To a cold (0 °C) solution of D-glyceraldehyde acetonide **9** (10.3 g, 79.5 mmol) in Et_2O (145 mL) was added vinyl magnesium bromide (81 mL, 81 mmol, 1.0 M THF) dropwise over 30 minutes. The reaction was allowed to warm to room temperature over 45 minutes and then quenched with a saturated aqueous NH_4Cl solution (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL x 3). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to give an oil. The crude residue was purified by flash chromatography on silica gel [Hex/EtOAc 1:1] to give 10.2 g (81%) of desired allylic alcohol **10** as a clear oil. For spectroscopic data see reference (14).

Preparation of Epoxy alcohol (11):



11

Kinetic resolution conditions:

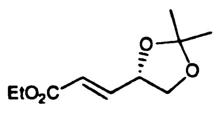
To a solution of Ti(O-*i*-Pr)$_4$ (1.94 mL, 6.51 mmol) in CH_2Cl_2 (10 mL) at -30 °C was added (-)-diisopropyl tartrate (1.64 mL, 7.71 mmol) in CH_2Cl_2 (10 mL). After 15 minutes of stirring, allylic alcohol **10** (1.0 g, 6.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise, followed by anhydrous *t*-BuOOH in toluene (4.35 M, 0.75

mL, 3.30 mmol). The reaction was allowed to proceed at -20 °C for 24 hours and then quenched with saturated aqueous Na_2SO_3 (10 mL) and Na_2SO_4 (10 mL). The resulting mixture was stirred for two hours and then filtered through a pad of Celite on a glass frit filter. The filter cake was washed with anhydrous Et_2O until the paste became granular. The granular filter cake was scraped off into a flask with EtOAc (50 mL) and stirred at reflux for 5 minutes. It was then filtered through the same pad of Celite and washed with hot EtOAc (50 mL). The filtrate was washed with 50% KOH (15 mL x 2) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give 5.3 g of a yellow oil. The crude residue was purified by flash chromatography on alumina basic, activity III, (hexanes/EtOAc, 1:1) to provide 95 mg of epoxy alcohol **11** as a clear oil. For spectroscopic data see reference (19).

Standard conditions:

To a solution of $Ti(O\text{-}i\text{-}Pr)_4$ (2.27 mL, 7.63 mmol) in CH_2Cl_2 (10 mL) at -30 °C was added (-)-diisopropyl tartrate (1.70 mL, 8.01 mmol) in CH_2Cl_2 (10 mL). After 15 minutes of stirring, allylic alcohol **10** (1.15 g, 7.28 mmol) in CH_2Cl_2 (20 mL) was added dropwise, followed by anhydrous *t*-BuOOH in toluene (4.35 M, 0.75 mL, 3.30 mmol). The reaction was allowed to proceed at -20 °C for 24 hours and then quenched with saturated aqueous Na_2SO_3 (10 mL) and Na_2SO_4 (10 mL). The resulting mixture was stirred for two hours and then filtered through a pad of Celite on a glass frit filter. The filter cake was washed with anhydrous Et_2O until the paste became granular. The granular filter cake was scraped off into a flask with EtOAc (50 mL) and stirred at reflux for 5 minutes. It was then filtered through the same pad of Celite and washed with hot EtOAc (50 mL). The filtrate was washed with 50% KOH (15 mL x 2) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give 5.26 g of a yellow oil. For spectroscopic data see reference (19).

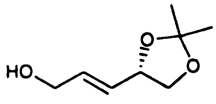
Preparation of allylic ester (12):



12

To a cold (0 °C) solution of bisisopropylidene acetal **8** (9.45 g, 19.8 mmol, 55% purity) in 5% aqueous $NaHCO_3$ (50 mL) was added dropwise a solution of $NaIO_4$ (6.3 g, 30 mmol) in water (50 mL). The ice bath was removed and stirred at room temperature for 1 hour. The reaction temperature was lowered back to 0 °C and then triethyl-α-phosphonacetate (20.0 mL, 100 mmol) and 6 M K_2CO_3 (150 mL) were added. The ice bath was removed and stirred at room temperature for 24 hours. The reaction mixture was extracted with CH_2Cl_2 (200 mL x 4). The combined extracts were dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 1:1] to give 7.43 g (94%) of allylic ester **12** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 6.86$ (dd, $J = 15.7, 5.5$ Hz, 1 vinyl H), 6.08 (dd, $J = 15.7, 1.6$ Hz, 1 vinyl H), 4.67 (dd, $J = 12.64, 6.59$ Hz, 1 H), 4.18 (q, $J = 7.14$ Hz, 2 H), 4.16 (dd, $J = 8.2, 6.6$ Hz, 1 H), 3.65 (dd, $J = 8.2, 7.1$ Hz, 1H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.27 (t, $J = 7.14$ Hz, 3 H). The spectroscopic data is in complete agreement with the reported literature.[16]

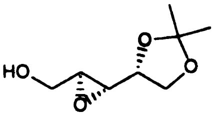
Preparation of allylic alcohol (13):



13

To a –78 °C solution of allylic ester **12** (5.99 g, 29.9 mmol) in CH_2Cl_2 (150 mL) was added DIBAL (75 mL, 1.0 M hexanes, 75 mmol) dropwise over 30 minutes. After stirring for 2 hours at –78 °C, the reaction was quenched with water (5 mL) and a saturated aqueous Rochelle's salt solution (150 mL). The mixture was allowed to warm to room temperature and stir overnight. The biphasic mixture was separated, and the organic phase washed twice with saturated aqueous Rochelle's salt solution. The combined aqueous phase was extracted three times with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 5.5 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/Et_2O 1:3] to give 3.54 g (75%) of allylic alcohol **13** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 5.96 (dt, *J* = 15.4, 4.94 Hz, 1 vinyl H), 5.71 (ddt, *J* = 15.4, 7.69, 1.65 Hz, 1 vinyl H), 4.52 (app q, *J* = 7.14 Hz, 1 H), 4.15 (dd, *J* = 4.94, 1.65 Hz, 2 H), 4.07 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.59 (t, *J* = 8.0 Hz, 1H), 1.46 (s, 1H), 1.41 (s, 3H), 1.38 (s, 3H). The spectroscopic data is in complete agreement with the reported literature.[16]

Preparation of 2,3-epoxy-1-ol (14):

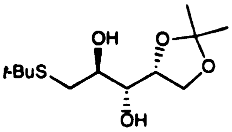


14

To a solution of Ti(O-*i*-Pr)$_4$ (4.52 mL, 15.2 mmol) in CH_2Cl_2 (20 mL) at –30 °C was added (+)-diethyl tartrate (2.72 mL, 15.9 mmol) in CH_2Cl_2 (20 mL). After

15 minutes of stirring, allylic alcohol **13** (2.28 g, 14.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise, followed by anhydrous *t*-BuOOH in toluene (2.18 M, 14.4 mL, 31.2 mmol). The reaction was allowed to proceed at -20 °C for 24 hours and then quenched with saturated aqueous Na_2SO_3 (20 mL) and Na_2SO_4 (20 mL). The resulting mixture was stirred for two hours and then filtered through a pad of Celite on a glass frit filter. The filter cake was washed with anhydrous Et_2O (~ 1 L) until the paste became granular. The granular filter cake was scraped off into a flask with EtOAc (50 mL) and stirred at reflux for 5 minutes. It was then filtered through the same pad of Celite and washed with hot EtOAc (50 mL). The filtrate was washed with 50% KOH (30 mL x 2) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil. The crude residue was purified by flash chromatography on silica gel [pet ether/Et_2O 1:7] to give 1.40 g (56%) of epoxy alcohol **14** as a clear oil. The spectroscopic data is in complete agreement with the reported literature.[19]

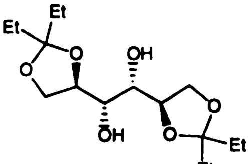
Preparation of diol sulfide (17):



17

Water and *t*-BuOH were deoxygenated prior to use by the rapid passage of nitrogen through the solvent for at least 30 minutes. A solution of epoxy alcohol **14** (1.0 g, 5.7 mmol) in 0.5 M NaOH (29 mL) and *t*-BuOH (29 mL) was immersed in a preheated (70 °C) oil bath and stirred vigorously. A solution of *t*-butylthiol (0.82 mL, 7.2 mmol) in *t*-BuOH (10 mL) was added dropwise over 45 minutes. After stirring an additional 20 minutes, the reaction was allowed to cool to room temperature and was then neutralized with a saturated aqueous NH_4Cl solution. After water was added to clarify the aqueous phase, the phases were separated. The aqueous phase extracted 5 times with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, filtered and concentrated to give a yellow oil. Flash chromatography on silica gel [hexanes/EtOAc 1:1] afforded 1.1 g (75%) of diol sulfide **17** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 4.32$ (dt, $J = 6.59$, 3.85 Hz, 1 H), 4.06 (dd, $J = 8.24$, 6.59 Hz, 1 H), 3.89 (dd, $J = 8.24$, 7.14 Hz, 1 H), 3.61 (dt, $J = 7.69$, 3.85 Hz, 1 H), 3.39 (dd, $J = 7.69$, 3.85 Hz, 1 H), 3.00 (dABq, $J = 13.19$, 3.85 Hz, 1 H), 2.69 (dABq, $J = 13.19$, 8.24 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.25 (s, 9 H). The spectroscopic data is in complete agreement with the reported literature.[19]

Preparation of bisisopentylidene (18):

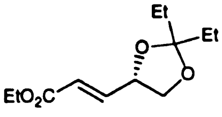


18

To a 40 °C slurry of D-mannitol (50 g, 27 mmol) in 126 mL of DMF containing camphosulfonic acid (CSA) (1.92 g, 8.2 mmol) was added 3,3-dimethoxypentane (76 g, 58 mol) dropwise over 15 minutes. After stirring for 3 hours, the reaction was quenched with triethylamine (1.4 g, 14 mmol). The resultant solution was concentrated under vacuum at 60 °C to afford a crude oil. The oil was diluted with 400 mL of EtOAc and then washed with brine (270 mL x 2). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum at 60 °C to yield a white solid. The solid was dried overnight under high vacuum at 60 °C to give 77.31 g of bisisopentylidene acetal **19**. According to literature,[20] the purity of the bis-acetal is ~70% and the spectroscopic data is in complete agreement.

^{1}H NMR 300 MHz ($CDCl_3$): δ = 3.72 – 4.20 (m, 8 H), 1.6 (m, 8 H), 0.86 (t, J = 7.42 Hz, 6 H), 0.89 (t, J = 7.42 Hz, 6 H).

Preparation of allylic ester (20):

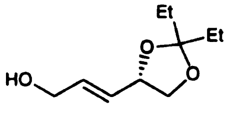


20

To a slurry of KIO_4 (6.12 g, 26.6 mmol) and $KHCO_3$ (0.28 g, 0.25 mmol) in H_2O (50 mL) at room temperature was added a solution of bisisopentylidene acetal **18** (11.0 g, 24.2 mmol, 70% purity) in THF (20 mL) dropwise over 5 - 10 minutes. After stirring for 3 hours at room temperature, the reaction mixture was cooled to 0 °C and followed by the addition of triethyl α-phosphonacetate (22.6 g, 20 mL, 100 mmol) and 150 mL of 6 M K_2CO_3. The resulting mixture was allowed to warm to room temperature and was stirred for 24 hr. The reaction mixture was extracted four times with CH_2Cl_2 and the combined extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 38 g of an oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc, 3:1) to provide 7.59 g (70%) of allylic ester **19** and 2.08 g (18%) of a diastereomeric mixture. IR (neat, 4 cm^{-1}): ν = 2978, 2884, 1724, 1665, 1464, 1305, 1175, 1080, 978, 920; $[\alpha]_D$ +41.6° (c 2.985, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.82 (dd, J = 15.66, 5.77 Hz, 1 H), 6.06 (d, J = 15.66 Hz, 1 H), 4.60 (m, 1 H), 4.13 (m, 1 H), 4.15 (q, J = 7.14 Hz, 2 H), 3.56 (m, 1 H), 1.62 (q, J = 7.42

Hz, 2 H), 1.61 (q, J = 7.42 Hz, 2 H), 1.24 (t, J = 7.14 Hz, 3 H), 0.88 (t, J = 7.42 Hz, 3 H), 0.86 (t, J = 7.42 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.91, 144.18, 122.39, 114.03, 75.22, 69.22, 60.49, 29.71, 29.33, 14.13, 8.04, 7.95; HRMS (CH_4) *m/z* 229.1441 [(M + H)$^+$; calcd for $C_{12}H_{21}O_4$, 229.1440].

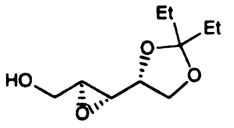
Preparation of allylic alcohol (20):



20

To a stirred solution of allylic ester **19** (3.40 g, 14.9 mmol) in 75 mL of CH_2Cl_2 at –78 °C was added DIBAL (38 mL, 1M hexanes, 38 mmol) over 30 min. The mixture was stirred at –78 °C for 3 hr, quenched with 3 mL of water and treated with 75 mL of saturated aqueous Rochelle's salt. The solution was allowed to warm to room temperature, and the phases were separated. The organic phase was washed twice with Rochelle's salt, and the combined aqueous phases were extracted with CH_2Cl_2. The combined extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel [hexanes/EtOAc, 1:3] to provide 2.39 g (86%) of allylic alcohol **20**. IR (neat, 4 cm^{-1}): ν = 3418, 2974, 2941, 2882, 1464, 1172, 1078, 918; $[\alpha]_D$ +27.2° (c 2.665, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.91 (dtd, J = 15.38, 4.95, 0.824 Hz, 1 H), 5.64 (ddt, J = 15.38, 7.69, 1.65 Hz, 1 H), 4.47 (q_{app} 7.69 Hz, 1 H), 4.10 (dd, J = 4.94, 1.65 Hz, 2 H), 4.04 (qAB, J = 8.24, 6.32 Hz, 1 H), 3.50 (t, J = 8.24 6 H), 1.60 (dq, J = 7.42 Hz, 4 H), 0.86 (dt, J = 7.42 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.86, 128.19, 113.44, 77.64, 69.99, 62.63, 30.05, 29.84, 8.25, 8.16; HRMS (CH_4) *m/z* 187.1335 [$(M + H)^+$; calcd for $C_{10}H_{19}O_3$, 187.1334].

Preparation of epoxy alcohol (21):

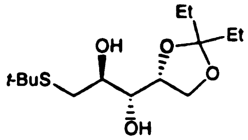


21

A solution of Ti(O-i-Pr)$_4$ (3.70 mL, 12.4 mmol) in 20 mL CH_2Cl_2 was added to a flask filled with nitrogen and cooled to -30 °C. (+)-diethyl-L-tartrate (2.3 mL, 13 mmol) in 20 mL of dry CH_2Cl_2 was added under stirring. After 15 minutes, allylic alcohol **20** (2.20 g, 11.8 mmol) in 40 mL of CH_2Cl_2 was added dropwise over 1 hour, followed by the addition of *t*-BuOOH in toluene (6.0 mL, 4.35 M, 26 mmol). The reaction was allowed to proceed at –20 °C for 26 hours, before being diluted with Et_2O (50 mL) and then quenched with saturated aqueous solutions of Na_2SO_3 and Na_2SO_4 (15 mL each). The resulting heterogeneous mixture was stirred vigorously for 2 hours and then filtered through a pad of Celite. The yellow paste was washed with anhydrous ether until granular. The yellow paste was scraped into a flask with 50 mL of EtOAc. The heterogeneous mixture was heated to reflux for 5 minutes. The resulting mixture was filtered through the same Celite pad. The cake was washed with 50 mL of hot EtOAc. The filtrate was washed with 50% KOH (2 x 15 mL) and then brine, dried over $MgSO_4$, filtered and concentrated to give 3.95 g of a crude oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 1:3] afforded 1.75 g (70%) of epoxy alcohol **21**. IR (neat, 4 cm^{-1}): ν = 3443, 2976, 2941, 2883, 1464, 1358, 1201, 1172, 1129, 1078, 916, 768; $[\alpha]_{589}^{20}$ -12.2° (c 1.40, $CHCl_3$); ^1H

NMR (300 MHz, $CDCl_3$) δ = 4.06 (m, 2 H), 3.92 (ddd, *J* = 12.64, 4.94, 2.20 Hz, 1 H), 3.77 (t, *J* = 6.59 Hz, 1 H), 3.64 (ddd, *J* = 12.64, 7.69, 3.85 Hz, 1 H), 3.12 (dt, *J* = 3.85, 2.20 Hz, 1 H), 3.07 (dd, J = 4.94, 2.20 Hz, 1 H), 2.01 (s, -OH), 1.60 (m, 4 H), 0.89 (t, *J* = 7.14 Hz, 3 H), 0.85 (t, *J* = 7.69 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 113.9, 75.5, 66.3, 60.8, 55.3, 54.8, 29.5, 29.2, 8.0, 7.9; HRMS (CH_4) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

Preparation of diol sulfide (22):

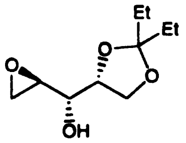


22

Water and *t*-BuOH were deoxygenated prior to use by the rapid passage of nitrogen through the solvent for at least 30 minutes. A solution of the epoxy alcohol **21** (3.01 g, 14.8 mmol) in 74 mL of 0.5 M NaOH and 74 mL of *t*-BuOH was immersed in a preheated (70 °C) oil bath and stirred vigorously. A solution of *t*-butylthiol (2.2 mL, 20 mmol) in *t*-BuOH (30 mL) was added dropwise over 60 minutes. After stirring for an additional 30 minutes, the reaction was allowed to cool to room temperature and then neutralized with a saturated aqueous NH_4Cl solution. After water was added to clarify the aqueous phase, the phases were separated. The aqueous phase extracted 5 times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [Hex/EtOAc, 3:1] afforded 3.56 g (82%) of diol sulfide **22**. IR (neat, 4 cm^{-1}): ν = 3464, 2973, 2941, 2884, 1462, 1366, 1169, 1080, 1059, 920; $[\alpha]_{589}^{20}$ +51.3° (c 2.545, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 4.26 (ddd, *J* = 7.69, 6.59, 4.40 Hz, 1 H), 4.07 (dt, *J* = 8.24, 6.59 Hz, 1

H), 3.84 (t, $J = 7.69$ Hz, 1 H), 3.63 (m, 1 H), 3.41 (dt, $J = 4.40, 6.59$ Hz, 1 H), 2.98 (dd, $J = 13.19, 4.40$ Hz, 1 H), 2.75 (d, $J = 5.49$ Hz, 1 H), 2.70 (dd, $J = 13.19, 7.69$ Hz, 1 H), 2.51 (d, $J = 7.14$ Hz, 1 H), 1.62 (m, 4 H), 1.31 (s, 9 H), 0.88 (q, $J = 7.69$ Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 112.9, 79.3, 73.1, 71.4, 66.7, 42.6, 32.2, 31.0, 29.5, 29.0, 8.2, 8.0$; HRMS ($CH_4$) *m/z* 293.1785 [$(M + H)^+$; calcd for $C_{14}H_{29}O_4S$, 293.1787].

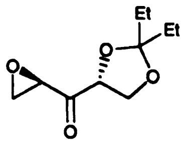
Preparation of epoxy alcohol (23):



23

To a solution of diol sulfide **22** (2.9 g, 9.9 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (6.13 g, 24.8 mmol) in CH_2Cl_2 (60 mL) was added Me_3OBF_4 (2.26 g, 15.3 mmol) portionwise until TLC indicated that the diol was completely consumed (~ 1.5 hour @ 15 minute intervals). NaH (0.53 g, 21 mmol), which was washed prior to use with pentane or used as a 95% mineral oil suspension, was added dropwise as a suspension in CH_2Cl_2 (10 mL). After stirring for 5 minutes, the solution was quenched with a saturated aqueous solution of NH_4Cl. Water was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give a red oil. Purification by flash chromatography on silica gel [Hex/EtOAc, 1:3] afforded 1.46 g (73%) of epoxy alcohol **23** and 6.10 g of recovered 2,6-di-*tert*-butyl-4-methyl pyridine. IR (neat, 4 cm^{-1}): $\nu = 3458, 2975, 2942, 2884, 1464, 1173, 1082, 918, 858$; $[\alpha]_D$ +4.8° (c 1.335, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 4.22$ (dt, $J = 4.94, 6.59$ Hz, 1 H), 4.07 (dd, $J = 8.24$, 6.59 Hz, 1 H), 3.83 (dd, *J* = 8.24, 7.14 Hz, 1 H), 3.37 (q, *J* = 5.49 Hz, 1 H), 2.98 (ddd, *J* = 6.59, 3.85, 2.75 Hz, 1 H), 2.82 (dd, *J* = 4.94, 3.85 Hz, 1 H), 2.74 (dd, *J* = 4.94, 2.75 Hz, 1 H), 2.36 (d, *J* = 4.94 Hz, 1 H), 1.64 (m, 4 H), 0.90 (t, *J* = 7.69 Hz, 3 H), 0.89 (t, *J* = 7.14 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 113.4, 77.0, 71.8, 65.9, 51.7, 45.3, 29.4, 28.9, 8.2, 8.0; HRMS (CH_4) *m/z* 203.1283 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

Preparation of epoxy ketone (24):

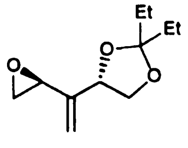


24

To a room temperature solution of epoxy alcohol **23** (0.42 g, 2.1 mmol) in CH_2Cl_2 (20 mL) were added DMSO (5.90 mL, 82.8 mmol), diisopropylethylamine (2.16 mL, 12.4 mmol), and sulfur trioxide pyridine (0.99 g, 6.21 mmol). After stirring for 30 mintues the reaction was quenched by the addition of an aqueous saturated solution of NH_4Cl (15 mL), followed by the addition of ether (40 mL). The phases were separated, and the organic layer was washed with brine (2x). The combined aqueous layers were extracted with ether (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel [hexanes/EtOAc, 3:1] to give 0.34 g (83%) of ketone **24** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2977, 2944, 2884, 1730, 1464, 1383, 1361, 1201, 1173, 1130, 1078, 1061, 912; $[\alpha]^{20}_{589}$ +151.6° (c 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.63 (dd, *J* = 7.69, 5.77 Hz, 1 H), 4.17 (dd, *J* = 8.51, 7.69 Hz, 1 H), 4.00 (m, 2 H), 2.99 (dd, *J* = 6.59, 4.67 Hz, 1 H), 2.79 (dd, *J* = 6.59, 2.47 Hz, 1 H), 1.64 (m, 4 H), 0.87 (t, *J* = 7.69

Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 205.1, 115.2, 79.7, 66.4, 50.4, 47.8, 29.0, 28.4, 8.0, 7.9$; HRMS ($CH_4$) *m/z* 201.1122 [$(M + H)^+$; calcd for $C_{10}H_{17}O_4$, 201.1127].

Preparation of alkene (25):



25

*Three step tandem reaction via diol sulfide **22**:*

To a solution of diol sulfide **22** (0.60 g, 2.0 mmol) and 2,6-di-*tert*-butyl-4-metylpyridine (1.05 g, 5.13 mmol) in CH_2Cl_2 (10 mL) was added Me_3OBF_4 (0.42 g, 2.6 mmol) portionwise until the diol was completely consumed (~ 1 hour). NaH (0.10 g, 4.3 mmol), which was washed prior to use with pentane, was added dropwise as a suspension in CH_2Cl_2 (3 mL). After stirring for 1 hour, the solution was quenched with a saturated aqueous solution of NH_4Cl. The phases were separated, and the aqueous layer extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated to give 1.45 g of crude material.

Swern Oxidation:

To a solution of oxalyl chloride (0.36 mL, 4.1 mmol) in CH_2Cl_2 (12 mL) at -78 °C was slowly added a solution of DMSO (0.58 mL, 8.2 mmol) solution in CH_2Cl_2 (1 mL). After 5 minutes, a solution of crude epoxy alcohol **23** in CH_2Cl_2 (6 mL) was added dropwise. After another 15 minutes, diisopropylethylamine (2.86 mL, 16.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction was diluted with ether (40 mL) and water (20 mL), and the phases were separated. The organic phase was washed with water, brine and then dried over Na_2SO_4, filtered and concentrated to give crude **24** as a yellow oil.

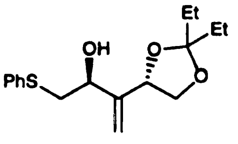
Wittig Olefination:

To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (0.81 g, 2.3 mmol) in THF (8 mL) was added *n*-BuLi (1.5 mL, 2.4 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 30 minutes, cooled back to 0 °C and then a solution of crude ketone **24** in THF (5 mL) was added dropwise. After stirring for 1 hour, the reaction was quenched with a saturated aqueous NH_4Cl solution. Ether was added and the phases were separated. The aqueous phase was extracted with ether (2x). The combined organics were washed with water, brine and then dried over Na_2SO_4, filtered and concentrated to give 1.65 g of crude material. Purification by flash chromatography on basic alumina, activity III [hexanes/EtOAc 5%] afforded 0.15 g (36%) of alkene **25**. For spectroscopic data see below.

Optimized olefination procedure:

To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (7.03 g, 19.7 mmol) in THF (30 mL) was added NaHMDS (18.3 mL, 18.3 mmol) dropwise over ~ 20 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes and then cooled to 0 °C at which time a solution of ketone **24** in THF (4 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3.5 hours. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (30 mL). Water (30 mL) and Et_2O (90 mL) were added, and the phases separated. The aqueous layer was extracted with Et_2O (25 mL x 2). The combined organic phase was washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated to give 6.83 g of crude material. Purification by flash chromatography on silica gel [hexanes/EtOAc, 3:1] afforded 0.60 g (80%) of alkene **25**. IR (neat, 4 cm^{-1}): ν = 2977, 2944, 2884, 1464, 1198, 1173, 1080, 1059, 918; $[\alpha]^{20}_{589}$ +101.9° (c 1.245, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.27 (s, 1 H), 5.22 (s, 1 H), 4.57 (dd, *J* = 8.79, 6.32 Hz, 1 H), 4.10 (qAB, *J* = 7.97, 6.32 Hz, 1 H), 3.61 (qAB, *J* = 8.79, 7.97 Hz, 1 H), 3.43 (dt, *J* = 3.85, 0.82 Hz, 1 H), 2.90 (qAB, *J* = 5.77, 4.12 Hz, 1 H), 2.54 (qAB, *J* = 5.77, 2.75 Hz, 1 H), 1.66 (m, 4 H), 0.90 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.0, 113.2, 113.1, 76.7, 69.4, 50.5, 49.4, 29.6, 29.2, 8.1; HRMS (CH_4) *m/z* 199.1326 [$(M + H)^+$; calcd for $C_{11}H_{19}O_3$, 199.1334].

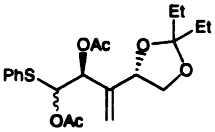
Preparation of hydroxy sulfide (26):



26

To a solution of sodium benzenethiolate (0.17 g, 1.2 mmol) in THF (10 mL) at room temperature was added dropwise (~ 15 minutes) a solution of epoxide **25** (0.19 g, 0.96 mmol) in THF (2 mL). After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous NH_4Cl solution. Et_2O and water were added and the phases were separated. The aqueous phase was extracted with ether (2x). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.34 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 10 %] afforded 0.20 g (67%) of hydroxy sulfide **26** as an oil. IR (neat, 4 cm^{-1}): ν = 3451, 2975, 2940, 2882, 1584, 1482, 1464, 1439, 1356, 1287, 1198, 1173, 1080, 1059, 1026, 918, 739, 691; $[\alpha]^{20}_{589}$ +53.8° (c 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30 (m, 5 H), 5.28 (s, 1 H), 5.24 (s, 1 H), 4.57 (dd, *J* = 8.79, 6.32 Hz, 1 H), 4.17 (m, 1 H), 4.13 (qAB, *J* = 7.97, 6.32 Hz, 1 H), 3.59 (qAB, *J* = 8.79, 7.97 Hz, 1 H), 3.28 (qAB, *J* = 13.74, 8.52 Hz, 1 H), 3.04 (qAB, *J* = 13.74, 8.52 Hz, 1 H), 2.94 (d, *J* = 3.85 Hz, -OH), 1.64 (m, 4 H), 0.89 (t, *J* = 7.42 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.3, 135.0, 130.0, 129.1, 126. 7, 113.2, 113.0, 76.9, 70.4, 69.8, 40.4, 29.7, 29.3, 8.1; HRMS (CH_4) *m/z* 307.1362 [(M - H)$^+$; calcd for $C_{17}H_{23}O_3S$, 307.1368].

Preparation of α-acetoxy sulfide (27) via pummerer rearrangement:



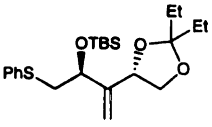
27

To a solution of phenyl sulfide **26** (0.101 g, 0.327 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added dropwise (~10 minutes) a solution of *m*-CPBA (0.056 g, 0.33 mmol) in CH_2Cl_2 (1 mL). After stirring for 5 minutes at –78 °C, the reaction mixture was allowed to warm to room temperature over 30 minutes. The reaction mixture was quenched by washing with 1 M NaOH (0.5 mL x 2), water (2x) and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give 0.12 g (100%) of a yellow oil.

Pummerer Rearrangement:

The above crude sulfoxide and sodium acetate (0.10 g, 1.0 mmol) were dissolved in acetic anhydride (2 mL). The reaction mixture was heated to reflux over 30 minutes and then stirred at reflux for 3 hours. The reaction mixture was concentrated. The resulting residue was diluted with CH_2Cl_2 (10 mL) and filtered to remove the excess sodium acetate. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution (4 mL x 2), water and brine. The combined organic phase was dried over $MgSO_4$, filtered and concentrated. The residue was evaporated from toluene several times under high vacuum to remove the residual acetic anhydride. Purification by flash chromatography on silica gel [hexanes/EtOAc, 10%] afforded 42 mg (38%) of a diastereomeric mixture of α-acetoxy sulfide **27** as a thick yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27-7.49 (m, 10 H) 6.30 (d, J = 5.77 Hz, 1 H), 6.24 (d, J = 5.49 Hz, 1 H), 5.55 (s, 1 H), 5.42 (d, J = 5.77 Hz, 1 H), 5.39 (s, 1 H), 5.35 (d, J = 5.49 Hz, 1 H), 5.25 (s, 2 H), 4.53 (m, 2 H), 4.18 (m, 2 H), 3.58 (m, 2 H), 2.08 (s, 3 H), 2.05 (s, 3 H), 2.03 (s, 3 H), 2.03 (s, 3 H) 1.62 (m, 8 H), 0.90 (t, J = 7.42 Hz, 6 H), 0.89 (t, J = 7.42 Hz, 6 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169. 5, 169.4, 169.2, 169.2, 142.0, 133.6, 133.4, 131.5, 131.2, 129.1, 129.1, 128.6, 128.5, 115.9, 115.4, 113.2, 113.2, 81.7, 79.7, 76.0, 74.1, 73.4, 70.3, 70.2, 29.7, 29.3, 20.9, 20.8, 8.2, 8.0.

Preparation of TBS-ether (29):



29

To a solution of alcohol **26** (0.13 g, 0.42 mmol) in CH_2Cl_2 (5 mL) at –78 °C were added diisopropylethylamine (0.24 mL, 1.3 mmol) and TBSOTf (0.15 mL, 0.67 mmol). After stirring for 20 minutes at –78 °C, the reaction was quenched with water (1 mL) and then allowed to warm to room temperature. The reaction mixture was diluted with Et_2O and saturated aqueous NH_4Cl and then the phases were separated. The organic phase was washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give 0.27 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 10%] afforded 0.13 g (75%) of TBS-ether **29** as an oil. For spectroscopic data see below.

*In situ protection via epoxide **25**:*

To a solution of sodium benzenethiolate (0.59 g, 4.5 mmol) in THF (35 mL) at room temperature was added dropwise (~ 10 minutes) a solution of epoxide **25** (0.68 g, 3.4 mmol) in THF (8 mL). After stirring for 2.5 hours, the reaction was quenched by the addition of a solution of TBSOTf (1.30 mL, 5.47 mmol) and *i*-Pr_2NEt (1.90 mL, 10.9 mmol) in THF (10 mL). After stirring for an additional 5 minutes, Et_2O (70 mL) and water was added, and the phases were separated. The aqueous phase was extracted with ether (2x). The combined organics were was washed with brine, dried over $MgSO_4$, filtered and concentrated to give 1.95 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 0 → 5%] afforded 0.80 g (55%) of TBS-ether **29** as a yellow oil, 0.38 g (36%) of unprotected alcohol **26** as a yellow oil and 59 mg (9%) of recovered epoxide **25** as an oil. For spectroscopic data see below.

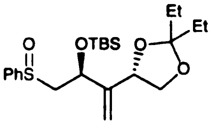
*Oxidation and olefination via **35**:*

To a solution of alcohol **35** (2.26 g, 5.30 mmol) in CH_2Cl_2 (55 mL) at 0 °C was added *i*-Pr_2NEt (5.50 mL, 31.8 mmol), DMSO (10 mL) and a heterogenous solution of SO_3•pyridine (2.53 g, 15.9 mmol) in DMSO (5 mL). The ice bath was removed and the reaction was stirred at room temperature for 30 minutes. The reaction was quenched with the addition of a saturated aqueous solution of

NH_4Cl (90 mL). The reaction mixture was diluted with Et_2O (190 mL), and the phases were separated. The organic phase was washed with brine (25 mL x 2). The combined aqueous phases were extracted with Et_2O (30 mL x 2). The organics were dried over $MgSO_4$, filtered and concentrated to give 3.09 g of crude **36** as a yellow oil.

To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (2.83 g, 7.95 mmol) in THF (30 mL) was added NaHMDS (6.4 mL, 6.4 mmol, 1 M THF) dropwise over ~ 20 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes, cooled to 0 °C and then a solution of crude ketone **36** in THF (7 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 4 hours. The reaction was quenched with the addition of a saturated aqueous NH_4Cl solution (7 mL). Water (7 mL) and Et_2O (110 mL) were added and the phases separated. The organic phase was washed with brine (10 mL x 2), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography on silica gel [hexanes/EtOAc, 10 → 25%] afforded 1.78 g (79%, 2 steps) of alkene **29** as an oil. IR (neat, 4 cm^{-1}): ν = 2930, 2884, 2859, 1471, 1464, 1439, 1256, 1173, 1080, 1005, 920, 837, 777, 737, 691; $[\alpha]^{20}_{589}$ +43.1° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 5.34 (s, 1 H), 5.23 (s, 1 H), 4.57 (dd, J = 9.07, 6.04 Hz, 1 H), 4.27 (dd, J = 7.42, 4.94 Hz, 1 H), 4.10 (dd, J = 7.69, 6.04 Hz, 1 H), 3.52 (dd, J = 9.06, 7.69 Hz, 1 H), 3.05 (qAB, J = 13.46, 4.94 Hz, 1 H), 2.97 (qAB, J = 13.46, 7.42 Hz, 1 H), 1.66 (m, 4 H), 0.89 (m, 6 H), 0.85 (s, 9 H), 0.035 (s, 3 H), -0.021 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.9, 136.8, 129.1, 128.9, 125.9, 112.9, 112.5, 75.2, 73.4, 70.6, 41.6, 29.9, 29.6, 25.8, 25.7, 18.2, 8.2, 8.1, -4.7, -4.9; HRMS (CH_4) m/z 421.2228 [$(M - H)^+$; calcd for $C_{23}H_{37}O_3SSi$, 421.2233].

Preparation of sulfoxide (30):

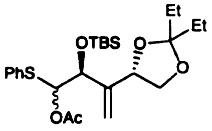


30

To a solution of phenyl sulfide **29** (1.05 g, 2.48 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added dropwise (~10 minutes) a solution of *m*-CPBA (0.43 g, 2.5 mmol) in CH_2Cl_2 (10 mL). After stirring for 5 minutes at –78 °C the reaction mixture was judged complete by TLC, and was then quenched by the addition of 1 M NaOH (3 mL) and allowed to warm to room temperature over 30 minutes. The phases were separated, and the organic phase washed with 1M NaOH (3 mL), water (3 mL x 2) and brine (4 mL), dried over $MgSO_4$, filtered and concentrated to give 1.13 g (100%) of crude sulfoxide **30** as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45 – 7.65 (m, 10 H), 5.45 (s, 1 H), 5.40 (s, 1 H), 5.35 (s, 1 H), 5.34 (s, 1 H), 4.45 – 4.70 (m, 4 H), 4.10 (dd, *J* = 7.42, 6.04 Hz, 1 H), 4.05 (dd, *J* = 7.42, 6.04 Hz, 1 H), 3.57 (dd, *J* = 9.07, 7.69 Hz, 1 H), 3.47 (dd, *J* = 9.07, 7.69 Hz, 1 H), 3.10 (qAB, *J* = 13.19, 6.59 Hz, 1 H), 2.95 (qAB, *J* = 13.19, 6.87 Hz, 1 H), 2.83 (qAB, *J* = 12.91, 2.20 Hz, 1 H), 2.70 (qAB, *J* = 12.91, 10.44 Hz, 1 H), 1.62 (m, 8 H), 0.79 – 0.96 (m, 30 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.1, 147.5, 146.0, 144.5, 132.9, 131.3, 130.8, 129.3, 129.0, 127.4, 127.1, 124.2, 123.6, 115.3, 113.2, 112.7, 75.5, 75.0, 70.6, 70.3, 70.1, 68.2, 66.2, 29.7, 29.4, 25.8, 25.7, 18.2, 18.0, 8.0, -2.9, -4.5, -5.0, -5.2.

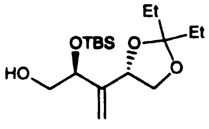
Preparation of α-acetoxy sulfide (31):



31

A solution of trifluoroacetic acid anhydride (0.20 mL, 1.4 mmol) in acetic anhydride (1 mL) was stirred at room temperature for 6 hours. A solution of crude sulfoxide **30** (0.42 g, 0.95 mmol) in Ac_2O (1 mL) was added and followed by the addition of 2,6-lutidine (0.22 mL, 1.9 mmol). After stirring for 15 hours at room temperature, the reaction was concentrated to give a dark red residue. CH_2Cl_2 was added to the residue and the solution was washed with a saturated aqueous $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to give a red oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 0.34 g (80%) of α-acetoxy sulfide **31** as a diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22- 7.46 (m, 10 H) 6.14 (d, *J* = 4.12 Hz, 1 H), 6.10 (d, *J* = 7.14 Hz, 1 H), 5.55 (s, 1 H), 5.50 (s, 1 H), 5.43 (s, 1 H), 5.22 (s, 1 H), 4.62 (m, 2 H), 4.42 (d, *J* = 3.85 Hz, 1 H), 4.35 (d, *J* = 7.14 Hz, 1 H), 4.21 (dd, *J* = 7.69, 6.04 Hz, 1 H), 4.14 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.59 (dd, *J* = 9.07, 7.69 Hz, 1 H), 3.54 (dd, *J* = 9.07, 7.69 Hz, 1 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.65 (m, 8 H), 0.90 (m, 30 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.03 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.5, 169.4, 169.2, 169.2, 142.0, 133.6, 133.4, 131.5, 131.2, 129.1, 129.1, 128.6, 128.5, 115.9, 115.4, 113.2, 113.1, 81.7, 79.7, 76.0, 74.0, 73.4, 70.3, 70.2, 29.7, 29.3, 20.9, 20.8, 8.2, 8.0; HRMS (CI) *m/z* 479.2277 [(M - H)$^+$; calcd for $C_{25}H_{39}O_5SSi$, 479.2287].

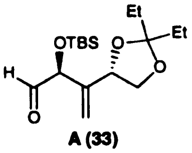
Reduction of α-acetoxy sulfide (31) to give alcohol (32):



32

To a solution of α-acetoxy sulfide **31** (0.80g, 1.8 mmol) in THF (30 mL) at 0 °C was added $LiBEt_3H$ (Super-Hydride®) (5.6 mL, 5.6 mmol, 1.0 M THF) dropwise (~15 minutes). The ice bath was removed and the reaction stirred at room temperature for 45 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (6 mL) and glycerol (1.7 mL, 0.3 mL/mmol). After stirring for 4 hours, the reaction mixture was diluted with Et_2O (30 mL) and the phases separated. The organic phase was washed with brine (5 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 1.2 g of a greenish-yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 25%] afforded 0.46 g (79%) of alcohol **32** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 5.38 (s, 1 H), 5.26 (s, 1 H), 4.52 (dd, *J* = 8.79, 6.59 Hz, 1 H), 4.22 (dd, *J* = 6.59, 3.85 Hz, 1 H), 4.12 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.53 (dd, *J* = 8.79, 7.69 Hz, 1 H), 3.53 (m, 1 H), 3.44 (m, 1 H), 1.65 (m, 4 H), 0.89 (m, 6 H) 0.89 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.1, 113.7, 112.8, 75.7, 74.5, 70.2, 66.9, 29.8, 29.4, 25.8, 18.1, 8.2, 8.1, -4.6, -5.1; HRMS (CI) *m/z* 331.2311 [(M + H)$^+$; calcd for $C_{17}H_{35}O_4Si$, 331.2305].

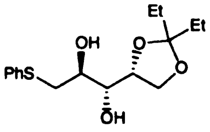
Oxidation of alcohol (32) to give aldehyde A (33):



A (33)

To a solution of oxalyl chloride (0.10 mL, 1.2 mmol) in CH_2Cl_2 (4 mL) at -78 °C was slowly added a solution of DMSO (0.17 mL, 2.4 mmol) in CH_2Cl_2 (0.1 mL). After 5 minutes, a solution of alcohol **32** (0.195 g, 0.594 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise. After another 15 minutes, *i*-Pr_2NEt (0.83 mL, 4.8 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction was diluted with ether (12 mL) and water (3 mL), and the phases were separated. The organic phase was washed with water (3 mL) and brine (3 mL). The combined aqueous phases were extracted with Et_2O (5 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated to give 0.22 g a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 0.16 g (82%) of aldehyde **33** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 9.40 (d, *J* = 1.65 Hz, 1 H), 5.49 (s, 1 H), 5.33 (d, *J* = 0.82 Hz, 1 H), 4.52 (dd, *J* = 8.79, 6.32 Hz, 1 H), 4.41 (s, 1 H), 4.07 (dd, *J* = 7.69, 6.32 Hz, 1 H), 3.60 (dd, *J* = 9.07, 7.69 Hz, 1 H), 1.68 (m, 4 H), 0.90 (s, 9 H), 0.89 (m, 6 H), 0.07 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.7, 142.5, 115.9, 113.3, 79.4, 76.1, 69.5, 29.7, 29.2, 25.6, 18.2, 8.2, 8.0, -5.0.

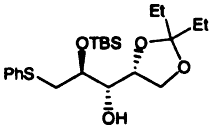
Preparation of sulfide diol (34):



34

Aqueous NaOH and *t*-BuOH were deoxygenated prior to use by the rapid passage of nitrogen through the solvent for at least 30 minutes. A solution of epoxy alcohol **21** (2.0 g, 9.9 mmol) in 50 mL of 0.5 M NaOH and 50 mL of *t*-BuOH was immersed in a preheated (~88 °C) oil bath. The reaction mixture was stirred vigorously. Thiophenol (1.42 mL, 13.8 mmol) was dissolved in *t*-BuOH (20 mL) and added dropwise over 2 hours. After stirring for an additional 10 minutes, the reaction was allowed to cool to room temperature and was then neutralized with a saturated aqueous NH_4Cl solution (50 mL). The phases were separated, and the aqueous phase extracted with CH_2Cl_2 (75 mL x 5). The combined organic extracts were washed with a saturated aqueous NH_4Cl solution (50 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated to give 4.6 g of yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 2.1 g (69%) of diol sulfide **34**. IR (neat, 4 cm^{-1}): ν = 3460, 2973, 2928, 2884, 1584, 1481, 1464, 1440, 1378, 1337, 1292, 1172, 1092, 1080, 1026, 912, 740; $[\alpha]_{589}^{20}$ +31.0° (c 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.3 (m, 5 H), 4.25 (ddd, *J* = 7.69, 6.59, 4.40 Hz, 1 H), 4.05 (dd, *J* = 8.2, 6.59 Hz, 1 H), 3.85 (app t, *J* = 7.97 Hz, 1 H), 3.65 (m, 1 H), 3.49 (m, 1 H), 3.56 (ABq, *J* = 14.01, 3.57 Hz, 1 H), 2.99 (ABq, *J* = 14.01, 8.52 Hz, 1 H), 2.76 (d, *J* = 5.22 Hz, -OH), 2.52 (d, *J* = 6.32 Hz, -OH), 1.64, (m, 4 H), 0.88 (t, *J* = 7.14 Hz, 3 H), 0.86 (t, *J* = 7.14 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.8, 129.8, 129.1, 126.6, 113.0, 76.3, 72.9, 70.9, 66.7, 38.7, 29.5, 28.9, 8.2, 8.0; HRMS (EI) *m/z* 312.1403 [M^+; calcd for $C_{16}H_{24}O_4S$, 312.1395].

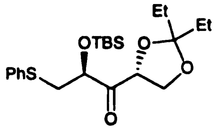
Selective mono-protection of diol (34) to give TBS-ether (35):



35

To a solution of diol sulfide **34** (4.01 g, 12.8 mmol) in CH_2Cl_2 (180 mL) at to 0 °C were added *i*-Pr_2NEt (2.67 mL, 15.4 mmol) and TBSTOf (3.23 mL, 14.1 mmol). The reaction mixture was stirred for ~1.5 hours and then quenched by the addition of an aqueous solution of NH_4Cl (10 mL). The reaction mixture was concentrated to ~ half volume. Water (6 mL) and Et_2O (160 mL) were and the phases were separated. The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to give 5.26 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/ EtOAc 5% → 10%] to afford 3.82 g (70%) of mono-protected TBS-ether **35** as an oil and 0.84 g (21%) of recovered diol **34**. For **35**: IR (neat, 4 cm^{-1}): ν = 2931, 2886, 2858, 1585, 1482, 1472, 1464, 1439, 1360, 1253, 1172, 1082, 923, 837, 777, 738; $[\alpha]_{589}^{20}$ –25.0° (c 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.35 (m, 5 H), 4.29 (dt, *J* = 3.02, 6.59 Hz, 1 H), 4.00 (dd, *J* = 6.59, 7.69 Hz, 1 H), 3.81 (app t, *J* = 7.69 Hz, 1 H), 3.70 (dt, *J* = 7.42, 3.30 Hz, 1 H), 3.62 (dt, *J* = 3.30, 7.69 Hz, 1 H), 3.33 (ABq, *J* = 13.18, 4.39 Hz, 1 H), 3.21 (ABq, *J* = 13.18, 4.39 Hz, 1 H), 2.32 (d, *J* = 7.97 Hz, -OH), 1.61 (m, 4 H), 0.92 (m, 15 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 129.2, 128.8, 125.8, 113.1, 74.6, 72.5, 72.1, 66.6, 38.6, 29.2, 28.8, 25.8, 18.1, 8.3, 8.0, -4.3, -4.8; HRMS (EI) *m/z* 426.2267 [M^+; calcd for $C_{22}H_{38}O_4SSi$, 426.2260].

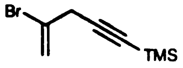
Preparation of ketone (36):



36

To a solution of alcohol **35** (3.82 g, 8.95 mmol) in CH_2Cl_2 (90 mL) at 0 °C were added *i*-Pr_2NEt (9.35 mL, 53.7 mmol), DMSO (18 mL) and a heterogenous solution of SO_3•pyridine (4.27 g, 26.9 mmol) in DMSO (7 mL). The ice bath was removed and stirred at room temperature for 30 minutes. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (65 mL). The reaction mixture was diluted with Et_2O (150 mL) and the phases were separated. The organic phase was washed with brine (20 mL x 2). The combined aqueous phases were extracted with Et_2O (30 mL x 2). The organics were dried over $MgSO_4$, filtered and concentrated to give 4.73 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to afford 2.73 g (72%) of ketone **36** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2932, 2884, 2859, 1734, 1472, 1464, 1441, 1362, 1256, 1201, 1173, 1086, 1026, 914, 839, 810, 779, 741; $[\alpha]^{20}_{589}$ +6.7° (c 1.015, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.3 (m, 5 H), 4.84 (dd, *J* = 7.69, 7.14 Hz, 1 H), 4.54 (t, *J* = 5.22 Hz, 1 H), 4.27 (dd, *J* = 8.52, 7.69 Hz, 1 H), 4.07 (dd, *J* = 8.52, 7.14 Hz, 1 H), 3.35 (ABq, *J* = 13.19, 5.22 Hz, 1 H), 3.18 (ABq, *J* = 13.19, 5.22 Hz, 1 H), 1.63 (dq, *J* = 3.30, 7.42 Hz, 4 H), 0.88 (m, 15 H), 0.08 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.5, 135.9, 129.6, 128.9, 126.4, 114.8, 78.4, 75.2, 66.0, 37.9, 29.2, 28.7, 25.7, 18.1, 8.0, -4.8, -5.0; HRMS (EI) *m/z* 395.1712 [(M - Et)$^+$; calcd for $C_{20}H_{31}O_4SSi$, 395.1718].

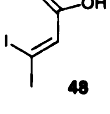
Preparation of fragment B:



B

To a cold (0 °C) solution of EtMgBr (11 mL, 33 mmol, 3.0 M Et_2O) was added dropwise (~45 minutes) a solution of trimethylsilylacetylene (4.2 mL, 30 mmol) in THF (45 mL). After stirring for an additional 10 minutes at 0 °C, the reaction was immersed into a preheated oil bath (55 °C) and stirred for 1 hour and then recooled to 0 °C. The septum was quickly removed and CuI (0.11 g, 0.60 mmol) was added. The reaction vessel was reimmersed into the oil bath (55 °C) and 2,3-dibromopropene (3.7 mL, 36 mmol) was added dropwise over 1.5 hours. After stirring an additional 4 hours, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL) and then diluted with Et_2O (125 mL). The phases were separated, and the organics were washed with brine (5 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 9.73 g of a reddish-yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to afford 6.02 g (93%) of fragment **B** as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 6.0$ (q, $J = 1.65$ Hz, 1 H), 5.53 (q, $J = 1.65$ Hz, 1 H), 3.35 (t, $J = 1.65$ Hz, 2 H), 0.16 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 126.7, 117.9, 101.0, 88.9, 32.7, -0.12$; HRMS (EI) *m/z* 215.9967 [M^+; calcd for $C_8H_{13}BrSi$, 215.9970].

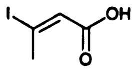
Preparation of (Z)-β-iodo acid (48):



48

Ethyl 2-butynoate (4.16 mL, 35.7 mmol) was added to a sealed tube containing hydriodic acid (7 mL, 48% aq) and heated to 110 °C. After heating for 12 hours, the sealed tube was removed from the oil bath and allowed to cool to room temperature. The resultant crystals were filtered with the aid of a glass frit filter and washed three times with cold water. If crystallization was slow the sealed tube was inserted into an ice bath. The wet crystals were dried overnight in vacuo over KOH to give 3.0 g (40%) of (Z)-β-iodo acid **48** as a white solid. The aqueous filtrate was diluted with Et_2O and separated the phases. The aqueous phase was extracted twice with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 4.45 g (52%) of (Z)-β-iodo ethyl ester **49**. Resubjection of the ethyl ester to the reaction conditions afforded the desired (Z)-β-iodo acid **48** quantitatively. mp = 66 °C; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 12.54$ (s, 1 H), 6.42 (s, 1 H), 3.32 (s, 1 H). The spectroscopic data is in complete agreement with the reported literature.[34]

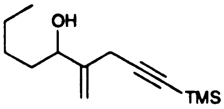
Isomerization of (Z)-β-iodo acid (48) to give (E)-β-iodo acid fragment (D):



D

The (Z)-β-iodo acid **48** was heated to 135 °C in a sealed tube for 24 hours. From ^1H NMR, the isomerization was not total but gave the desired E-isomer (**D**) in a 3:1 ratio. With careful flash chromatography on silica gel [hexanes/EtOAc 25%, 1% MeOH] the two isomers were separated. mp = 66 °C; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 12.54$ (s, 1 H), 6.42 (s, 1 H), 3.32 (s, 1 H). The spectroscopic data is in complete agreement with the reported literature.[34]

Preparation of alcohol (50) [model A/B coupling]:



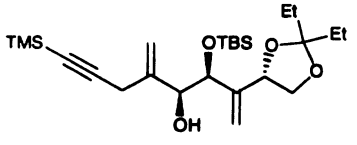
50

Vinyl bromide **B** (0.20 g, 0.92 mmol) and $MgBr_2{\bullet}Et_2O$ (0.39 g, 1.5 mmol) were dissolved in THF (10 mL) and cooled to –78 °C. *t*-BuLi (1.1 mL, 1.8 mmol, 1.7 M pentane) was added dropwise over ~8 minutes. After stirring for an additional 5 minutes at –78 °C, valeraldehyde (0.065 mL, 0.61 mmol) was added dropwise. After stirring for 1 hour at –78 °C, the reaction was allowed to warm to room temperature over 30 minutes and then stirred for an additional 15 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (2 mL). Et_2O (20 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (2x). The combined organics were washed with brine, dried over $MgSO_4$, filtered and concentrated to give 0.26 g of an yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to afford 75.5 mg (55%) of alcohol **50** and 43.3 mg (32%) of allylic addition by-product, alcohol **51**. For spectroscopic data see below.

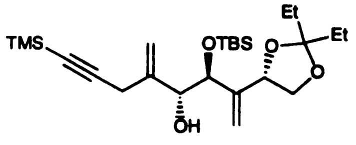
Zincate derivative:

t-BuLi (0.90 mL, 1.5 mmol, 1.7 M pentane) was added dropwise to Et_2O (3 mL) at –78 °C. A solution of vinyl bromide **B** (0.16 g, 0.74 mmol) in Et_2O (2 mL) was added dropwise to the *t*-BuLi solution. After stirring for 10 minutes, $ZnMe_2$ (0.38 mL, 0.75 mmol, 2.0 M toluene) was added. After stirring for an additional 15 minutes, valeraldehyde (0.054 mL, 0.50 mmol) was added dropwise. After stirring for 1 hour at –78 °C, the reaction was allowed to warm to room temperature over 30 minutes and then stirred for an additional 15 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1 mL). Et_2O (15 mL) was added and the phases separated. The organic phase was washed with water (3 mL x 2). The combined aqueous phases were extracted with Et_2O (5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to give 0.17 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to afford 0.10 g (90%) of alcohol **50** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.22 (dd, J = 3.02, 1.37 Hz, 1 H), 5.10 (t, J = 1.10 Hz, 1 H), 4.15 (t, J = 6.59 Hz, 1 H), 3.08 (ABq t, J = 19.79, 1.37, 1 H), 2.96 (ABq t, J = 19.79, 1.37 Hz, 1 H), 1.55 (m, 2 H), 1.30 (m, 4 H), 0.88 (t, J = 7.14 Hz, 3 H), 0.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.1, 112.3, 87.7, 74.9, 34.8, 27.8, 22.6, 14.0, 0.04.

Preparation of alcohol (52) [fragment A/B coupling]:



52a



52b

Vinyl bromide **B** (0.12 g, 0.59 mmol) and $MgBr_2 \bullet Et_2O$ (0.30 g, 1.2 mmol) were dissolved in THF (6 mL) and cooled to –78 °C. *t*-BuLi (0.70 mL, 1.2 mmol, 1.7 M pentane) was added dropwise over ~5 minutes. After stirring for an additional 10 minutes, a solution of aldehyde **33** (38 mg, 0.12 mmol) in THF (1 mL) was added dropwise. After stirring for 1.5 hours at –78 °C, the reaction was allowed to warm to room temperature over 30 minutes and then stirred an additional 15 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1 mL). Et_2O was added, and the phases separated. The aqueous phase was extracted with Et_2O (2x). The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated to give 76 mg of a crude yellow oil. The crude residue was purified by flash chromatography on silica gel [Hex/EtOAc 5%] to afford

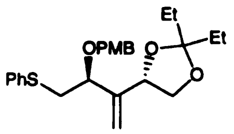
Zincate derivative:

t-BuLi (0.86 mL, 1.5 mmol, 1.7 M pentane) was added dropwise to Et_2O (3 mL) at –78 °C. A solution of vinyl bromide **B** (0.16 g, 0.74 mmol) in Et_2O (2 mL) was added dropwise to the *t*-BuLi solution. After stirring for 10 minutes, $ZnMe_2$ (0.50 mL, 1.0 mmol, 2.0 M toluene) was added and the reaction stirred for an additional 15 minutes. In a separate flask, to a –78 °C solution of aldehyde **33** (0.16 g, 0.487 mmol) in Et_2O (3 mL) was added $ZnMe_2$ (0.25 mL, 0.50 mmol, 2.0 M pentane) and the mixture stirred for 15 minutes. The zincate derivative of fragment **B** was quickly transferred via cannula to the pre-complexed aldehyde solution. After stirring for 1 hour at –78 °C, the reaction was allowed to warm to room temperature over 60 minutes and was then quenched by the addition of a saturated aqueous NH_4Cl solution (1.5 mL). Et_2O (15 mL) was added and the phases separated. The organic phase was washed with water (3 mL x 2). The combined aqueous phases were extracted with Et_2O (5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to give 0.16 g of a yellow oil. Purification by flash chromatography on silica gel [Hex/EtOAc 5%] afforded several products.

52a: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.45$ (s, 1 H), 5.30 (s, 1 H), 5.25 (s, 1 H), 5.12 (s, 1 H), 4.55 (dd, $J = 9.07, 5.77$ Hz, 1 H), 4.19 (dd, $J = 7.59, 5.77$ Hz, 1 H), 4.17 (d, $J = 4.67$ Hz, 1 H), 3.99 (app t, $J = 5.22 / 4.95$ Hz, 1 H), 3.50 (dd, $J = 9.07, 7.69$ Hz, 1 H), 3.10 (ABq, $J = 19.50$ Hz, 1 H), 2.98 (ABq, $J = 19.78$ Hz, 1 H), 2.78 (d, $J = 5.77$ Hz, 1 H), 1.68 (m, 4 H), 0.90 (m, 6 H), 0.89 (s, 9 H), 0.14 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 146.2$, 142.5, 114.4, 114.2, 113.6, 103.3, 77.4, 76.3, 75.3, 75.1, 70.8, 38.6, 29.9, 29.6, 25.8, 18.2, 8.1 (2), 0.03, -4.5, -5.1; HRMS (EI) *m/z* 466.2922 [M^+; calcd for $C_{25}H_{46}O_4Si_2$, 466.2935].

52b: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 5.49$ (s, 1 H), 5.31 (d, $J = 1.37$ Hz, 1 H), 5.25 (m, 1 H), 5.15 (s, 1 H), 4.58 (dd, $J = 9.07, 5.77$ Hz, 1 H), 4.20 – 4.14 (m, 2 H), 4.07 (dd, $J = 3.85, 6.59$ Hz, 1 H), 3.59 (dd, $J = 9.0, 7.69$ Hz, 1 H), 3.12 (ABq, $J = 19.78$ Hz, 1 H), 2.97 (ABq, $J = 19.50$ Hz, 1 H), 2.46 (d, $J = 3.85$ Hz, 1 H), 1.65 (m, 4 H), 0.90 (m, 6 H), 0.86 (s, 9 H), 0.14 (s, 9 H), 0.04 (s, 3 H), 0.01 (s, 3 H).

Preparation of PMB-ether (54):

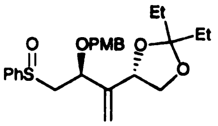


54

To a stirred suspension of NaH (0.23 g, 8.9 mmol, 95% in mineral oil) in DMSO (10 mL) was added dropwise a solution of alcohol **29** (1.84 g, 5.96 mmol) in THF (30 mL) at room temperature. After stirring for 25 minutes, *p*-methoxybenzyl chloride (1.30 mL, 9.54 mmol) was added. After stirring for 3.5

hours, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (4 mL). The reaction mixture was diluted with Et_2O (80 mL) and water (5 mL) and the phases were separated. The organic phase was washed with brine (5 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 3.53 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5% → 10%] afforded 2.36 g (93%) of PMB-ether **54** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2973, 2938, 2880, 1613, 1586, 1514, 1481, 1464, 1439, 1302, 1246, 1173, 1080, 1059, 1038, 920, 822, 741, 693; $[\alpha]^{20}_{589}$ +103.4° (c 0.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 – 7.30 (m, 7 H), 6.84 (d, J = 8.79 Hz, 2 H), 5.54 (app t, J = 1.10 Hz, 1 H), 5.29 (s, 1 H), 4.53 (dd, J = 8.79, 5.49 H, 1 H), 4.51 (ABq, J = 11.26 Hz, 1 H), 4.26 (ABq, J = 11.26 Hz, 1 H), 4.07 (dd, J = 7.69, 6.04 Hz, 1 H), 3.96 (dd, J = 7.69, 5.49 Hz, 1 H), 3.78 (s, 3 H), 3.51 (dd, J = 9.07, 7.69 Hz, 1 H), 3.11 (dABq, J = 7.97, 13.46 Hz, 1 H), 2.99 (dABq, J = 5.22, 13.46 Hz, 1 H), 1.65 (m, 4 H), 0.91 (t, J = 7.42 Hz, 3 H), 0.90 (t, J = 7.42 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 145.1, 136.2, 129.9, 129.6, 129.5, 128.9, 126.1, 115.1, 113.7, 112.7, 78.5, 75.3, 70.6, 70.5, 55.3, 69.0, 29.8, 29.5, 8.2, 8.1; HRMS (CI) *m/z* 429.2096 [(M + H)$^+$; calcd for $C_{25}H_{33}O_4S$, 429.2100].

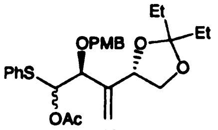
Preparation of sulfoxide (55):



55

To a solution of phenyl sulfide **54** (2.34 g, 5.46 mmol) in CH_2Cl_2 (120 mL) at –78 °C was added dropwise (~20 minutes) a solution of *m*-CPBA (1.13 g, 6.55 mmol) in CH_2Cl_2 (25 mL). After stirring for 10 minutes the reaction was judged complete by TLC. The reaction was quenched by the addition of 1M NaOH (6.5 mL). The reaction mixture was allowed to warm to room temperature and the phases were separated. The organic phase was washed with 1 M NaOH (6.5 mL), water (10 mL x 2) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 2.43 g (100%) of a cloudy oil, which was used without further purification.

Preparation of α-acetoxy sulfide (56):

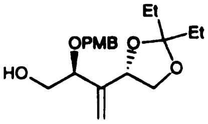


56

Trifluroacetic anhydride (1.15 mL, 2.69 mmol) was dissolved in acetic anhydride (5.5 mL) and the solution stirred at room temperature for 8 hours. A solution of crude sulfoxide **55** (2.43 g, 5.46 mmol) in Et_2O/Ac_2O (5 mL) was added and after a few minutes 2,6-lutidine (1.27 mL, 10.9 mmol) was added. After stirring for 12 hours at room temperature, the reaction was concentrated under high vacuum. CH_2Cl_2 (40 mL) was added and the solution was then washed with a saturated aqueous $NaHCO_3$ solution (5 mL x 3) and brine (5 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 3.24 g of a dark red oil. Purification by flash chromatography on silica gel [hexanes/EtOAc, 10%] afforded 2.03 g (76%) of α-acetoxy sulfide **56** as a thick yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.41$ (m, 4 H), 7.25 (m, 10 H), 6.84 (d, $J = 8.79$ Hz, 4 H), 6.23 (d, $J = 5.49$ Hz, 1 H), 6.13 (d, $J = 5.77$ Hz, 1 H), 5.64 (s, 1 H), 5.57 (app t, $J = 1.10$ Hz, 1 H), 5.44 (s, 1 H), 5.34 (s, 1 H), 4.57 (m, 4 H), 4.30 (d, $J = 11.26$ Hz, 1 H), 4.28 (ABq, $J = 11.54$ Hz, 1 H), 3.99 - 4.13 (m, 4 H), 3.79

(s, 6 H), 3.57 (dd, *J* = 9.07, 7.97 Hz, 1 H), 3.50 (dd, *J* = 9.07, 7.97 Hz, 1 H), 2.20 (s, 3 H), 1.96 (s, 3 H), 1.65 (m, 8 H), 0.90 (m, 12 H)

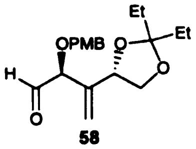
Reduction of α-acetoxy sulfide to give alcohol (57):



57

To a cold (0 °C) solution of α-acetoxy sulfide **56** (2.0 g, 4.1 mmol) in THF (55 mL) was added dropwise (~20 minutes) Super-Hydride® (13.6 mL, 13.6 mmol, 1.0 M THF). The ice bath was removed and the reaction stirred at room temperature for 45 minutes. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (12 mL) and glycerol (4.1 mL, 0.3 mL/mmol). The reaction mixture was diluted with Et_2O (80 mL) and stirred for several hours. The phases were separated, and the organic phase was washed with brine (5 mL x 2), dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 1.2 g (87%) of alcohol **57** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3466, 2973, 2940, 2881, 1613, 1515, 1465, 1249, 1174, 1077, 1036, 920, 823; $[\alpha]^{20}_{589}$ +50.4 (c 0.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 5.53 (app t, *J* = 1.10 Hz, 1 H), 5.35 (s, 1 H), 4.55 (ABq, *J* = 11.26 Hz, 1 H), 4.53 (dd, *J* = 8.24, 6.32 Hz, 1 H), 4.26 (ABq, *J* = 11.26 Hz, 1 H), 4.12 (dd, *J* = 7.69, 6.32 Hz, 1 H), 3.98 (dd, *J* = 7.14, 4.40 Hz, 1 H), 3.78 (s, 3 H), 3.52 (m, 3 H), 1.68 (m, 4 H), 0.93 (t, *J* = 7.42 Hz, 3 H), 0.89 (t, *J* = 7.42 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 143.6, 129.8, 129.6, 115.4, 113.9, 113.0, 80.3, 75.9, 70.4, 70.1, 65.5, 55.2, 29.8, 29.3, 8.2, 8.1; HRMS (CI) *m/z* 203.1280 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

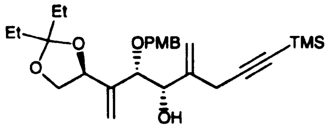
Oxidation of alcohol (57) to give aldehyde (58):



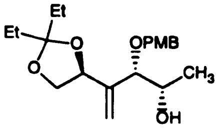
58

To a stirred solution of the Dess-Martin periodinane (0.28 g, 0.65 mmol) in CH_2Cl_2 (10 mL) were added pyridine (0.053 mL, 0.653 mmol) and a solution of alcohol **57** (0.20 g, 0.59 mmol) in CH_2Cl_2 (0.5 mL). The reaction stirred at room temperature until judged complete by TLC (~1 hour). The reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% $Na_2S_2O_3$ (1:1) solution (5 mL) and diluted with Et_2O (25mL). After stirring for 1 hour, the phases were separated. The organic phase was washed with water (2 mL), aqueous saturated $CuSO_4$ solution (2 mL x 2), water (2 mL) and brine (2 mL). The organics were dried over Na_2SO_4, filtered and concentrated to give 0.18 g (90%) of aldehyde **58** as a yellow oil. $[\alpha]^{20}_{589}$ +6.9° (c 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 1.65 Hz, 1 H), 7.25 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 5.61 (app t, *J* = 1.10 Hz, 1 H), 5.34 (d, *J* = 0.55 Hz, 1 H), 4.58 (ABq, *J* = 11.54 Hz, 1 H), 4.52 (dd, *J* = 8.79, 6.32 Hz, 1 H), 4.43 (ABq, *J* = 11.54 Hz, 1 H), 4.23 (s, 1 H), 4.05 (dd, *J* = 7.97, 6.32 Hz, 1 H), 3.79 (s, 3 H), 3.60 (dd, *J* = 9.07, 7.97 Hz, 1 H), 1.68 (m, 4 H), 0.93 (t, *J* = 7.42 Hz, 3 H), 0.89 (t, *J* = 7.42 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.1, 159.5, 140.4, 129.8, 128.8, 118.2, 113.9, 113.3, 83.9, 76.3, 70.9, 69.5, 55.3, 29.7, 29.2, 8.3, 8.0.

Preparation of alcohol (60) [fragment A/B coupling]:



60



61

t-BuLi (0.30 mL, 0.50 mmol, 1.7 M pentane) was added dropwise to Et_2O (1 mL) at –78 °C. A solution of vinyl bromide **B** (0.055 g, 0.25 mmol) in Et_2O (0.7 mL) was added dropwise (~7 minutes) to the *t*-BuLi solution. After stirring for 10 minutes, $ZnMe_2$ (0.17 mL, 0.34 mmol, 2.0 M toluene) was added. In a separate flask, to a solution of aldehyde **58** (0.056 g, 0.167 mmol) in Et_2O (1 mL) at –78 °C was added $ZnMe_2$ (0.09 mL, 0.167 mmol, 2.0 M toluene). After both solutions had stirred for 15 minutes at –78 °C, the zinc reagent was quickly transferred via cannula to the pre-complexed aldehyde solution. After stirring for 1.5 hours at -78 °C, the reaction was allowed to warm to room temperature over 60 minutes and was then quenched by the addition of a saturated aqueous NH_4Cl solution (1mL) dropwise. Et_2O (5 mL) was added, and the phases were separated. The organic phase was washed with water (1 mL x 2) and brine (1 mL). The combined aqueous phases were extracted with Et_2O (5 mL). The combined organics were washed with brine (3 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] afforded 32 mg (41%) of alcohol **60** as a yellow oil.

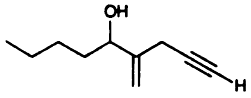
Grignard protocol:

t-BuLi (3.8 mL, 6.56 mmol, 1.7 M pentane) was added dropwise to Et_2O (15 mL) at –78 °C. A solution of vinyl bromide **B** (0.70 g, 3.2 mmol) in Et_2O (6 mL) was added dropwise (~12 minutes) to the *t*-BuLi solution. After stirring for 10 minutes, $MgBr_2\bullet Et_2O$ (3.5 mL, 1.0 M Et_2O/PhH (3:1), 3.5 mmol) was added and stirred at –78 °C for 15 minutes and then at 0 °C for 10 minutes and then the reaction temperature lowered back to –78 °C. In a separate flask, to a solution of aldehyde **58** (0.72 g, 2.15 mmol) in Et_2O/PhH (3:1) (2mL) at 0 °C was added $MgBr_2\bullet Et_2O$ (2.2 mL, 1.0 M Et_2O/PhH (3:1), 2.2 mmol). The aldehyde solution was transferred via cannula to the Grignard solution. After stirring for 1 hour at -78 °C, the reaction was allowed to warm to 0 °C and stirred for 2 hours. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (2 mL) and water (2 mL). Et_2O (2 mL) was added, and the phases were separated. The organic phase was washed with brine (2x). The combined aqueous phases were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.2 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 10%, 1% Et_3N] to give 0.65 g (64%) of alcohol **60** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3546, 2969, 2883, 2178, 1613, 1515, 1465, 1303, 1250, 1173, 1078, 1036, 918, 843, 761; $[\alpha]_{589}^{20}$ +55.1° (c 0.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, J = 8.52 Hz, 2 H), 6.85 (d, J = 8.52 Hz, 2 H), 5.63 (t, J = 1.37 Hz, 1 H), 5.35 (s, 1 H), 5.33 (d, J = 1.37 Hz, 1 H), 5.13 (s, 1 H), 4.55 (ABq, J = 10.99 Hz, 1 H), 4.51 (dd, J = 9.07, 6.04 Hz, 1 H), 4.22 (ABq, J = 10.99 Hz, 1 H), 4.15 (dd, J = 7.69, 6.04 Hz, 1 H), 4.08 (m, 1 H), 3.84 (d, J = 6.04 Hz, 1 H), 3.79 (s, 3 H), 3.51 (dd, J = 9.07, 7.69 Hz, 1 H), 3.07 (ABq, J = 19.78 Hz, 1 H), 2.86 (d, J = 3.57 Hz, 1 H), 2.88 (ABq, J = 19.78 Hz, 1 H), 1.65 (m, 4 H), 0.94 (t, J = 7.42 Hz, 3 H), 0.90 (t, J = 7.42 Hz, 3

H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 143.5, 141.9, 129.7, 129.5, 116.3, 115.2, 113.9, 112.8, 103.3, 87.7, 81.3, 76.2, 75.3, 70.6, 70.5, 55.2, 29.9, 29.5, 23.2, 8.2, 8.1, 0.01; HRMS (EI) *m/z* 443.2248 [(M - Et)$^+$; calcd for $C_{25}H_{35}O_5Si$, 443.2254].

By-product alcohol **61**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 5.66 (t, *J* = 1.37 Hz, 1 H), 5.31 (d, *J* = 1.10 Hz, 1 H), 4.56 (m, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.22 (ABq, *J* = 10.99 Hz, 1 H), 4.11 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.79 (s, 3 H), 3.60 (m, 2 H), 3.49 (dd, *J* = 9.07, 7.69 Hz, 1 H), 2.78 (br s, -OH), 1.68 (m, 4 H), 1.06 (d, *J* = 6.04 Hz, 3 H), 0.93 (t, *J* = 7.42 Hz, 3 H), 0.91 (t, *J* = 7.42 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 143.7, 129.7, 117.4, 113.9, 112.7, 86.1, 74.9, 70.9, 70.3, 68.9, 55.3, 29.9, 29.6, 18.3, 8.2, 8.1.

TMS-deprotection to give alkyne (62):

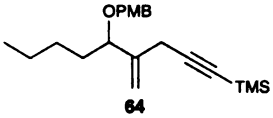


62

To a cold (0 °C) solution of TMS-alkyne **50** (0.127 g, 0.566 mmol) in THF (5 mL) was added dropwise (~5 minutes) an acetic acid buffered TBAF solution (1.05:1) (0.60 mL, 0.60 mmol, 1.0 M THF). After stirring for 2 hours, Et_2O (12 mL) was added and then the reaction was quenched by the addition of water (2 mL). The phases were separated, and the organic phase was washed with brine (1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.12 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 78 mg (90%) of alkyne **62** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ

= 0.88 (t, J = 7.14 Hz, 3 H), 1.30 (m, 4 H), 1.55 (m, 2 H), 2.13 (t, J = 2.75 Hz, 1 H), 2.92 (dtABq, J = 2.75, 1.37, 19.50 Hz, 1 H), 3.06 (dtABq, J = 2.75, 1.10, 19.50 Hz, 1 H), 4.15 (t, J = 6.59 Hz, 1 H), 5.12 (m, 1 H), 5.25 (dt, J = 1.65, 1.37 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.9, 112.3, 81.3, 74.8, 71.0, 34.7, 27.7, 22.5, 21.0, 14.0.

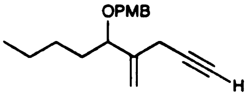
Preparation of PMB-ether (64):



64

To a solution of alcohol **50** (0.14 g, 0.624 mmol) and *p*-$CH_3OPhCH_2OC(NH)CCl_3$ (0.70 g, 2.49 mmol)[78] in cyclohexane/CH_2Cl_2 (1:1) (4 mL) was added CSA (15 mg, 0.062mmol). The reaction vessel was immersed into a preheated oil bath (~40 °C). After stirring for 3 hours, more CSA (20 mg) was added. After stirring for a total of 12 hours, the reaction mixture was allowed to cool to room temperature, diluted with ether (15 mL), and quenched by the addition of a saturated aqueous $NaHCO_3$ solution (2 mL). The phases were separated, and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 mL x 2) and brine (3 mL), dried over $MgSO_4$, filtered and concentrated to give a white-yellow solid. Hexanes were added to the residue which was stirred for 30 minutes and then filtered. The solid was washed several times with hexanes. The filtrate was concentrated to give 0.43 g of an yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 0.11 g (51%) of PMB-ether **64** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.17 (s, 9 H), 0.85 (t, J = 6.87 Hz, 3 H), 1.30 (m, 4 H), 1.55 (m, 2 H), 2.93 (ABq, J = 20.33 Hz, 1 H), 3.03 (ABq, *J* = 20.05 Hz, 1 H), 3.78 (m, 1 H), 3.79 (s, 3 H), 4.16 (ABq, *J* = 11.26 Hz, 1 H), 4.42 (ABq, *J* = 11.54 Hz, 1 H), 5.11 (d, *J* = 1.37 Hz, 1 H), 5.41 (d, *J* = 1.65 Hz, 1 H), 6.85 (d, *J* = 8.52 Hz, 2 H), 7.22 (d, *J* = 8.52 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 143.3, 130.60, 129.4, 114.4, 113.7, 103.9, 87.7, 81.9, 69.9, 55.2, 33.6, 28.0, 22.5, 21.4, 14.0, 0.09.

Preparation of alkyne (65):



65

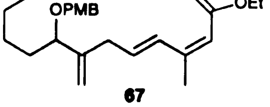
To a solution of TMS-alkyne **64** (0.11 g, 0.32 mmol) in THF (3 mL) was added dropwise an acetic acid buffered TBAF solution (0.39 mL, 0.39 mmol, 1.0 M THF). After stirring for 3.5 hours at room temperature, Et_2O (10 mL) was added and then quenched with the addition of a saturated aqueous $NaHCO_3$ solution (0.4 mL) and water (0.4 mL). The phases were separated, and the organic phase washed with brine (0.5 mL), dried over $MgSO_4$, filtered and concentrated to give 93 mg of a yellow oil. Purification by flash chromatography on silica gel [Hexanes/EtOAc 5%] afforded 79 mg (91%) of alkyne **65** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (t, *J* = 6.87 Hz, 3 H), 1.28 (m, 4 H), 1.60 (m, 2 H), 2.16 (t, *J* = 2.75 Hz, 1 H), 2.89 (app qABq, *J* = 1.92, 20.05 Hz, 1 H), 3.01 (dtABq, *J* = 2.75, 1.37, 20.05 Hz, 1 H), 3.78 (m, 1 H), 3.78 (s, 3 H), 4.17 (ABq, *J* = 11.26 Hz, 1 H), 4.42 (ABq, *J* = 11.54 Hz, 1 H), 5.12 (d, *J* = 1.10 Hz, 1 H), 5.43 (app q, *J* = 1.65 Hz, 1 H), 6.85 (d, *J* = 9.07 Hz, 2 H), 7.23 (d, *J* = 9.07 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 143.0, 130.5, 129.4, 114.6, 113.7, 81.9, 81.3, 71.2, 69.7, 55.3, 33.5, 27.9, 22.5, 19.8, 14.0.

Hydrostannylation of alkyne (65) to give vinyl stannane (66):

66

$(Ph_3P)_2PdCl_2$ (1 mg, 0.002 mmol) and Red-Sil[75a,b] (0.22 g, 0.463 mmol, 2.1 mmol/g) were added to Et_2O (1.5 mL) and followed by the addition of a solution of alkyne **62** (0.042 g, 0.15 mmol) in Et_2O (0.5 mL), Bu_3SnF (0.057 g, 0.19 mmol) and a few crystals of TBAF. After stirring for 1.5 hours at room temperature, more Red-Sil (70 mg) was added and the reaction stirred for an additional 2 hours. The reaction was filtered through a pad of Celite on a glass frit. The residual Red-Sil was washed several times with Et_2O. The filtrate was concentrated to give 86 mg of a brown cloudy oil. From ^1H NMR, the crude vinyl stannane **66** was a mixture of E- and internal isomers (1.5:1). ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.24$ (d, $J = 8.79$ Hz, 2 H), 7.23 (d, $J = 8.79$ Hz, 2 H), 6.85 (d, $J = 8.79$ Hz, 4 H), 5.95 (m, 2 H), 5.70 (m, 1 H), 5.29 (m, 1 H), 5.05 (s, 1 H), 5.01 (s, 1 H), 4.96 (s, 1 H), 4.84 (d, $J = 1.65$ Hz, 1 H), 4.46 (ABq, $J = 10.99$ Hz, 1 H), 4.43 (ABq, $J = 10.99$ Hz, 1 H), 4.18 (ABq, $J = 11.54$ Hz, 1 H), 4.16 (ABq, $J = 11.54$ Hz, 1 H), 3.78 (s, 6 H), 3.70 (m, 2 H), 3.0 – 2.70 (m, 4 H), 1.60 – 0.80 (3 series of m, 72 H).

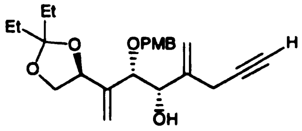
Preparation of diene (67) – Model Stille coupling:



67

To a solution of $(MeCN)_2PdCl_2$ (2 mg, 0.008 mmol) in DMF (1 mL) were added a solution of (Z)-β-iodo ethyl ester **49** (37 mg, 0.15 mmol) in DMF (0.1 mL) and a solution of crude vinyl stannane **66** (86 mg, 0.15 mmol) in DMF (0.1 mL). After stirring for 12 hours at room temperature, the reaction was diluted with ether (10 mL) and then washed with brine (1 mL x 3), a saturated aqueous KF solution (1 mL x 2) and brine (1 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.16 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to give 61.2 mg of a diene **67** contaminated with residual vinyl iodide **49** as a yellow oil after two columns.

Preparation of terminal alkyne (68):

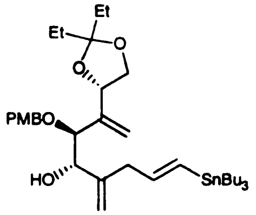


68

To a solution of TMS-alkyne **60** (0.14 g, 0.30 mmol) in THF (3 mL) was added an acetic acid buffered TBAF (1.05:1) solution (0.36 mL, 1.0 M THF, 0.36 mmol) dropwise. After stirring for 3.5 hours at room temperature, the reaction was diluted with ether (10 mL) and then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (0.4 mL) and water (0.4 mL). The phases were separated, and the organic phase was washed with brine (0.5 mL), dried over $MgSO_4$, filtered and concentrated to give 0.11 g (93%) of alkyne **68** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.24 Hz, 2 H), 6.86 (d, *J* = 8.24 Hz, 2 H), 5.64 (s, 1 H), 5.35 (s, 2 H), 5.14 (s, 1 H), 4.56 (ABq, *J* = 10.44 Hz, 1 H), 4.51 (dd, *J* = 9.34, 6.04 Hz, 1 H), 4.22 (ABq, *J* = 10.99 Hz, 1 H), 4.14 (dd, *J* = 7.69, 6.04 Hz, 1 H), 4.08 (d, *J* = 6.59 Hz, 1 H), 3.83 (d, *J* = 6.59 Hz, 1 H), 3.79 (s, 3 H), 3.51 (dd, *J* = 9.34, 7.69 Hz, 1 H), 3.03 (ABq, *J* = 19.78 Hz, 1 H), 2.86 (ABq,

J = 19.78 Hz, 1 H), 2.10 (t, J = 2.75 Hz, 1 H), 1.64 (m, 4 H), 0.92 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 143.5, 141.6, 129.7, 129.4, 116.4, 115.3, 113.8, 112.8, 81.3, 80.9, 76.3, 75.3, 71.2, 70.6, 70.4, 55.2, 29.8, 29.4, 21.7, 8.2, 8.1.

Preparation of vinyl stannane (69):



69

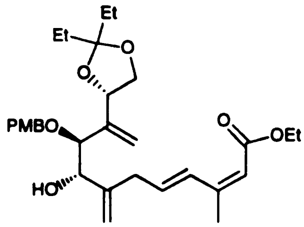
Red-Sil (0.53 g, 2.1 mmol/g, 1.1 mmol) and $(Ph_3P)_2PdCl_2$ (2 mg, 0.003 mmol) were dissolved in Et_2O (2 mL) and followed by the addition of a solution of crude alkyne **68** (0.11 g, 0.28 mmol) in Et_2O (1 mL), Bu_3SnF (0.11 g, 0.36 mmol), and a few crystals of TBAF. After stirring for 4 hours at room temperature, the reaction mixture was filtered through a glass frit filter with a pad of Celite. The Red-Sil was washed several times with Et_2O. The filtrate was concentrated to give 0.16 g of a yellow oil, which was purified by flash chromatography on silica gel [Hexanes/EtOAc 10%] to give 27 mg (14%) of pure E-vinyl stannane **69**, 51 mg (27%) as a mixture of regioisomers (E-stannane major) and 44 mg (23%) of a regio-mixture (internal major).

E-isomer. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, J = 8.79 Hz, 2 H), 6.86 (d, J = 8.79 Hz, 2 H), 5.90 (m, 2 H), 5.62 (s, 1 H), 5.33 (s, 1 H), 5.09 (s, 1 H), 4.96 (d, J = 1.10 Hz, 1 H), 4.56 (ABq, J = 10.44 Hz, 1 H), 4.51 (dd, J = 8.79, 6.04 Hz, 1 H), 4.23 (ABq, J = 10.99 Hz, 1 H), 4.14 (dd, J = 7.69, 6.04 Hz, 1 H), 3.98 (dd, J =

6.04, 3.85 Hz, 1 H), 3.82 (d, *J* = 6.04 Hz, 1 H), 3.79 (s, 3 H), 3.50 (dd, *J* = 8.79, 7.69 Hz, 1 H), 2.92 (dABq, *J* = 4.40, 19.32 Hz, 1 H), 2.86 (d, *J* = 3.85 Hz, -OH), 2.70 (dABq, *J* = 4.40, 19.23 Hz, 1 H), 1.65 (m, 4 H), 1.46 (m, 6 H), 1.26 (m, 12 H), 0.87 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 146.0, 145.7, 143.9, 130.9, 129.7, 129.6, 116.1, 114.1, 113.8, 112.7, 81.5, 76.8, 75.2, 70.8, 70.4, 55.3, 40.7, 29.9, 29.5, 29.1, 27.3, 13.7, 9.4, 8.2, 8.1.

internal isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.79 Hz, 2 H), 6.85 (d, *J* = 8.24 Hz, 2 H), 5.60 (s, 1 H), 5.59 (m, 1 H), 5.33 (s, 1 H), 5.21 (m, 1 H), 5.15 (s, 1 H), 4.90 (s, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.52 (dd, *J* = 7.69, 6.59 Hz, 1 H), 4.23 (ABq, *J* = 10.99 Hz, 1 H), 4.17 (dd, *J* = 7.69, 6.59 Hz, 1 H), 3.93 (t, *J* = 5.49 / 4.40 Hz, 1 H), 3.82 (d, *J* = 4.94 Hz, 1 H), 3.79 (s, 3 H), 3.52 (dd, *J* = 8.79, 7.69 Hz, 1 H), 3.01 (ABq, *J* = 15.93 Hz, 1 H), 2.71 (ABq, *J* = 15.93 Hz, 1 H), 2.68 (d, *J* = 4.94 Hz, -OH), 1.66 (m, 4 H), 1.44 (m, 6 H), 1.26 (m, 12 H), 0.87 (m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 152.4, 146.3, 144.2, 129.7, 129.6, 127.4, 115.7, 114.2, 113.8, 112.7, 80.7, 75.8, 75.2, 70.8, 70.3, 55.2, 44.0, 29.9, 29.5, 29.0, 27.4, 13.7, 9.8, 8.2, 8.1.

Preparation of diene (70) "ABD":



70

Stille Cross-coupling:

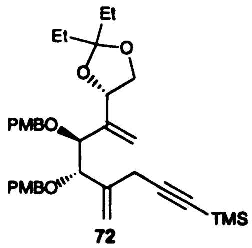
A solution of Pd_2dba_3 (1 mg, 0.001 mmol) and $AsPh_3$ (1.3 mg, 0.0044 mmol) in NMP (0.2 mL) was stirred at room temperature for 10 minutes and then a solution of (Z)-β-iodo ethyl ester **49** (0.013 g, 0.055 mmol) in NMP (0.2 mL) was added. The reaction vessel was immersed into a preheated oil bath (~50 °C) and a solution of vinyl stannane **69** (0.038 g, 0.055 mmol) in NMP (0.2 mL) was immediately added. After stirring for 16 hours at 50 °C, the reaction was allowed to cool to room temperature and then diluted with Et_2O (6 mL). The organic phase was washed with water (0.2 mL), brine (0.2 mL), a saturated aqueous KF solution (0.2 mL x 2) and brine (0.2 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 95 mg of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 15 mg (52%) of diene **70** as a yellow oil. For spectroscopic data see below.

Liebeskind's Cross-coupling:

To a solution of (Z)-β-iodo ethyl ester **49** (0.017 g, 0.072 mmol) in NMP (0.2 mL) was added copper (I) thiophene-2-carboxylate (CuTc) (0.010 g, 0.054 mmol). To this suspension was added a solution of vinyl stannane **69** (0.026 g, 0.036 mmol) in NMP (0.2 mL). After stirring for 30 minutes, the reaction was diluted with Et_2O (6 mL) and filtered through a bed of Celite. The green filter cake was washed with Et_2O (3 mL). The clear filtrate was washed with water (0.6 mL x 3), a saturated aqueous KF solution (0.5 mL x 2), and brine (0.6 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 48 mg of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 10 mg (56%) of diene **70** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.56$ (d, $J = 15.93$ Hz, 1 H), 7.22 (d, $J = 8.79$ Hz, 2 H), 6.86 (d, $J = 8.79$ Hz, 2 H), 6.06 (dt, $J = 15.38, 7.14$ Hz, 1 H), 5.62 (s, 1 H), 5.61 (s, 1 H), 5.34

(s, 1 H), 5.10 (s, 1 H), 4.95 (s, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.51 (dd, *J* = 8.79, 6.04 Hz, 1 H), 4.23 (ABq, *J* = 10.99 Hz, 1 H), 4.13 (m, 3 H), 4.0 (dd, *J* = 6.04, 3.30 Hz, 1 H), 3.83 (d, *J* = 6.59 Hz, 1 H), 3.79 (s, 3 H), 3.50 (dd, *J* = 8.79, 7.69 Hz, 1 H), 2.99 (dABq, *J* = 6.59, 16.48 Hz, 1 H), 2.90 (d, *J* = 3.30 Hz, -OH), 2.79 (dABq, *J* = 7.69, 16.48 Hz, 1 H), 1.95 (d, *J* = 1.10 Hz, 3 H), 1.65 (m, 4 H), 1.25 (t, *J* = 7.14 Hz, 3 H), 0.94 (t, *J* = 7.69 Hz, 3 H), 0.89 (t, *J* = 7.69 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 159.4, 150.6, 145.6, 143.7, 135.6, 129.8, 129.5, 116.5, 116.4, 114.9, 113.9, 112.8, 81.5, 76.8, 75.1, 70.7, 70.4, 59.7, 55.3, 35.8, 29.9, 29.5, 21.1, 14.3, 8.2, 8.1; HRMS (CI) *m/z* 515.3001 [$(M + H)^+$; calcd for $C_{30}H_{43}O_7$, 515.3009].

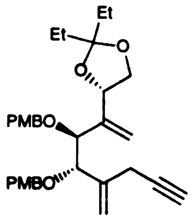
Preparation of PMB-ether (72):



72

To a solution alcohol **60** (0.095 g, 0.201 mmol) and *p*-$CH_3OPhCH_2OC(NH)CCl_3$[78] (0.23 g, 0.80 mmol) in cyclohexane/CH_2Cl_2 (3:1) (2 mL) was added CSA (5 mg, 0.02 mmol). The reaction vessel was immersed into a preheated oil bath (~40 °C). After stirring for 3 hours at 40 °C, more CSA (11 mg) was added. After stirring for a total of 12 hours, the reaction mixture was allowed to cool to room temperature, diluted with Et_2O (15 mL), and quenched by the addition of a saturated aqueous $NaHCO_3$ solution (1 mL). The phases were separated, and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 mL x 2) and brine (3 mL), dried over $MgSO_4$, filtered and concentrated to give a white-yellow solid. Hexanes were added to the residue, stirred for 30 minutes and then filtered. The solid was washed several times with hexanes. The filtrate was concentrated to give 0.21 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 49 mg (41%) of PMB-ether **72** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.27 (d, *J* = 8.79 Hz, 2 H), 7.22 (d, *J* = 8.24 Hz, 2 H), 6.87 (d, *J* = 8.24 Hz, 2 H), 6.83 (d, *J* = 8.79 Hz, 2 H), 5.54 (s, 1 H), 5.45 (s, 1 H), 5.31 (s, 1 H), 5.16 (s, 1 H), 4.53 (ABq, *J* = 10.99 Hz, 1 H), 4.46 (ABq, *J* = 11.54 Hz, 1 H), 4.45 (m, 1 H), 4.27 (ABq, *J* = 10.99 Hz, 1 H), 4.23 (ABq, *J* = 11.54 Hz, 1 H), 3.99 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.95 (d, *J* = 5.49 Hz, 1 H), 3.84 (d, *J* = 6.04 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.41 (dd, *J* = 8.79, 7.69 Hz, 1 H), 3.04 (ABq, *J* = 20.33 Hz, 1 H), 2.94 (ABq, *J* = 20.33 Hz, 1 H), 1.64 (m, 4 H), 0.91 (t, *J* = 7.14 Hz, 3 H), 0.87 (t, *J* = 7.14 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 159.0, 143.7, 140.8, 130.4, 130.2, 130.1, 129.7, 115.9, 115.3, 113.8 (2), 112.6, 103.6, 87.6, 83.0, 81.2, 75.5, 71.4, 70.7, 70.6, 55.2, 29.8, 29.5, 23.6, 8.1, 0.08.

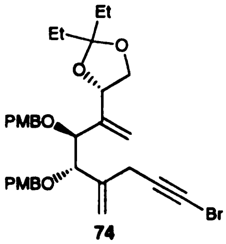
Preparation of terminal alkyne (73):



73

To a solution TMS-alkyne **72** (0.049 g, 0.083 mmol) in THF (0.8 mL) was added an acetic acid buffered TBAF (1.05:1) solution (0.10 mL, 1.0 M THF, 0.10 mmol) dropwise. After stirring for 5 hours at room temperature, the reaction was diluted with Et_2O (5 mL) and then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (0.1 mL) and water (0.1 mL). The phases were separated, and the organic phase was washed with brine (0.2 mL), dried over $MgSO_4$, filtered and concentrated to give 40 mg (93%) of crude alkyne **73** as a yellow oil.

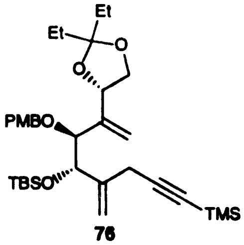
Preparation of 1-bromo-alkyne (74):



74

To a solution of crude alkyne **73** (0.040 g, 0.077 mmol) in acetone (0.2 mL) were added NBS (0.0164 g, 0.0924 mmol) and $AgNO_3$ (1.3 mg, 0.0077 mmol). The flask was wrapped with aluminum foil and stirred at room temperature for one hour. The reaction was quenched by the addition of water (0.2 mL), diluted with Et_2O (1.5 mL) and the phases were separated. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated to give 37 mg of crude 1-bromo-alkyne **74** as a yellow oil.

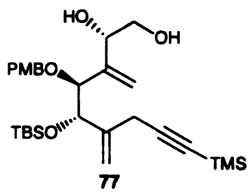
Preparation of TBS-ether (76):



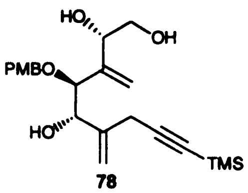
76

To a solution of alcohol **60** (0.45 g, 0.95 mmol) in CH_2Cl_2 (4.5 mL) was added 2,6-lutidine (0.22 mL, 1.9 mmol) and TBSOTf (0.33 mL, 1.4 mmol). After stirring for 60 minutes, the reaction was quenched with water (1 mL) and a saturated aqueous NH_4Cl solution (1 mL). The reaction was diluted with Et_2O (50 mL), and the phases were separated. The organic phase was washed with brine (2 mL x 2), a saturated aqueous $CuSO_4$ solution (2 mL x 2) and brine (2 mL). The combined aqueous phases were extracted with Et_2O (3 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.59 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 5% → 10%] to give 0.50 g (89%) of TBS-ether **76** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2957, 2929, 2857, 2178, 1613, 1514, 1464, 1258, 1173, 1079, 1040, 920, 842, 777, 760, 699; $[\alpha]_{589}^{20}$ +16.9° (c 0.825, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.52 Hz, 2 H), 6.83 (d, *J* = 8.52 Hz, 2 H), 5.52 (s, 1 H), 5.24 (s, 2 H), 5.07 (s, 1 H), 4.52 (app d, *J* = 9.07 Hz, 1 H), 4.50 (ABq, *J* = 11.26 Hz, 1 H), 4.28 (d, *J* = 5.49 Hz, 1 H), 4.24 (ABq, *J* = 11.26 Hz, 1 H), 4.05 (dd, *J* = 7.42, 6.04 Hz, 1 H), 3.78 (s, 3 H), 3.63 (d, *J* = 5.49 Hz, 1 H), 3.43 (dd, *J* = 9.07, 7.69 Hz, 1 H), 3.07 (ABq, *J* = 19.78 Hz, 1 H), 2.90 (ABq, *J* = 19.78 Hz, 1 H), 1.65 (m, 4 H), 0.92 (t, *J* = 7.42 Hz, 3 H), 0.88 (t, *J* = 7.42 Hz, 3 H), 0.84 (s, 9 H), 0.14 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.4, 130.3, 129.3, 114.2, 113.6, 104.1, 100.3, 82.0, 70.6, 55.3, 30.1, 29.7, 25.8, 25.7, 23.9, 18.2, 8.2, 8.1, 0.11, -2.9, -4.9; HRMS (CI) *m/z* 587.3573 [$(M + H)^+$; calcd for $C_{33}H_{55}O_5Si_2$, 587.3588].

Hydrolysis of isopentylidene acetal (76) to give diol (77) and triol (78):



77



78

p-toluenesulfonic acid monohydrate:

To a solution of isopentylidene acetal **76** (0.12 g, 0.20 mmol) in MeOH (2 mL) was added *p*-toluenesulfonic acid monohydrate (PTSA) (4 mg, 0.02 mmol). After stirring at room temperature for 12 hours, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution (0.4 mL). The reaction mixture was diluted with Et_2O (10 mL) and water (2 mL) and then the phases were separated. The organic phase was washed with brine (0.5 mL x 2). The combined aqueous phases were extracted with Et_2O (3 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 63 mg of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 6.7 mg of desired diol **77** (6%) as a yellow oil, 19 mg (23%) of triol **78** via acetonide hydrolysis and loss of the TBS moiety, and 16.4 mg (17%) of alcohol **60** via loss of the TBS group only. For spectroscopic data see below.

10-camphorsulfonic acid:

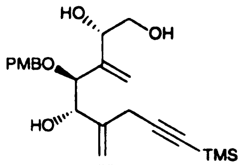
To a solution of isopentylidene acetal **76** (0.46 g, 0.78 mmol) in MeOH/ CH_2Cl_2 (2:1) (9 mL) was added 10-camphorsulfonic acid (CSA) (0.018 g, 0.078 mmol). The reaction was immersed into a preheated oil bath (40 °C). After stirring for 6 hours, additional CSA (18 mg) was added. A second portion of CSA (18 mg) was made after 24 hours. After stirring for a total of 31 hours, the reaction was allowed to cool to room temperature and was then neutralized with

Et_3N (0.5 mL). The reaction mixture was then concentrated to give 0.45 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/ EtOAc 25% → 50%, 0.5% MeOH] to give 0.145 g (46%) of triol **78** and 92 mg (25%) of alcohol **60** as clear oils.

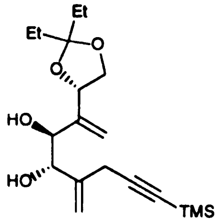
diol **77**: IR (neat, 4 cm^{-1}): ν = 3417, 2957, 2931, 2858, 2177, 1613, 1515, 1471, 1464, 1303, 1250, 1174, 1084, 1037, 915, 842, 777, 760; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, J = 8.79 Hz, 2 H), 6.84 (d, J = 8.79 Hz, 2 H), 5.30 (s, 1 H), 5.28 (d, J = 1.65 Hz, 1 H), 5.21 (s, 1 H), 5.07 (s, 1 H), 4.49 (ABq, J = 11.54 Hz, 1 H), 4.43 (d, J = 6.04 Hz, 1 H), 4.34 (ABq, J = 11.54 Hz, 1 H), 4.19 (m, 1 H), 3.83 (d, J = 6.04 Hz, 1 H), 3.79 (m, 4 H), 3.56 (m, 1 H), 3.09 (ABq, J = 19.78 Hz, 1 H), 2.94 (ABq, J = 19.78 Hz, 1 H), 0.86 (s, 9 H), 0.14 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 144.6, 143.1, 129.4, 115.2, 114.6, 113.7, 103.9, 84.4, 77.2, 75.2, 72.1, 71.2, 65.4, 55.3, 25.8, 23.5, 18.2, 0.08, -5.0; HRMS (CI) m/z 519.2948 [$(M + H)^+$; calcd for $C_{28}H_{47}O_5Si_2$, 519.2962].

triol **78**: IR (neat, 4 cm^{-1}): ν = 3397, 2958, 2929, 2178, 1612, 1515, 1457, 1420, 1303, 1251, 1174, 1036, 922, 845, 760; $[\alpha]^{20}_{589}$ +56.9° (c 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.20 (d, J = 8.52 Hz, 2H), 6.85 (d, J = 8.52 Hz, 2 H), 5.45 (s, 1 H), 5.34 (s, 2 H), 5.16 (s, 1 H), 4.53 (ABq, J = 10.99 Hz, 1 H), 4.25 (ABq, J = 10.99 Hz, 1 H), 4.22 – 4.18 (m, 2 H), 3.88 (d, J = 5.77 Hz, 1 H), 3.78 (s, 3 H), 3.69 (dd, J = 11.26, 3.57 Hz, 1 H), 3.57 (dd, J = 11.26, 7.14 Hz, 1 H), 3.06 (ABq, J = 19.78 Hz, 1 H), 2.90 (ABq, J = 19.78 Hz, 1 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.5, 145.2, 142.2, 129.7, 129.2, 116.6, 114.9, 113.9, 103.4, 87.8, 82.0, 76.4, 72.4, 70.8, 65.8, 55.3, 23.3, 0.01; HRMS (CI) *m/z* 405.2079 [(M + H)$^+$; calcd for $C_{22}H_{33}O_5Si$, 405.2097].

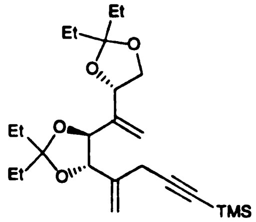
Hydrolysis of isopentylidene acetal (60) to give triol (78):



78



79



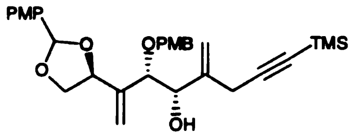
80

To a solution of isopentylidene acetal **60** (0.38 g, 0.80 mmol) in MeOH was added PTSA (0.015 g, 0.080 mmol). The reaction vessel was immersed into a preheated oil bath (~40 °C). After 11.5 hours, additional PTSA (15 mg) was added, as well as THF (1 mL). After stirring for 24 hours, CSA (19 mg) and THF (2 mL) was added. After stirring an additional 4.5 hours, the reaction was neutralized by the addition of Et_3N (0.5 mL) and then concentrated to give 0.49 g of a yellow oil. CH_2Cl_2 (5 mL) was added to residue. The residue was washed with brine (0.5 mL), water (0.5 mL), a saturated aqueous $NaHCO_3$ solution (0.5 mL), and brine (0.5 mL). The combined aqueous phases were extracted with Et_2O. The organics were dried over $MgSO_4$, filtered and concentrated to give 0.38 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25% → 50%, 0.5% MeOH] to give 0.16 g (50%) of desired triol **78** as a yellow oil, 65 mg (17%) of recovered alcohol **60** and small amounts of by-products **79** and **80**.

by-product **79**: IR (neat, 4 cm^{-1}): ν = 3426, 2971, 2944, 2884, 2180, 1464, 1250, 1199, 1175, 1076, 1034, 928, 843, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.38 (s, 1 H), 5.34 (s, 1 H), 5.30 (s, 1 H), 5.18 (s, 1 H), 4.33 (s, 2 H), 4.27 (m, 1 H), 3.69 (m, 2 H), 3.14 (ABq, *J* = 19.23 Hz, 1 H), 3.0 (ABq, *J* = 19.23 Hz, 1 H), 2.94 (s, 1 H), 2.33 (s, 1 H), 1.75 – 1.62 (m, 4 H), 0.93 (t, *J* = 7.69 Hz, 3 H), 0.92 (t, *J* = 7.69 Hz, 3 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 143.6, 139.1, 116.5, 116.1, 112.9, 88.0, 83.1, 80.8, 76.3, 71.9, 65.4, 30.2, 30.1, 22.3, 8.1, -0.06; LRMS (CI) *m/z* 353 [$(M + H)^+$; calcd for $C_{19}H_{33}O_4Si$, 353].

by-product **80**: IR (neat, 4 cm^{-1}): ν = 2957, 2926, 2855, 2180, 1746, 1464, 1250, 1198, 1173, 1080, 1059, 1034, 922, 843, 760; ^{1}H NMR (300 MHz, CDCl$_3$) δ = 5.53 (s, 1 H), 5.40 (d, *J* = 1.10 Hz, 1 H), 5.34 (s, 1 H), 5.22 (s, 1 H), 4.53 (dd, *J* = 8.79, 6.04 Hz, 1 H), 4.26 (d, *J* = 8.79 Hz, 1 H), 4.22 (d, *J* = 9.07 Hz, 1 H), 4.17 (dd, *J* = 7.69, 6.04 Hz, 1 H), 3.49 (dd, *J* = 8.79, 7. 69 Hz, 1 H), 3.15 (ABq, *J* = 19.50 Hz, 1 H), 3.01 (ABq, *J* = 19.78 Hz, 1 H), 1.70 (m, 8 H), 0.90 (m, 12 H), 0.14 (s, 9 H); ^{13}C NMR (75 MHz, CDCl$_3$) δ = 143.4, 139.7, 116.6, 113.4, 112.8, 112.6, 87.9, 83.7, 79.3, 77.2, 75.5, 70.9, 30.1, 29.9, 29.6, 29.4, 22.7, 22.3, 8.1, 8.0, -0.02; LRMS (CI) *m/z* 421 [$(M + H)^+$; calcd for $C_{24}H_{41}O_4Si$, 421].

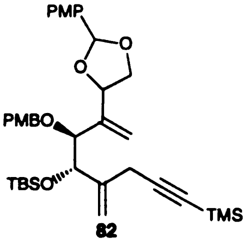
Preparation of *p*-methoxybenzylidene acetal (81):



81

To a solution of triol **78** (0.16 g, 0.40 mmol) in DMF (1 mL) were added PTSA (4 mg, 0.02 mmol) and *p*-MeOC$_6$H$_4$CH(OMe)$_2$ (0.080 mL, 0.47 mmol). The reaction was immersed into a preheated oil bath (~55 °C) and stirred for 2.5 hours. The reaction was neutralized with Et$_3$N (0.1 mL). The resulting mixture was diluted with EtOAc (10 mL). The phases were separated, and the organic phase washed with brine (1 mL x 2) and H$_2$O (1 mL). The combined aqueous phases were extracted with EtOAc. The organics dried over $MgSO_4$, filtered and concentrated to give 0.49 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 0.16 g (78%) of a diastereomeric mixture of *p*-methoxybenzylidene acetal **81** as an oil.

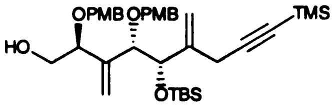
Preparation of TBS-ether (82):



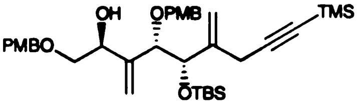
82

To a solution of alcohol **81** (0.16 g, 0.31 mmol) in CH_2Cl_2 (1.5 mL) were added 2,6-lutidine (0.071 mL, 0.61 mmol) and TBSOTf (0.10 mL, 0.46 mmol). After stirring at room temperature for 1 hour, the reaction was quenched by the addition of water (0.3 mL) and a saturated aqueous NH_4Cl solution (0.3 mL). The mixture was diluted with ether (15 mL) and then the phases were separated. The organic phase was washed with brine (0.6 mL), a saturated aqueous $CuSO_4$ solution (0.6 mL x 2) and brine (0.6 mL). The combined aqueous phases were extracted with Et_2O (1 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.26 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.11 g (56%) of TBS-ether **82** as a clear oil.

Reduction of benzylidene acetal (82) to give PMB-ether (83):



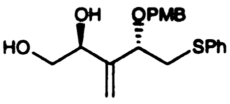
83a



83b

To a solution of *p*-methoxybenzylidene acetal **82** (0.11 g, 0.17 mmol) in CH_2Cl_2 (1 mL) at -78 °C was added DIBAL-H (0.51 mL, 1.0 M hexanes, 0.51 mmol) dropwise. After stirring for 1 hour at –78 °C, the reaction was gradually allowed to warm to room temperature and stirred overnight (~20 hours). The reaction was quenched by the addition of EtOAc (0.2 mL) and a aqueous solution of Rochelle's salt (1 mL). The mixture solidified and therefore, CH_2Cl_2 was added. After stirring overnight, the reaction mixture was separated. The organic phase was washed with Rochelle's salt (2x). The combined aqueous phases were extracted with CH_2Cl_2 (3x). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 82 mg of an yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 49 mg (50%) of a mixture of PMB-ethers **83**.

Preparation of diol (84):

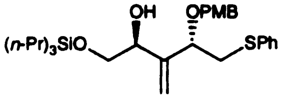


84

To a solution of isopentylidene acetal **54** (1.68 g, 3.92 mmol) were added CSA (0.091 g, 0.39 mmol) and water (0.25 mL). The reaction was immersed into a preheated oil bath (40 °C). After stirring for 12 hours, the reaction was allowed to cool to room temperature and was then neutralized with Et_3N (0.17 mL). The reaction solution was concentrated and Et_2O (20 mL) was added to the residue. The resulting solution was washed with brine (1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 1.48 g of a thick yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 50%, 1% MeOH] to give 1.26

g (89%) of diol **84** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3409, 2932, 2870, 2836, 1613, 1586, 1514, 1482, 1464, 1439, 1302, 1248, 1175, 1080, 1034, 928, 822, 741; $[\alpha]_{589}^{20}$ +73.1° (c 0.73, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.13 (m, 7 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.36 (s, 1 H), 5.26 (s, 1 H), 4.49 (ABq, *J* = 10.99 Hz, 1 H), 4.32 (ABq, *J* = 10.99 Hz, 1 H), 4.26 (m, 1 H), 3.99 (t, *J* = 7.14 Hz, 1 H), 3.78 (s, 3 H), 3.67 (m, 1 H), 3.57 (m, 1 H), 3.25 (dABq, *J* = 7.14, 13.19 Hz, 1 H), 3.11 (dABq, *J* = 6.04, 13.19 Hz, 1 H), 2.69 (m, -OH), 2.23 (m, -OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 146.0, 135.9, 129.6, 129.5, 128.9, 126.2, 116.4, 113.8, 79.9, 76.6, 72.0, 70.8, 65.8, 55.3, 38.5; HRMS (CI) *m/z* 361.1462 [(M + H)$^+$; calcd for $C_{20}H_{25}O_4S$, 361.1474].

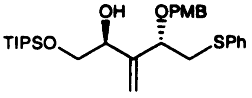
Preparation of mono-protected 1,2-diol (85):



85

To a solution of diol **84** (0.420 g, 1.17 mmol) in CH_2Cl_2 (12 mL) was added imidazole (0.16 g, 2.3 mmol), DMAP (0.014 g, 0.12 mmol), and tri-*n*-propylsilyl chloride (0.26 mL, 1.2 mmol). After stirring for 2 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (4 mL). Ether (25 mL) was added, and the phases were separated. The organic phase was washed with brine (3 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.60 g of a clear oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.39 g (65%) of mono-silylated **85** and 0.17 g (22%) of the fully disilylated diol as clear oils. IR (neat, 4 cm^{-1}): ν = 3480, 2955, 2926, 2869, 1612, 1586, 1514, 1481, 1462, 1439, 1302, 1248, 1209, 1173, 1090, 1067, 1038, 924, 822, 739; $[\alpha]_{589}^{20}$ +65.0° (c 0.785, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.10 (m, 7 H), 6.83 (d, *J* = 8.79 Hz, 2 H), 5.42 (s, 1 H), 5.33 (s, 1 H), 4.52 (ABq, *J* = 10.99 Hz, 1 H), 4.27 (ABq, *J* = 11.54 Hz, 1 H), 4.17 (m, 1 H), 3.97 (dd, *J* = 7.69, 4.94 Hz, 1 H), 3.78 (s, 3 H), 3.60 (dd, *J* = 9.89, 3.30 Hz, 1 H), 3.44 (dd, *J* = 10.44, 8.24 Hz, 1 H), 3.16 (dd, *J* = 13.19, 7.69 Hz, 1 H), 3.07 (dd, *J* = 13.19, 5.49 Hz, 1 H), 2.75 (d, *J* = 2.75 Hz, -OH), 1.32 (m, 6 H), 0.93 (t, *J* = 7.14 Hz, 9 H), 0.57 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 146.4, 136.5, 129.9, 129.5, 129.2, 128.8, 125.9, 115.5, 113.7, 78.7, 71.6, 70.4, 66.8, 55.2, 39.2, 18.3, 16.7, 16.2; HRMS (CI) *m/z* 517.2807 [(M + H)$^+$; calcd for $C_{29}H_{45}O_4SSi$, 517.2808].

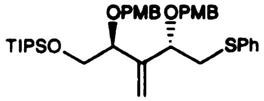
Preparation of mono-protected 1,2-diol (87):



87

To a solution of diol **84** (1.41 g, 3.91 mmol) in CH_2Cl_2 (40 mL) were added imidazole (0.53 g, 7.8 mmol), DMAP (0.048 g, 0.391 mmol), and triisopropylsilyl chloride (0.88 mL, 4.1 mmol). After stirring for 24 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL). Et_2O (80 mL) was added, and the phases were separated. The organic phase was washed with brine (5 mL x 2). The combined aqueous phases were extracted with Et_2O (5 mL x 2). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 2.34 g of a clear oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 1.84 g (91%) of mono-silylated **87**. IR (neat, 4 cm^{-1}): ν = 3474, 2944, 2889, 1613, 1586, 1514, 1464, 1439, 1385, 1302, 1248, 1173, 109/, 1038, 920, 884, 820, 739; $[\alpha]^{20}_{589}$ +64.1° (c 0.695, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.11 (m, 7 H), 6.82 (d, *J* = 8.79 Hz, 2 H), 5.44 (s, 1 H), 5.33 (s, 1 H), 4.52 (ABq, *J* = 10.99 Hz, 1 H), 4.28 (ABq, *J* = 10.99 Hz, 1 H), 4.20 (m, 1 H), 3.97 (dd, *J* = 5.49, 7.69 Hz, 1 H), 3.78 (s, 3 H), 3.70 (dd, *J* = 3.85, 9.89 Hz, 1 H), 3.55 (dd, *J* = 8.24, 9.89 Hz, 1 H), 3.16 (dABq, *J* = 7.69, 13.19 Hz, 1 H), 3.08 (dABq, *J* = 5.49, 13.19 Hz, 1 H), 2.84 (d, *J* = 2.20 Hz, -OH), 1.03 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 146.3, 136.5, 129.9, 129.5, 128.8, 125.9, 115.5, 113.7, 78.6, 77.2, 71.8, 70.4, 67.5, 55.2, 39.3, 17.9, 11.8; HRMS (CI) *m/z* 517.2805 $[(M + H)^+$; calcd for $C_{29}H_{45}O_4SSi$, 517.2808].

Preparation of fully protected triol (89):

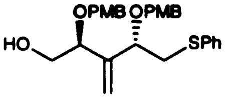


89

To a cold (0 °C) solution of alcohol **87** (0.46 g, 0.89 mmol) in THF (8 mL) was added NaHMDS (1.34 mL, 1.0 M THF, 1.34 mmol) dropwise. The ice bath was removed and the reaction stirred at room temperature for 30 minutes, after which time DMSO (2.5 mL) and PMBCl (0.20 mL, 1.4 mmol) were added. After stirring for 1.5 hours, the reaction was quenched with a saturated aqueous NH_4Cl solution (1 mL) and diluted with Et_2O (20 mL) and water (0.5 mL). The phases were separated, and the organic phase was washed with brine (1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.85 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5% → 10%] to give 0.45 g (79 %) of fully protected triol **89** as a clear oil. IR (neat, 4

cm^{-1}): ν = 2940, 2865, 1613, 1514, 1464, 1302, 1246, 1173, 1086, 1038, 884; $[\alpha]^{20}_{589}$ +71.9° (c 0.705, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.10 (m, 9 H), 6.85 (d, *J* = 8.79 Hz, 2 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.45 (s, 1 H), 5.44 (s, 1 H), 4.59 (ABq, *J* = 11.54 Hz, 1 H), 4.53 (ABq, *J* = 11.54 Hz, 1 H), 4.43, (ABq, *J* = 11.54 Hz, 1 H), 4.29 (ABq, *J* = 11.54 Hz, 1 H), 3.98 (t, *J* = 6.59 Hz, 1 H), 3.89 (dd, *J* = 4.40, 6.59 Hz, 1 H), 3.82 – 3.74 (m, 7 H), 3.65 (dd, *J* = 4.40, 10.44 Hz, 1 H), 3.11 (d, *J* = 6.59 Hz, 2 H), 1.03 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 145.7, 136.7, 130.5, 130.2, 129.4, 129.3, 129.2, 128.8, 125.8, 115.4, 113.7, 80.0, 77.9, 70.6, 70.5, 66.8, 55.2, 39.6, 17.9, 11.9; HRMS (CI) *m/z* 637.3365 [$(M + H)^+$; calcd for $C_{37}H_{53}O_5SSi$, 637.3383].

Preparation of alcohol (90):

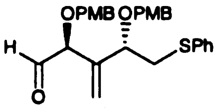


90

To a solution of TIPS-silyl ether **89** (0.126 g, 0.198 mmol) in THF (2 mL) was added TBAF (0.24 mL, 1.0 M THF, 0.24 mmol) dropwise. After stirring for 20 minutes, the reaction was diluted with Et_2O (5 mL) and water (0.2 mL). The phases were separated, and the organic phase was washed with brine (0.2 mL x 2). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.13g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 25% → 50%] to give 80 mg (84%) of alcohol **90** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3409, 2932, 2870, 2836, 1613, 1586, 1514, 1482, 1464, 1439, 1302, 1248, 1175, 1080, 1034, 928, 822, 741; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.21 (d, *J* = 8.79 Hz, 2 H), 7.20 (d, *J* = 8.79

Hz, 2 H), 7.20 (m, 4 H), 6.85 (d, *J* = 8.79 Hz, 2 H), 6.84 (m, 1 H), 6.83 (d, *J* = 8.79 Hz, 2 H), 5.48 (s, 1 H), 5.44 (s, 1 H), 4.57 (ABq, *J* = 11.54 Hz, 1 H), 4.51 (ABq, *J* = 11.54 Hz, 1 H), 4.30 (ABq, *J* = 11.54 Hz, 1 H), 4.28 (ABq, *J* = 11.54 Hz, 1 H), 3.93 (m, 2 H), 3.78 (s, 6 H), 3.50 (m, 2 H), 3.18 (dABq, *J* = 7.69, 13.19 Hz, 1 H), 3.07 (dABq, *J* = 5.49, 13.19 Hz, 1 H).

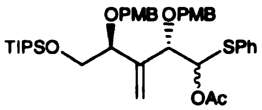
Preparation of aldehyde (91):



91

To a stirred solution of Dess-Martin periodinane (0.074 g, 0.18 mmol) in CH_2Cl_2 (3 mL) were added pyridine (0.014 mL, 0.18 mmol) and a solution of alcohol **90** (0.080 g, 0.17 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 50 minutes at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ /10% aqueous $Na_2S_2O_3$ (1:1) solution (2 mL) and diluted with Et_2O (10 mL). After stirring for 30 minutes, the phases were separated. The organic phase was washed with water (0.4 mL), a saturated aqueous $CuSO_4$ solution (0.4 mL x 2), water (0.4 mL) and brine (0.5 mL), dried over Na_2SO_4, filtered and concentrated to give 77 mg (97%) of crude aldehyde **91** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 1.65 Hz, 1 H), 7.19 (m, 8 H), 6.85 (d, *J* = 8.24 Hz, 2 H), 6.84 (m, 1 H), 6.83 (d, *J* = 8.24 Hz, 2 H), 5.47 (s, 1 H), 5.43 (s, 1 H), 4.58 (ABq, *J* = 10.99 Hz, 1 H), 4.45 (ABq, *J* = 11.54 Hz, 1 H), 4.36 (ABq, *J* = 11.54 Hz, 1 H), 4.22 (d, *J* = 1.65 Hz, 1 H), 4.14 (ABq, *J* = 10.99 Hz, 1 H), 3.97 (dd, *J* = 7.14, 6.04 Hz, 1 H), 3.78 (s, 6 H), 3.22 (dABq, *J* = 7.14, 13.73 Hz, 1 H), 3.11 (dABq, *J* = 6.04, 13.73 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.2, 159.5, 159.3, 141.7, 136.2, 129.7, 129.6, 129.1, 128.9, 128.8, 125.9, 120.5, 113.9, 113.7, 84.2, 78.9, 71.0, 70.7, 55.3, 38.2.

Preparation of α-acetoxy sulfide (93):



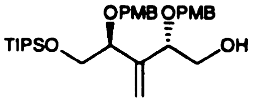
93

To a solution of phenyl sulfide **89** (0.43 g, 0.68 mmol) in CH_2Cl_2 (13 mL) at −78 °C was added dropwise (~8 minutes) a solution of *m*-CPBA (0.14 g, 0.81 mmol) in CH_2Cl_2 (4 mL). After stirring for 10 minutes (until judged complete by TLC), the reaction was quenched with 1 M NaOH (0.81 mL) and then allowed to warm to room temperature. The phases were separated, and the organic phase was washed with 1 M NaOH (0.81 mL x 2) and brine (1 mL), dried over $MgSO_4$, filtered and concentrated to give 0.43 g (100%) of crude sulfoxide **92** as a clear oil.

Pummerer rearrangement:

Trifluoroacetic anhydride (0.14 mL, 1.0 mmol) was dissolved in acetic anhydride (0.7 mL) and the solution stirred at room temperature for 7.5 hours. A solution of crude sulfoxide **92** (0.43 g, 0.68 mmol) in Ac_2O (0.7 mL) was added and after a few minutes 2,6-lutidine (0.16 mL, 1.4 mmol) was added. After stirring for 12 hours at room temperature, the reaction mixture was concentrated under high vacuum. CH_2Cl_2 (15 mL) was added to the residue and the resultant solution was then washed with a saturated aqueous $NaHCO_3$ solution (1.5 mL x 2) and brine (2 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.47 g of a dark red oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc, 10 %] to give 0.28 g (60 %) of α-acetoxy sulfide **93** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2942, 2867, 1750, 1613, 1514, 1464, 1370, 1302, 1246, 1219, 1173, 1090, 1036, 884, 821, 745; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.41 (m, 4 H), 7.23 (m, 14 H), 6.82 (m, 8 H), 6.34 (d, *J* = 3.85 Hz, 1 H), 6.22 (d, *J* = 3.85 Hz, 1 H), 5.61 (s, 1 H), 5.56 (s, 1 H), 5.52 (s, 1 H), 5.50 (s, 1 H), 4.63 – 4.49 (m, 4 H), 4.29 – 4.41 (m, 4 H), 4.22 (d, *J* = 3.30 Hz, 1 H), 4.11 (d, *J* = 3.30 Hz, 1 H), 3.96 (t, *J* = 5.49 Hz, 1 H), 3.91 (dd, *J* = 4.40, 6.59 Hz, 1 H), 3.79 – 3.64 (m, 16 H), 1.96 (s, 3 H), 1.94 (s, 3 H), 1.01 (m, 42 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.5, 169.4, 159.2, 159.1, 158.9, 142.8, 142.4, 132.9, 132.7, 130.8, 130.6, 129.8, 129.5, 129.2 (2), 129.1, 128.9, 127.9, 127.8, 117.4, 116.3, 113.7, 113.6, 113.5, 83.5, 81.5, 80.5, 80.4, 79.1, 78.9, 70.9, 70.7, 70.6, 67.2, 66.9, 55.2, 20.9, 20.8, 18.0, 17.9, 11.8; HRMS (CI) *m/z* 712.3697 [(M + $NH_4)^+$; calcd for $C_{39}H_{58}O_7SSiN$, 712.3703].

Preparation of alcohol (94):

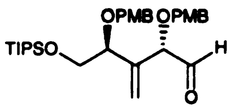


94

To a cold (0 °C) solution of α-acetoxy sulfide **93** (0.28 g, 0.43 mmol) in THF (5 mL) was added dropwise (~4 minutes) Super-Hydride® (1.4 mL, 1.0 M THF, 1.4 mmol). The ice bath was removed. After stirring at room temperature for 30 minutes, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (2.2 mL) and glycerol (0.66 mL, 0.3 mL/mmol) and diluted with Et_2O (20 mL). After stirring for several hours, the phases were separated. The organic phase was washed with brine (2 mL x 2), dried over

$MgSO_4$, filtered and concentrated to give 0.45 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 0.18 g (82%) of alcohol **94** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3453, 2944, 2867, 1613, 1514, 1464, 1302, 1248, 1173, 1094, 1067, 1038, 884, 822; $[\alpha]_{589}^{20}$ +64.9° (c 0.5825, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (m, 4 H), 6.84 (m, 4 H), 5.46 (s, 1 H), 5.44 (s, 1 H), 4.56 (ABq, *J* = 11.54 Hz, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.38 (ABq, *J* = 11.54 Hz, 1 H), 4.26 (ABq, *J* = 10.99 Hz, 1 H), 4.01 (dd, *J* = 4.40, 7.14 Hz, 1 H), 3.90 (t, *J* = 6.04 Hz, 1 H), 3.78 (m, 7 H), 3.68 (dd, *J* = 5.49, 10.44 Hz, 1 H), 3.62 – 3.48 (m, 2 H), 2.40 (dd, *J* = 4.40, 8.79, -OH), 1.02 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 144.0, 130.3, 130.2, 129.4, 129.2, 116.9, 113.9, 113.7, 80.3, 79.9, 70.7, 70.3, 66.3, 65.3, 55.3, 17.9, 11.9; HRMS (FAB, NBA + KI) *m/z* 583.2838 [$(M + K)^+$; calcd for $C_{31}H_{48}O_6SiK$, 583.2857].

Preparation of aldehyde (95):

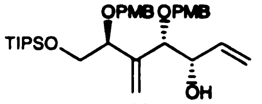


95

To a stirred solution of Dess-Martin periodinane (0.24 g, 0.57 mmol) in CH_2Cl_2 (10 mL) were added pyridine (0.050 mL, 0.57 mmol) and a solution of alcohol **94** (0.28 g, 0.51 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 3 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (8 mL) and diluted with hexanes (40 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with water (1 mL), a saturated aqueous $CuSO_4$

solution (1 mL x 2), water (1 mL) and brine (1 mL), dried over Na_2SO_4, filtered and concentrated to give 0.26 g (91%) of aldehyde **95** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2944, 2867, 1734, 1613, 1514, 1464, 1302, 1250, 1175, 1092, 1036, 884, 820; $[\alpha]^{20}_{589}$ +21.2° (c 0.865, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.46 (d, J = 1.47 Hz, 1 H), 7.23 (m, 4 H), 6.85 (d, J = 8.79 Hz, 2 H), 6.82 (d, J = 8.79 Hz, 2 H), 5.48 (s, 1 H), 5.46 (s, 1 H), 4.56 (ABq, J = 11.72 Hz, 1 H), 4.43 (ABq, J = 11.72 Hz, 1 H), 4.41 (ABq, J = 11.72, 1 H), 4.26 (s, 1 H), 4.24 (ABq, J = 11.72 Hz, 1 H), 3.94 (app t, J = 5.37 and 6.35 Hz, 1 H), 3.84 (dd, J = 6.84, 10.25 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.68 (dd, J = 5.37, 10.25 Hz, 1 H), 1.0 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.0, 159.1, 141.4, 130.2, 129.5, 129.4, 129.1, 119.4, 113.8, 113.6, 84.2, 80.9, 70.7, 70.6, 66.2, 55.2, 17.9, 11.8.

Preparation of alcohol (96):

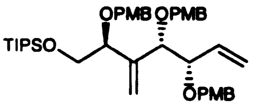


96

To a solution of crude aldehyde **95** (0.16 g, 0.30 mmol) in Et_2O/PhH (3:1) (4 mL) was added $MgBr_2 \bullet Et_2O$ (0.31 mL, 1.0 M Et_2O/PhH (3:1), 0.31 mmol). The mixture was then cooled to 0 °C. Vinyl magnesium bromide (0.44 mL, 1.0 M THF, 0.44 mmol) was added dropwise. After stirring for 40 minutes at 0 °C, the reaction was quenched with a saturated aqueous NH_4Cl solution (0.5 mL) and water (0.1 mL). Et_2O (1 mL) was added, and the phases separated. The organic phase was washed with water (0.2 mL) and brine (0.2 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.16 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%

→ 25%] to give 0.12 g (71 %) of vinyl addition alcohol **96** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3456, 2961, 2944, 2867, 1613, 1514, 1464, 1302, 1250, 1173, 1090, 1038, 922, 884, 801; $[\alpha]^{20}_{589}$ +51.3° (c 0.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.24 Hz, 2 H), 7.20 (d, *J* = 8.79 Hz, 2 H), 6.85 (d, *J* = 8.79 Hz, 2 H), 6.83 (d, *J* = 8.24 Hz, 2 H), 5.81 (ddd, *J* = 17.03, 10.99, 6.04 Hz, 1 H), 5.52 (s, 1 H), 5.43 (s, 1 H), 5.32 (dt, *J* = 17.03, 1.65 Hz, 1 H), 5.15 (dt, *J* = 10.44, 1.65 Hz, 1 H), 4.57 (ABq, *J* = 11.54 Hz, 1 H), 4.56 (ABq, *J* = 11.54 Hz, 1 H), 4.43 (ABq, *J* = 11.54 Hz, 1 H), 4.23 (ABq, *J* = 10.99 Hz, 1 H), 4.09 (m, 1 H), 3.93 (t, *J* = 5.49 Hz, 1 H), 3.80 – 3.70 (m, 9 H), 2.89 (d, *J* = 3.85 Hz, -OH), 1.03 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 159.0, 143.7, 136.7, 130.6, 129.9, 129.4, 129.2, 116.8, 113.8, 113.7, 82.3, 80.4, 74.4, 71.0, 70.4, 66.7, 55.3, 17.8, 11.9; HRMS (CI) *m/z* 588.3718 [$(M + NH_4)^+$; calcd for $C_{33}H_{54}O_6NSi$, 588.3720].

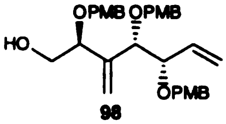
Protection of alcohol (96) to give PMB-ether (97):



97

To a cold (0 °C) solution of alcohol **96** (0.16 g, 0.28 mmol) in THF (4 mL) was added NaHMDS (0.31 mL, 1.0 M THF, 0.31 mmol) dropwise. The ice bath was removed and the reaction stirred at room temperature for 20 minutes, after which time DMSO (1.3 mL) and PMBCl (0.053 mL, 0.392 mmol) were added. After stirring for 3 hours, the reaction was quenched with a saturated aqueous NH_4Cl solution (0.3 mL) and water (0.3 mL) and then diluted with Et_2O (15 mL). The phases were separated, and the organic phase was washed with brine (0.3 mL x 2). The combined aqueous phase was extracted with Et_2O (1 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.47 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.15 g (79 %) of fully protected tetra-ol **97** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2961, 2865, 1613, 1586, 1512, 1464, 1302, 1250, 1173, 1068, 1036, 922, 882, 802; $[\alpha]^{20}_{589}$ +40.3° (c 0.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 8.24 Hz, 6 H), 6.81 (m, 6 H), 5.82 (m, 1 H), 5.50 (s, 1 H), 5.39 (s, 1 H), 5.27 (d, *J* = 2.75 Hz, 1 H), 5.22 (s, 1 H), 4.50 (series ABq, 3 H), 4.30 (series ABq, 3 H), 3.91 (m, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.63 (m, 2 H), 1.01 (s, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.9, 158.8, 143.9, 135.3, 131.2, 130.6, 130.5, 129.4, 129.3, 129.1, 118.3, 114.9, 113.7, 113.6, 113.5 (2), 81.9, 81.0, 80.3, 70.8, 70.5, 70.4, 67.2, 55.2, 18.0, 11.9; HRMS (CI) *m/z* 708.4292 [$(M + NH_4)^+$; calcd for $C_{41}H_{62}O_7NSi$, 708.4296].

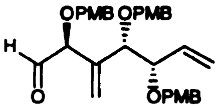
Deprotection of TIPS-silyl ether (97) to give alcohol (98):



98

To a solution of TIPS-silyl ether **97** (0.15 g, 0.22 mmol) in THF (2 mL) was added TBAF (0.24 mL, 1.0 M THF, 0.24 mmol) dropwise. After stirring for 30 minutes, the reaction was diluted with Et_2O (12 mL) and water (0.4 mL). The phases were separated, and the organic phase was washed with brine (0.30 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.15 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/ EtOAc 25%] to give 0.11 g (94 %) of alcohol **98** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3445, 2961, 2865, 1613, 1586, 1514, 1464, 1302, 1248, 1173, 1068, 1034, 926, 816; $[\alpha]_{589}^{20}$ +62.2° (c 0.31, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.21$ (m, 6 H), 6.84 (m, 6 H), 5.86 (ddd, $J = 17.03, 10.44, 6.59$ Hz, 1 H), 5.53 (s, 1 H), 5.46 (s, 1 H), 5.31 (m, 2 H), 4.56 (ABq, $J = 11.54$ Hz, 2 H), 4.50 (ABq, $J = 10.99$ Hz, 1 H), 4.34 (ABq, $J = 11.54$ Hz, 1 H), 4.33 (ABq, $J = 12.09$ Hz, 1 H), 4.12 (ABq, $J = 10.99$ Hz, 1 H), 4.00 (m, 2 H), 3.87 (d, $J = 4.94$ Hz, 1 H), 3.80 (s, 6 H), 3.77 (s, 3 H), 3.54 (m, 1 H), 3.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 159.1$, 159.0, 142.7, 134.8, 130.3, 130.2, 130.1, 129.5, 129.4, 129.2, 118.8, 116.1, 113.7, 113.6, 81.6, 80.6, 79.6, 70.6, 70.4, 70.4, 64.9, 55.1.

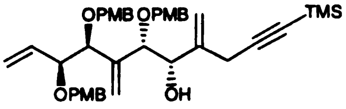
Preparation of aldehyde (99):



99

To a stirred solution of Dess-Martin periodinane (0.096 g, 0.23 mmol) in CH_2Cl_2 (4 mL) were added pyridine (0.020 mL, 0.23 mmol) and a solution of alcohol **98** (0.11 g, 0.21 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 2 hours at room temperature, the reaction was quenched with the addition of a saturated aqueous $NaHCO_3$ /10% aqueous $Na_2S_2O_3$ (1:1) solution (4 mL) and diluted with Et_2O (25 mL). After stirring for 2 hours, the phases were separated. The organic phase was washed with water (0.8 mL), a saturated aqueous $CuSO_4$ solution (0.8 mL x 2), water (0.8 mL) and brine (1.5 mL), dried over Na_2SO_4, filtered and concentrated to give 0.10 g (92 %) of aldehyde **99** as a yellow oil. IR (neat, 4 cm^{-1}): $\nu = 2944$, 2867, 1734, 1613, 1514, 1464, 1302, 1250, 1175, 1092, 1036, 884, 820; $[\alpha]_{589}^{20}$ +10.8° (c 0.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 9.36$ (d, $J = 1.65$ Hz, 1 H), 7.20 (m, 6 H), 6.83 (m, 6 H), 5.76 (m, 1 H), 5.51 (s, 1 H), 5.45 (s, 1 H), 5.27 (s, 1 H), 5.23 (dd, *J* = 6.59, 1.65 Hz, 1 H), 4.49 (ABq, *J* = 11.54 Hz, 2 H), 4.44 (ABq, *J* = 11.54 Hz, 1 H), 4.33 (ABq, *J* = 11.54 Hz, 1 H), 4.32 (m, 1 H), 4.31 (ABq, *J* = 10.99 Hz, 1 H), 4.23 (ABq, *J* = 11.54 Hz, 1 H), 4.0 (m, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.1, 159.3, 159.1, 159.0, 140.3, 134.7, 130.3, 130.1, 129.5, 129.4, 129.3, 118.7, 113.8, 113.6, 84.3, 81.6, 80.6, 71.1, 70.9, 70.5, 55.2.

Preparation of alcohol (100):

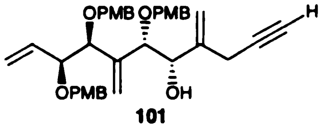


100

t-BuLi (0.30 mL, 1.7 M pentane, 0.507 mmol) was added dropwise to a Et_2O (1.5 mL) at –78 °C. A solution of vinyl bromide **B** (0.55 g, 0.25 mmol) in Et_2O (0.6 mL) was added dropwise to the *t*-BuLi solution. After stirring for 10 minutes, $MgBr_2 \bullet Et_2O$ (0.27 mL, 1.0 M Et_2O/PhH (3:1), 0.27 mmol) was added and stirred at –78 °C for 15 minutes and then at 0 °C for 10 minutes and then lowered back to –78 °C. In a separate flask, crude aldehyde **99** (90 mg, 0.17 mmol) was dissolved in an Et_2O/benzene/CH_2Cl_2 (3:1:1) solution (1.5 mL) and cooled to 0 °C and $MgBr_2 \bullet Et_2O$ (0.17 mL, 1.0 M Et_2O/PhH (3:1), 0.17 mmol) was added. The Grignard solution of **B** was transferred via cannula to the precomplexed aldehyde solution. After stirring for 2 hours at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (0.2 mL) and water (0.1 mL). The phases were separated, and the organic phase was washed with water (0.2 mL) and brine (0.2 mL x 2). The combined aqueous phases were extracted with Et_2O (2x). The combined organics were dried over

$MgSO_4$, filtered and concentrated to give 0.11 g of a yellow oil, which was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 63 mg (56 %) of a diastereomeric mixture of alcohol **100** as a yellow oil.

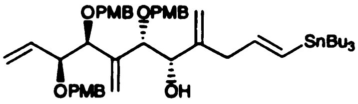
Preparation of alkyne (101) via TMS deprotection:



101

To a solution of TMS-alkyne **100** (0.033 g, 0.049 mmol) in THF (1 mL) was added dropwise an acetic acid buffered TBAF solution (1.05:1) (0.060 mL, 0.060 mmol, 1.0M THF). After stirring for 4 hours at room temperature, Et_2O (4 mL) was added to the reaction and which was then quenched by the addition of a saturated aqueous $NaHCO_3$ solution (0.06 mL) and water (0.1 mL). The phases were separated. The organic phase was washed with brine (0.2 mL), dried over $MgSO_4$, filtered and concentrated to give 29 mg (98 %) of alkyne **101** as a yellow oil, which was used crude in the subsequent reaction.

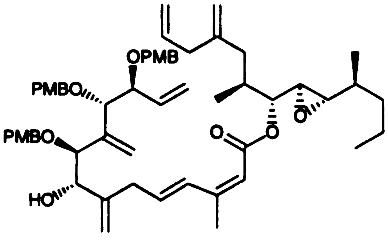
Hydrostannylation of alkyne "101" to give vinyl stannane "102":



102

$(Ph_3P)_2PdCl_2$ (0.3 mg, 0.0005 mmol) and Red-Sil (0.089 g, 0.1872 mmol, 2.1 mmol/g) were added to Et_2O (0.5mL). A solution of crude alkyne **101** (0.028 g, 0.047 mmol) in Et_2O (0.5 mL), Bu_3SnF (0.019 g, 0.0608 mmol) and a drop of TBAF (1.0 M THF) were added. After stirring for 2.5 hours at room temperature, the reaction was filtered through a pad of Celite on a glass frit . The Red-Sil filter cake was washed several times with ether. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 31 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 17 mg (41%) of (E)-vinyl stannane **102** as a diastereomeric regio-mixture.

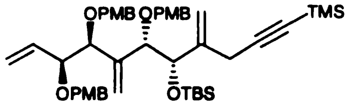
Preparation of diene (103) via Stille reaction:



103

A solution of Pd_2dba_3 (0.6 mg, 0.0006 mmol) and $AsPh_3$ (0.8 mg, 0.0025 mmol) in NMP (0.1 mL) was stirred at room temperature for 10 minutes and followed by the addition of vinyl iodide **300**[50] (0.014 g, 0.0315 mmol) as an NMP solution (0.1 mL) to the yellowish-green solution. The reaction was immersed into a preheated oil bath (~45 °C) and a solution of vinyl stannane **102** (0.028 g, 0.0315 mmol) in NMP (0.2 mL) was added immediately. After stirring for 18 hours at 50 °C, the reaction was allowed to cool to room temperature and was then diluted with Et_2O (6 mL). The organic phase was washed with water (0.2 mL), brine (0.2 mL), a saturated aqueous KF solution (0.2 mL x 2) and brine (0.2 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.11 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 7 mg (24%) of a diastereomeric mixture of diene **103** as a yellow oil.

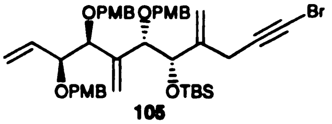
Preparation of TBS-ether (104):



104

To a solution of alcohol **100** (0.057 g, 0.085 mmol) in CH_2Cl_2 (0.5 mL) were added 2,6-lutidine (0.020 mL, 0.17 mmol) and TBSOTf (0.030 mL, 0.13 mmol). After stirring for 10 minutes, the reaction was quenched with water (0.1 mL) and a saturated aqueous NH_4Cl solution (0.1 mL). The reaction was diluted with Et_2O (5 mL), and the phases were separated. The organic phase was washed with brine (0.2 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 91 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 48 mg (72%) of a diastereomeric mixture of TBS-protected alcohol **104** as a clear oil.

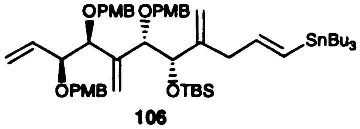
Preparation of 1-bromo-alkyne (105):



105

TMS-alkyne **104** (0.048 g, 0.06 mmol) were dissolved in acetone (0.5 mL). NBS (0.013 g, 0.073 mmol) and $AgNO_3$ (1 mg, 0.006 mmol) were added to the solution. After stirring for 65 minutes, the reaction mixture was diluted with water (0.25 mL) and Et_2O (2.5 mL). The phases were separated, and the organic phase was washed with brine (0.1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 44 mg (90%) of a yellow oil, which was used crude in the subsequent reaction.

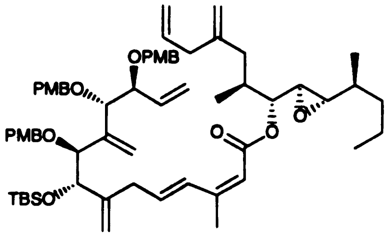
Preparation of vinyl stannane (106):



106

$(Ph_3P)_2PdCl_2$ (0.4 mg, 0.0005 mmol) and Red-Sil (0.21 g, 0.43 mmol, 2.1 mmol/g) were added to Et_2O (0.6 mL). A solution of crude 1-bromo-alkyne **105** (0.043 g, 0.054 mmol) in Et_2O (0.6 mL), Bu_3SnF (0.037 g, 0.12 mmol) and a drop of TBAF (1.0 M THF) were added. After stirring for 1.5 hours at room temperature, the reaction was filtered through a pad of Celite on a glass frit. The residual Red-Sil was washed several times with Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 69 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 31 mg (57%) of diastereomeric mixture of vinyl stannane **106** as a yellow oil.

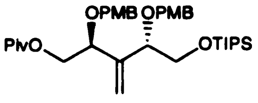
Preparation of diene (107) via Liebeskind's coupling:



107

To a solution of (Z)-vinyl iodide **300**^{50} (0.014 g, 0.031 mmol) in NMP (0.2 mL) was added copper (I) thiophene-2-carboxylate (CuTc) (0.009 g, 0.05 mmol). To this suspension was added a solution of vinyl stannane **106** in NMP (0.2 mL). After stirring for 50 minutes, the reaction was diluted with Et_2O (10 mL) and filtered through a bed of Celite. The green filter cake was washed with Et_2O (3 mL). The clear filtrate was washed with water (0.6 mL x 3), a saturated aqueous KF solution (0.5 mL x 2), and brine (0.6 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 51 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 16 mg (49%) of a diastereomeric mixture of diene **107** as a pink oil.

Preparation of Piv-ester (108):



108

To a cold (0 °C) solution of alcohol **94** (0.092 g, 0.17 mmol) in CH_2Cl_2 (1.5 mL) were added pyridine (0.027 mL, 0.34 mmol) and a solution of PivCl (0.025 mL, 0.20 mmol) in CH_2Cl_2 (0.2 mL) dropwise. After stirring for 2.5 hours, the ice bath was removed and the reaction stirred at room temperature for 30 minutes. The reaction was quenched by the addition of water (0.1 mL) and then diluted with Et_2O (4 mL). The phases were separated, and the organic phase was washed with a saturated aqueous $CuSO_4$ solution (0.2 mL x 2), water (0.2 mL x 2) and brine. The organics were dried over $MgSO_4$, filtered and concentrated to give 0.15 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 78 mg (74%) of fully protected tetra-ol **108** as a clear oil.

Preparation of alcohol (109):

109

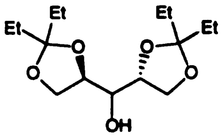
To a solution of crude fully protected tetra-ol **108** (1.69 g, 2.31 mmol) in THF (15 mL) was added TBAF (2.8 mL, 1.0 M THF, 2.8 mmol) dropwise. After stirring for 5.5 hours the reaction was judged complete by TLC analysis. The reaction was then diluted with Et_2O (40 mL) and water (2.5 mL) and the phases were separated. The organic phase was washed with brine (2.5 mL x 2). The combined aqueous phase was extracted with Et_2O (2 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.53 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 1.05 g (96% yield, 2 steps from **94**) of alcohol **109** as a clear oil.

*via diol (**118**):*

To a cold (0 °C) solution of diol **118** (1.19 g, 3.06 mmol) in CH_2Cl_2 (30 mL) were added pyridine (0.50 mL, 6.1 mmol) and a solution of PivCl (0.38 mL, 3.1 mmol) in CH_2Cl_2 (2 mL) dropwise (~3 minutes). After stirring for 18 hours between 0 °C and room temperature, the reaction was quenched by the addition of water (1 mL) and a saturated aqueous NH_4Cl solution (1 mL). Et_2O (35 mL) was added, and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (7 mL x 2), water (5 mL x 2) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated to give 1.40 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 35% → 75%] afforded 0.68 g (47%) of alcohol **109** as a clear oil and 0.33 g (28%) of recovered diol **118**. For **109**: IR (neat, 4 cm^{-1}): ν = 3492, 2965, 2872, 2838, 1728, 1613, 1588, 1514, 1646, 1399, 1364, 1302, 1285, 1250, 1173, 1139, 1073, 1036, 927, 820; $[\alpha]_{589}^{20}$ +91.3° (c 1.095, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* =

8.79 Hz, 4 H), 6.86 (d, J = 8.79 Hz, 2 H), 6.84 (d, J = 8.79 Hz, 2 H), 5.50 (s, 2 H), 4.55 (ABq, J = 11.54 Hz, 1 H), 4.54 (ABq, J = 11.54 Hz, 1 H), 4.33 (ABq, J = 11.54 Hz, 1 H), 4.25 (ABq, J = 11.54, 1 H), 4.14 – 4.07 (m, 2 H), 4.03 – 3.95 (m, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.56 (m, 2 H), 2.22 (dd, J = 8.79, 4.94 Hz, 1 H), 1.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.3, 159.3 (2), 142.5, 129.9, 129.8, 129.5, 129.3, 117.2, 113.9, 113.8, 80.0, 70.5, 65.7, 65.3, 60.4, 55.2, 38.7, 27.2.

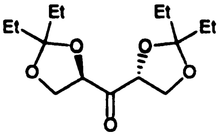
Preparation of bisisopentylidene acetal (111):



111

To a 40 °C slurry of D-arabitol (15 g, 99 mmol) in DMF (15 mL) containing CSA (0.70 g, 3.0 mmol) was added 3,3-dimethoxypentane (29.0 g, 217 mmol) dropwise (~40 minutes). After stirring for an additional 5.5 hours, the reaction was quenched with Et_3N (0.45 mL) and then concentrated via rotovap at 60 °C to afford a crude oil. The residue was diluted with Et_2O (200 mL) and then washed with brine (50 mL x 4), dried over $MgSO_4$, filtered and concentrated to give 26 g (90%) of acetal **111** as a clear oil.

Preparation of ketone (112):

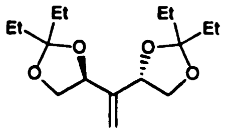


112

To a solution of alcohol **111** (1.0 g, 3.5 mmol) in CH_2Cl_2 (35 mL) were added DMSO (2.46 mL, 34.7 mmol), i-Pr_2NEt (3.62 mL, 20.8 mmol) and

SO_3•pyridine (1.65 g, 10.4 mmol). After stirring at room temperature for 90 minutes, the reaction was quenched with a saturated aqueous NH_4Cl solution (70 mL) and water (6 mL). Et_2O (140 mL) was added, and the phases were separated. The organic phase was washed with brine (20 x 2). The combined aqueous phase was extracted with Et_2O (20 mL x 3). The combined organics were dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 0.68 g (68%) of ketone **112** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2975, 2944, 2884, 1736, 1464, 1360, 1262, 1201, 1173, 1082, 1061, 912, 799; $[\alpha]^{20}_{589}$ +62.4° (c 0.66, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 4.82 (t, J = 7.14 or 7.69 Hz, 2 H), 4.31 (t, J = 7.69 or 8.24 Hz, 2 H), 3.96 (dd, J = 7.14, 8.79 Hz, 2 H), 1.69 (m, 8 H), 0.93 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.3, 114.9, 78.7, 66.2, 29.1, 28.2, 8.2, 8.0.

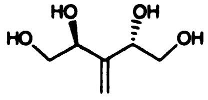
Preparation of alkene (113):



113

To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (1.35 g, 3.77 mmol) in THF (5 mL) was added NaHMDS (3.5 mL, 1.0 M THF, 3.5 mmol) dropwise. The ice bath was removed and the reaction stirred at room temperature for 30 minutes before the temperature was lowered back to 0 °C. A solution of ketone **112** (0.20 g, 0.70 mmol) in THF (1 mL) was added dropwise and the reaction stirred for 3 hours at room temperature. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (5 mL) and water (5 mL). The reaction was diluted Et_2O (15 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (5 mL x 2). The combined organic phase was washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated to give an oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 0.196 g (99%) of alkene **113** as a clear oil. IR (neat, 4 cm^{-1}): $\nu = 2975, 2942, 2882, 1464, 1356, 1271, 1198, 1173, 1132, 1080, 1059, 1040, 920$; $[\alpha]^{20}_{589}$ +63.1° (c 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 5.29 (br s, 2 H), 4.50 (dd, *J* = 6.04, 8.79 Hz, 2 H), 4.18 (dd, *J* = 6.04, 7.69 Hz, 2 H), 3.55 (dd, *J* = 7.69, 8.79 Hz, 2 H), 1.64 (m, 4 H), 0.90 (t, *J* = 7.69 Hz, 3 H), 0.89 (t, *J* = 7.69 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6, 112.8, 76.1, 70.0, 29.7, 29.4, 8.1 (2).

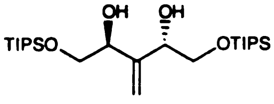
Hydrolysis of acetal (113) to give tetra-ol (114):



114

To a solution of bisisopentylidene acetal **113** (5.08 g, 17.9 mmol) in $MeOH/CH_2Cl_2$ (2:1) (180 mL) was added CSA (0.83 g, 3.6 mmol) and water (3 mL). The reaction flask was immersed into a preheated oil bath (~40 °C). After stirring for 8.5 hours, the reaction was allowed to cool to room temperature and then concentrated under high vacuum overnight to give 3.73 g of crude tetra-ol **114** as a yellow oil.

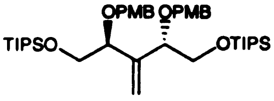
Preparation of TIPS-ether (115):



115

To a solution of crude tetra-ol **114** (from above) in CH_2Cl_2/DMF (1:1) (130 mL) were added imidazole (4.86 g, 71.4 mmol), DMAP (0.22 g, 1.8 mmol) and TIPSCl (8.0 mL, 37 mmol). After stirring for 12 hours, the reaction was concentrated to give a yellow residue. CH_2Cl_2 (150 mL) was added to the residue and then washed with water (25 mL) and brine (25 mL x 2). The organics were dried over $MgSO_4$, filtered and concentrated to give 9.54 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10% → 50%] afforded 6.3 g (77% yield, 2 steps) of TIPS disilylated tetra-ol **115** as a clear oil and 1.04 g (19% yield, 2 steps) of TIPS monosilylated tetra-ol **115a** as a white solid.

Preparation of fully protected tetra-ol (116):

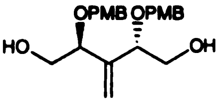


116

To a solution of tetra-ol **115** (2.30 g, 4.99 mmol) in cyclohexane/CH_2Cl_2 (3:1) (44 mL) were added PMB-imidate (5.64 g, 20 mmol) and CSA (0.12 g, 0.50 mmol). The reaction flask was immersed into a preheated oil bath (~40 °C). After stirring for 24 hours, additional CSA (60 mg) and PMB-imidate (2.8 g) were added. After stirring for a total of 50 hours, the reaction was allowed to cool to room temperature and was then quenched with a saturated aqueous $NaHCO_3$ solution (3 mL). Et_2O (80 mL) was added and the phases were separated. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (3 mL x

2) and brine (4 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give a milky white solid. Hexanes were added to the residue. After stirring for several hours, the mixture was filtered and concentrated to give 5.3 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 1.35 g (38%) of fully protected tetra-ol **116** as a clear oil and 1.06 g (37%) of mono-protected PMB-ether derivative **117**.

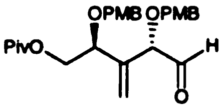
Deprotection of TIPS-ether (116) to give diol (118):



118

To a solution of TIPS disilylated tetra-ol **116** (5.97 g, 8.51 mmol) in THF (90 mL) was added TBAF (19 mL, 1.0 M THF, 19 mmol) dropwise (~25 minutes). After stirring an additional 1.5 hours, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL) and water (10 mL). Et_2O (300 mL) was added and the phases were separated. The organic phase was washed with brine (10 mL x 2). The combined aqueous phases were extracted with Et_2O (10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 7.6 g of a yellow oil, which was used crude in subsequent reactions.

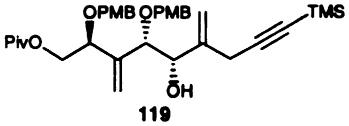
Preparation of aldehyde (110):



110

To a stirred solution of Dess-Martin periodinane (0.50 g, 1.2 mmol) in CH_2Cl_2 (20 mL) were added pyridine (0.10 mL, 1.187 mmol) and a solution of alcohol **109** (0.51 g, 1.1 mmol) in CH_2Cl_2 (2 mL). After stirring for 4 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (20 mL) and diluted with Et_2O (100 mL). After stirring for 30 minutes, the phases were separated. The organic phase was washed with water (4 mL), a saturated aqueous $CuSO_4$ solution (4 mL x 2), water (4 mL x 2) and brine (8 mL), dried over Na_2SO_4, filtered and concentrated to give 0.50 g (100%) of crude aldehyde **110** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2963, 2870, 2837, 1730, 1613, 1514, 1464, 1397, 1366, 1283, 1250, 1173, 1157, 1078, 1034, 822; $[\alpha]_{589}^{20}$ +50.1° (c 0.685, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.51 (d, J = 1.65 Hz, 1 H), 7.23 (d, J = 8.79 Hz, 1 H), 7.19 (d, J = 8.79 Hz, 2 H), 6.85 (d, J = 8.79 Hz, 2 H), 6.83 (d, J = 8.79 Hz, 2 H), 5.51 (s, 1 H), 5.48 (s, 1 H), 4.57 (ABq, J = 11.54 Hz, 1 H), 4.44 (s, 1 H), 4.38 (ABq, J = 11.54 Hz, 1 H), 4.13 – 4.22 (m, 3 H), 4.06 – 4.12 (m, 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.1, 178.1, 159.5, 159.2, 140.3, 129.6, 129.5, 128.7, 120.5, 113.9, 113.7, 84.0, 77.9, 70.9, 70.5, 65.6, 55.2, 38.6, 27.1.

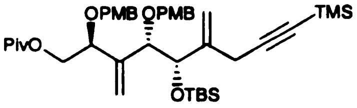
Preparation of alcohol (119) – Fragment AB coupling:



119

t-BuLi (2.85 mL, 1.7 M pentane, 4.85 mmol) was added dropwise to Et_2O (12 mL) at –78 °C. A solution of vinyl bromide **B** (0.52 g, 2.4 mmol) in Et_2O (5 mL) was added dropwise to the *t*-BuLi solution. After stirring for 10 minutes, $MgBr_2 \bullet Et_2O$ (2.60 mL, 1.0 M Et_2O/PhH (3:1), 2.60 mmol) was added and the reaction stirred at –78 °C for 15 minutes and then at 0 °C for 10 minutes. In a separate flask, to a 0 °C solution of crude aldehyde **110** (0.76 g, 1.62 mmol) in CH_2Cl_2 (8 mL) was added $MgBr_2{\bullet}Et_2O$ (1.60 mL, 1.0 M Et_2O/PhH (3:1) 1.60 mmol) and the solution stirred for several minutes. The Grignard solution was transferred via cannula to the precomplexed aldehyde solution. After stirring for 45 minutes at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1.5 mL) and water (1.5 mL). The reaction was diluted with Et_2O and the phases were separated. The organic phase was washed with water (0.7 mL) and brine (0.7 mL x 2). The combined aqueous phases were extracted with Et_2O (2x). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.11 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 0.57 g (58%) of alcohol **119** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3382, 2961, 2917, 2885, 2178, 1727, 1653, 1617, 1514, 1458, 1250, 1154, 1036, 843, 760; $[\alpha]^{20}_{589}$ +72.3° (c 0.495, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.39 Hz, 2 H), 7.19 (d, *J* = 8.39 Hz, 2 H), 6.85 (d, *J* = 8.39 Hz, 2 H), 6.84 (d, *J* = 8.39 Hz, 2 H), 5.57 (s, 1 H), 5.48 (s, 1 H), 5.36 (s, 1 H), 5.19 (s, 3 H), 4.53 (ABq, *J* = 10.99 Hz, 1 H), 4.51 (ABq, *J* = 11.54 Hz, 1 H), 4.36 (ABq, *J* = 11.54 Hz, 1 H), 4.29 (d, *J* = 9.34 Hz, 1 H), 4.24 (ABq, *J* = 10.99 Hz, 1 H), 3.97 – 4.14 (series m, 2 H), 3.90 (d, *J* = 4.94 Hz, 1 H), 3.78 (m, 1 H), 3.78 (s, 1 H), 3.77 (s, 3 H), 3.06 (ABq, *J* = 19.78 Hz, 1 H), 2.92 (ABq, *J* = 19.78 Hz, 1 H), 2.85 (d, *J* = 4.40 Hz, 1 H), 1.18 (s, 9 H), 0.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.3, 159.5, 159.4, 143.1, 142.7, 130.3, 129.7, 129.5, 129.2, 116.8, 114.7, 114.0, 113.9, 103.6, 87.8, 80.4, 77.6, 76.0, 71.2, 70.9, 66.1, 55.3, 38.8, 27.2, 23.4, 0.07; HRMS (CI) *m/z* 626.3513 [(M + NH_4)$^+$; calcd for $C_{35}H_{52}O_7SiN$, 626.3501].

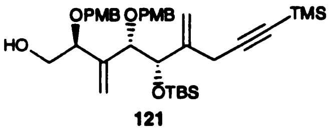
Preparation of TBS-ether (120):



120

To a cold (0 °C) solution of alcohol **119** (1.11 g, 1.82 mmol) in CH_2Cl_2 (18 mL) was added 2,6-lutidine (0.27 mL, 2.3 mmol) and TBSOTf (0.48 mL, 2.1 mmol). After stirring for 30 minutes at 0 °C, the reaction was quenched with water (1.4 mL) and a saturated aqueous NH_4Cl solution (1.4 mL). The reaction was diluted with Et_2O (90 mL) and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (1 mL x 2), water (1 mL x 2) and brine (2 mL), dried over $MgSO_4$, filtered and concentrated to give 1.36 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 1.07 g (81 %) of TBS-silylated alcohol **120** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2955, 2858, 2174, 1720, 1613, 1587, 1514, 1464, 1362, 1302, 1157, 1099, 862, 841; $[\alpha]_{589}^{20}$ +19.8° (c 0.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.79 Hz, 4 H), 6.89 (d, *J* = 8.24 Hz, 4 H), 5.57 (s, 1 H), 5.41 (s, 1 H), 5.33 (d, *J* = 1.65 Hz, 1 H), 5.16 (s, 1 H), 4.56 (ABq, *J* = 11.54 Hz, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.46 (d, *J* = 4.94 Hz, 1 H), 4.35 (ABq, *J* = 10.99 Hz, 1 H), 4.33 (ABq, *J* = 10.99 Hz, 1 H), 4.23 – 4.27 (m, 2 H), 3.90 – 4.0 (m, 2 H), 3.83 (s, 3 H), 3.82 (s, 3 H), 3.20 (ABq, *J* = 19.78 Hz, 1 H), 3.10 (ABq, *J* = 19.78 z, 1 H), 1.24 (s, 9 H), 0.87 (s, 9 H), 0.19 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.4, 159.0, 142.9, 142.6, 130.7, 130.4, 129.0 (2), 114.3, 113.7, 104.3, 86.9, 81.0, 78.1, 77.3, 71.2, 70.9, 66.1, 55.2, 38.7, 27.2, 25.6, 24.4, 18.1, 0.1, -5.1; HRMS (FAB) *m/z* 723.4119 [$(M + NH_4)^+$; calcd for $C_{41}H_{66}O_7Si_2N$, 723.4112].

Preparation of alcohol (121):

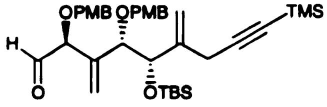


121

To a cold (0 °C) solution of Piv-ester **120** (1.07 g, 1.48 mmol) in THF (12 mL) was added dropwise (~3 minutes) Super-Hydride® (3.11 mL, 1.0 M THF, 3.11 mmol). After stirring for 35 minutes, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (3.1 mL), glycerol (0.93 mL, 0.3 mL/mmol) and water (3.1 mL) and then the reaction mixture was diluted with Et_2O (100 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with brine (1.5 mL), 0.5 M NaOH (1.5 mL x 2), and brine (1.5 mL). The combined aqueous phases were extracted with Et_2O (3 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.33 g of a clear oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 0.83 g (88 %) of alcohol **121** as a clear oil. IR (neat, 4 cm^{-1}): ν =3455, 2957, 2932, 2897, 2859, 2176, 1613, 1514, 1464, 1302, 1250, 1173, 1096, 1063, 1038, 841, 777, 760; $[\alpha]_{589}^{20}$ +26.3° (c 0.51, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.79 Hz, 2 H), 7.22 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.47 (s, 1 H), 5.35 (s, 1 H), 5.29 (s, 1 H), 5.11 (s, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.50 (ABq, *J* = 12.09 Hz, 1 H), 4.40 (d, *J* = 5.49 Hz, 1 H), 4.28 (ABq, *J* = 11.54 Hz, 1

H), 4.23 (ABq, *J* = 10.99 Hz, 1 H), 4.08 (m, 1 H), 3.78 (s, 6 H), 3.78 (m, 1 H), 3.63 (m, 1 H), 3.39 (ddd, *J* = 4.40, 7.14, 11.54 Hz, 1 H), 3.16 (ABq, *J* = 19.29 Hz, 1 H), 3.04 (ABq, *J* = 19.78 Hz, 1 H), 2.14 (dd, *J* = 9.34, 3.85 Hz, 1 H), 0.84 (s, 9 H), 0.14 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 159.1, 142.9, 142.8, 130.5, 130.3, 129.3, 129.0, 114.5, 113.8, 113.7, 104.2, 80.7, 80.6, 70.9, 70.7, 64.8, 55.2, 25.8, 24.4, 18.2, 0.08, -5.1; HRMS (CI) *m/z* 639.3510 [(M + H)$^+$; calcd for $C_{36}H_{55}O_6Si_2$, 639.3537].

Preparation of aldehyde (122):



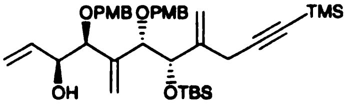
122

To a stirred solution of Dess-Martin periodinane (0.64 g, 1.5 mmol) in CH_2Cl_2 (25 mL) were added pyridine (0.13 mL, 1.5 mmol) and a solution of alcohol **121** (0.80 g, 1.3 mmol) in CH_2Cl_2 (5 mL). After stirring for 1.5 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (22 mL) and then diluted with Et_2O (170 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with water (4 mL), a saturated aqueous $CuSO_4$ solution (4 mL x 2), water (4 mL x 2) and brine (8 mL), dried over Na_2SO_4, filtered and concentrated to give 0.74 g (93%) of crude aldehyde **122** as a yellow oil.

IR ($CHCl_3$, 4 cm^{-1}): ν = 2955, 2857, 2174, 1730, 1613, 1588, 1514, 1464, 1362, 1304, 1101, 1003, 910, 862, 841; $[\alpha]_{589}^{20}$ -55.2° (c 0.545, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.33 (d, *J* = 2.75 Hz, 1 H), 7.24 (d, *J* = 8.79 Hz, 2 H), 7.20 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 6.83 (d, *J* = 8.79 Hz, 2 H), 5.52 (s, 1

H), 5.41 (s, 1 H), 5.26 (s, 1 H), 5.05 (s, 1 H), 4.52 (ABq, *J* = 11.54 Hz, 1 H), 4.42 (ABq, *J* = 11.54 Hz, 1 H), 4.42 – 4.32 (m, 3 H), 4.18 (ABq, *J* = 10.99 Hz, 1 H), 3.91 (d, *J* = 5.49 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.11 (ABq, *J* = 19.78 Hz, 1 H), 2.98 (ABq, *J* = 19.78 Hz, 1 H), 0.83 (s, 9 H), 0.14 (s, 9 H), -0.02 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.1, 159.4, 159.0, 142.9, 139.7, 130.3, 129.5, 129.4, 129.2, 117.0, 114.4, 113.9, 113.5, 104.3, 87.0, 84.3, 81.2, 71.6, 70.9, 55.2, 25.8, 24.0, 18.2, 0.08, -5.1, -5.2.

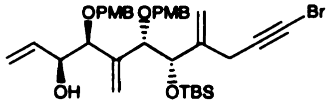
Preparation of alcohol (123):



123

To a cold (0 °C) solution of crude aldehyde **122** (0.74 g, 1.2 mmol) in a $Et_2O/PhH/CH_2Cl_2$ (3:1:1) solution (18 mL) was added $MgBr_2•Et_2O$ (1.3 mL, 1.0 M Et_2O/PhH (3:1), 1.3 mmol). After stirring for 6 minutes, vinyl magnesium bromide (2.3 mL, 1.0 M THF, 2.3 mmol) was added dropwise (~ 12 minutes). After stirring for 60 minutes at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1 mL) and water (1 mL). The reaction mixture was diluted with Et_2O (40 mL) and the phases separated. The organic phase was washed with water (2 mL) and brine (2 mL). The combined aqueous phases were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.74 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.45 g (58%) of alcohol **123** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3552, 2958, 2932, 2900, 2858, 2176, 1614, 1514, 1464, 1362, 1303, 1250, 1173, 1091, 1037, 921, 841, 779, 760; $[\alpha]_{589}^{20}$ +6.8° (c 0.575, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.39 Hz, 2 H), 7.22 (d, *J* = 8.39 Hz, 2 H), 6.86 (d, *J* = 8.39 Hz, 4 H), 5.90 (ddd, *J* = 17.23, 10.16, 5.30 Hz, 1 H), 5.50 (s, 1 H), 5.42 (s, 1 H), 5.33 (s, 1 H), 5.31 (m, 1 H), 5.18 (s, 1 H), 5.15 (m , 1 H), 4.55 (ABq, *J* = 11.49 Hz, 1 H), 4.54 (ABq, *J* = 11.05 Hz, 1 H), 4.50 (d, *J* = 4.86 Hz, 1 H), 4.35 (ABq, *J* = 11.49 Hz, 1 H), 4.23 (ABq, *J* = 10.60 Hz, 1 H), 4.03 (br s, 2 H), 3.93 (d, *J* = 4.86 Hz, 1 H), 3.79 (s, 6 H), 3.17 (ABq, *J* = 19.44 Hz, 1 H), 3.10 (ABq, *J* = 19.88 Hz, 1 H), 0.86 (s, 9 H), 0.16 (s, 9 H), 0.01 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 159.1, 143.1, 142.9, 138.2, 130.6, 130.5, 129.3, 129.1, 128.9, 116.1, 114.4, 113.8, 113.7, 104.5, 86.8, 82.1, 80.5, 73.5, 71.7, 70.8, 55.2, 25.9, 24.8, 18.3, 14.1, 0.10, -5.0, -5.1; HRMS (CI) *m/z* 665.3695 [(M + H)$^+$; calcd for $C_{38}H_{57}O_6Si_2$, 665.3694].

Preparation of 1-bromo-alkyne (124):

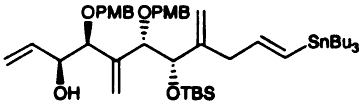


124

TMS-alkyne **123** (0.31 g, 0.47 mmol) was dissolved in acetone (5 mL) and NBS (0.10 g, 0.56 mmol) and $AgNO_3$ (0.020 g, 0.12 mmol) were added. After stirring for 3 hours the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of water (1 mL) and then diluted with Et_2O (35 mL). The phases were separated, and the organic phase was washed with brine (1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.43 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/ EtOAc 10%] afforded 0.28 g (92%) of 1-bromo-alkyne **124** as a clear oil. ^1H NMR (500

MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.84 Hz, 2 H), 7.22 (d, *J* = 8.39 Hz, 2 H), 6.86 (d, *J* = 8.84 Hz, 4 H), 5.89 (ddd, *J* = 16.79, 10.16, 5.30 Hz, 1 H), 5.50 (s, 1 H), 5.41 (s, 1 H), 5.32 (s, 1 H), 5.29 (s, 1 H), 5.18 (s, 1 H), 5.16 (s, 1 H), 4.55 (ABq, *J* = 11.93 Hz, 1 H), 4.53 (ABq, *J* = 10.60 Hz, 1 H), 4.41 (d, *J* = 4.86 Hz, 1 H), 4.31 (ABq, *J* = 11.93 Hz, 1 H), 4.23 (ABq, *J* = 11.05 Hz, 1 H), 4.02 (m, 2 H), 3.92 (d, *J* = 4.86 Hz, 1 H), 3.79 (s, 6 H), 3.17 (ABq, *J* = 19.44 Hz, 1 H), 3.04 (ABq, *J* = 19.44 Hz, 1 H), 2.45 (br s, -OH), 0.85 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 159.1, 142.9, 142.8, 138.1, 130.5, 130.4, 129.3, 129.0, 116.2, 114.5, 114.4, 113.7, 82.0, 80.5, 77.7, 77.5, 73.5, 71.7, 70.8, 55.2, 40.2, 29.5, 25.9, 24.3, 18.3, -5.1 (2); HRMS (FAB, NBA + KI) *m/z* 709.1994 [(M + K)$^+$; calcd for $C_{35}H_{47}O_6BrSiK$, 709.1962].

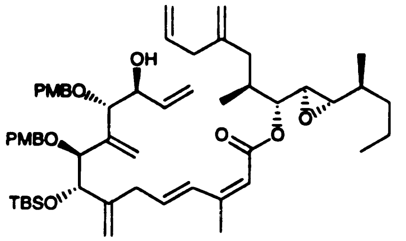
Preparation of vinyl stannane (125):



125

To a solution of $(Ph_3P)_2PdCl_2$ (2 mg, 0.003 mmol), Red-Sil (0.94 g, 2.0 mmol, 2.1 mmol/g), and Bu_3SnF (0.17 g, 0.55 mmol) in Et_2O (4.5 mL) was added of a solution of 1-bromo-alkyne **124** (0.167 g, 0.248 mmol) in Et_2O (0.5 mL) and a drop of TBAF (1.0 M THF). After stirring for 2.5 hours at room temperature, the reaction was filtered through a pad of Celite on a glass frit. The residual Red-Sil was washed several times with Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 0.27 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 15%] to give 0.16 g (73%) of E-vinyl stannane **125** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2955, 2928, 2855, 1613, 1514, 1464, 1361, 1302, 1250, 1173, 1084, 1040, 920, 835, 777; $[\alpha]^{20}_{589}$ +3.6° (c 0.555, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.84 Hz, 2 H), 7.21 (d, *J* = 8.84 Hz, 2 H), 6.85 (d, *J* = 8.84 Hz, 2 H), 6.84 (d, *J* = 8.84 Hz, 2 H), 5.95 – 5.85 (m, 3 H), 5.50 (s, 1 H), 5.45 (s, 1 H), 5.30 (m, 1 H), 5.16 (m, 1 H), 5.07 (s, 1 H), 4.94 (s, 1 H), 4.56 (ABq, *J* = 11.49 Hz, 1 H), 4.54 (ABq, *J* = 11.05 Hz, 1 H), 4.34 (m, 2 H), 4.20 (ABq, *J* = 11.05 Hz, 1 H), 4.03 (m, 2 H), 3.92 (d, *J* = 5.30 Hz, 1 H), 3.79 (s, 6 H), 3.0 (m, 2 H), 2.39 (d, *J* = 5.74 Hz, 1 H), 1.50 (m, 6 H), 1.30 (m, 6 H), 0.87 (m, 24 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 159.1, 146.6, 143.2, 138.3, 130.7, 130.6, 130.2, 129.3, 129.0, 116.0, 114.2, 113.7, 113.7, 113.1, 81.9, 80.8, 78.0, 73.4, 71.7, 70.7, 55.3, 55.2, 41.5, 29.1, 27.3, 25.9, 18.3, 13.7, 9.4, -4.9, -5.0; HRMS (EI) *m/z* 823.3694 $[(M - Bu)^+$; calcd for $C_{43}H_{37}O_6SiSn$, 823.3726].

Preparation of diene (126) via Liebeskind's coupling:

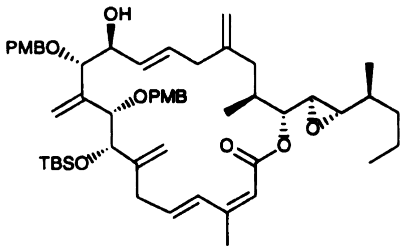


126

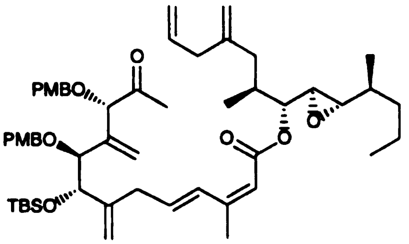
To a cold (0 °C) solution of (Z)-vinyl iodide **300**[50] (0.12 g, 0.27 mmol) in NMP (1 mL) was added copper (I) thiophene-2-carboxylate (CuTc) (0.039 g, 0.204 mmol). To this suspension was added a solution of vinyl stannane **125** (0.12 g, 0.14 mmol) in NMP (0.5 mL). After stirring 15 minutes at 0 °C, the ice bath was removed and the reaction stirred at room temperature for 15 minutes. The reaction mixture was diluted with Et_2O (20 mL) and filtered through a pad of

Celite on a glass frit. The green filter cake was washed with Et_2O (3x). The yellow filtrate was washed with water (2 mL x 3), a saturated aqueous KF solution (2 mL x 2), and brine (2 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.23 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 15%] to give 75 mg (60%) of diene **126** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3513, 3077, 2959, 2930, 1715, 1636, 1613, 1588, 1514, 1464, 1381, 1302, 1248, 1173, 1150, 1074, 1036, 914, 835, 779; $[\alpha]^{20}_{589}$ -6° (c 0.205, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.64 (d, *J* = 15.91 Hz, 1 H), 7.25 (d, *J* = 8.39 Hz, 2 H), 7.21 (d, *J* = 8.39 Hz, 2 H), 6.85 (m, 4 H), 6.11 (dt, *J* = 15.91, 7.51 Hz, 1 H), 5.90 (m, 1 H), 5.76 (s, 1 H), 5.68 (s, 1 H), 5.51 (s, 1 H), 5.45 (s, 1 H), 5.31 (d, *J* = 17.23 Hz, 1 H), 5.16 (d, *J* = 10.60 Hz, 1 H), 5.09 (s, 1 H), 5.03 (d, *J* = 7.51 Hz, 1 H), 5.01 (s, 1 H), 4.93 (m, 1 H), 4.83 (s, 1 H), 4.76 (s, 1 H), 4.65 (t, *J* = 6.19 Hz, 1 H), 4.57 (ABq, *J* = 11.93 Hz, 1 H), 4.54 (ABq, *J* =11.05 Hz, 1 H), 4.34 (m, 1 H), 4.32 (ABq, *J* = 11.49 Hz, 1 H), 4.22 (ABq, *J* = 11.05 Hz, 1 H), 4.04 (br s, 2 H), 3.94 (d, *J* = 4.86 Hz, 1 H), 3.78 (s, 6 H), 3.09 (dABq, *J* = 6.63, 16.35 Hz, 1 H), 3.00 (dABq, *J* = 7.95, 15.91 Hz, 1 H), 2.87 (dd, *J* = 2.21, 6.19 Hz, 1 H), 2.71 (t, *J* = 7.51 Hz, 2 H), 2.62 (dd, *J* = 2.21, 7.07 Hz, 1 H), 2.44 (d, *J* = 5.30 Hz, 1 H), 2.30 (dABq. *J* = 4.42, 13.70 Hz, 1 H), 2.05 (m, 1 H), 1.98 (s, 3 H), 1.83 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 0.95 (d, *J* = 6.63 Hz, 3 H), 0.91 (d, *J* = 7.07 Hz, 3 H), 0.85 (m, 3 H), 0.84 (s, 9 H), -0.03 (s, 3 H), -0.04 (s, 3 H).

Ring-closing metathesis of diene (126) to give (Z)-macrocycle (127):



127



128

To a slightly refluxing solution of diene **126** (74 mg, 0.081 mmol) in CH_2Cl_2 (74 mL) was added dropwise (~8 hours) a solution of bis(tricyclohexylphosphine) benzylidene ruthenium dichloride (33 mg, 0.040 mmol) in CH_2Cl_2 (8 mL). After stirring an additional 18 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 0.14 g of a black residue. The black residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 34 mg (47%) of (Z)-macrocycle **127** and 10 mg (14%) of ketone **128** as oils. For spectroscopic data see below.

2nd generation catalyst:

To a slightly refluxing solution of diene **126** (26 mg, 0.029 mmol) in CH_2Cl_2 (26 mL) was added dropwise (~2 hours) a solution of $PhHC{=}Ru(PCy_3)(IMes\text{-}H_2)Cl_2$ (5 mg, 0.006 mmol) in CH_2Cl_2 (2 mL). After stirring an additional 8 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 33 mg of a black residue. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 22 mg (88%) of macrocycle **127**.

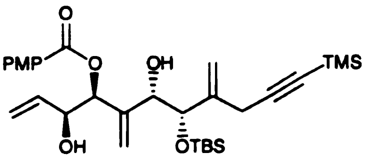
macrocycle **127:** IR (neat, 4 cm^{-1}): ν = 3515, 2957, 2930, 2857, 1709, 1636, 1613, 1514, 1464, 1381, 1302, 1248, 1173, 1154, 1074, 1038, 909, 835, 777; $[\alpha]^{20}_{589}$ +37.5° (c 0.557, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.41 (d, J = 15.91

Hz, 1 H), 7.23 (d, *J* = 8.84 Hz, 2 H), 7.19 (d, *J* = 8.84 Hz, 2 H), 6.84 (d, *J* = 8.84 Hz, 2H), 6.82 (d, *J* = 8.84 Hz, 2 H), 6.19 (dt, *J* = 15.91, 7.51 Hz, 1 H), 5.65 (s, 1 H), 5.61 (m, 2 H), 5.54 (dd, *J* = 4.86, 15.46 Hz, 1 H), 5.50 (s, 1 H), 5.13 (s, 1 H), 4.95 (s, 1 H), 4.86 (s, 1 H), 4.74 (s, 1 H), 4.64 (dd, *J* = 3.53, 6.63 Hz, 1 H), 4.52 (ABq, *J* = 11.49 Hz, 1 H), 4.48 (ABq, *J* =10.60 Hz, 1 H), 4.26 (ABq, *J* = 11.05 Hz, 1 H), 4.20 (ABq, *J* = 11.49 Hz, 1 H), 4.19 (d, *J* = 6.19 Hz, 1 H), 3.96 (br s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.78 (m, 1 H), 3.69 (br s, 1 H), 3.07 (dABq, *J* = 7.51, 15.91 Hz, 1 H), 2.96 (dABq, *J* = 6.19, 15.46 Hz, 1 H), 2.90 (dd, *J* = 2.21, 6.63 Hz, 1 H), 2.78 (dABq, *J* = 6.19, 14.58 Hz, 1 H), 2.64 (dABq. *J* = 5.74, 14.58 Hz, 1 H), 2.59 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.30 – 2.20 (m, 3 H), 1.86 (d, *J* = 1.33 Hz, 3 H), 1.78 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 0.98 (d, *J* = 7.07 Hz, 3 H), 0.92 (d, *J* = 6.63 Hz, 3 H), 0.88 (m, 12 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

ketone **128:** IR (neat, 4 cm^{-1}): ν = 2957, 2930, 2857, 1715, 1636, 1613, 1514, 1464, 1389, 1358, 1302, 1250, 1173, 1150, 1074, 1038, 912, 835, 777; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 15.46 Hz, 1 H), 7.22 (d, *J* = 8.39 Hz, 2 H), 7.19 (d, *J* = 8.84 Hz, 2 H), 6.85 (d, *J* = 8.39 Hz, 2H), 6.83 (d, *J* = 8.84 Hz, 2 H), 6.06 (dt, *J* = 15.91, 7.51 Hz, 1 H), 5.75 (m, 1 H), 5.66 (s, 1 H), 5.60 (s, 1 H), 5.39 (s, 1 H), 5.00 (series m, 3 H), 4.82 (s, 2 H), 4.75 (s, 1 H), 4.64 (dd, *J* = 4.86, 6.19 Hz, 1 H), 4.44 (ABq, *J* = 11.49 Hz, 1 H), 4.35 (ABq, *J* = 11.49 Hz, 1 H), 4.33 (s, 1 H), 4.32 (ABq, *J* = 11.05 Hz, 1 H), 4.23 (d, *J* = 5.74 Hz, 1 H), 4.14 (ABq, *J* = 11.49 Hz, 1 H), 3.93 (d, *J* = 5.74 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.02 (dABq, *J* = 6.63, 16.35 Hz, 1 H), 2.90 (dABq, *J* = 6.63, 16.35 Hz, 1 H), 2.86 (dd, *J* = 2.21, 6.19 Hz, 1 H), 2.70 (t, *J* = 7.51 Hz, 2 H), 2.60 (dd, *J* = 2.21, 7.07 Hz, 1 H), 2.29

(dABq, J = 4.86, 13.70 Hz, 1 H), 2.11 (s, 3 H), 2.03 (m, 1 H), 1.97 (s, 3 H), 1.81 (dABq, J = 9.72, 13.70 Hz, 1 H), 1.50 – 1.20 (series m, 5 H), 0.95 (d, J = 7.07 Hz, 3 H), 0.90 (d, J = 7.07 Hz, 3 H), 0.87 (t, J = 7.07 Hz, 3 H), 0.82 (s, 9 H), -0.04 (s, 3 H), -0.06 (s, 3H).

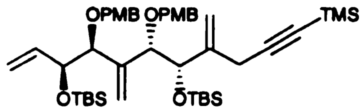
DDQ deprotection of PMB-ether (123) to give alcohol (130):



or other possible regioisomers

To a solution of PMB-ether **123** (24 mg, 0.036 mmol) in *t*-BuOH/aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (1.4 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (33 mg, 0.14 mmol). After stirring for 2 hours, the red reaction mixture was diluted with CH_2Cl_2 (10 mL) and a saturated aqueous $NaHCO_3$ solution (10 mL) and then separated the phases. The aqueous phase was extracted with CH_2Cl_2 (5 mL x 3). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 24 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 11 mg (56%) of PMB-ester **130** as a clear oil, which is a mixture of regioisomers.

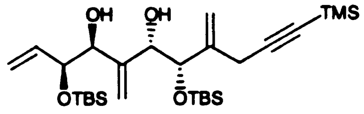
Preparation of TBS-ether (131):



131

To a cold (0 °C) solution of alcohol **123** (0.26 g, 0.39 mmol) in CH_2Cl_2 (4 mL) were added 2,6-lutidine (0.060 mL, 0.51 mmol) and TBSOTf (0.11 mL, 0.47 mmol). After stirring for 20 minutes, the reaction was quenched with water (0.20 mL) and a saturated aqueous NH_4Cl solution (0.20 mL). The reaction was diluted with Et_2O (20 mL) and the phases were separated. The organic phase was washed with brine (0.5 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.35 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5% →10%] to give 0.25 g (82 %) of fully protected tetra-ol **131** as a clear oil. IR ($CHCl_3$, 4 cm^{-1}): ν = 2930, 2857, 2174, 1711, 1613, 1588, 1514, 1464, 1362, 1302, 1099, 1005, 912, 864, 841; $[\alpha]^{20}_{589}$ -22.5° (c 0.525, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.24 (app t, *J* = 7.95 or 8.84 Hz, 4 H), 6.85 (app t, *J* = 7.51 or 8.39 Hz, 4 H), 5.91 (ddd, *J* = 4.86, 10.60, 17.23 Hz, 1 H), 5.40 (s, 1 H), 5.37 (s, 1 H), 5.33 (d, *J* = 1.33 Hz, 1 H), 5.20 (m, 1 H), 5.14 (s, 1 H), 5.10 (m, 1 H), 4.57 (ABq, *J* = 11.05 Hz, 1 H), 4.53 (ABq, *J* = 11.05 Hz, 1 H), 4.32 (m, 4 H), 4.20 (d, *J* = 5.74 Hz, 1 H), 3.94 (d, *J* = 4.86 Hz, 1 H), 3.79 (s, 6 H), 3.21 (ABq, *J* = 20.32 Hz, 1 H), 3.10 (ABq, *J* = 20.32 Hz, 1 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.14 (s, 9 H), 0.08 (s, 3 H), 0.02 (s, 3 H), 0.017 (s, 3 H), 0.002 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 158.9, 158.8, 144.2, 143.3, 137.4, 131.6, 131.4, 128.8, 128.7, 115.5, 114.5, 113.7, 113.6, 113.5, 104.5, 87.3, 82.2 (2), 78.8, 76.5, 71.2, 70.9, 55.2, 31.6, 26.0, 25.9, 24.5, 22.6, 18.3, 18.2, 14.1, 0.12, -4.7, -4.8, -4.9, -4.9.

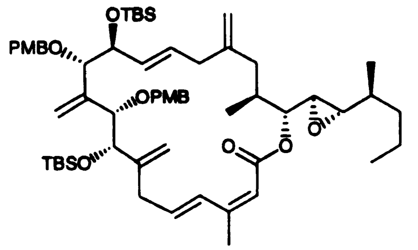
DDQ deprotection of PMB-ether (131) to give diol (132):



132

To a solution of PMB-ether **131** (0.22 g, 0.28 mmol) in *t*-BuOH/ aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (14 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.19 g, 0.85 mmol). After stirring for 60 minutes, additional DDQ (65 mg) was added. After stirring an additional 5.5 hours, the red reaction mixture was diluted with CH_2Cl_2 (30 mL) and a saturated aqueous $NaHCO_3$ solution (10 mL) and then the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL x 3). The combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.21 g of a red oil. The crude residue was purified by flash chromatography on silica gel [hexanes/ EtOAc 5%] to give 90 mg (59%) of diol **132** as a light yellow oil. IR (neat, 4 cm^{-1}): ν = 3560, 2957, 2930, 2899, 2859, 2178, 1701, 1603, 1580, 1512, 1471, 1464, 1406, 1362, 1252, 1161, 1074, 1032, 930, 839, 779; $[\alpha]^{20}_{589}$ -23.4° (c 0.435, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 5.83 (ddd, *J* = 6.63, 10.60, 17.23 Hz, 1 H), 5.34 – 5.14 (series m, 6 H), 4.31 (d, *J* = 4.42 Hz, 1 H), 4.10 (t, *J* = 6.19 Hz, 1 H), 3.89 (t, *J* = 5.30 or 4.86 Hz, 1 H), 3.80 (t, *J* = 5.30 or 4.86 Hz, 1 H), 3.10 (ABq, *J* = 19.88 Hz, 1 H), 3.01 (ABq, *J* = 19.88 Hz, 1 H), 2.87 (d, *J* = 5.74 Hz, -OH), 2.86 (d, *J* = 3.98 Hz, -OH), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.16 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 147.4, 143.4, 137.8, 116.9, 114.5, 114.0, 87.5, 77.7, 76.7, 75.9, 74.6, 31.6, 25.9, 23.6, 22.6, 18.2 (2), 14.1, 0.05, -4.2, -4.7, -4.8, -5.0.

TBS-protection of macrocycle (127) to give TBS-ether (133):

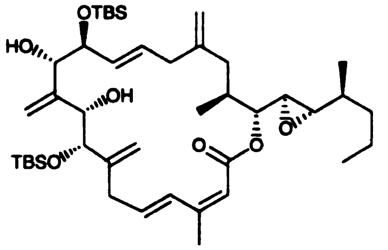


133

To a cold (0 °C) solution of alcohol **127** (0.017 g, 0.019 mmol) in CH_2Cl_2 (0.4 mL) were added 2,6-lutidine (3 drops) and TBSOTf (4 drops). After stirring for 4 hours, additional 2,6-lutidine (3 drops) and TBSOTf (4 drops) were added. After stirring yet an additional 4 hours at 0 °C, the ice bath was removed and the reaction stirred at room temperature for 4 hours. The reaction was diluted with Et_2O (6 mL) and washed with water (0.2 mL), a saturated aqueous $CuSO_4$ solution (0.2 mL x 2), water (0.2 mL) and brine (0.2 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 36 mg of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 18 mg (92%) of fully protected macrocycle **133** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2957, 2928, 2857, 1709, 1614, 1514, 1464, 1389, 1360, 1302, 1248, 1173, 1152, 1082, 1038, 914, 835, 777; $[\alpha]^{20}_{589}$ +18.2° (c 0.80, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 15.91 Hz, 1 H), 7.22 (d, *J* = 8.84 Hz, 2 H), 7.18 (d, *J* = 8.39 Hz, 2 H), 6.82 (d, *J* = 8.84 Hz, 2 H), 6.81 (d, *J* = 8.84 Hz, 2 H), 6.11 (dt, *J* = 15.92, 6.63 Hz, 1 H), 5.64 (m, 3 H), 5.48 (s, 1 H), 5.47 (s, 1 H), 5.20 (s, 1 H), 4.94 (s, 1 H), 4.83 (s, 1 H), 4.77 (s, 1 H), 4.71 (dd, *J* = 3.53, 6.19 Hz, 1 H), 4.51 (ABq, *J* = 11.05 Hz, 1 H), 4.47 (ABq, *J* = 11.05 Hz, 1 H), 4.27 (ABq, *J* = 11.05 Hz, 1 H), 4.19 (d, *J* = 4.86 Hz, 1 H), 4.14 (app t, *J* = 4.86/6.19 Hz, 1 H), 4.06 (ABq, *J*

= 11.49 Hz, 1 H), 3.78 (s, 6 H), 3.74 (d, J = 4.42 Hz, 1 H) 3.57 (d, J = 4.86 Hz, 1 H), 3.01 (d, J = 6.19 Hz, 2 H), 2.83 (dd, J = 1.77, 6.19 Hz, 1 H), 2.70 – 2.50 (series m, 3 H), 2.16 (m, 2 H), 1.86 (s, 3 H), 1.86 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 1.01 (d, J = 6.63 Hz, 3 H), 0.92 (d, J = 7.07 Hz, 3 H), 0.90 – 0.80 (series m, 21 H), -0.02 (s, 6 H), -0.04 (s, 3 H), -0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.6, 158.8, 158.6, 150.4, 146.6, 145.7, 143.5, 136.6, 132.7, 131.6, 131.3, 129.4, 129.1, 128.8, 128.5, 128.1, 116.5, 115.7, 115.2, 113.5, 113.4, 112.1, 83.6, 81.1, 78.9, 75.9, 75.8, 71.3, 70.2, 61.1, 56.6, 55.2, 39.6, 39.0, 36.7, 35.3, 35.1, 34.6, 26.0, 25.9, 21.1, 20.0, 18.4, 15.9, 15.4, 14.2, -3.6, -4.2, -4.5, -4.7.

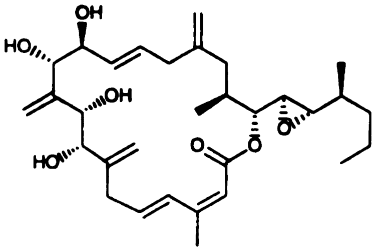
DDQ deprotection of PMB-macrocycle (133) to give macrocycle diol (134):



134

To a solution of PMB-ether **133** (16.4 mg, 0.0164 mmol) in *t*-BuOH/ aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (1 mL) was added DDQ (15 mg, 0.066 mmol). After stirring for 3.5 hours, the red reaction mixture was diluted with CH_2Cl_2 (6 mL) and a saturated aqueous $NaHCO_3$ solution (6 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 mL x 3). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (3 mL), water (3 mL) and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated to give 27 mg of a dark red oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 6.4 mg (52%) of diol **134** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3567, 2965, 2928, 2857, 1707, 1636, 1603, 1464, 1379, 1262, 1154, 1098, 1030, 905, 801; $[\alpha]^{20}_{589}$ +15° (c 0.23, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.54 (d, J = 15.91 Hz, 1 H), 6.14 (m, 1 H), 5.70 (s, 1 H), 5.56 (dt, J = 15.02, 6.63 Hz, 1 H), 5.42 (dd, J = 4.86, 15.02 Hz, 1 H), 5.32 (s, 2 H), 5.23 (s, 1 H), 5.09 (s, 1 H), 4.83 (s, 1 H), 4.74 (s, 1 H), 4.57 (dd, J = 3.53, 7.07 Hz, 1 H), 4.01 (d, J = 2.65 Hz, 1 H), 3.91 (t, J = 3.53 Hz, 1 H), 3.85 (m, 1 H), 3.69 (dd, J = 3.53, 6.10 Hz, 1 H), 3.16 (dABq, J = 15.02, 5.30 Hz, 1 H), 2.90 (dd, J = 2.21, 6.63 Hz, 1 H), 2.85 (dABq, J = 15.02, 8.84 Hz, 1 H), 2.66 (m, 3 H), 2.64 (dd, J = 2.21, 7.51 Hz, 1 H), 2.30 (m, 2 H), 1.99 (s, 3 H), 1.78 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 0.96 (d, J = 7.07 Hz, 3 H), 0.94 (d, J = 7.07 Hz, 3 H), 0.89 (m, 3 H), 0.88 (s, 9 H), 0.85 (s, 9 H), 0.01 (s, 3 H), -0.02 (s, 3 H), -0.04 (s, 3 H), -0.05 (s, 3 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ =

Preparation of Z-amphidinolide A (135):

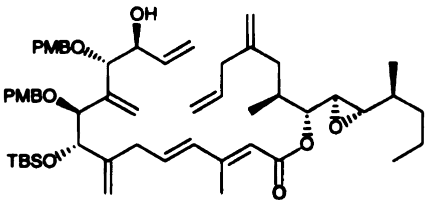


135

To a solution of disilylated macrocycle **134** in THF (0.5 mL) was added dropwise an acetic acid buffered TBAF (1.05:1) solution (0.07 mL, 0.2 M THF, 0.014 mmol). After stirring for 4.5 hours at room temperature, the reaction was directly loaded onto a silica gel (0.5 g) column [hexanes/EtOAc 75%] and eluted with EtOAc to give 3.4 mg of an oil. Purification by flash chromatography on silica gel (0.3 g) [hexanes/EtOAc 75% → 100%] afforded 1.1 mg (33%) of z-amphidinolide A **135** as a white solid. ^{1}H NMR (500 MHz, CDCl$_3$) δ = 7.52 (d, J

= 15.91 Hz, 1 H), 6.10 (m, 1 H), 5.70 (s, 1 H), 5.68 (m, 1 H), 5.45 (s, 1 H), 5.42 (dd, J = 5.74, 15.63 Hz, 1 H), 5.40 (s, 1 H), 5.35 (s, 1 H), 5.13 (s, 1 H), 4.87 (s, 1 H), 4.73 (s, 1 H), 4.64 (dd, J = 3.09, 6.63 Hz, 1 H), 4.24 (br s, 1 H), 4.14 (br s, 1 H), 4.12 (br s, 1 H), 4.04 (br s, 1 H), 3.09 (dABq, J = 15.02, 5.74 Hz, 1 H), 2.94 (d, J = 8.39 Hz, 1 H), 2.91 (dd, J = 2.21, 6.63 Hz, 1 H), 2.82 (dABq, 14.58, 6.19 Hz, 1 H), 2.63 (m, 3 H), 2.0 (s, 3 H), 1.73 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 0.99 (d, J = 6.63 Hz, 3 H), 0.93 (d, J = 7.07 Hz, 3 H), 0.88 (t, J = 7.07 Hz, 3 H); HRMS (CI) *m/z* 553.3115 [(M + Na)$^+$; calcd for $C_{31}H_{46}O_7Na$, 553.3141].

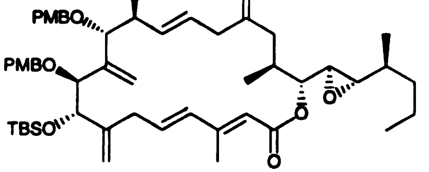
Preparation of diene (136) via Liebeskind's coupling:



136

To a cold (0 °C) solution of (E)-vinyl iodide **301**[50] (0.27 g, 0.31 mmol) in NMP (2.2 mL) was added copper (I) thiophene-2-carboxylate (CuTc) (0.12 g, 0.61 mmol). To this suspension was added a solution of vinyl stannane **125** (0.27 g, 0.31 mmol) in NMP (1.1 mL). After stirring for 15 minutes at 0 °C, the ice bath was removed and the reaction stirred at room temperature until judged complete by TLC analysis (~ 30 minutes). The reaction mixture was diluted with Et_2O (30 mL) and filtered through a pad of Celite on a glass frit. The green filter cake was washed with Et_2O (3x). The yellow filtrate was washed with water (3 mL x 3), a saturated aqueous KF solution (3 mL x 2), and brine (3 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.60 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 15%] to give 0.17 g (62%) of diene **136** as a light yellow oil. IR (neat, 4 cm^{-1}): ν = 3513, 3077, 2959, 2930, 1715, 1636, 1613, 1588, 1514, 1464, 1381, 1302, 1248, 1173, 1150, 1074, 1036, 914, 835, 779; $[\alpha]^{20}_{589}$ -2° (c 0.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.39 Hz, 2 H), 7.21 (d, *J* = 8.84 Hz, 2 H), 6.86 (d, *J* = 8.39 Hz, 2 H), 6.84 (d, *J* = 8.39 Hz, 2 H), 6.07 (s, 1 H), 5.90 (m, 2 H), 5.76 (m, 1 H), 5.71 (s, 1 H), 5.50 (m, 1 H), 5.44 (m, 1 H), 5.30 (d, *J* = 17.23 Hz, 1 H), 5.16 (m, 1 H), 5.10 (s, 1 H), 5.03 (m, 2 H), 4.93 (s, 1 H), 4.83 (s, 1 H), 4.76 (s, 1 H), 4.66 (dd, *J* = 5.30, 6.19 Hz, 1 H), 4.55 (m, 2 H), 4.34 (t, *J* = 5.30 Hz, 1 H), 4.30 (ABq, *J* = 11.93 Hz, 1 H), 4.21 (ABq, *J* = 11.05 Hz, 1 H), 4.03 (m, 2 H), 3.95 (d, *J* = 4.86 Hz, 1 H), 3.79 (s, 6 H), 3.0 (m, 2 H), 2.88 (dd, *J* = 2.21, 6.19 Hz, 1 H), 2.71 (t, *J* = 7.51 Hz, 2 H), 2.62 (dd, *J* = 2.21, 7.07 Hz, 1 H), 2.40 (dd, *J* = 5.74, 8.84 Hz, 1 H), 2.31 (dABq, *J* = 4.86, 13.70 Hz, 1 H), 2.25 (s, 3 H), 2.06 (m, 1 H), 1.84 (dABq, *J* = 9.72, 13.70 Hz, 1 H), 1.50 – 1.20 (m, 5 H), 0.97 (d, *J* = 7.07 Hz, 3 H), 0.92 (d, *J* = 7.07 Hz, 3 H), 0.86 (t, *J* = 7.07 Hz, 3 H), 0.84 (s, 9 H), -0.02 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = ; HRMS (FAB) *m/z* 913.5652 [$(M + H)^+$; calcd for $C_{55}H_{81}O_9Si$, 913.5650].

Ring-closing metathesis of diene (136) to give (E)-macrocycle (140):



140

To a slightly refluxing solution of diene **136** (26 mg, 0.029 mmol) in CH_2Cl_2 (25 mL) was added dropwise (~6 hours) a solution of bis(tricyclohexylphosphine) benzylidene ruthenium dichloride (12 mg, 0.014 mmol) in CH_2Cl_2 (3 mL). After stirring an additional 18 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 43 mg of a black residue. The black residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 8.7 mg (34%) of truncated ketone **137** as an oil and 6 mg (23%) of the recovered diene.

2^{nd} generation catalyst:

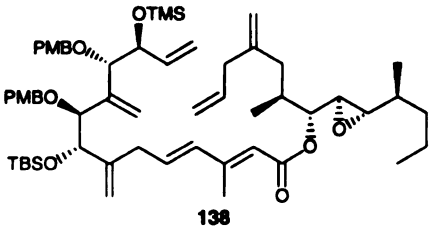
To a slightly refluxing solution of diene **136** (20 mg, 0.022 mmol) in CH_2Cl_2 (20 mL) was added dropwise (~8 hours) a solution of PhHC=Ru(PCy_3)(IMes-H_2)Cl_2 (19 mg, 0.022 mmol) in CH_2Cl_2 (5 mL). After stirring an additional 10 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 34 mg of a black residue. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 7 mg (36%) of macrocycle **140**.

macrocycle **136**: : IR (neat, 4 cm^{-1}): ν = 3515, 2957, 2930, 2857, 1709, 1636, 1613, 1514, 1464, 1381, 1302, 1248, 1173, 1154, 1074, 1038, 909, 835, 777; HRMS (FAB) *m/z* 907.5197 [$(M + Na)^+$; calcd for $C_{53}H_{76}O_9SiNa$, 907.5156].

ketone **137**: IR (neat, 4 cm^{-1}): ν = 2957, 2930, 2857, 1715, 1636, 1613, 1514, 1464, 1389, 1358, 1302, 1250, 1173, 1150, 1074, 1038, 912, 835, 777; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 8.84 Hz, 2 H), 7.19 (d, *J* = 8.84 Hz, 2 H), 6.86 (d, *J* = 8.84 Hz, 2 H), 6.83 (d, *J* = 8.39 Hz, 2 H), 6.05 (m, 2 H), 5.76 (m, 1 H), 5.72 (s, 1 H), 5.63 (s, 1 H), 5.40 (s, 1 H), 5.01 (m, 3 H), 4.83 (s, 1 H), 4.82 (s, 1 H), 4.76 (s, 1 H), 4.66 (dd, *J* = 4.86, 6.19 Hz, 1 H), 4.43 (ABq, *J* = 11.49 Hz, 1 H), 4.36 (ABq, *J* = 11.49 Hz, 1 H), 4.32 (m, 2 H), 4.23 (d, *J* = 5.74 Hz, 1 H), 4.13

(ABq, *J* = 11.05 Hz, 1 H), 3.94 (d, *J* = 5.30 Hz, 1 H), 3.78 (s, 6 H), 2.95 (m, 1 H), 2.88 (dd, *J* = 2.21, 6.19 Hz, 1 H), 2.86 (m, 1 H), 2.71 (t, *J* = 7.51 Hz, 2 H), 2.62 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.31 (dABq, *J* = 4.42, 13.70 Hz, 1 H), 2.24 (s, 3 H), 2.12 (s, 3 H), 2.05 (m, 1 H), 1.83 (dABq, *J* = 10.16, 13.70 Hz, 1 H), 1.50 –1.20 (series m, 5 H), 0.96 (d, *J* = 7.07 Hz, 3 H), 0.92 (d, *J* = 7.07 Hz, 3 H), 0.88 (t, *J* = 7.07 Hz, 3 H), 0.84 (s, 9 H), -0.03 (s, 3 H), -0.05 (s, 3 H); HRMS (CI) *m/z* 203.1280 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

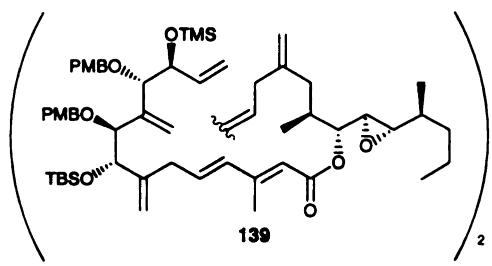
Preparation of TMS-ether (138):



138

To a cold (0 °C) solution of diene **136** (0.017 g, 0.019 mmol) in CH_2Cl_2 (0.3 mL) were added 2,6-lutidine (2 drops) and TMSOTf (2 drops). After stirring for 3.5 hours, additional 2,6-lutidine (2 drops) and TMSOTf (2 drops) were added. After stirring an additional 10 hours at 0 °C, the reaction was diluted with Et_2O (5 mL) and washed with water (0.2 mL), a saturated aqueous $CuSO_4$ solution (0.2 mL x 2), water (0.2 mL x 2) and brine (0.2 mL). The organics were dried over Na_2SO_4, filtered and concentrated to give 13 mg (70%) of crude TMS-ether **138** as a yellow oil.

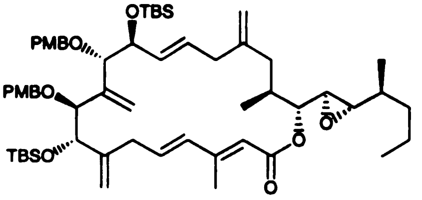
Ring-closing metathesis of diene (138) to give dimer (139):



139

To a slightly refluxing solution of diene **138** (13 mg, 0.013 mmol) in CH_2Cl_2 (11 mL) was added dropwise (~5.5 hours) a solution of $PhHC{=}Ru(PCy_3)(IMes\text{-}H_2)Cl_2$ (4 mg, 0.004 mmol) in CH_2Cl_2 (2 mL). After stirring an additional 14 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 22 mg of a black residue. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 10 mg (79%) of dimer **139**.

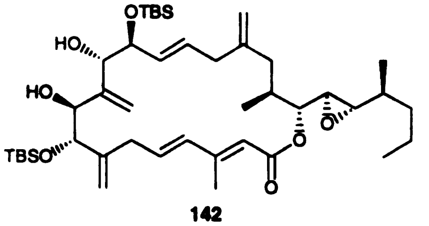
TBS-protection of macrocycle (140) to give TBS-ether (141):



141

To a cold (0 °C) solution of alcohol **140** (0.021 g, 0.024 mmol) in CH_2Cl_2 (0.6 mL) were added 2,6-lutidine (6 drops) and TBSOTf (6 drops). After stirring for 7.5 hours, additional 2,6-lutidine (3 drops) and TBSOTf (3 drops) were added. After stirring an additional 60 minutes, the reaction was diluted with Et_2O (8 mL) and washed with water (0.5 mL), a saturated aqueous $CuSO_4$ solution (0.5 mL x 2), water (0.5 mL) and brine (0.5 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 59 mg of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 21 mg (90%) of fully protected macrocycle **141** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2957, 2928, 2857, 1709, 1614, 1514, 1464, 1389, 1360, 1302, 1248, 1173, 1152, 1082, 1038, 914, 835, 777; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.39 Hz, 1 H), 7.19 (d, *J* = 8.39 Hz, 1 H), 7.18 (d, *J* = 8.39 Hz, 1 H), 7.15 (d, *J* = 8.39 Hz, 1 H), 6.85 (d, *J* = 8.84 Hz, 1 H), 6.83 (d, *J* = 8.84 Hz, 1 H), 6.78 (d, *J* = 8.84 Hz, 1 H), 6.76 (d, *J* = 8.39 Hz, 1 H), 5.96 (m, 1 H), 5.92 (d, *J* = 15.46 Hz, 1 H), 5.65 (s, 1 H), 5.57 (dd, *J* = 7.51, 15.46 Hz, 1 H), 5.57 (s, 1 H), 5.54 (s, 1 H), 5.46 (m, 1 H), 5.36 (s, 1 H), 5.14 (s, 1 H), 5.0 (s, 1 H), 4.95 (s, 1 H), 4.73 (d, *J* = 6.63 Hz, 1 H), 4.59 (ABq, *J* = 11.49 Hz, 1 H), 4.50 (m, 3 H), 4.41 (ABq, *J* = 11.49 Hz, 1 H), 4.32 (d, *J* = 5.30 Hz, 1 H), 4.31 (ABq, *J* = 12.37 Hz, 1 H), 4.14 (d, *J* = 6.63 Hz, 1 H), 4.13 (ABq, *J* = 12.37 Hz, 1 H), 4.05 (dd, *J* = 2.21, 7.07 Hz, 1 H), 3.58 (d, *J* = 6.63 Hz, 1 H), 3.36 (s, 1 H), 3.0 (dABq, *J* = 9.28, 14.14 Hz, 1 H), 2.96 (dd, *J* = 2.21, 7.07 Hz, 1 H), 2.85 (m, 2 H), 2.70 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.53 (m, 2 H), 2.47 (dABq, *J* = 4.86, 13.25 Hz, 1 H), 2.16 (m, 1 H), 2.05 (s, 3 H), 1.86 (dABq, *J* = 7.95, 13.25 Hz, 1 H), 1.50 – 1.20 (series m, 4 H), 1.01 (d, *J* = 7.07 Hz, 3 H), 0.97 (d, *J* = 6.63 Hz, 3 H), 0.90 – 0.80 (series m, 21 H), -0.07 (series s, 12 H); HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

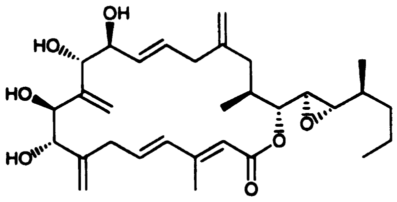
DDQ deprotection of PMB-macrocycle (141) to give macrocycle diol (142):



142

To a solution of PMB-ether **141** (21 mg, 0.021 mmol) in *t*-BuOH/ aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (1.6 mL) was added DDQ (19 mg, 0.086 mmol). After stirring for 3.5 hours, the red reaction mixture was diluted with CH_2Cl_2 (6 mL) and a saturated aqueous $NaHCO_3$ solution (6 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2.5 mL x 3). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (3 mL), water (3 mL) and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated to give 25 mg of a dark red oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 4.6 mg (52%) of diol **142** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3567, 2965, 2928, 2857, 1707, 1636, 1603, 1464, 1379, 1262, 1154, 1098, 1030, 905, 801; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.17 (d, *J* = 15.91 Hz, 1 H), 6.07 (m, 1 H), 5.78 (s, 1 H), 5.59 (s, 1 H), 5.37 (s, 1 H), 5.34 (s, 1 H), 5.24 (dd, *J* = 3.53, 15.02 Hz, 1 H), 5.21 (s, 1 H), 5.11 (s, 1 H), 4.78 (s, 1 H), 4.74 (s, 1 H), 4.44 (dd, *J* = 3.53, 7.51 Hz, 1 H) 4.13 (d, *J* = 2.65 Hz, 1 H), 4.08 (d, *J* = 3.53 Hz, 1 H), 3.89 (m, 1 H), 3.57 (d, *J* = 8.39 Hz, 1 H), 3.09 (m, 1 H), 2.90 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.67 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.66 (m, 1 H), 2.53 (dABq, *J* = 8.84, 15.02 Hz, 1 H), 2.51 (d, *J* = 7.07 Hz, 1 H), 2.44 (d, *J* = 8.39 Hz, 1 H), 2.42 (dABq, *J* = 4.86, 13.25 Hz, 1 H), 2.27 (s, 3 H), 2.15 (m, 1 H), 1.78 (dABq, *J* = 8.84, 13.25 Hz, 1 H), 1.50 – 1.20 (series m, 5 H), 0.99 (d, *J* = 7.07 Hz, 3 H), 0.97 (d, *J* = 7.07 Hz, 3 H), 0.90 (m, 3 H), 0.90 (s, 9 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H), 0.005 (s, 3 H).

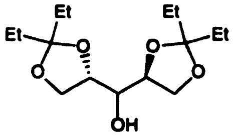
Preparation of the assigned structure of amphidinolide A (1):



1

To a solution of disilylated macrocycle **142** (1.8 mg, 0.0024 mmol) in THF (0.2 mL) was added dropwise an acetic acid buffered TBAF (1.05:1) solution (0.05 mL, 0.1 M THF, 0.005 mmol). After stirring for 21 hours at room temperature, the reaction was directly loaded onto a silica gel (0.3 g) column [hexanes/EtOAc 25%, 1% MeOH] and eluted with hexanes/EtOAc (1:3) to give 0.3 mg (25%) of amphidinolide A (**1**) as a white solid. HRMS (CI) *m/z* 553.3115 [(M + Na)$^+$; calcd for $C_{31}H_{46}O_7Na$, 553.3141].

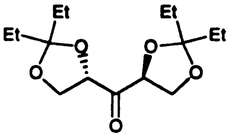
Preparation of bisisopentylidene acetal (143):



143

To a 40 °C slurry of L-arabitol (14.80 g, 97.27 mmol) and CSA (0.70 g, 3.0 mmol) in DMF (15 mL) was added 3,3-dimethoxypentane (29.0 g, 217 mmol) dropwise (~30 minutes). After stirring an additional 6 hours, the reaction was quenched with Et_3N (0.5 mL) and then concentrated via rotovap at 60 °C to afford a crude oil. The residue was diluted with Et_2O (200 mL) and washed with brine (50 mL x 4), dried over $MgSO_4$, filtered and concentrated to give 27.84 g of crude acetal **143** as a clear oil.

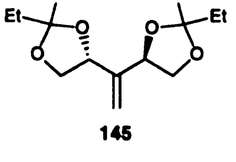
Preparation of ketone (144):



144

To a cold (0 °C) solution of alcohol **143** (3.42 g, 11.9 mmol) in CH_2Cl_2 (40 mL) were added DMSO (7 mL), TEA (9.9 mL, 71.156 mmol) and a suspension of SO_3•pyridine in DMSO (10 mL). The ice bath was removed and the reaction stirred at room temperature for 90 minutes and was then quenched with a saturated aqueous NH_4Cl solution (25 mL) and water (6 mL). Et_2O (50 mL) was added, and the phases were separated. The organic phase was washed with brine (15 mL x 2). The combined aqueous phases were extracted with Et_2O (15 mL x 2). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 6.02 g of a reddish-yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 2.32 g (68%) of ketone **144** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2975, 2944, 2884, 1736, 1464, 1360, 1262, 1201, 1173, 1082, 1061, 912, 799; $[\alpha]_{589}^{20}$ -63.6° (c 0.66, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 4.82 (t, *J* = 7.14 or 7.69 Hz, 2 H), 4.31 (t, *J* = 7.69 or 8.24 Hz, 2 H), 3.96 (dd, *J* = 7.14, 8.79 Hz, 2 H), 1.69 (m, 8 H), 0.93 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 205.3, 114.9, 78.7, 66.2, 29.1, 28.2, 8.2, 8.0; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

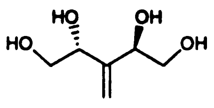
Preparation of alkene (145):



145

To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (15.9 g, 44.5 mmol) in THF (60 mL) was added NaHMDS (36 mL, 1.0 M THF, 36 mmol) dropwise. The ice bath was removed and the reaction stirred at room temperature for 30 minutes. A solution of ketone **144** (8.50 g, 29.7 mmol) in THF (10 mL) was added dropwise and the reaction stirred for 3.5 hours at room temperature. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL) and water (10 mL). The reaction was diluted Et_2O (120 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (10 mL x 2). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated to give 13.7 g of a red oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 6.96 g (83%) of alkene **145** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2975, 2942, 2882, 1464, 1356, 1271, 1198, 1173, 1132, 1080, 1059, 1040, 920; $[\alpha]^{20}_{589}$ -63.9° (c 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 5.29 (br s, 2 H), 4.50 (dd, *J* = 6.04, 8.79 Hz, 2 H), 4.18 (dd, *J* = 6.04, 7.69 Hz, 2 H), 3.55 (dd, *J* = 7.69, 8.79 Hz, 2 H), 1.64 (m, 8 H), 0.90 (t, *J* = 7.69 Hz, 6 H), 0.89 (t, *J* = 7.69 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.6, 112.8, 76.1, 70.0, 29.7, 29.4, 8.1 (2); HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

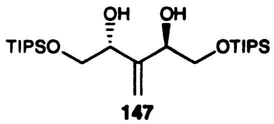
Hydrolysis of acetal (145) to give tetra-ol (146):



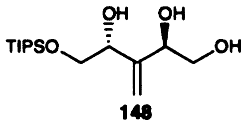
146

To a solution of bisisopentylidene acetal **145** (6.96 g, 24.5 mmol) in MeOH/CH_2Cl_2 (2:1) (250 mL) were added CSA (1.14 g, 4.89 mmol) and water (3 mL). The reaction flask was immersed into a preheated oil bath (~40 °C) and the reaction stirred for 8.5 hours. The reaction was allowed to cool to room temperature and then concentrated under high vacuum overnight to give 4.84 g of crude tetra-ol **146** as a yellow oil.

Preparation of TIPS-ether (147):



147

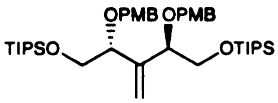


148

To a solution of crude tetra-ol **146** (from above) in CH_2Cl_2/DMF (1:1) (180 mL) were added imidazole (6.66 g, 97.9 mmol), DMAP (0.30 g, 2.4 mmol) and TIPSCl (11 mL, 51 mmol). After stirring for 24 hours at room temperature, the reaction was concentrated to give a yellow residue. CH_2Cl_2 (150 mL) was added to the residue, which was then washed with water (25 mL) and brine (25 mL x 2). The organics were dried over $MgSO_4$, filtered and concentrated to give 15.9 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10% → 50%] afforded 7.61 g (68% yield, 2 steps) of TIPS disilylated tetra-ol **147** as a clear oil and 1.61 g (22% yield, 2 steps) of TIPS monosilylated tetra-ol **148** as a white solid.

tetra-ol **147**: IR (neat, 4 cm^{-1}): ν = 3422, 2944, 2894, 2887, 1464, 1385, 1260, 1107, 1061, 1015, 920, 884, 801; $[\alpha]_{589}^{20}$ -11.5° (c 0.925, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 5.27 (br s, 2 H), 4.23 (m, 2 H), 3.83 (dd, J = 4.40, 9.89 Hz, 2 H), 3.60 (dd, J = 8.24, 9.89 Hz, 2 H), 3.10 (d, J = 2.75 Hz, -OH), 1.03 (m, 42 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.3, 113.4, 73.4, 67.3, 17.9, 11.9; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

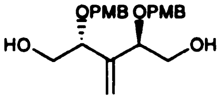
Preparation of fully protected tetra-ol (149):



149

To a solution of tetra-ol **147** (8.20 g, 17.8 mmol) in cyclohexane/CH_2Cl_2 (1:1) (180 mL) was added PMB-imidate (20.11 g, 71.18 mmol) and CSA (0.41 g, 1.8 mmol). The reaction flask was immersed into a preheated oil bath (~40 °C). After stirring for 48 hours, additional CSA (0.2 g) and PMB-imidate (3.6 g) were added and the reaction continued to stir an additional 23 hours. The reaction was allowed to cool to room temperature and then quenched with a saturated aqueous $NaHCO_3$ solution (8 mL). Et_2O (200 mL) was added and the phases were separated. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (5 mL x 2) and brine (10 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give a milky white solid. Hexanes were added to the residue. After stirring for several hours, the mixture was filtered and concentrated to give 16 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 6.03 g (48%) of fully protected tetra-ol **149** as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.24 (d, J = 8.24 Hz, 4 H), 6.82 (d, J = 8.24 Hz, 2 H), 6.80 (d, J = 8.79 Hz, 2 H), 5.38 (br s, 2 H), 4.56 (ABq, J = 11.54 Hz, 2 H), 4.37 (ABq, J = 11.54 Hz, 2 H), 3.92 – 3.60 (series m, 12 H), 1.02 (m, 42 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.9, 144.7, 130.8, 129.0, 113.7, 113.5, 80.5, 70.4, 67.0, 55.2, 117.9, 11.9; HRMS (CI) *m/z* 203.1280 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

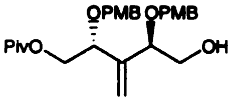
Deprotection of TIPS-ether to give diol (150):



150

To a solution of TIPS disilylated tetra-ol **149** (6.03 g, 8.61 mmol) in THF (90 mL) was added TBAF (19 mL, 1.0 M THF, 19 mmol) dropwise (~30 minutes). After stirring an additional 2.5 hours, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (10 mL) and water (10 mL). Et_2O (200 mL) was added and the phases were separated. The organic phase was washed with brine (10 mL x 2). The combined aqueous phases were extracted with Et_2O (10 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 8.2 g of a reddish-yellow oil. IR (neat, 4 cm^{-1}): ν = 3443, 2926, 1612, 1586, 1514, 1464, 1393, 1302, 1248, 1175, 1034, 818; $[\alpha]^{20}_{589}$ -98.3° (c 0.65, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.79 Hz, 4 H), 6.86 (d, *J* = 8.24 Hz, 4 H), 5.48 (s, 2 H), 4.55 (ABq, *J* = 10.99 Hz, 2 H), 4.27 (ABq, *J* = 10.99 Hz, 2 H), 3.93 (dd, *J* = 4.40, 6.59 Hz, 2 H), 3.78 (s, 6 H), 3.58 (m, 4 H), 2.42 (br s, -OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 142.7, 129.7, 129.5, 117.2, 113.9, 80.1, 70.5, 65.1, 55.2; HRMS (CI) *m/z* 203.1280 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

Preparation of alcohol (153):



153

To a cold (0 °C) solution of diol **150** (1.12 g, 2.88 mmol) in CH_2Cl_2 (30 mL) were added pyridine (0.47 mL, 5.8 mmol) and a solution of PivCl (0.36 mL, 2.9

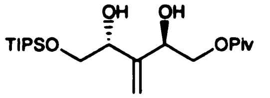
mmol) in CH_2Cl_2 (2 mL) dropwise (~3 minutes). After stirring for 12 hours between 0 °C and room temperature, the reaction was quenched by the addition of water (1 mL) and a saturated aqueous NH_4Cl solution (1 mL). Et_2O (40 mL) was added and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (3 mL x 2), water (3 mL x 2) and brine (4 mL), dried over $MgSO_4$, filtered and concentrated to give 1.50 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 35% → 75%] afforded 0.71 g (52%) of Piv-ester **153**, 0.25 g (16%) of the di-pivaloyl derivative and 0.30 g (27%) of recovered diol **150** as oils. For spectroscopic data see below.

*via fully protected tetra-ol (**152**):*

To a solution of TIPS protected alcohol **152** (2.49 g, 3.96 mmol) in THF (35 mL) was added TBAF (4.7 mL, 1.0 M THF, 4.7 mmol) dropwise. After stirring for 2 hours, the reaction was diluted with Et_2O (85 mL) and water (3 mL), and then the phases were separated. The organic phase was washed with brine (4 mL x 2). The combined aqueous phases were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 3.10 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25% → 35%] afforded 1.40 g (75%) of alcohol **153** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3492, 2965, 2872, 2838, 1728, 1613, 1588, 1514, 1646, 1399, 1364, 1302, 1285, 1250, 1173, 1139, 1073, 1036, 927, 820; $[\alpha]^{20}_{589}$ -82.1° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.79 Hz, 4 H), 6.86 (d, J = 8.79 Hz, 2 H), 6.84 (d, J = 8.79 Hz, 2 H), 5.50 (s, 2 H), 4.55 (ABq, J =

11.54 Hz, 1 H), 4.54 (ABq, *J* = 11.54 Hz, 1 H), 4.33 (ABq, *J* = 11.54 Hz, 1 H), 4.25 (ABq, *J* = 11.54, 1 H), 4.14 – 4.07 (m, 2 H), 4.03 – 3.95 (m, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.56 (m, 2 H), 2.22 (dd, *J* = 8.79, 4.94 Hz, 1 H), 1.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.3, 159.3, 159.2, 142.5, 129.9, 129.8, 129.5, 129.3, 117.2, 113.9, 113.8, 80.0, 70.5, 65.7, 65.3, 60.4, 55.2, 38.7, 27.2; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

Pivaloyl protection of tetra-ol (148) to give diprotected tetra-ol (151):



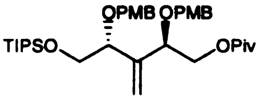
151

To a cold (0 °C) solution of monosilylated tetra-ol **148** (1.85 g, 6.08 mmol) in CH_2Cl_2 (60 mL) were added pyridine (0.98 mL, 12 mmol) and a solution of PivCl (0.82 mL, 6.7 mmol) in CH_2Cl_2 (4 mL) dropwise. After stirring for 23 hours between 0 °C and room temperature, the reaction was quenched by the addition of water (1 mL) and a saturated aqueous NH_4Cl solution (1 mL). Et_2O (150 mL) was added and the phases were separated. The organic phase was washed with water (5 mL), a saturated aqueous $CuSO_4$ solution (6 mL x 2), water (6 mL x 2) and brine (7 mL), dried over $MgSO_4$, filtered and concentrated to give 3.03 g of a clear oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25 %] afforded 1.91 g (81%) of diprotected tetra-ol **151** as a clear oil, and 0.24 g (13%) of recovered monosilylated tetra-ol **148** as a white solid.

For **151**: IR (neat, 4 cm^{-1}): ν = 3430, 2965, 2944, 2889, 1732, 1464, 1285, 1262, 1157, 1101, 920, 884, 801; $[\alpha]_{589}^{20}$ -19.9° (c 0.605, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 5.22 (s, 1 H), 5.20 (s, 1 H), 4.40 (dd, *J* = 4.94, 6.04 Hz, 1 H), 4.32 (dd,

J = 3.85, 7.69 Hz, 1 H), 4.21 (m, 2 H), 3.80 (dd, J = 3.85, 9.89 Hz, 1 H), 3.68 (dd, J = 7.69, 9.89 Hz, 1 H), 3.10 (br s, -OH), 1.18 (s, 9 H), 1.05 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.7, 146.2, 114.0, 73.6, 71.7, 67.3, 67.1, 38.8, 27.1, 17.9, 11.8; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

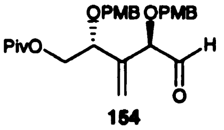
PMB protection of tetra-ol (151) to give fully protected tetra-ol (152):



152

To a solution of tetra-ol **151** (1.91 g, 4.92 mmol) in cyclohexane/CH_2Cl_2 (1:1) (50 mL) was added PMB-imidate (5.55 g, 19.7 mmol) and CSA (0.11 g, 0.49 mmol). The reaction flask was immersed into a preheated oil bath (~40 °C). After stirring for 50 hours, the reaction was allowed to cool to room temperature and was then quenched with a saturated aqueous $NaHCO_3$ solution (6 mL). Et_2O (125 mL) was added and the phases were separated. The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (6 mL x 2) and brine (6 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give a milky white solid. Hexanes were added to the residue. After stirring for several hours, the mixture was filtered and concentrated to give 5.26 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 2.49 g (81%) of fully protected tetra-ol **152** as a clear oil.

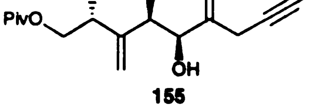
Preparation of aldehyde (154):



154

To a stirred solution of Dess-Martin periodinane (1.63 g, 3.85 mmol) in CH_2Cl_2 (60 mL) were added pyridine (0.31 mL, 3.9 mmol) and a solution of alcohol **153** (1.40 g, 2.96 mmol) in CH_2Cl_2 (6 mL). After stirring for 45 minutes at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (60 mL) and diluted with Et_2O (300 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with water (10 mL), a saturated aqueous $CuSO_4$ solution (10 mL x 2), water (10 mL x 2) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated to give 1.37 g (98%) of crude aldehyde **154** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2963, 2870, 2837, 1730, 1613, 1514, 1464, 1397, 1366, 1283, 1250, 1173, 1157, 1078, 1034, 822; $[\alpha]^{20}_{589}$ -41.9° (c 0.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.51 (d, *J* = 1.65 Hz, 1 H), 7.23 (d, *J* = 8.79 Hz, 2 H), 7.19 (d, *J* = 8.79 Hz, 2 H), 6.85 (d, *J* = 8.79 Hz, 2 H), 6.83 (d, *J* = 8.79 Hz, 2 H), 5.51 (s, 1 H), 5.48 (s, 1 H), 4.57 (ABq, *J* = 11.54 Hz, 1 H), 4.44 (s, 1 H), 4.38 (ABq, *J* = 11.54 Hz, 1 H), 4.13 – 4.22 (m, 3 H), 4.06 – 4.12 (m, 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.2, 178.2, 159.5, 159.2, 140.3, 129.6, 129.5, 128.7, 120.5, 113.9, 113.7, 84.0, 77.9, 71.0, 70.5, 65.6, 55.2, 38.6, 27.1.

Preparation of alcohol (155) – Fragment AB coupling:

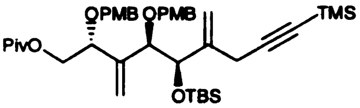


155

t-BuLi (3.95 mL, 1.5 M pentane, 5.93 mmol) was added dropwise to Et_2O (15 mL) at –78 °C. A solution of vinyl bromide **B** (0.64 g, 3.0 mmol) in Et_2O (4 mL) was added dropwise (~18 minutes) to the *t*-BuLi solution. After stirring for 10 minutes, $MgBr_2 \bullet Et_2O$ (3.20 mL, 1.0 M Et_2O/PhH (3:1), 3.20 mmol) was added and the reaction stirred at –78 °C for 15 minutes and then at 0 °C for 10 minutes. In a separate flask, to a 0 °C solution of crude aldehyde **154** (0.93 g, 2.0 mmol) in CH_2Cl_2 (9 mL) was added $MgBr_2 \bullet Et_2O$ (2.0 mL, 1.0 M Et_2O/PhH (3:1), 2.0 mmol) and the reaction stirred for several minutes. The Grignard solution was transferred via cannula to the precomplexed aldehyde solution. After stirring for 50 minutes at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (3 mL) and water (1 mL). The reaction was diluted with Et_2O, stirred for 30 minutes and then the phases were separated. The organic phase was washed with brine (1 mL x 2). The combined aqueous phases were extracted with Et_2O (2x). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.5 g of a reddish-yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 0.68 g (57%) of alcohol **155** as a yellow oil. IR ($CHCl_3$, 4 cm^{-1}): ν = 3381, 2961, 2917, 2865, 2178, 1727, 1684, 1616, 1514, 1458, 1250, 1154, 1036, 843, 760; $[\alpha]^{20}_{589}$ -61.9° (c 0.60, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.20 Hz, 2 H), 7.19 (d, *J* = 8.20 Hz, 2 H), 6.85 (d, *J* = 8.20 Hz, 2 H), 6.84 (d, *J* = 8.20 Hz, 2 H), 5.58 (s, 1 H), 5.49 (s, 1 H), 5.36 (s, 1 H), 5.20 (s, 3 H), 4.53 (ABq, *J* = 10.77 Hz, 1 H), 4.51 (ABq, *J* = 11.02 Hz, 1 H), 4.34 (ABq, *J* = 11.28 Hz, 1 H), 4.29 (dd, *J* = 2.31, 11.29 Hz, 1 H), 4.23 (ABq, *J* = 11.02 Hz, 1 H), 3.97 – 4.14 (series m, 2 H), 3.90 (d, *J* = 5.13 Hz, 1 H), 3.78 (m, 1 H), 3.79 (s, 1 H), 3.78 (s, 3 H), 3.06 (ABq, *J* = 19.99 Hz, 1 H), 2.92 (ABq, *J* = 19.99 Hz, 1 H), 2.85 (d, *J* = 4.36 Hz, 1 H), 1.19 (s, 9 H), 0.13

(s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 178.4, 159.4, 159.2, 142.7, 142.3, 130.1, 129.6, 129.5, 129.3, 116.8, 114.9, 113.9, 113.8, 103.4, 87.8, 80.1, 76.0, 71.0, 70.7, 66.0, 55.2, 38.8, 27.2, 23.3, 0.05; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

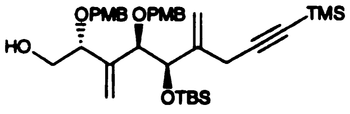
Preparation of TBS-ether (156):



156

To a cold (0 °C) solution of alcohol **155** (0.445 g, 0.731 mmol) in CH_2Cl_2 (7 mL) were added 2,6-lutidine (0.10 mL, 0.91 mmol) and TBSOTf (0.19 mL, 0.84 mmol). After stirring for 40 minutes at 0 °C, the reaction was quenched with water (0.3 mL) and a saturated aqueous NH_4Cl solution (0.3 mL). The reaction was diluted with Et_2O (25 mL) and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (0.5 mL x 2), water (0.5 mL x 2) and brine (1 mL), dried over $MgSO_4$, filtered and concentrated to give 0.54 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.40 g (77%) of TBS-silylated alcohol **156** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2955, 2858, 2174, 1720, 1613, 1587, 1514, 1464, 1362, 1302, 1157, 1099, 862, 841; $[\alpha]^{20}_{589}$ -18.1° (c 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.39 Hz, 4 H), 6.84 (d, *J* = 8.39 Hz, 2 H), 6.83 (d, *J* = 8.84 Hz, 2 H), 5.52 (t, *J* = 1.33 Hz, 1 H), 5.35 (s, 1 H), 5.28 (d, *J* = 1.335 Hz, 1 H), 5.11 (s, 1 H), 4.50 (ABq, *J* = 11.49 Hz, 1 H), 4.49 (ABq, *J* = 11.49 Hz, 1 H), 4.41 (d, *J* = 5.30 Hz, 1 H), 4.32 (ABq, *J* = 11.05 Hz, 1 H), 4.29 (ABq, *J* = 11.05 Hz, 1 H), 4.24 (dABq, *J* = 2.21, 11.93 Hz, 1 H), 4.19 (d, *J* = 7.51 Hz, 1 H), 3.90 (dABq, *J* = 7.51, 11.49 Hz, 1 H),3.88 (d, *J* = 5.30 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.14 (ABq, *J* = 19.44 Hz, 1 H), 3.05 (ABq, *J* = 19.88 z, 1 H), 1.19 (s, 9 H), 0.83 (s, 9 H), 0.14 (s, 9 H), -0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.4, 159.0, 142.9, 142.6, 130.8, 130.4, 129.0 (2), 113.7 (2), 104.4, 86.9, 81.0, 78.1, 77.4, 71.2, 70.9, 66.1, 55.3, 38.8, 27.2, 25.8, 24.4, 18.1, 0.12, -5.1 (2); HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

Preparation of alcohol (157):

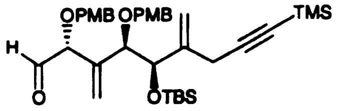


157

To a cold (0 °C) solution of Piv-ester **156** (1.01 g, 1.38 mmol) in THF (14 mL) was added dropwise (~10 minutes) Super-Hydride® (2.9 mL, 1.0 M THF, 2.9 mmol). After stirring for 55 minutes, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (2.9 mL), glycerol (0.87 mL, 0.3 mL/mmol) and water (2.9 mL). The reaction mixture was diluted with Et_2O (125 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with brine (1.5 mL), 0.5 M NaOH (1.5 mL x 2), and brine (1.5 mL). The combined aqueous phases were extracted with Et_2O (3 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.13 g of a clear oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 25%] to give 0.80 g (91%) of alcohol **157** as a clear oil. IR (neat, 4 cm^{-1}): ν =3455, 2957, 2932, 2897, 2859, 2176, 1613, 1514, 1464, 1302, 1250, 1173, 1096, 1063, 1038, 841, 777, 760; $[\alpha]^{20}_{589}$ -22.8° (c 0.61, $CHCl_3$); ^{1}H

NMR (500 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.84 Hz, 2 H), 7.22 (d, *J* = 8.84 Hz, 2 H), 6.86 (d, *J* = 8.84 Hz, 2 H), 6.84 (d, *J* = 8.84 Hz, 2 H), 5.47 (s, 1 H), 5.35 (s, 1 H), 5.30 (s, 1 H), 5.11 (s, 1 H), 4.55 (ABq, *J* = 11.05 Hz, 1 H), 4.50 (ABq, *J* = 11.49 Hz, 1 H), 4.40 (d, *J* = 5.74 Hz, 1 H), 4.29 (ABq, *J* = 11.49 Hz, 1 H), 4.24 (ABq, *J* = 11.05 Hz, 1 H), 4.08 (dd, *J* = 3.09, 7.07 Hz, 1 H), 3.78 (s, 6 H), 3.78 (m, 1 H), 3.63 (m, 1 H), 3.40 (ddd, *J* = 3.98, 7.07, 11.49 Hz, 1 H), 3.15 (ABq, *J* = 19.44 Hz, 1 H), 3.05 (ABq, *J* = 19.44 Hz, 1 H), 2.12 (dd, *J* = 4.42, 9.29 Hz, 1 H), 0.85 (s, 9 H), 0.15 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 159.1, 142.9, 142.8, 130.5, 130.3, 129.3, 129.0, 114.5, 113.8, 113.7, 104.2, 80.7, 80.6, 70.9, 70.7, 64.8, 55.2, 25.8, 24.4, 18.2, 0.08, -5.1;

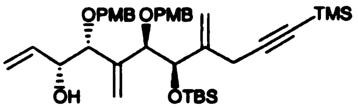
Preparation of aldehyde (158):



158

To a stirred solution of Dess-Martin periodinane (0.69 g, 1.6 mmol) in CH_2Cl_2 (22 mL) were added pyridine (0.14 mL, 1.6 mmol) and a solution of alcohol **157** (0.80 g, 1.25 mmol) in CH_2Cl_2 (5 mL). After stirring for 40 minutes at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (24 mL) and diluted with Et_2O (125 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with water (5 mL), a saturated aqueous $CuSO_4$ solution (5 mL x 2), water (5 mL x 2) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated to give 0.79 g (98%) of crude aldehyde **158** as a yellow oil. IR ($CHCl_3$, 4 cm^{-1}): ν = 2955, 2857, 2174, 1730, 1613, 1588, 1514, 1464, 1362, 1304, 1101, 1003, 910, 862, 841; $[\alpha]_{589}^{20}$ +58.1° (c 0.40, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ = 9.35 (d, *J* = 2.31 Hz, 1 H), 7.26 (d, *J* = 8.46 Hz, 2 H), 7.22 (d, *J* = 8.46 Hz, 2 H), 6.88 (d, *J* = 8.46 Hz, 2 H), 6.85 (d, *J* = 8.46 Hz, 2 H), 5.53 (s, 1 H), 5.43 (s, 1 H), 5.22 (s, 1 H), 5.07 (s, 1 H), 4.55 (ABq, *J* = 11.28 Hz, 1 H), 4.44 (ABq, *J* = 11.28 Hz, 1 H), 4.41 (d, *J* = 5.90 Hz, 1 H), 4.38 (ABq, *J* = 11.53 Hz, 1 H), 4.35 (s, 1 H), 4.20 (ABq, *J* = 11.28 Hz, 1 H), 3.93 (d, *J* = 5.90 Hz, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.12 (ABq, *J* = 19.74 Hz, 1 H), 3.02 (ABq, *J* = 19.74 Hz, 1 H), 0.84 (s, 9 H), 0.16 (s, 9 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.1, 159.4, 159.0, 142.9, 139.7, 130.3, 129.5, 129.4, 129.2, 117.0, 114.4, 113.9, 113.5, 104.3, 87.0, 84.3, 81.2, 71.6, 70.9, 55.2, 25.8, 24.0, 18.2, 0.08, -5.1, -5.2.

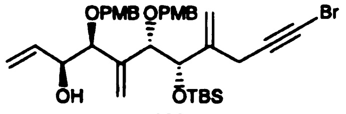
Preparation of alcohol (159):



159

To a cold (0 °C) solution of crude aldehyde **158** (0.79 g, 1.2 mmol) in CH_2Cl_2 (20 mL) was added $MgBr_2{\bullet}Et_2O$ (1.24 mL, 1.0 M Et_2O/PhH (3:1), 1.24 mmol). After stirring for 6 minutes, vinyl magnesium bromide (2.5 mL, 1.0 M THF, 2.5 mmol) was added dropwise (~ 12 minutes). After stirring for 60 minutes at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1.3 mL) and water (1.3 mL). The reaction mixture was diluted with Et_2O (40 mL), stirred at room temperature for 30 minutes, and then the phases were separated. The organic phase was washed with brine (1.5 mL x 2). The combined aqueous phases were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 1.0 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.51 g (61%) of alcohol **159** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3552, 2958, 2932, 2900, 2858, 2176, 1614, 1514, 1464, 1362, 1303, 1250, 1173, 1091, 1037, 921, 841, 779, 760; $[\alpha]^{20}_{589}$ -6.8° (c 0.325, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.72 Hz, 2 H), 7.22 (d, *J* = 8.72 Hz, 2 H), 6.86 (d, *J* = 8.20 Hz, 4 H), 5.89 (ddd, *J* = 16.66, 11.02, 5.38 Hz, 1 H), 5.49 (s, 1 H), 5.41 (s, 1 H), 5.32 – 5.29 (m, 2 H), 5.16 (m, 1 H), 5.14 (s , 1 H), 4.54 (ABq, *J* = 11.53 Hz, 1 H), 4.53 (ABq, *J* = 10.77 Hz, 1 H), 4.49 (d, *J* = 4.87 Hz, 1 H), 4.34 (ABq, *J* = 10.77 Hz, 1 H), 4.21 (ABq, *J* = 10.77 Hz, 1 H), 4.01 (m, 2 H), 3.91 (d, *J* = 4.87 Hz, 1 H), 3.79 (s, 6 H), 3.17 (ABq, *J* = 19.48 Hz, 1 H), 3.10 (ABq, *J* = 19.48 Hz, 1 H), 2.41 (d, *J* = 5.90 Hz, -OH), 0.85 (s, 9 H), 0.14 (s, 9 H), 0.00 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 159.1, 143.1, 142.9, 138.1, 130.5, 130.4, 129.3, 129.1, 128.9, 116.1, 114.2, 113.7, 113.6, 104.4, 86.8, 82.0, 80.5, 77.1, 73.5, 71.6, 70.7, 55.2, 25.9, 24.8, 18.3, 14.1, 0.10, -5.0, -5.1.

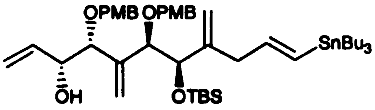
Preparation of 1-bromo-alkyne (160):



160

TMS-alkyne **159** (0.34 g, 0.51 mmol) was dissolved in acetone (5.5 mL) and NBS (0.11 g, 0.61 mmol) and $AgNO_3$ (0.013 g, 0.077 mmol) were added. After stirring for 11 hours the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of water (1 mL) and was then diluted with Et_2O (35 mL). The phases were separated. The organic phase was washed with brine (1 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.49 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/ EtOAc 10%] afforded 0.27 g (78%) of 1-bromo-alkyne **160** as a clear oil.

Preparation of vinyl stannane (161):

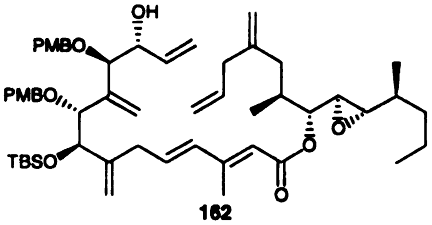


161

To a solution of $(Ph_3P)_2PdCl_2$ (3 mg, 0.004 mmol), Red-Sil (1.4 g, 2.9 mmol, 2.1 mmol/g), and Bu_3SnF (0.25 g, 0.80 mmol) in Et_2O (6 mL) were added a solution of 1-bromo-alkyne **160** (0.245 g, 0.365 mmol) in Et_2O (1 mL) and a drop of TBAF (1.0 M THF). After stirring for 2 hours at room temperature, the reaction was filtered through a pad of Celite on a glass frit. The residual Red-Sil was washed several times with Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 0.39 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 15%] to give 0.233 g (72%) of E-vinyl stannane **161** as a clear oil. IR (neat, 4 cm^{-1}): $\nu = 2955$, 2928, 2855, 1613, 1514, 1464, 1361, 1302, 1250, 1173, 1084, 1040, 920, 835, 777; $[\alpha]^{20}_{589}$ -2.0° (c 0.67, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) $\delta = 7.25$ (d, $J = 8.72$ Hz, 2 H), 7.21 (d, $J = 8.72$ Hz, 2 H), 6.85 (d, $J = 8.72$ Hz, 2 H), 6.84 (d, $J = 8.72$ Hz, 2 H), 5.95 – 5.85 (m, 3 H), 5.50 (s, 1 H), 5.45 (s, 1 H), 5.30 (md, $J = 10.51$ Hz, 1 H), 5.16 (md, $J = 10.51$ Hz, 1 H), 5.07 (s, 1 H), 4.94 (s, 1 H), 4.56 (ABq, $J = 10.77$ Hz, 1 H), 4.54 (ABq, $J = 10.51$ Hz, 1 H), 4.35 (d, $J = 5.13$ Hz, 1 H), 4.33 (ABq, $J = 11.79$ Hz, 1 H), 4.19 (ABq, $J = 11.02$ Hz, 1 H), 4.01 (m, 2 H), 3.91 (d, J

= 5.38 Hz, 1 H), 3.79 (s, 6 H), 3.0 (m, 2 H), 2.40 (d, J = 5.64 Hz, 1 H), 1.50 (m, 6 H), 1.30 (m, 6 H), 0.87 (m, 24 H), -0.02 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.2, 159.1, 146.6, 143.2, 138.3, 130.7, 130.6, 130.2, 129.3, 129.0, 116.0, 114.2, 113.7, 113.7, 113.1, 81.9, 80.8, 78.0, 73.4, 71.7, 70.7, 55.3, 55.2, 41.5, 29.1, 27.3, 25.9, 18.3, 13.7, 9.4, -4.9, -5.0; HRMS (CI) *m/z* 203.1280 [$(M + H)^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

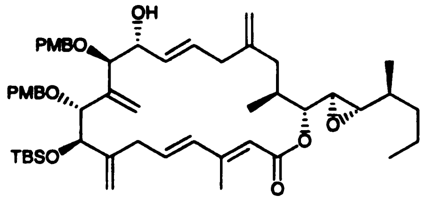
Preparation of diene (162) via Liebeskind's coupling:



162

To a cold (0 °C) solution of (E)-vinyl iodide **301**[50] (0.23 g, 0.52 mmol) and vinyl stannane **161** (0.23 g, 0.26 mmol) in NMP (3 mL) was added copper (I) thiophene-2-carboxylate (CuTc) (0.10 g, 0.52 mmol). The ice bath was removed and the reaction stirred at room temperature until judged complete by TLC (~40 minutes). The reaction mixture was diluted with Et_2O (30 mL) and filtered through a pad of Celite on a glass frit. The green filter cake was washed with Et_2O (3x). The yellow filtrate was washed with water (3 mL x 3), a saturated aqueous KF solution (3 mL x 2), and brine (3 mL). The combined aqueous phases were extracted with Et_2O. The organics were dried over $MgSO_4$, filtered and concentrated to give 0.52 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 15%] to give 0.15 g (63%) of diene **162** as a clear yellow oil. IR (neat, 4 cm^{-1}): ν = 3501, 3075, 2957, 2928, 2857, 1715, 1613, 1514, 1464, 1391, 1360, 1302, 1250, 1173, 1150, 1076, 1038, 914, 835, 779; $[\alpha]^{20}_{589}$ -8.0° (c 0.415, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.72 Hz, 2 H), 7.21 (d, *J* = 8.72 Hz, 2 H), 6.87 (d, *J* = 8.46 Hz, 2 H), 6.85 (d, *J* = 8.46 Hz, 2 H), 6.07 (m, 1 H), 5.89 (m, 2 H), 5.76 (m, 1 H), 5.71 (s, 1 H), 5.52 (s, 1 H), 5.44 (s, 1 H), 5.31 (d, *J* = 17.17 Hz, 1 H), 5.17 (d, *J* = 8.97 Hz, 1 H), 5.10 (s, 1 H), 5.03 (m, 2 H), 4.93 (s, 1 H), 4.83 (s, 1 H), 4.76 (s, 1 H), 4.65 (dd, *J* = 5.13, 6.41 Hz, 1 H), 4.57 (ABq, *J* = 11.53 Hz, 1 H), 4.54 (ABq, *J* = 11.02 Hz, 1 H), 4.34 (m, 1 H), 4.30 (ABq, *J* = 11.53 Hz, 1 H), 4.21 (ABq, *J* = 11.02 Hz, 1 H), 4.03 (m, 2 H), 3.94 (d, *J* = 4.61 Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.0 (m, 2 H), 2.88 (dd, *J* = 2.05, 6.41 Hz, 1 H), 2.71 (dABq, *J* = 6.41, 15.64 Hz, 1 H), 2.69 (dABq, *J* = 7.18, 15.38 Hz, 1 H), 2.63 (dd, *J* = 2.05, 7.43 Hz, 1 H), 2.40 (dABq, *J* = 5.90, 11.28 Hz, 1 H), 2.31 (m, 1 H), 2.25 (s, 3 H), 2.05 (m, 1 H), 1.83 (dABq, *J* = 9.99, 13.84 Hz, 1 H), 1.50 – 1.20 (series m, 5 H), 0.96 (d, *J* = 7.18 Hz, 3 H), 0.92 (d, *J* = 6.92 Hz, 3 H), 0.88 (t, *J* = 7.18 Hz, 3 H), 0.84 (s, 9 H), -0.03 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = ; HRMS (CI) *m/z* 203.1280 [(M + H)$^+$; calcd for $C_{10}H_{19}O_4$, 203.1283].

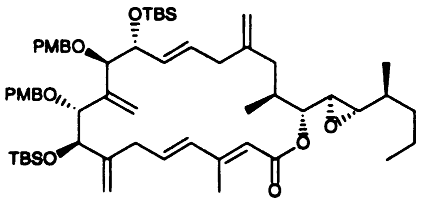
Ring-closing metathesis of diene (162) to give (E)-macrocycle (163):



163

To a slightly refluxing solution of diene **162** (0.15 g, 0.16 mmol) in CH_2Cl_2 (150 mL) was added dropwise (~9 hours) a solution of PhHC=Ru(PCy_3)(IMes-H_2)Cl_2 (70 mg, 0.082 mmol) in CH_2Cl_2 (18 mL). After stirring an additional 15 hours at reflux, the reaction was allowed to cool to room temperature and then concentrated to give 0.26 g of a black residue. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 39 mg (27%) of macrocycle **163**.

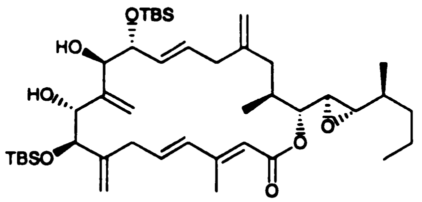
TBS-protection of macrocycle (163) to give TBS-ether (164):



164

To a cold (0 °C) solution of alcohol **163** (0.039 g, 0.044 mmol) in CH_2Cl_2 (0.6 mL) were added 2,6-lutidine (0.02 mL, 0.088 mmol) and TBSOTf (0.013 mL, 0.11 mmol). After stirring for 75 minutes at 0 °C, the reaction was diluted with Et_2O (15 mL) and was then washed with water (1 mL), a saturated aqueous $CuSO_4$ solution (1mL x 2), water (1 mL x 2) and brine (1 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 75 mg of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 37 mg (82%) of fully protected macrocycle **164** as a clear oil.

DDQ deprotection of PMB-macrocycle (164) to give macrocycle diol (165):

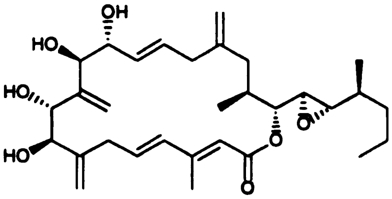


165

To a solution of PMB-ether **164** (36 mg, 0.037 mmol) in *t*-BuOH/aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (2 mL) was added DDQ (33 mg, 0.15 mmol). After stirring for 4 hours, the red reaction mixture was diluted with CH_2Cl_2 (12 mL) and a saturated aqueous $NaHCO_3$ solution (12 mL). The phases were separated.

The aqueous phase was extracted with CH_2Cl_2 (5 mL x 3). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (3 mL), water (3 mL) and brine (3 mL), dried over $MgSO_4$, filtered, and concentrated to give 33 mg of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 12 mg (43%) of diol **165** as an oil.

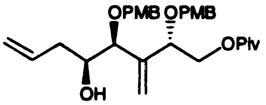
Preparation of the amphidinolide A isomer (166):



166

To a solution of TBS-silylated macrocycle **165** (7.8 mg, 0.010 mmol) in THF (1 mL) was added dropwise an acetic acid buffered TBAF solution (1.05:1) (0.11 mL, 0.2 M THF, 0.022 mmol). After stirring for 21 hours, the reaction was directly loaded onto a silica gel (0.4 g) column [hexanes/EtOAc 25%, 1% MeOH] and eluted with hexanes/EtOAc (1:3) to give 2.1 mg of amphidinolide A isomer **166** as a white solid.

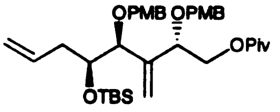
Preparation of alcohol (167):



167

To a -23 °C solution of crude aldehyde **110** (0.58 g, 1.24 mmol) in CH_2Cl_2 (18 mL) was added $MgBr_2 \bullet Et_2O$ (1.36 mL, 1.0 M Et_2O/PhH 3:1, 1.36 mmol) and allyltributyltin (0.50 mL, 1.6 mmol). The reaction was allowed to warm to 0 °C over 1 hour and then stirred an additional 2 hours at 0 °C. The reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1.5 mL) and water (1.5 mL). Et_2O (60 mL) was added and the phases were separated. The organic phase was washed with a saturated aqueous KF solution (1.5 mL x 2) and brine (1 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 1.1 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 0.46 g (72%) of alcohol **167** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3511, 2961, 2936, 2909, 2870, 2838, 1727, 1613, 1514, 1479, 1464, 1397, 1302, 1282, 1250, 1173, 1157, 1064, 1036, 920, 820; $[\alpha]_{589}^{20}$ +79.0° (c 0.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.24 Hz, 2 H), 7.21 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.24 Hz, 2 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.77 (m, 1 H), 5.58 (s, 1 H), 5.45 (s, 1 H), 5.06 – 4.97 (m, 2 H), 4.56 (ABq, *J* = 10.99 Hz, 1 H), 4.55 (ABq, *J* = 11.54 Hz, 1 H), 4.37 (ABq, *J* = 11.54 Hz, 1 H), 4.22 (ABq, *J* = 10.99 Hz, 1 H), 4.21 (m, 1 H), 4.10 (m, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.72 (d, *J* = 4.97 Hz, 1 H), 3.64 (m, 1 H), 2.51 (br d, *J* = 3.30 Hz, 1 H), 2.22 (br t, *J* = 7.14 Hz, 2 H), 1.18 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.4, 159.4, 159.2, 142.6, 134.7, 130.0, 129.6, 129.3, 118.1, 117.4, 113.9, 113.8, 81.8, 76.7, 71.7, 70.7, 66.1, 55.3, 38.7, 37.7, 27.2; HRMS (FAB) *m/z* 513.2869 [$(M + H)^+$; calcd for $C_{30}H_{41}O_7$, 513.2852].

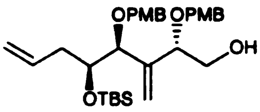
Preparation of TBS-ether (168):



168

To a cold (0 °C) solution of alcohol **167** (0.46 g, 0.90 mmol) in CH_2Cl_2 (9 mL) were added 2,6-lutidine (0.14 mL, 1.2 mmol) and TBSOTf (0.23 mL, 0.99 mmol). After stirring for 40 minutes at 0 °C, the reaction was quenched with water (0.5 mL) and a saturated aqueous NH_4Cl solution (0.5 mL). The reaction was diluted with Et_2O (30 mL) and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (0.5 mL x 2), water (0.5 mL x 2) and brine (1 mL), dried over $MgSO_4$, filtered and concentrated to give 0.63 g of a light pink oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 10%] to give 0.51 g (91%) of TBS-silylated alcohol **168** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2959, 2934, 2907, 2859, 1730, 1613, 1514, 1464, 1302, 1284, 1250, 1173, 1155, 1101, 1067, 1038, 912, 828, 810, 777; $[\alpha]_{589}^{20}$ +48.0° (c 0.585, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.79 Hz, 2 H), 7.23 (d, *J* = 8.24 Hz, 2 H), 6.85 (app d, *J* = 8.24 Hz, 2 H), 6.84 (app d, *J* = 8.79 Hz, 2 H), 5.85 – 5.71 (m, 1 H), 5.61 (s, 1 H), 5.45 (s, 1 H), 5.01 (m, 1 H), 4.97 (m, 1 H), 4.57 (ABq, *J* = 10.99 Hz, 1 H), 4.53 (ABq, *J* = 11.54 Hz, 1 H), 4.37 (m, 1 H), 4.37 (ABq, *J* = 10.99 Hz, 1 H), 4.22 (ABq, *J* = 11.54 Hz, 1 H), 4.20 – 4.16 (m, 1 H), 3.96 (dd, *J* = 7.69, 11.54 Hz, 1 H), 3.84 – 3.76 (m, 2 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 2.4 – 2.3 (m, 1 H), 2.03 (dt, *J* = 13.73, 8.24 Hz, 1 H), 1.19 (s, 9 H), 0.79 (s, 9 H), -0.03 (s, 3 H), -0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.3, 159.1 (2), 142.4, 135.9, 130.6, 130.4, 129.2, 129.1, 11639, 115.1, 113.7, 80.8, 74.5, 70.9, 70.6, 66.1, 55.3, 38.8, 37.5, 27.2, 25.9, 18.1, -4.4, -4.7; HRMS (FAB) *m/z* 627.3735 [(M + H)$^+$; calcd for $C_{36}H_{55}O_7Si$, 627.3717].

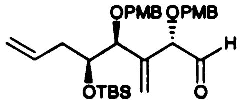
Preparation of alcohol (169):



169

To a cold (0 °C) solution of Piv-ester **168** (0.51 g, 0.812 mmol) in THF (8 mL) was added dropwise (~12 minutes) Super-Hydride® (1.71 mL, 1.0 M THF, 1.71 mmol). After stirring for 30 minutes, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (1.7 mL), glycerol (0.51 mL, 0.3 mL/mmol) and water (1.7 mL). The reaction mixture was diluted with Et_2O (60 mL) and stirred for 90 minutes. The phases were separated. The organic phase was washed with 0.5 M NaOH (1 mL x 2), and brine (1 mL). The combined aqueous phases were extracted with Et_2O (2 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.52 g of a clear oil. The crude residue was purified by flash chromatography on silica gel [hexanes/ EtOAc 25%] to give 0.40 g (91%) of alcohol **169** as a clear oil. IR (neat, 4 cm^{-1}): ν = 3468, 2957, 2930, 2857, 1613, 1588, 1514, 1464, 1362, 1302, 1250, 1173, 1061, 1038, 912, 826, 777; $[\alpha]_{589}^{20}$ +56.9° (c 0.37, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.79 Hz, 2 H), 7.22 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.80 (m, 1 H), 5.54 (s, 1 H), 5.42 (s, 1 H), 5.02 (s, 1 H), 4.98 (m, 1 H), 4.60 (ABq, *J* = 11.12 Hz, 1 H), 4.53 (ABq, *J* = 11.54 Hz, 1 H), 4.29 (ABq, *J* = 10.99 Hz, 1 H), 4.25 (ABq, *J* = 11.40 Hz, 1 H), 4.22 (dd, *J* = 3.02, 7.69 Hz, 1 H), 3.80 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.72 (d, *J* = 5.08 Hz, 1 H), 3.62 (m, 1 H), 3.43 (ddd, *J* = 3.85, 7.28, 11.26 Hz, 1 H), 2.35 (m, 1 H), 2.24 (dd, *J* = 3.85, 9.20 Hz, -OH), 2.06 (tABq, *J* = 7.83, 14.01 Hz, 1 H), 0.82 (s, 9 H), -0.01 (s, 3 H), -0.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 159.1, 142.7, 135.6, 130.4, 130.2, 129.4, 129.2, 117.0, 115.4, 113.9, 113.7, 81.0, 80.1, 74.2, 70.7, 70.5, 65.2, 55.3, 37.6, 25.9, 18.1, -4.3, -4.7; HRMS (FAB) *m/z* 543.3130 [$(M + H)^+$; calcd for $C_{31}H_{47}O_6Si$, 543.3142].

Preparation of aldehyde (170):

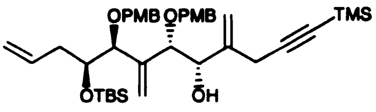


170

To a stirred solution of Dess-Martin periodinane (0.38 g, 1.6 mmol) in CH_2Cl_2 (14 mL) were added pyridine (0.070 mL, 0.88 mmol) and a solution of alcohol **169** (0.40 g, 0.74 mmol) in CH_2Cl_2 (2 mL). After stirring for 2 hours at room temperature, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$/10% aqueous $Na_2S_2O_3$ (1:1) solution (14 mL) and diluted with Et_2O (65 mL). After stirring for 60 minutes, the phases were separated. The organic phase was washed with water (3 mL), a saturated aqueous $CuSO_4$ solution (3 mL x 2), water (3 mL x 2) and brine (3 mL), dried over Na_2SO_4, filtered and concentrated to give 0.35 g (88%) of crude aldehyde **170** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 2955, 2930, 1732, 1613, 1514, 1464, 1362, 1302, 1250, 1173, 1070, 1038, 912, 830, 777; $[\alpha]_{589}^{20}$ -29.9° (c 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 9.41 (d, *J* = 2.20 Hz 1 H), 7.25 (d, *J* = 8.24 Hz, 2 H), 7.19 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 6.83 (d, *J* = 8.24 Hz, 2 H), 5.84 – 5.70 (m, 1 H), 5.58 (s, 1 H), 5.48 (s, 1 H), 5.10 – 4.92 (m, 2 H), 4.45 (m, 1 H), 4.57 (ABq, *J* = 10.99 Hz, 1 H), 4.46 (ABq, *J* = 10.99 Hz, 1 H), 4.38 (ABq, *J* = 11.54 Hz, 1 H), 4.13 (ABq, *J* = 11.54 Hz, 1 H), 3.86 (m, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.29 (m, 1 H), 2.02 (m, 1 H), 0.81 (s, 9 H), -0.04 (s, 3 H), -0.07 (s, 3 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ = 199.1, 159.4, 159.1, 140.0, 135.5, 130.2, 129.5, 129.4, 118.1, 117.0, 113.9, 113.6, 84.1, 81.6, 73.7, 71.3, 70.6, 55.2, 37.7, 25.9, 18.1, -4.3, -4.7.

Preparation of alcohol (171):

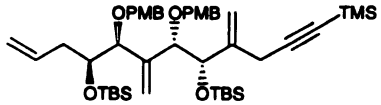


171

t-BuLi (0.98 mL, 1.7 M pentane, 1.7 mmol) was added dropwise to Et_2O (4 mL) at –78 °C. A solution of vinyl bromide **B** (0.18 g, 0.83 mmol) in Et_2O (1 mL) was added dropwise (~7 minutes) to the *t*-BuLi solution. After stirring for 10 minutes, $MgBr_2•Et_2O$ (0.88 mL, 1.0 M Et_2O/PhH (3:1), 0.88 mmol) was added and the reaction stirred at –78 °C for 15 minutes and then at 0 °C for 10 minutes. In a separate flask, to a 0 °C solution of crude aldehyde **170** (0.30 g, 0.55 mmol) in CH_2Cl_2 (3 mL) was added $MgBr_2•Et_2O$ (0.55 mL, 1.0 M Et_2O/PhH (3:1), 0.55 mmol) and the reaction stirred for several minutes. The Grignard solution was transferred via cannula to the precomplexed aldehyde solution. After stirring for 90 minutes at 0 °C, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (0.4 mL) and water (0.4 mL). The reaction was diluted with Et_2O (3 mL) and stirred for 30 minutes. The phases were separated. The organic phase was washed with brine (0.5 mL x 2). The combined aqueous phases were extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered and concentrated to give 0.38 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 0.20 g (53%) of alcohol **171** as a yellow oil. IR (neat, 4 cm^{-1}): ν = 3553, 2957, 2930, 2857, 2178, 1613, 1514, 1464, 1362, 1302, 1250, 1173, 1062, 1038, 912, 841, 777;

$[\alpha]^{20}_{589}$ +44.0° (c 0.338, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.84 Hz, 2 H), 7.21 (d, *J* = 8.84 Hz, 2 H), 6.85 (d, *J* = 8.84 Hz, 4 H), 5.86 (m, 1 H), 5.56 (s, 1 H), 5.52 (s, 1 H), 5.39 (d, *J* = 1.33 Hz, 1 H), 5.19 (d, *J* = 1.33 Hz, 1 H), 5.0 (m, 2 H), 4.57 (ABq, *J* = 11.05 Hz, 1 H), 4.55 (ABq, *J* = 11.49 Hz, 1 H), 4.28 (ABq, *J* = 11.05 Hz, 1 H), 4.27 (ABq, *J* = 11.49 Hz, 1 H), 4.13 (d, *J* = 3.09 Hz, 1 H), 4.05 (t, *J* = 4.42 Hz, 1 H), 3.86 (dt, *J* = 7.51, 4.42 Hz, 1 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.75 (d, *J* = 4.86 Hz, 1 H), 3.09 (ABq, *J* = 20.32 Hz, 1 H), 2.98 (ABq, *J* = 20.32 Hz, 1 H), 2.71 (d, *J* = 5.30 Hz, -OH), 2.42 (m, 1 H), 2.13 (dt, *J* = 14.14, 7.51 Hz, 1 H), 0.85 (s, 9 H), 0.15 (s, 9 H), 0.01 (s, 3 H), -0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 159.1, 143.4, 143.2, 135.8, 130.5, 130.1, 129.4, 129.1, 116.9, 115.4, 114.0, 113.8, 113.7, 103.6, 87.9, 81.0, 80.6, 75.4, 74.6, 71.1, 70.6, 55.3, 37.6, 26.0, 23.5, 18.2, 0.10, -4.1, -4.5; HRMS (FAB) *m/z* 679.3833 [$(M + H)^+$; calcd for $C_{39}H_{59}O_6Si_2$, 679.3850].

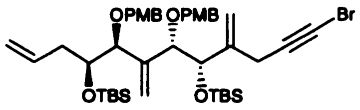
Preparation of TBS-ether (172):



172

To a cold (0 °C) solution of alcohol **171** (0.198 g, 0.291 mmol) in CH_2Cl_2 (3 mL) were added 2,6-lutidine (0.044 mL, 0.38 mmol) and TBSOTf (0.080 mL, 0.35 mmol). After stirring for 30 minutes at 0 °C, the reaction was quenched with water (0.2 mL) and a saturated aqueous NH_4Cl solution (0.2 mL). The reaction was diluted with Et_2O (15 mL) and the phases were separated. The organic phase was washed with a saturated aqueous $CuSO_4$ solution (0.2 mL x 2), water (0.2 mL x 2) and brine (0.4 mL), dried over $MgSO_4$, filtered and concentrated to give 0.29 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to give 185 mg (80%) of TBS-silylated alcohol **172** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2957, 2930, 2896, 2857, 2178, 1614, 1588, 1514, 1472, 1302, 1250, 1173, 1094, 1040, 912, 839, 777; $[\alpha]_{589}^{20}$ -5.4° (c 0.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 8.84 Hz, 4 H), 6.87 (d, *J* = 8.84 Hz, 2 H), 6.85 (d, *J* = 8.39 Hz, 2 H), 5.80 (m, 1 H), 5.48 (s, 1 H), 5.46 (s, 1 H), 5.36 (s, 1 H), 5.16 (s, 1 H), 4.98 (m, 2 H), 4.59 (ABq, *J* = 11.05 Hz, 1 H), 4.56 (ABq, *J* = 11.49 Hz, 1 H), 4.42 (ABq, *J* = 11.05 Hz, 1 H), 4.29 (m, 2 H), 4.14 (d, *J* = 5.74 Hz, 1 H), 3.89 (dt, *J* = 7.51, 3.53 Hz, 1 H), 3.84 (d, *J* = 3.53 Hz, 1 H), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.22 (ABq, *J* = 20.32 Hz, 1 H), 3.09 (ABq, *J* = 20.32 Hz, 1 H), 2.45 (m, 1 H), 2.18 (dt, *J* = 14.14, 7.51 Hz, 1 H), 0.91 (s, 9 H), 0.88 (s, 9 H), 0.15 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H), 0.03 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.0, 158.8, 144.4, 143.4, 136.3, 131.4, 131.3, 128.8 (2), 116.7, 115.1, 114.8, 113.6, 113.6, 104.3, 87.5, 82.3, 82.0, 79.1, 74.5, 71.3, 55.2 (2), 37.7, 26.1, 25.4, 24.4, 18.2, 0.10, -4.0, -4.1; HRMS (FAB) *m/z* 793.4742 [(M + H)$^+$; calcd for $C_{45}H_{73}O_6Si_3$, 793.4715].

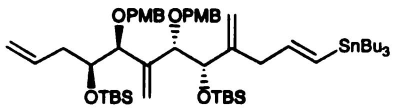
Preparation of bromo-alkyne (173):



173

To a solution of TMS-alkyne **172** (0.14 g, 0.18 mmol) in acetone (2 mL) was added NBS (0.038 g, 0.21 mmol) and $AgNO_3$ (0.007 g, 0.04 mmol). After stirring for 7 hours the reaction was judged complete by TLC analysis. The reaction was quenched by the addition of water (0.4 mL) and was then diluted with Et_2O (14 mL). The phases were separated. The organic phase was washed with brine (0.4 mL x 2), dried over $MgSO_4$, filtered and concentrated to give 0.18 g of a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 5%] afforded 92 mg (66%) of 1-bromo-alkyne **173** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2953, 2928, 2894, 2857, 1613, 1587, 1514, 1464, 1362, 1302, 1248, 1173, 1094, 1040, 1005, 911, 837, 777; $[\alpha]_{589}^{20}$ +1.3° (c 0.49, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.26 (d, *J* = 8.84 Hz, 2 H), 7.24 (d, *J* = 8.39 Hz, 2 H), 6.88 (d, *J* = 8.84 Hz, 2 H), 6.85 (ABq, *J* = 8.39 Hz, 2 H), 5.80 (m, 1 H), 5.48 (s, 2 H), 5.33 (d, *J* = 1.77 Hz, 1 H), 5.15 (s, 1 H), 5.0 (s, 1 H), 4.97 (br d, *J* = 4.86 Hz, 1 H), 4.59 (ABq, *J* = 11.05 Hz, 1 H), 4.55 (ABq, *J* = 11.49 Hz, 1 H), 4.39 (ABq, *J* = 11.05 Hz, 1 H), 4.28 (ABq, *J* = 11.49 Hz, 1 H), 4.25 (d, *J* = 5.74 Hz, 1 H), 4.13 (d, *J* = 5.74 Hz, 1 H), 3.89 (dt, *J* = 7.51, 4.42 Hz, 1 H), 3.84 (d, *J* = 3.98 Hz, 1 H), 3.80 (s, 3 H), 3.80 (s, 3 H), 3.21 (ABq, *J* = 20.32 Hz, 1 H), 3.05 (ABq, *J* = 20.32 Hz, 1 H), 2.45 (m, 1 H), 2.17 (dt, *J* = 14.14, 7.51 Hz, 1 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.0, 158.9, 144.1, 143.3, 136.2, 131.3, 131.2, 128.8 (2), 116.7, 115.3, 114.9, 113.7, 113.6, 82.2, 81.9, 79.0, 77.7, 74.5, 71.2, 55.3, 55.2, 40.6, 37.7, 26.1, 25.9, 24.0, 18.2 (2), -4.1 (2), -4.8, -4.9;

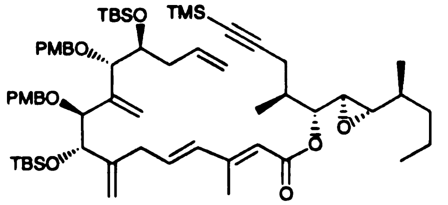
Preparation of vinyl stannane (174):



174

To a mixture of $(Ph_3P)_2PdCl_2$ (0.8 mg, 0.001 mmol), Red-Sil (0.44 g, 0.92 mmol, 2.1 mmol/g), Bu_3SnF (0.078 g, 0.25 mmol) and 1-bromo-alkyne **173** (0.092 g, 0.12 mmol) in Et_2O (2.5 mL) was added a drop of TBAF (1.0 M THF). After stirring for 2 hours at room temperature, the reaction was diluted with Et_2O (5 mL) and then filtered through a pad of Celite on a glass frit. The residual Red-Sil was washed several times with Et_2O. The filtrate was dried over $MgSO_4$, filtered, and concentrated to give 0.14 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/ EtOAc 2% → 5%] to give 74 mg (64%) of E-vinyl stannane **174** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2955, 2928, 2857, 1614, 1514, 1464, 1302, 1250, 1173, 1090, 1040, 910, 837, 777; $[\alpha]_{589}^{20}$ -4.5° (c 0.59, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.39 Hz, 2 H), 7.21 (d, *J* = 8.84 Hz, 2 H), 6.84 (d, *J* = 8.84 Hz, 2 H), 6.83 (d, *J* = 8.39 Hz, 2 H), 5.91 (m, 2 H), 5.78 (m, 1 H), 5.48 (s, 1 H), 5.44 (s, 1 H), 5.06 (s, 1 H), 4.97 – 4.91 (m, 3 H), 4.59 (ABq, *J* = 11.05 Hz, 1 H), 4.54 (ABq, *J* = 11.49 Hz, 1 H), 4.41 (ABq, *J* = 11.05 Hz, 1 H), 4.24 – 4.20 (series m, 2 H), 4.09 (d, *J* = 5.74 Hz, 1 H), 3.88 (m, 2 H), 3.79 (s, 6 H), 3.06 (ABq, *J* = 18.56 Hz, 1 H), 2.91 (ABq, *J* = 18.99 Hz, 1 H), 2.42 (m, 1 H), 2.17 (dt, *J* = 14.58, 7.07 Hz, 1 H), 1.47 (m, 6 H), 1.27 (m, 6 H), 0.87 (m, 33 H), 0.03 (s, 3 H), 0.02 (s, 3 H), -0.001 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.8, 158.7, 147.7, 146.5, 144.3, 136.3, 131.5, 131.3, 130.2, 128.7 (2), 116.7, 115.1, 113.8, 113.6, 113.4, 82.2, 82.0, 79.5, 74.4, 71.1, 71.0, 55.3, 55.2, 41.3, 37.7, 29.1, 27.3, 26.1, 25.9, 18.3, 18.2, 13.7, 9.4, -4.0, -4.7, -4.8; HRMS (FAB) *m/z* 955.4766 $[(M - Bu)^+]$; calcd for $C_{50}H_{83}O_6Si_2Sn$, 955.4750].

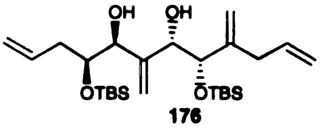
Preparation of diene (175) via Stille cross-coupling:



175

A solution of Pd_2dba_3 (1.3 mg, 0.0014 mmol) and $AsPh_3$ (1.8 mg, 0.0058 mmol) in NMP (0.3 mL) were stirred at room temperature for 10 minutes, at which time a solution of (E)-vinyl iodide **302**[50] (0.035 g, 0.072 mmol) in NMP (0.2 mL) was added to the yellowish-green solution. The reaction flask was immersed into a preheated oil bath (~50 °C) and a solution of vinyl stannane **174** (0.073 g, 0.072 mmol) in NMP (0.2 mL) was added immediately. After stirring for 21 hours at 50 °C, the reaction was allowed to cool to room temperature and was then diluted with Et_2O (10 mL). The organic phase was washed with water (0.3 mL x 2), a saturated aqueous KF solution (0.3 mL x 2) and brine (0.4 mL). The organics were dried over $MgSO_4$, filtered and concentrated to give 0.16 g of a yellow oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to give 23 mg (30%) of diene **175** as a clear oil. IR (neat, 4 cm^{-1}): ν = 2959, 2930, 2857, 2176, 1717, 1614, 1587, 1514, 1464, 1388, 1362, 1302, 1250, 1173, 1148, 1094, 1038, 912, 839, 777; $[\alpha]_{589}^{20}$ -5.6° (c 0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.23 (d, J = 8.39 Hz, 2 H), 7.21 (d, J = 8.39 Hz, 2 H), 6.85 (d, J = 8.84 Hz, 2 H), 6.84 (d, J = 8.39 Hz, 2 H), 6.04 (m, 2 H), 5.78 (m, 1 H), 5.67 (s, 1 H), 5.48 (s, 2 H), 5.08 (s, 1 H), 4.98 (s, 1 H), 4.96 (m, 1 H), 4.88 (s, 1 H), 4.75 (t, J = 6.19 Hz, 1 H), 4.60 (ABq, J = 11.05 Hz, 1 H), 4.53 (ABq, J = 11.49 Hz, 1 H), 4.37 (ABq, J = 11.05 Hz, 1 H), 4.25 (ABq, J = 11.05 Hz, 1 H), 4.21 (d, J = 5.74 Hz, 1 H), 4.13 (d, J = 5.74 Hz, 1 H), 3.90 (m, 2 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 3.05 (dABq, J = 5.74, 16.35 Hz, 1 H), 2.94 (dABq, J = 6.63, 16.35 Hz, 1 H), 2.91 (dd, J = 2.21, 6.19 Hz, 1 H), 2.66 (dd, J = 2.21, 7.51 Hz, 1 H), 2.44 (m, 1 H), 2.40 (dABq, J = 4.86, 16.79 Hz, 1 H), 2.28 (m, 1 H), 2.24 (s, 3 H), 2.18 (dt, J = 14.14, 7.07 Hz, 1 H), 2.07 (m, 1 H), 1.50 – 1.20 (series m, 5 H), 1.11 (d, J = 7.07 Hz, 3 H), 0.93 (d, J = 7.07 Hz, 3 H), 0.88 (m, 12 H), 0.87 (s, 9 H), 0.14 (s, 9 H), 0.03 (s, 6 H), 0.003 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 166.2, 158.9, 158.8, 153.2, 147.4, 144.1, 136.2, 135.4, 135.0, 131.4, 131.2, 128.8, 128.6, 117.6, 116.8, 115.4, 114.3, 113.7, 113.6, 104.7, 86.6, 82.2, 82.1, 79.2, 75.1, 74.5, 71.1 (2), 61.6, 56.8, 55.3, 37.8, 36.6, 36.3, 35.3, 26.1, 25.9, 23.6, 20.0, 18.3, 18.2, 15.8, 15.3, 14.2, 14.0, 0.06, -4.0, -4.7, -4.8; HRMS (FAB) *m/z* 1071.6600[(M + H)$^+$; calcd for $C_{62}H_{99}O_9Si_3$, 1071.6597].

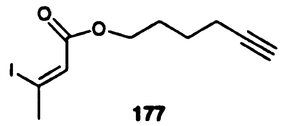
DDQ deprotection of PMB-ether (174) to give diol (176):



176

To a solution of PMB-ether **174** (40 mg, 0.040 mmol) in *t*-BuOH/aqueous pH=7 buffer/CH_2Cl_2 (1:1:5) (2 mL) was added DDQ (27 mg, 0.12 mmol). After stirring for 7 hours, the red reaction mixture was diluted with CH_2Cl_2 (12 mL) and a saturated aqueous $NaHCO_3$ solution (12 mL). The phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 mL x 3). The combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 41 mg of a red oil. The crude residue was purified by flash chromatography on silica gel [hexanes/EtOAc 5%] to give 10 mg (53%) of diol **176** as an oil. Note: the vinyl stannane moiety did not survive the reaction. IR (neat, 4 cm^{-1}): ν = 3551, 3079, 2955, 2930, 2895, 2859, 1472, 1464, 1390, 1362, 1255, 1070, 1005, 914, 837, 777; ^1H NMR (300 MHz, $CDCl_3$) δ = 5.77 (m, 2 H), 5.30 (s, 1 H), 5.26 (s, 1 H), 5.11 – 5.03 (series m, 5 H), 4.93 (d, *J* = 1.33 Hz, 1 H), 4.06 (d, *J* = 5.30 Hz, 1 H), 3.83 (m, 2 H), 3.76 (dt, *J* = 7.51, 4.42 Hz, 1 H), 2.89 (d, *J* = 4.86 Hz, -OH), 2.85 (m, 1 H), 2.74 (d, *J* = 7.51 Hz, -OH), 2.70 (m, 1 H), 2.43 (dt, *J* = 14.14, 7.51 Hz, 1 H), 2.23 (m, 1 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 148.5, 147.2, 135.6, 134.2, 118.1, 116.9, 113.6, 113.1, 78.6, 73.9, 73.4, 73.0, 38.9, 36.3, 25.9 (2), 18.2, 18.1, -4.4 (2), -4.5, -5.0; HRMS (FAB) *m/z* 483.3344 [$(M + H)^+$; calcd for $C_{26}H_{51}O_4Si_2$, 483.3326].

Preparation of β-iodo ester (177):



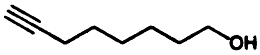
177

To a solution of (Z)-β-iodo acid **48** (0.50 g, 2.4 mmol) in CH_2Cl_2 (5 mL) were added 5-hexyn-1-ol (0.29 mL, 2.6 mmol) and DMAP (0.029 g, 0.24 mmol). The reaction flask was cooled to 0 °C after which a solution of DCC (0.54 g, 2.6 mmol) in CH_2Cl_2 (1 mL) was added. After stirring for 5 minutes at 0 °C, the ice bath was removed and the reaction continued to stir at room temperature for 6 hours. The reaction mixture was filtered through a pad of Celite on a glass frit. The filter cake was washed with CH_2Cl_2 several times. The filtrate was washed with 0.5 M HCl (2 mL x 2) and a saturated aqueous $NaHCO_3$ solution (2 mL).

The organics were dried over $MgSO_4$, filtered, and concentrated to give 1.05 g of an oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 0.54 g (78%) of (Z)-β-iodo ester **177** as a clear oil.

^{1}H NMR 300 MHz ($CDCl_3$): $\delta = 6.27$ (d, J = 1.37 Hz, 1 H), 4.15 (t, J = 6.32 Hz, 2 H), 2.70 (d, J = 1.37 Hz, 3 H), 2.20 (dt, J = 2.47, 6.87 Hz, 2 H), 1.93 (t, J = 2.47, 1 H), 1.76 (m, 2 H), 1.59 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 164.3$, 125.4, 113.5, 83.8, 68.7, 36.5, 27.6, 24.9, 18.1.

Isomerization of 3-octyn-1-ol to 7-octyn-1-ol via "Zipper Reaction":



Potassium 3-aminopropylamide (KAPA) was prepared by first washing the KH (8.2 g, 71.32 mmol, 35% mineral dispersion) suspension with hexanes (3x, 5 mL/g of dispersion). The light gray to white solid was cooled to 0 °C and 1,3-diaminopropane (50 mL) was added dropwise and the reaction stirred at 0 °C for 1 hour. The ice bath was removed, and the reaction was stirred at room temperature for 2 hours after which 3-octyn-1-ol (3.0 g, 24 mmol) was added dropwise. After stirring for 8 hours, the reaction was quenched by the slow addition of water (20 mL) and a saturated aqueous NH_4Cl solution (10 mL). The reaction mixture was further diluted with 1.0 M HCl (20 mL) and Et_2O (50 mL). The phases were separated. The aqueous phase was extracted with Et_2O (50 mL x 3). The combined organics were dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Purification by flash chromatography on silica gel [hexanes/EtOAc 25%] afforded 2.5 g (83%) of 7-octyn-1-ol as a clear oil.

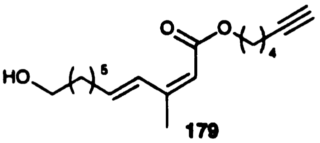
^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.58 (t, J = 6.59 Hz, 2H), 2.14 (dt, J = 2.74, 6.87 Hz, 2H), 1.90 (t, J = 2.74 Hz, 1H), 1.75 (s, –OH), 1.5 (m, 4 H), 1.35 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 84.5, 68.1, 62.7, 32.5, 28.4, 28.3, 25.2, 18.2.

Preparation of vinyl stannane (178):

178

To a solution of 7-octyn-1-ol (0.18 g, 1.4 mmol) in benzene (15 mL) were added AIBN (0.012 g, 0.071 mmol) and Bu_3SnH (0.57 mL, 2.1 mmol). The flask was immediately immersed in a preheated ~85 °C oil bath. After stirring for 3 hours, the reaction mixture was concentrated. Purification by flash chromatography on silica gel [hexanes/EtOAc 10%] afforded 0.47 g (79%) of a mixture (4.7:1) of E- and Z-vinyl stannane **178** as a clear oil.

Preparation of diene (179) via Stille coupling:



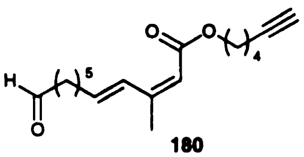
179

To a solution of bis(acetonitrile)palladium (II) chloride (13 mg, 0.052 mmol) in DMF (10 mL) were added a solution of vinyl iodide **177** (0.30 g, 1.0 mmol) in DMF (0.5 mL) and a solution of vinyl stannane **178** (0.47 g, 1.1 mmol) in DMF (0.5 mL). After stirring for 18 hours at room temperature, the reaction was quenched with the addition of a 10% aqueous NH_4OH solution (10 mL). The phases were separated. The aqueous phase was extracted with Et_2O (20 mL x 3). The combined organic phases were washed with water (10 mL x 2), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give 0.63 g of a red oil.

Purification by flash chromatography on silica gel [Hexanes/EtOAc 25%] afforded 0.11 g (37%) of diene **179** as a yellow oil.

^{1}H NMR 300 MHz ($CDCl_3$) $\delta = 7.53$ (dd, $J = 0.82, 15.93$ Hz, 1 H), 6.10 (dt, $J = 15.93, 6.87$ Hz, 1 H), 5.57 (d, $J = 0.55$ Hz, 1 H), 4.09 (t, $J = 6.59$ Hz, 2 H), 3.60 (dt, $J = 5.49$ Hz, 2 H), 2.20 (m, 4 H), 1.95 (d, $J = 1.1$ Hz, 3 H), 1.93 (t, $J = 2.75$ Hz, 1 H), 1.2 - 1.8 (m, 12 H); ^{13}C NMR 75 MHz ($CDCl_3$) $\delta = 166.44$, 151.48, 139.11, 127.64, 115.48, 83.89, 68.61, 63.08, 62.79, 33.11, 32.59, 28.89, 28.82, 27.71, 25.45, 24.96, 21.05, 18.03.

Preparation of aldehyde (180):



180

To a solution of alcohol **179** (0.11 g, 0.38 mmol) in CH_2Cl_2 (4 mL) were added DMSO (0.27 mL, 3.8 mmol), *i*-Pr_2NEt (0.39 mL, 2.3 mmol), and SO_3•pyridine (0.18 g, 1.1 mmol) at room temperature. After stirring for 25 minutes, the reaction was quenched by the addition of an aqueous saturated NH_4Cl solution (4 mL). The reaction mixture was diluted with Et_2O (12 mL), and the phases were separated. The organic phase was washed with brine (2 mL x 2). The combined aqueous phases were extracted with Et_2O (3 mL x 2). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give 0.10 g. The crude product was purified by flash chromatography on silica gel [hexanes/EtOAc 10% → 25%] to give 57 mg (53%) of aldehyde **180** as a yellow oil.

^{1}H NMR 300 MHz ($CDCl_3$): δ = 9.74 (t, *J* =1.65 Hz, 1 H), 7.54 (dd, *J* = 0.82, 15.93 Hz, 1 H), 6.10 (dt, *J* = 15.93, 6.87 Hz, 1 H), 5.58 (s, 1 H), 4.09 (t, *J* = 6.59 Hz, 2 H), 2.41(dt, *J* = 1.65, 7.42 Hz, 2 H), 2.20 (m, 4 H), 1.96 (d, *J* = 1.1 Hz, 3 H), 1.93 (t, *J* = 2.75 Hz, 1 H), 1.1 - 1.8 (m, 10 H).

Indium cyclization of aldehyde / alkyne (180):

Aldehyde-alkyne **180** (57 mg, 0.20 mmol), 1,3-dibromopropene (0.020 mL, 0.196 mmol), indium powder (45 mg, 0.393 mmol), and sodium iodide (59 mg, 0.393 mmol) were added to THF (2 mL). After stirring at room temperature for 6.5 hours, the reaction was quenched with the addition of a saturated aqueous NH_4Cl solution (0.5 mL). The reaction mixture was diluted with Et_2O (4 mL) and the phases were separated. The organic phase was washed with brine (1 mL). The combined aqueous phases were extracted with Et_2O (2 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to give 0.090 g of a yellow oil. The crude material was purified by flash chromatography on silica gel [Hexanes/EtOAc 10%] to give two identifiable products in very small quantities.

References and Notes:

1. Review: Ishibashi, M.; Kobayashi, J. *Heterocycles*, **1997**, *44*, 543 – 572.
2. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y. *Tetraheron Lett.* **1986**, *27*, 5755 – 5758.
3. Kobayashi, J.; Ishibashi, M. *J. Nat. Prod.* **1991**, *54*, 1435 – 1439.
4. Terrell, L. R.; Ward, J. S., III; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 3097 – 3100.
5. (a) Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198 – 11199. (b) Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765 - 766. (c) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945 – 948.
6. (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 619. (b) Zhang, H. X.; Guibe, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 623.
7. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413 – 4450. (b) Trnka, T. M. Grubbs, R. H. *Accts. Chem. Res.* **2001**, *34*, 18 – 29.
8. Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615 – 623.
9. O'Connor S. J.; Williard P. G. *Tetrahedron Lett.* **1989**, *30*, 4637 – 4640.
10. Yu, Y.; Williard, P. G.; 221st American Chemical Society National Meeting, April 1-5, San Diego, CA; The Division of Organic Chemistry of the American Chemical Society: Washington, DC, 2001; ORGN 580.
11. (a) Boden, C.; Pattenden, G. *Synlett* **1994**, 181 – 182. (b) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703 – 706.
12. (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813 – 817. (b) Mitchell, T. *Synthesis* **1992**, 803 – 815.
13. (a) Schmid, c. R.; Bryant, J. D.; Dowlatzadeh, M.; Phillips, J. L.; Prather, D. E.; Schantz, R. E.; Sear, N. L.; Vianco, C. S. *J. Org. Chem.* **1991**, *56*, 4056 – 4058. (b) Hertel, L. W.; Grossman, C. S.; Kroin, J. S. *Synth. Comm.* **1991**, *21*, 151 – 154.
14. Sharma, P. K.; Srivastava, S. K.; Sharma, S. *Synthetic Comm.* **1995**, *25*, 1249 – 1253.

15. Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373 – 1378.

16. Marshall, J. A.; Trometer, J. D.; Cleary, D. G. Tetrahedron 1989, 45, 391 – 402.

17. Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1375 – 1382.

18. Payne, G. B. *J. Am. Chem. Soc.* 1962, 3819 – 3822.

19. Behrens, C. H.; Ko, S. Y. K.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687 – 5696.

20. Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587 – 590.

21. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480 – 2482.

22. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287.

23. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505 – 5507.

24. Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282 – 2291.

25. The regiochemistry of TBS ether **35** was made obvious through the spectroscopic analysis of compounds later in the Scheme such as **29**.

26. Tanikaga, R.; Yabuki, Y.; Ono, N.; Kaji, A. *Tetrahedron Lett.* **1976**, 2257 – 2258.

27. Hall, J. A.; Keyworth, D. A. *In Brief Chemistry of the Elements with Qualitiative Analysis*, Benjamin: Meleno Park, 1971, p.119.

28. Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1967**, *89*, 5505.

29. Nakadaira, Y.; Sato, R.; Sakurai, H. *J. Organomet. Chem.* **1992**, *441*, 411 – 417.

30. (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1988**, 909 – 910. (b) Jeffery, T. *Tetrahedron Lett.* **1989**, *30*, 2225 – 2228.

31. (a) Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1994**, 1153 – 1160. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1996**, *37*, 1081 – 1084. (c) Desrut, M.; Kergomard, A.; Renard, M. F.; Veschambre, H. *Tetrahedron* **1981**, *37*, 3825 – 3829.

32. After consulting with Professor Carriera, these results should have been expected since he stated that an activated electrophile is needed for the alkylation.

33. This part of the project was taking over by Joe Ward.

34. (a) Le Noble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897-3899.

35. For a discussion on the addition of aqueous HI to alkynes see the following references: (a) Zoller, T.; Uguen, D. *Tetrahedron Lett.* **1998**, *39*, 6719 – 6720. (b) Abarbri, M.; Parrain, J.; Cintrat, J.; Duchene, A. *Synthesis* **1996**, 82 – 86.

36. (a) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775 – 1781. (b) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674 – 3680.

37. Tũckmantel, W.; Oshima, K. ; Nozaki H. *Chem. Ber.* **1986**, *119*, 1581 – 1593.

38. The aldehyde was not purified because during column chromatography on silica gel the exo-olefin internalized with similar substrates.

39. Smith, A. B., III; Chen, S. S. Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 12013 – 12014.

40. Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485 – 486.

41. (a) Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrehedron Lett.* **1992**, *33*, 5861 – 5864. (b) review: Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853 – 12909.

42. Kim, S.; Kim, K. H. *Tetrahedron Lett.* **1995**, *36*, 3725 – 3728.

43. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748 – 2749.

44. Mori, Y.; Yaegashi, K.; Furokawa, H *Tetrahedron* **1997**, *53*, 12917 – 12932.

45. Takano, S.; Akiyama, M.; Ogasawara, K. *Chem. Pharm. Bull.* **1984**, *32*, 791 – 794.

46. Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404 – 407.

47. Wang, Z. *Tetrahedron Lett.* **1989**, *30*, 6611 – 6614.

48. The lack of success of this reaction is probably due to the purity of the pivaloyl chloride, and with the success of the silyl protection, the pivaloyl protection was not repeated.

49. (a) Gill, D. M.; Pegg, N. A.; Rayner, C. M. *Tetrahedron* **1996**, *52*, 3609 – 3630. (b) McIntyre, S.; Warren, S. *Tetrahedron Lett.* **1990**, *31*, 3457 – 3460.

50. For the synthesis and characterization of this compound see the PhD dissertation of Feng Geng **2001**, Michigan State University.

51. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123 – 1125.

52. Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312 – 2313.

53. The lack of identification of the by-products was due to the scale of the reactions and the contamination of products with residual catalyst.

54. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.

55. For a leading reference see: Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942 – 3943.

56. The yield of the oxidation was higher if the reaction was ran on a smaller scale (12 mmol or less).

57. This investigation was necessary since no detailed experimental procedure is reported in the literature.

58. (a) Paquette, L.A.; Bennett, G.D.; Isaac, M.B.; Chhatriwalla, A. *J. Org. Chem.* **1998**, *63*, 1836 – 1845. (b) Paquette, L.A.; Mitzel, T.M.; Isaac, M.B.; Crasto, C.F.; Schomer, W.W. *J. Org. Chem.* **1997**, *62*, 4293 – 4301. (c) Cintas, P. *Synlett*, **1995**, 1087 – 1096. (d) Araki, S.; Shimizu, T.; Johar, P.S.; Jin, S.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538 – 2542.

59. Binder, W.H.; Prenner, R.H.; Schmid, W. *Tetrahedron*, **1994**, *50*, 749 – 758.

60. Ranu, B.C.; Majee, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1225 – 1226.

61. (a) Li, C.; Chen, D. *Tetrahedron Lett.* **1996**, *37*, 295 – 298. (b) Araki, S.; Hirashita, T.; Shimizu, H.; Yamarmura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1996**, *37*, 8417 – 8420. (c) Li, C. *Tetrahedron Lett.* **1995**, *36*, 517 – 518.

62. Brown, C.A.; Yamashita, A. *J. Chem. Soc., Chem. Commun.* **1976**, 959.

63. Macaulay, S. *J. Org. Chem.* **1980**, *45*, 734 – 735.

64. see ref. 6b

65. (a) Miyai, T.; Inoue, K.; Yasuda, M.; Baba, A. *Synlett*, **1997**, 699 – 700. (b) Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1995**, 36, 9497 – 9500. (c) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920 – 1921.

66. (a) Terstiege, I.; Maleczka, R. E., Jr. *J. Org. Chem.* **1999**, *64*, 342 – 343. (b) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622 – 9623.

67. Although successful, reactions carried out in the absence of TBAF or TBAI ran considerably slower.

68. CsF may be substituted for KF with little change in the outcome of the reaction.

69. Some substrate intolerance was observed when 6-(*tert*-butyldimethylsilyloxy)-1-hexyne (**185**) was subjected to conditions A. In this case, although the TBS group remained in place, a significant amount of destannylation occurred.

70. Mitchel, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257 – 265.

71. (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741 – 760. (b) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can J. Chem.* **1994**, *72*, 1181 – 1192. (c) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023 – 2035. (d) Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59 – 66. (e) Breslow, R. *Acc. Chem. Res.* **1991**, *6*, 159 – 164.

72. Kawakami, T.; Shibata, I.; Baba, A. *J. Org. Chem.* **1996**, *61*, 82 – 87.

73. Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371 – 1448.

74. Preliminary ^{119}Sn NMR data is consistent with this hypothesis, as is literature precedent, see Leibner, J. E.; Jacobus, J. *J. Org. Chem.* **1979**, *44*, 449 – 450.

75. (a) Corey, E. J.; Guzmann-Perexz, A.; Lazerwith, S. E.; *J. Am. Chem. Soc.* **1997**, *119*, 11769 – 11776. (b) Pearlman, B. A.; Putt, S. R.; Fleming, J. A. *J. Org. Chem.* **1985**, *50*, 3622 – 3624. (c) Harpp, D. N.; Gingras, M. *J. Am.*

Chem. Soc. **1988**, *110*, 7737 – 7745. (d) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079 – 4094.

76. This trend continues when the Bu_3SnCl/KF/PMHS method is used under free radical conditions that promote kinetic Z-olefin formation (excess alkyne, short reaction times; Leusink, A. J.; Budding, H. A. *J. Organomet. Chem.* **1968**, *11*, 533 – 539; Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L. *Synthesis* **1986**, 496 – 499; and ref (3b). However, for reasons that remain unclear, the reactions were significantly less selective for the cis vinylstannanes with the Bu_3SnF/TBAF/PMHS protocol.

77. (a) Reed-Mundell, J. J.; Nadkarni, D. V.; Kunz, J. M., Jr.; Fry, C. W.; Fry, J. L. *Chem. Mater.* **1995**, *7*, 1655 – 1660. (b) Kini, A. D.; Nadkarni, D. V.; Fry, J. L. *Tetrahedron Lett.* **1994**, *35*, 1507 – 1510. (c) For other immobilized hydrosilanes, see: Rudzinski, W. E.; Montgomery, T. L.; Frye, J. S.; Hawkins, B. L.; Maciel, G. E. *J. Catal.* **1986**, *98*, 444 – 456.

78. (a) Scott, W. J.; Moretto, A. F. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. Ed.; Wiley: New York, 1995; Vol. 7, 5327 – 5328. (b) Dyer, R. S.; Walsh, T. J.; Wonderlin, W. F.; Bercegeay, M. *Neurobehav. Toxicol. Teratol.* **1982**, *4*, 127 – 133.

79. At 9-20 mg/kg the LD50 of Me_3SnCl is similar to that of Me_3SnH (7 mg/kg in large rates). However, as a solid (mp 37-38 °C) the Me_3SnCl does not pose the same inhalation hazard as Me_3SnH. Furthermore, the reaction of R_3SnCl with KF/PMHS initially involves the conversion of the tin chlorides into the corresponding tin fluorides, which given their associated nature are generally only sparingly soluble in organic solvents. Thus, tin poisoning through absorption is also minimized by this protocol.

80. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139 – 4142.