This is to certify that the

dissertation entitled

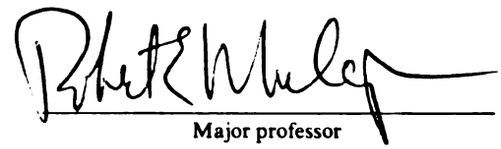
THE TOTAL SYNTHESIS OF THE
PROPOSED STRUCTURE OF AMPHIDINOLIDE A

presented by

Joseph Samuel Ward III

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry



Major professor

Date August 14, 2002

THE TOTAL SYNTHESIS OF THE PROPOSED STRUCTURE OF AMPHIDINOLIDE A

By

Joseph Samuel Ward III

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

2002

ABSTRACT

THE TOTAL SYNTHESIS OF THE PROPOSED STRUCTURE OF

AMPHIDINOLIDE A

By

Joseph Samuel Ward III

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 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. Our first-generation approach to the target molecule allowed us to investigate the synthesis of the requisite stereocenters and possible coupling strategies. The information gleaned from these studies directed our successful synthesis of the proposed structure of amphidinolide A.

To my grandfather,
John F. Weldon.

ACKNOWLEDGMENTS

I would like to thank Professor Robert E. Maleczka, Jr. for his patience, guidance and encouragement during my studies at Michigan State. I could not have asked for a better mentor. I hope I can be as understanding and wise with my own students. I would also like to thank Professors Peter Wagner, Gary Blanchard, and Aaron Odom for serving on my guidance committee. I wish to thank Professors William Reusch and Babak Borhan for helpful discussions over the years.

I have to thank my family for their understanding throughout my academic studies. In particular I thank my parents, Brenda and Joe, for encouraging me to follow my dreams. I also thank my sister, Jaimie, for her love and friendship. Without their understanding, encouragement, and support throughout my life, this achievement would not have been possible.

I would like to thank my colleagues from the Maleczka group for their friendship and help, especially Lamont Terrell and Feng Geng who labored hard to finish the total synthesis of proposed amphidinolide A. I also thank all my friends from the Blanchard group for all the comic relief they supplied over the years.

TABLE OF CONTENTS

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
h	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
Mes	mesityl
mL	milliliter
mmol	millimole
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
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TMS	trimethylsilyl
PTSA	*p*-toluenesulfonic acid

Chapter 1. Introduction and Prior Work

The amphidinolides,[1] were isolated by Jun'ichi Kobayashi (Hokkaido University) from the marine dinoflagellate *Amphidinium sp.* These macrocyclic lactones represent a novel class of natural products, which originate from this species of marine microorganism. 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 1. The potency of the amphidinolides varies from one of the weakest members amphidinolide T1[2] to the highly potent amphidinolide N.[3]

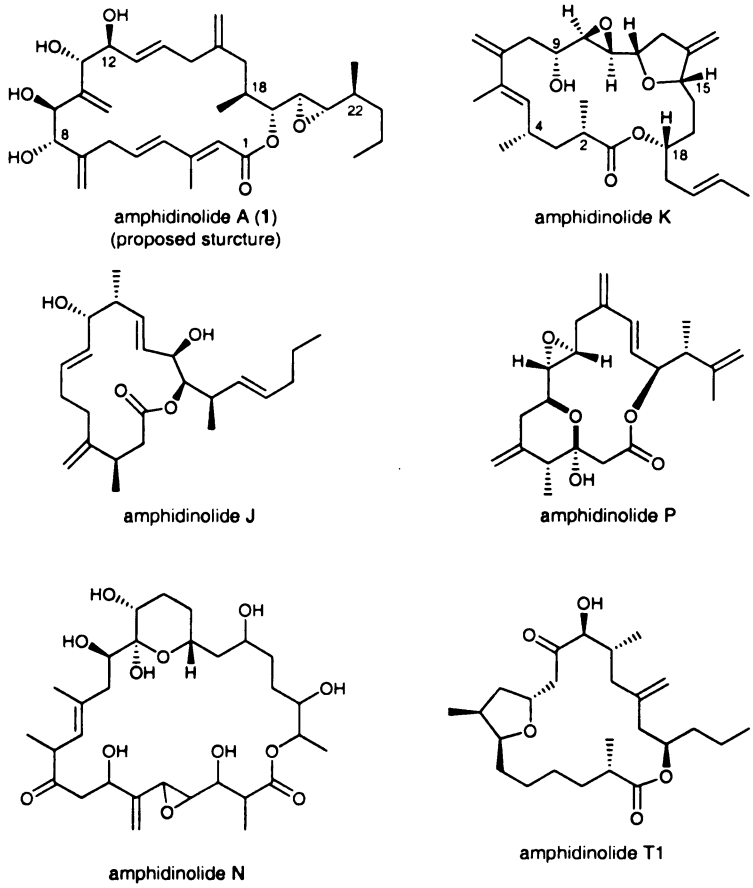
Table 1. Cytotoxicity Data of Several Amphidinolides

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
T1	19	18.0	35.0

Several of the amphidinolides have been synthesized in the laboratories of David Williams. These include amphidinolides J, K, and P (Scheme 1).[4] When the Williams' group finished amphidinolide K their data was inconsistant with Kobayashi's proposed stereochemical assignment. The syntheses of more than 20 isomers were ultimately required to assign the actual relative and absolute stereochemistry of this macrolactone. This is instructional because the reported absolute stereochemistries of many of the amphidinolides, including amphidinolide A, are only suggestions based on Kobayashi's extensive use of one- and two-dimensional NMR. Determining the stereochemistry of

complex natural products exclusively on NMR is difficult at best. While NMR has proven to be useful for determining the stereochemistry of adjacent stereocenters, use of NMR with isolated regions of stereochemistry, such as the C8-C12 and C18-C22 regions of amphidinolide A or the C9-C15, C18, C2, and C4 in amphidinolide K is difficult.

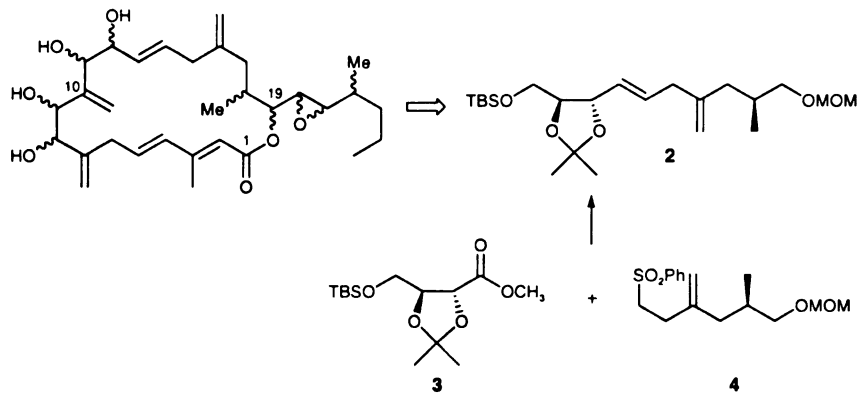
Scheme 1. Several Amphidniolides



Amphidinolide A (**1**), Scheme 1, isolated in 1986, was the first polyolefinic macrolactone of this unique series of compounds to be identified.[5] Since 1986 there have been over twenty-two of these unique macrolides isolated, with the complete stereochemistry of only a few elucidated. In addition to its impressive anti-cancer activity, amphidinolide A has several striking structural features, including both lipophilic and hydrophilic moieties, two exocyclic olefins, and both conjugated and non-

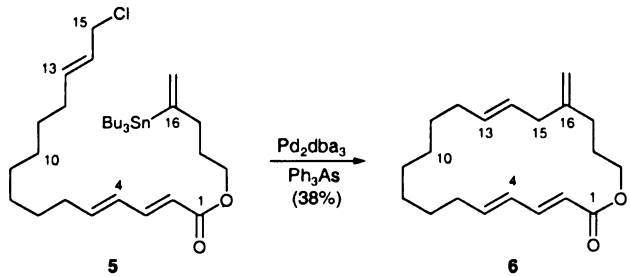
conjugated dienes. Because of these structural and biological features, amphidinolide A became a target for total synthesis.[6]

Scheme 2. Willard's Approach



To date only the groups of Paul Willard (Brown University), Gerrald Pattenden (Nottingham), and ourselves have reported synthetic efforts towards amphidinolide A. Williard's early work,[7] published in 1989, appeared prior to Kobayashi's proposed stereochemical elucidation of amphidinolide A.[8] Therefore his approach (Scheme 2) to the C_{10} – C_{19} fragment **2**, was developed to allow preparation of all possible stereoisomers. To facilitate an unambiguous assignment of the stereochemistry, the other stereoisomers could be readily constructed by changing chirality of the starting materials used to construct **2**. 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. Willard continues to progress towards the synthesis of amphidinolide A and presented a paper on this recent work at the April 2001 ACS meeting.[9]

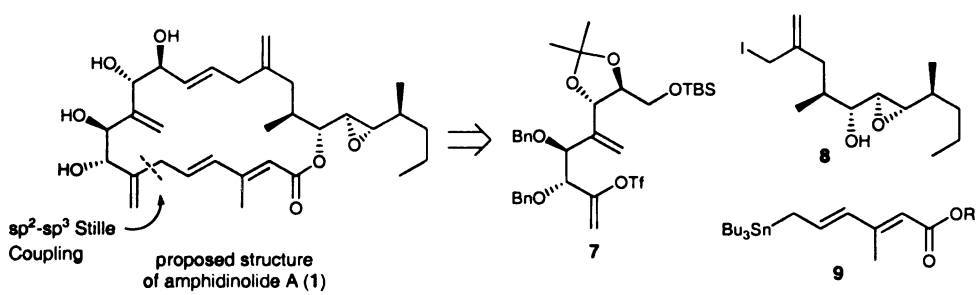
Scheme 3. Pattenden's General Approach



5 6

In 1994, Pattenden published his first report on his synthetic efforts.[10] A model study was used 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 intra-molecular coupling of a vinyl stannane and an allylic halide. The methodology proved moderately successful when applied to a model amphidinolide A system (Scheme 3). The desired macrocycle was obtained in 38% yield along with the (C13-C14) Z-isomer (6%) and the allylic isomer (2%, C13-C16 bond formation).

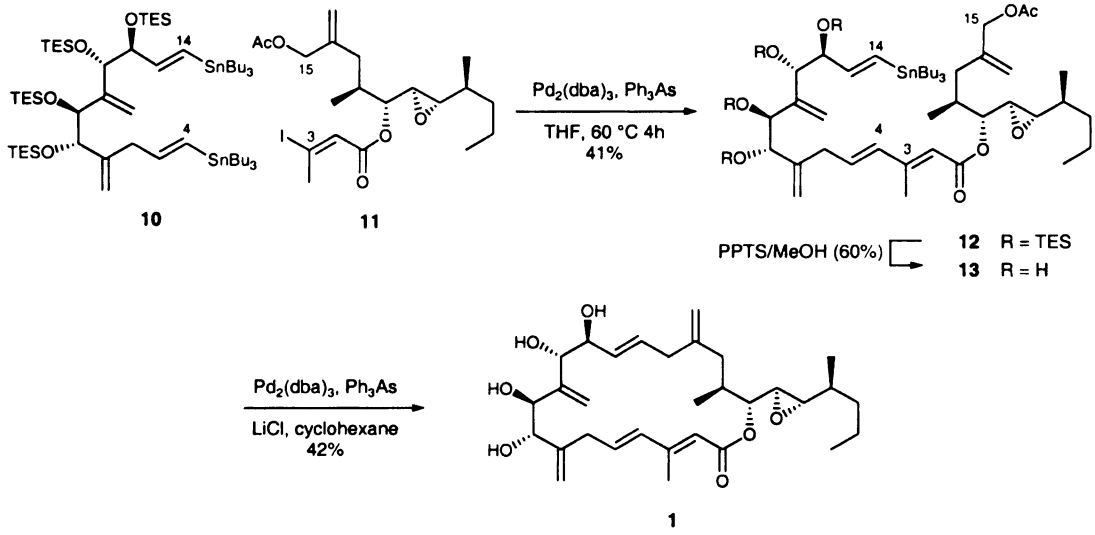
Scheme 4. Pattenden's First Generation Retroanalysis



Pattenden outlined his full synthetic approach toward the natural product in a 1998 publication (Scheme 4).[10b] The underlying theme of their retro-synthesis is the application of the above-mentioned sp^2-sp^3 coupling methodology to fragments **7** and **9**. At this time he had completed one (**7**) of the three proposed subunits (**7-9**). This subunit was derived from D-glucose, allowing Pattenden to purchase three of the four stereocenters of the tetraol portion of **1**. The syntheses of the other subunits or the

methodology to be used in the completion of the macrocyclic ring system were not disclosed in this publication.

Scheme 5. Pattenden's Total Synthesis of **1** .



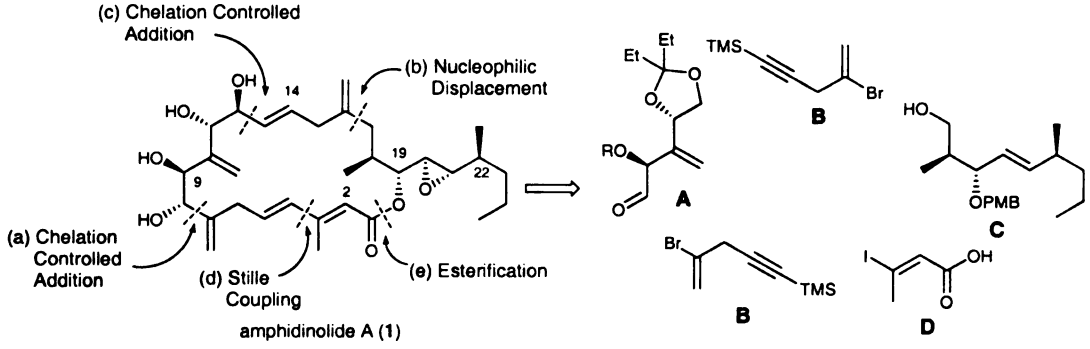
In February 2002 Pattenden published the total synthesis of **1**.[11] This publication included several revisions to the previous described retrosynthesis. The upper bond disconnection was clarified, and as with his previous reports, this bond was constructed using an sp^2-sp^3 Stille coupling. The tetraol portion of **1** was still derived from D-glucose, but the lower bond disconnection was moved from C6-C7 to C3-C4. This bond was constructed using a sp^2-sp^2 Stille coupling. This Stille coupling is elegant, as it not only discriminates between the two vinyl stannanes in **10** but also between the two possible electrophilic positions in **11**, the iodine on C3 and the allylic acetate on C15. Pattenden believed that because the upper stannane was stericly encumbered it would be the less reactive of the two positions and thus the coupling should occur at the lower stannane. Also, reactivity arguments can be made that the vinyl iodide is much more reactive than the allylic acetate. After removal of the silicon protective groups, the macrocycle was

closed using a Pattenden's sp^2-sp^3 coupling affording **1**. A comparison of his strategy to our own successful route[6b] to **1** is discussed in Chapter 4.

Chapter 2. First Generation Approach, Synthesis of Sub-targets

Our initial retrosynthetic analysis of amphidinolide A (Scheme 6) afforded four fragments **A**-**D**. Several factors guided this retrosynthetic plan, including the formation of multiple stereocenters early in the synthesis, the development and evaluation of new synthetic methods, and a flexible coupling strategy to allow for the evaluation of multiple pathways for coupling the fragments.

Scheme 6. First Generation Retrosynthetic Analysis

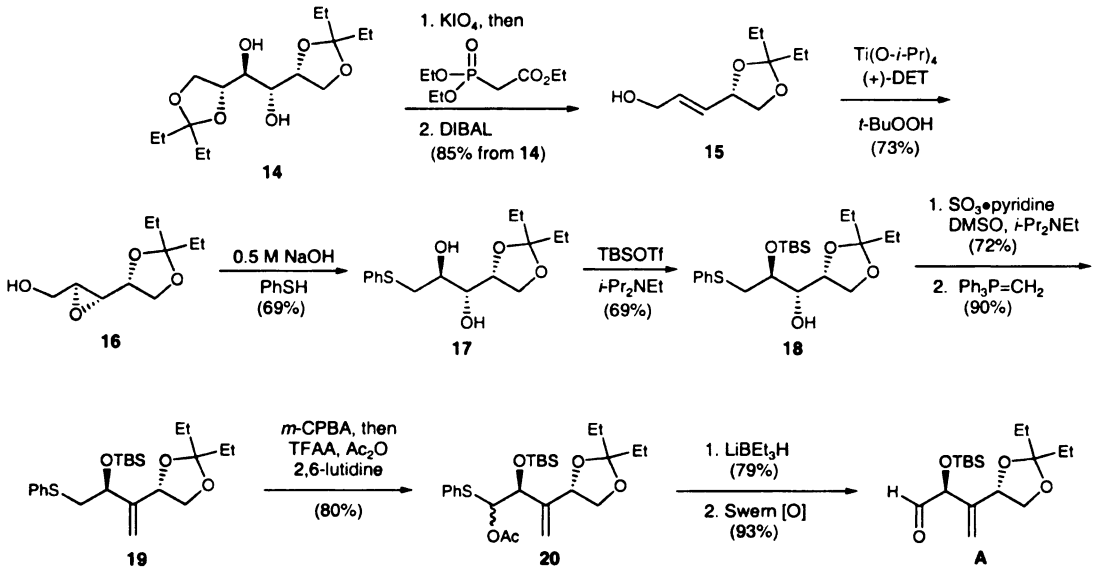


As initially envisioned the coupling of **A** and **B** would employ (a) a nucleophile (Grignard reagent or cuprate) derived from fragment **B**, which would be added in a chelation-controlled manner to fragment **A**. A similar nucleophile would be used to (b) displace an electrophile derived from the free alcohol of fragment **C**. The resulting **AB** and **BC** fragments would then be coupled via (c) another chelation-controlled addition. Finally, fragment **D** would be added via (d) a Stille coupling followed by (e) a macrolactonization to close the ring.

2.1. Synthesis of Fragment A

Fragment **A** contains two of the nine stereocenters of amphidinolide A and these two stereocenters will be used to control the stereochemistry of the two adjacent stereocenters in the molecule (C8 and C12). Since fragment **A** is highly oxygenated, a logical starting material for this fragment would be a commercially available sugar.

Scheme 7. Synthesis of Fragment A



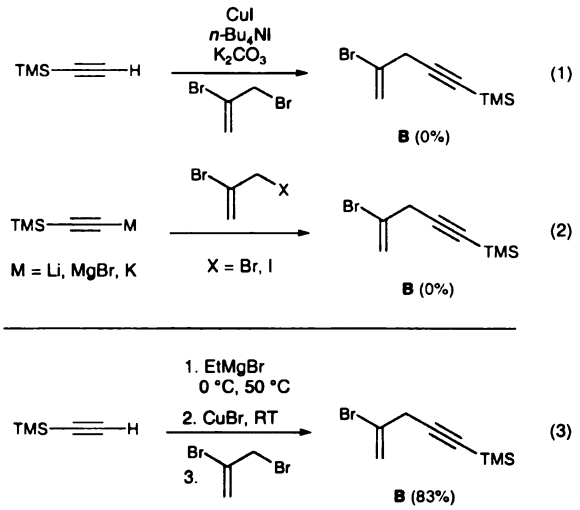
The synthesis of fragment **A** (Scheme 7), began with a conversion of the bisisopentylidene of D-mannitol to allylic alcohol **15**, which was based on literature precedence for the analogous acetonide.[12] As such, bisisopentylidene **14** was oxidatively cleaved by KIO_4 and then subjected to a Wittig olefination reaction. DIBAL reduction of the resultant ester provided allylic alcohol **15** in 85% yield over 3 steps. Sharpless asymmetric epoxidation[13] of **15** afforded 2,3-epoxy-1-ol **16** with complete stereocontrol. Sharpless[13] had already shown that exposure of 2,3-epoxy-1-ols to the equilibrating conditions of the Payne rearrangement[14] can result in selective opening of the epoxide terminal upon the addition of *t*-butylthiol. Therefore, we decided to follow a similar approach, substituting thiophenol for *t*-butylthiol as this would set up the molecule for a Pummerer rearrangement. In practice, this tactic provided sulfide **17**, which could be monoprotected at the C2 hydroxyl affording TBS ether **18** in 69% yield. A Doering-Parikh oxidation[15] of **18** followed by Wittig olefination efficiently installed the exo olefin of **19**. Oxidation of the sulfide with *m*-CPBA resulted in a sulfoxide, which was

immediately subjected to a Pummerer rearrangement[16] to affording acetoxy sulfide **20** in 80% yield as a mixture of diastereomers. Reduction of **20** with lithium triethylborohydride and subsequent Swern oxidation provided fragment **A**. The synthesis of fragment **A** requires 11 steps from readily available bisisopentylidene **14** and afforded the desired product with an overall yield of 12%.[17]

2.2. Synthesis of Fragment B

We anticipated the need for multi-gram quantities of fragment **B** as it is a common building block in both right and left hemispheres of amphidinolide A. Somewhat surprisingly, this relatively simple small molecule had yet to be described in the literature.

Scheme 8. Synthesis of Fragment **B**



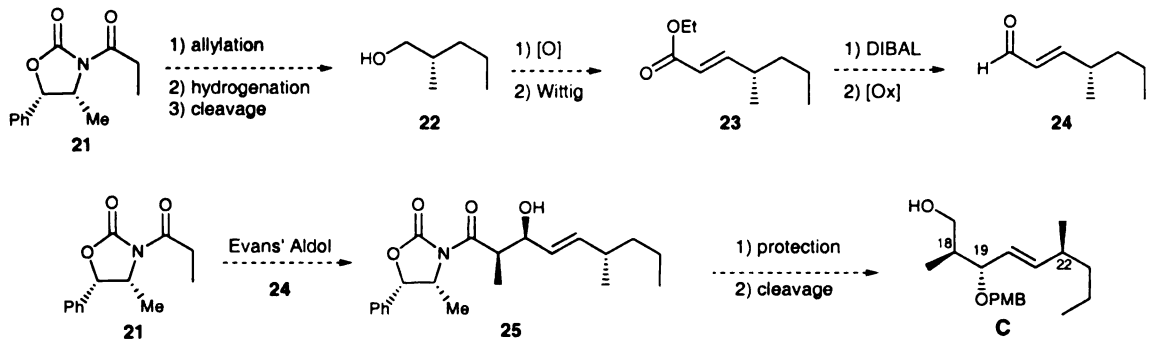
Initially, attempts were made to apply copper mediated phase transfer conditions (Scheme 8, reaction 1), however multiple variations of these conditions failed to afford the desired compound. Attempts were then made to apply more direct displacement conditions using alkynyl metal species derived from trimethylsilylacetylene (Scheme 8, reaction 2). These conditions also failed to afford the desired product. After

considerable experimentation, copper mediated conditions were discovered which afforded fragment **B** in high yield (Scheme 8, reaction 3). The key to this synthesis is the temperature at which each reaction and addition is performed. For the formation of the Grignard species of trimethylsilylacetylene, heating to 55 °C was found to be critical. The reaction is then allowed to cool to room temperature, after which CuBr was added. It was determined that CuI or CuCN could be substituted for CuBr with no loss in reactivity or yield. The reaction mixture was heated to 50 °C, again this temperature is crucial, followed by the addition of 2,3-dibromopropene dropwise over a 3 hour period. Workup and purification by chromatography affords fragment **B** in 83% yield as a yellow liquid.[17]

2.3. Synthesis of Fragment C

Fragment **C** contains three of the stereocenters and the side-chain of amphidinolide A. However, unlike fragment **A** there is no obvious strategy to allow for the purchase of any of the stereocenters of this fragment. Retrosynthetic analysis of fragment **C** led us to the conclusion that an iterative chiral auxiliary approach would be the most efficient route for the construction of this subunit. The first auxiliary based reaction would set the stereochemistry of the C22 methyl group. We concluded this stereocenter would be too distant from the reaction center in the subsequent aldol that was to set the stereochemistry at C18-C19, thus an auxiliary would also control the stereochemistry of the aldol reaction (Scheme 9). This methodology will also allow for the ability to change these stereocenters by simply changing the chiral auxiliary used, which will allow us to compensate in the event a stereochemical misassignment of the natural product was made.

Scheme 9. Proposed Route to Fragment **C**



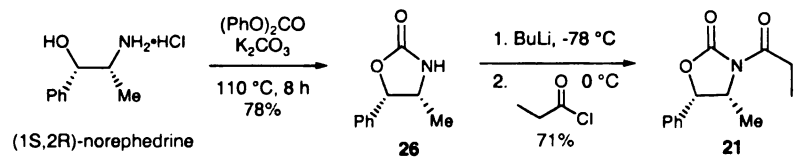
The first key intermediate for fragment **C** is (S)-2-methylpentanol (**22**). Prior to our synthesis, **22** was known in the literature,[18] but was derived from costly ($20/g) starting materials,[18a] a chiral resolution of racemic **22**,[18b] or low yielding biological reduction.[18c] As this intermediate is near the beginning of the overall synthesis, we needed a route that afforded **22** both enantiomericaly pure and with high throughput. Several routes were investigated to meet this demand.

2.3.1. Evans' Oxazolidinone Approach to 22

As we planned to employ an Evans aldol reaction to generate what would ultimately become the C18 and C19 asymmetric centers of amphidinolide A, it was decided to employ the same auxiliary system for the synthesis of (*S*)-2-methylpentanol **22** (Scheme 9). This would be efficient, as we would not need to generate different auxiliary systems for each of the stereogenic steps. The literature preparation for oxazolidinone auxiliary **26** used the light and temperature sensitive commercially available (1*S*, 2*R*)-norephedrine free amino alcohol.[19] By increasing the amount of K_2CO_3 used in the reaction to 2.2 equivalents, the more stable and commercially available hydrochloride salt could be used to afford the desired oxazolidinone in 78% yield (Scheme 10). The product was then acylated by first deprotonating with *n*-BuLi at –78 °C and quenching

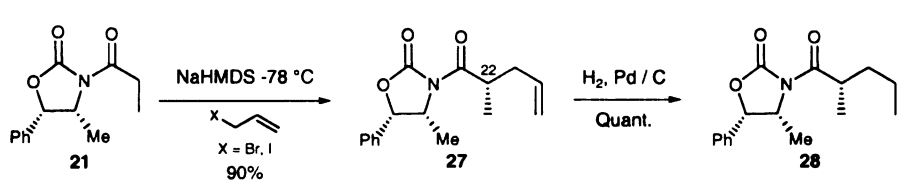
with proprionyl chloride. The product was purified by Kügelrohr distillation to afford the acylated auxiliary **21** in 71% yield.

Scheme 10. Synthesis of Acyloxazolidinone (**20**)



With the synthesis of the acyloxazolidinone complete it was time to install the three remaining carbons of (*S*)-2-methylpentanol (**22**) and set the stereocenter, which will become C22 in amphidinolide A. Since we need the saturated pentanol, it would be optimal to perform the chiral alkylation with an electrophile such as propyl bromine. Unfortunately, it was previously determined that alkylations of acyloxzaolinones require the use of an activated electrophile such as allyl bromine or iodide. After some optimization of known conditions,[20] allylation of **21** was performed by the dropwise addition of a THF solution of **21** to solution of NaHMDS in THF at –78 °C (Scheme 11). This was followed by the dropwise addition of allyl bromide via syringe pump and stirred at –78 °C for 16 hours. This afforded **27** in excellent yield as a light yellow crystalline material without the need for silica gel chromatography. Subsequent hydrogenation (10% Pd on carbon) afforded the desired product **28** in quantitative yield.

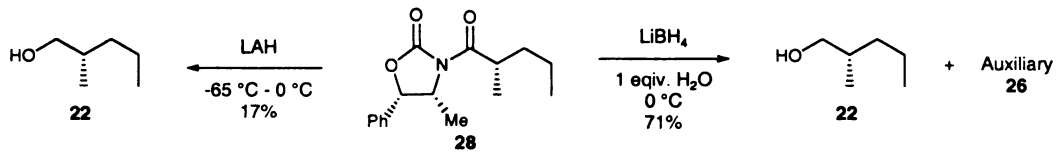
Scheme 11. Allylation of Acyloxazolidinone (**21**)



Now that the chiral auxiliary has served its purpose it needs to be removed thereby releasing the desired intermediate (*S*)-2-methylpentanol (**22**). There are several methods for removing the chiral auxiliary. The auxiliary can be cleaved oxidatively

(LiOH, H_2O_2) to afford the acid derivative of the side chain.[20b] However, for our purposes we desired a reductive method to cleave the auxiliary and give the alcohol derivative of the side chain. While an aldehyde of this side chain will ultimately be required, the alcohol should be a more storage stable intermediate since it will not be prone to epimerization due to enolization or degradation due to oxidation. Furthermore, the alcohol is more amenable to silica gel chromatography. The original Evans' strategy to reductively cleave the auxiliary was to use lithium aluminum hydride (LAH).[20a] This procedure required careful temperature control and a complicated work-up to quench the excess LAH and to isolate the desired product by vacuum distillation.[20a] When this was attempted with compound **28** a disappointing 17% yield was obtained along with byproducts from the degradation of the oxazolidinone ring.

Scheme 12. Synthesis of (S)-2-methylpentanol (**22**)



A second procedure for the reductive cleavage of the auxiliary employs the use of lithium borohydride ($LiBH_4$) in ether with 1.0 equivalent of water.[21] Presumably, the water reacts with $LiBH_4$ to afford $LiB(OH)H_3$, which is known to be a good reducing agent. Application of these conditions to the reduction of **28** (Scheme 12) afforded the alcohol in 71% yield. Unlike with the LAH method, the temperature was easy to maintain at the requisite 0 °C and auxiliary (**26**) was recovered, without degradation, for recycling.

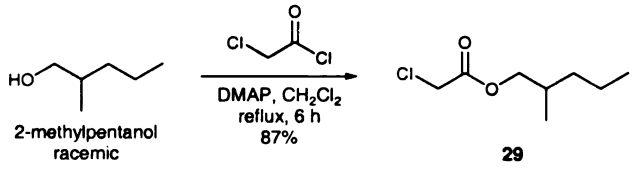
Although this method affords (S)-2-methylpentanol (**22**) in five steps and 35% overall yield, the largest this reaction sequence could be scaled up to was 10 g of the

norephedrine starting material. In our hands, scaling the synthesis above this level caused the reaction yields and selectivities to drop dramatically.

2.3.2. Enzymatic Resolution of 2-Methylpentanol

Since the above preparation of **22** was not sufficiently scalable, alternative routes were investigated. One such route was to use a lipase to resolve commercially available racemic 2-methylpentanol. Lipases differ from other esterases in that they are typically more efficient at a lipid/water interface than on single substrate molecules dissolved in solvent.[22] Because of this enhanced efficiency, lipases are commonly used to selectively hydrolyze an ester in aqueous medium. The ester chosen for studying the kinetic resolution of 2-methylpentanol was chloroacetate **29**, based on literature precedence.[23] Reaction of 2-methylpentanol with chloroacetyl chloride in the presence of DMAP afforded the desired chloroacetate (Scheme 13) in 87% yield and could be performed on large scale (42 g).

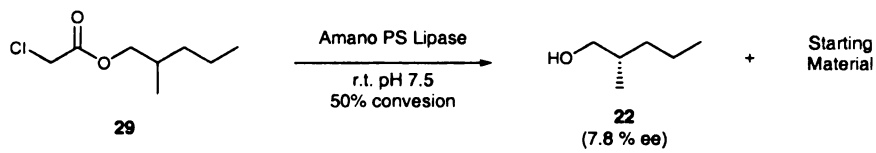
Scheme 13. Synthesis of Chloroacetate (**29**)



There are many commercially available lipases on the market. Amano P-30 has been successfully applied to similar kinetic resolutions,[24] however Amano replaced this particular lipase with a newer Amano PS lipase. With the enzyme and substrate in hand an attempt was made selectively hydrolyze **29** (Scheme 14). All reactions were run in pH 7.0 phosphate buffer and water. To ensure the maximum amount of interface between the water and substrate, the reactions were vigorously stirred with a mechanical stirrer. During the course of the reaction, chloroacetic acid will be produced, acidifying the

reaction medium, and will denature the enzyme without proper pH control. A ChemCadet pH controller was used to control a syringe pump charged with 1M NaOH. The first attempt was run at room temperature and a constant pH of 7.5. The reaction was allowed to run to 50% conversion by GC analysis. After workup and isolation, the optical rotation of the resultant 2-methylpentanol was measured, and the reaction was proceeding as planned affording enrichment in the S enantiomer. Unfortunately, there was only a 7.8% enantiomeric excess.

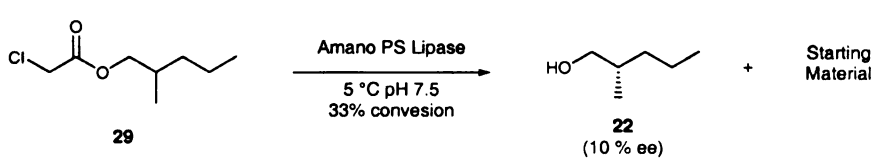
Scheme 14. Resolution of **29**, 50% Conversion



29 **22** (7.8 % ee)

As a lipase reaction continues, the % ee for the hydrolysis product typically decreases. Thus this first reaction should be the worse case scenario. The kinetic resolution was run a second time (Scheme 15) with two modifications. First, the reaction was run at 5 °C in order to slow the reaction down and afford better selectivity. Secondly, the reaction was stopped at 33% conversion in an effort to isolate the desired enantiomer of **22** before it could be reacylated in the possible equilibrium conditions, or before more of the undesired enantiomer was hydrolyzed. These modifications slightly improved the enantioselectivity, but enantiomeric excess of the product (10% ee) was still too low to be useful in our synthesis.

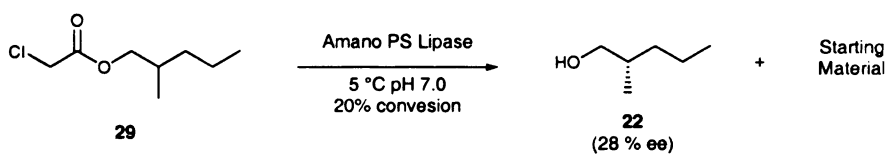
Scheme 15. Resolution of **29**, 33% Conversion



29 **22** (10 % ee)

After consulting with Amano about optimal conditions, the reaction was repeated a third time (Scheme 16). In this attempt the pH was maintained at 7.0 instead of 7.5 during the reaction. Also the reaction was stopped at 20% conversion. The resultant isolated alcohol was enriched in the desired isomer, but only at 28% ee.

Scheme 16. Resolution of **29**, 20% Conversion



29

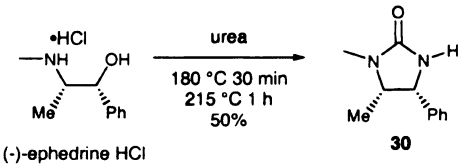
22
(28 % ee)

The enantiomeric excess of this resolution never approached a synthetically useful level. It is possible that another lipase could efficiently resolve this material, however that would require screening many enzymes and conditions. Also resubjecting the enriched material could afford further enrichment. Unfortunately, this particular reaction appears to have a fairly active equilibrium requiring the reaction be stopped at very low conversion levels. This would mandate the reaction be run on liters of reaction medium in order to obtain the same quantities of material for the oxazolidinone route.

2.3.3. Imidazolidinone Auxiliary Approach to 22

Since the original oxazolidinone route failed to scale and the chiral resolution with Amano PS lipase failed to give sufficient enantiomeric excess, another synthetic route to scalable quantities of (*S*)-2-methylpentanol (**22**) was needed. Fortunately, we were not the only group looking for ways to scale chiral auxiliary technology to larger scales. A literature report[25] illustrated that a variation of the oxazolidinone type auxiliary, imidazolidinone (**30**), could be used on pharmaceutical manufacturing scale (1000 kg). While this scale far exceeds what is required for the synthesis of amphidinolide A, it does indicate that this auxiliary should scale to fit our needs.

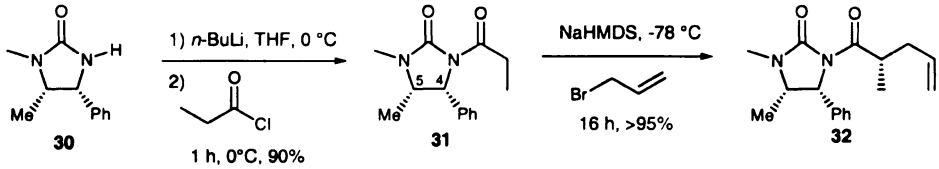
Scheme 17. Synthesis of Imidazolidinone Auxiliary (**30**)



(-)-ephedrine HCl **30**

The synthesis of **30** begins with the commercially available (1*R*,2*S*)-ephedrine hydrochloride and urea (Scheme 17). This solventless reaction was previously reported[26] using 50g starting material to afford 28g (60%) of the desired auxiliary (**30**) after recrystallization. In our hands, this reaction afforded between 50 and 55% yield on the same scale. Increasing the scale of this reaction to 100g resulted in significantly reduced yields (30-35%). The reason for the reduction in yields can be traced to the equipment used to run the reaction. On a 50g scale, the reaction vessel was small enough to fit in a large oil bath. However, the larger scale reaction required a larger flask, which could then only be heated with a heating mantle. This resulted in the visible charring of the material in the flask due to uneven heating. Thus scale for us was not limited by the reaction, but by our hardware.

Scheme 18. Acylation and Allylation of (**30**)



30 **31** **32**

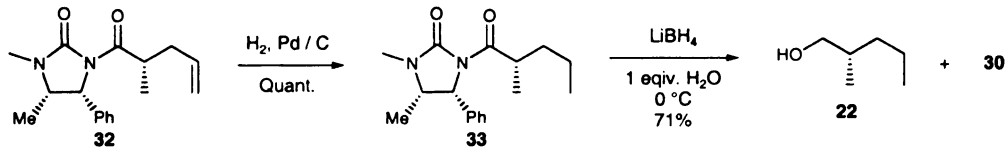
With imidazolidinone auxiliary **30** in hand the side chain was constructed (Scheme 18) in the same manner used for the oxazolidinone auxiliary (**26**). The auxiliary was deprotonated with *n*-BuLi in THF at 0 °C and quenched with proprionyl chloride to afford **31** in high yields with no need for purification. This reaction has a benefit over the oxazolidinone route: (a) the imidazolidinone auxiliary is acylated at 0 °C instead of the

cryogenic –78 °C for the oxazolidinone, and (b) **31** does not require purification, whereas the acylated oxazolidinone (**21**) required a tedious vacuum distillation. The only issue with this reaction upon scale-up is that **30** begins to precipitate near 0 °C. Though this does not appear to have a negative effect, the time for deprotonation was extended by 30 minutes if this occurred. The allylation was performed by adding a THF solution of **31** to a –78 °C solution of NaHMDS in THF dropwise via a syringe or cannula. Allyl bromide was added dropwise via a syringe pump, 25 minutes after the addition was complete and the reaction was allowed to stir overnight at –78 °C. Upon workup the product purity fluctuated and sometimes required silica gel chromatography to obtain sufficiently pure material. During experimentation with reaction conditions for scale-up it was found that cooling the THF solution of **31** to approximately –30 °C before addition to the NaHMDS solution via cannula resulted in nearly quantitative yield of **32**. Furthermore, the material was consistently pure, obviating the need for purification.

With either set of conditions, only one diastereomer was observed. This is in contrast to Evans' work with similarly substituted oxazolidinones. Evans found that the substituent at C4 (Scheme 18) was the stereocontrol element in this type of reaction. Experimentally it was found that a phenyl did not impart complete stereocontrol resulting in mixtures of diastereomers, even when using sodium enolates, which were found to be superior to lithium.[27] Cardillo reports diasteroselectivities for alkylation reactions of **31** to be on the order of 92% de when using a lithium enolate,[28] which is superior to what Evans observed for analogous oxazolidinone alkylations containing a phenyl at C4. For our system, the single observable isomer is attributed to the use of a sodium enolate, which is known to impart better diastereoselectives than lithium. The addition of **31** as a

cold solution and slow addition of allyl bromide prevents the enolate from decomposing and allowing the product to be isolated without the need for further purification.

Scheme 19. Reductive Cleavage of Imidazolidinone **33**

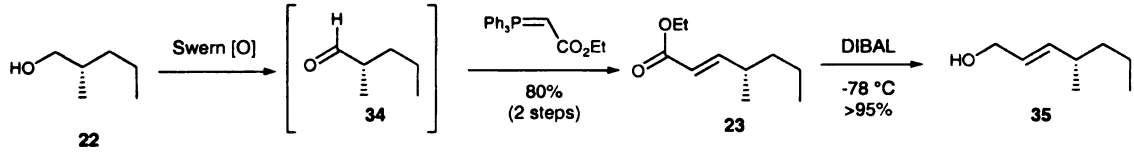


Hydrogenation of **32** quantitatively saturated the side chain in **33** (Scheme 19). As before we needed to cleave the auxiliary and release (*S*)-2-methylpentanol (**22**). The $LiBH_4$ protocol was used to reductively cleave the auxiliary affording **22** in 71% yield after chromatography. The imidazolidinone auxiliary (**30**) was recovered in moderate yield and could be reused with no loss in chiral activity.

This imidazolidinone-based route is far superior for the synthesis of (*S*)-2-methylpentanol (**22**) by either the oxazolidinone or kinetic resolution routes. It is scalable to the limits of the glassware available to handle the reactions and workups. Also with the modification to add **31** as a cold solution, this route does not require any chromatography until the final step for the separation of **22** from residual **30**. With this methodology, the synthesis of **22** is no longer the limiting factor to obtaining useful amounts of fragment **C**.

2.3.4. Elaboration of (*S*)-2-Methylpentanol (22)

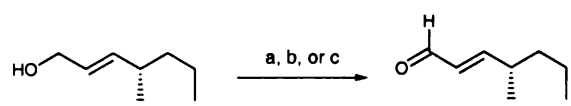
Scheme 20. Oxidation and Elongation of **22**



The first step in the elaboration of **22** is the oxidation of the primary alcohol to aldehyde **34** (Scheme 20). Initial attempts at isolating **34** in racemic form were

unsuccessful, possibly due to problems with volatility and stability. There was low crude mass recovery after rotary evaporation of the reaction solvent, indicating the product may have also evaporated. Silica gel chromatography afforded only minute amounts of material that corresponded spectrally to the desired product. This was not the first time a volatile/unstable aldehyde was required for use in a Wittig reaction. Ireland reported[29] the linking of a Swern oxidation with a Wittig reaction in a single pot. This eliminated the need to isolate the problematic aldehyde and allowed for the isolation of the stable α,β-unsaturated ester (**23**) in high yield and with the desired *trans* geometry of the double bond. DIBAL reduction of this ester was performed under standard conditions and required only the use of a silica gel plug to remove residual aluminum salts and afford pure allylic alcohol (**35**).

Scheme 21. Oxidation of Allylic Alcohol (**35**)



35 **24**

Conditions: a) Swern [O] 75%
b) SO_3 • pyridine [O] 83%
c) Dess-Martin Periodane [O] 95%

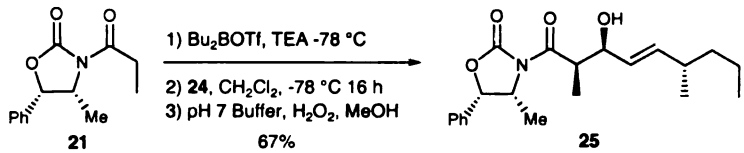
With allylic alcohol **35** in hand, the final step before the asymmetric aldol reaction could be attempted was the oxidation of the alcohol to α,β-unsaturated aldehyde **24** (Scheme 21). Initially, **35** was oxidized under Swern conditions, which proceeded in approximately 75% average yield. The product aldehyde was sensitive to the pH of the silica gel used for chromatographic purification. Even buffering the column with TEA, the mass recovery was variable. A SO_3•pyridine[15] oxidation afforded a much cleaner reaction mixture. In this case the byproducts were of sufficiently different R_f to allow for the use of less silica gel, and in turn the mass recovery was more consistant. In an

attempt to completely eliminate the need for chromatography all together, Dess-Martin periodane[30] was studied. This proved to be an excellent oxidant providing the desired product with only trace byproducts, which ultimately did not interfere with the subsequent aldol reaction. Although this reaction afforded the desired product in sufficient purity and in high yield, the oxidant is not stable and if not properly handled, can decompose during storage resulting in a poor oxidation and loss of substantial amounts of **35**. Thus special care was taken to ensure the oxidant was stored properly to minimize the problems associated with its use.

2.3.5. Asymmetric Aldol and Final Elaboration of Fragment C

With a viable route to aldehyde **24**, the key aldol step was investigated. As mentioned previously we initially envisioned a route to fragment **C** that would utilize the same starting auxiliary (**21**). Although this auxiliary proved less than satisfactory for the moderate scale synthesis of (S)-2-methylpentanol (**22**), it was an established auxiliary for the Evans' asymmetric aldol reaction.[31]

Scheme 22. Asymmetric *syn*-Aldol



21 **25**

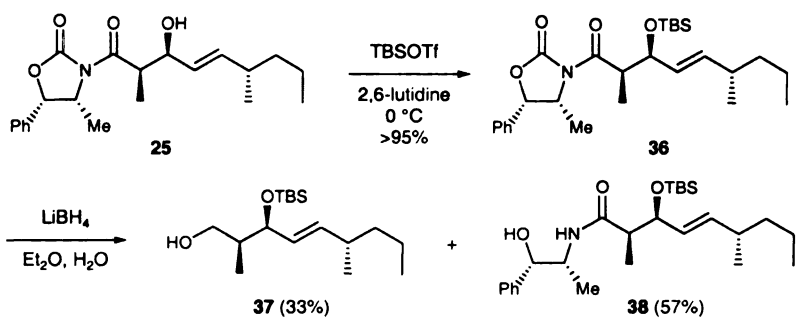
Paralleling the work by Evans and co-workers, the oxazolidinone auxiliary (**21**) was subjected to enolization with dibutyl boron triflate and triethylamine (Scheme 22).[31] After the prescribed period of time, the aldehyde (**24**) was added dropwise as a solution via syringe pump and reacted for 2 hours at –78 °C to 0 °C, per Evans' established protocols. Unfortunately after the oxidative workup at pH 7, the reaction afforded only a 10% yield of the desired product. The reaction suffered from poor conversion as

indicated by the recovery of **21**. This indicated either the enolization was incomplete at the time of the aldehyde addition or that reaction of **24** is sluggish and a 2 hour reaction time was insufficient.

After several variations on reaction times and addition rates, it was determined that adding **24** dropwise via syringe pump was essential. Also allowing the reaction to proceed overnight (ca. 16h) afforded an acceptable 67% yield with excellent diasteroselectivity. This reaction appears sensitive to temperature variations after the addition of the aldehyde, as the reaction yields can vary with varying temperatures. However, the average yield for the reaction is 65-67%.

With the Evans aldol completed the auxiliary had to be removed to release fragment **C**. The $LiBH_4$ reduction protocol used previously would afford the desired primary alcohol, however the basic nature of this reaction means that **25** needs to be protected to prevent a retro-aldol reaction from occurring. Protection at this stage was also needed to provide differentiation of the two alcohols in fragment **C**. Two different protective groups were simultaneously explored. This would allow for easy changes in the protecting scheme should the need arise.

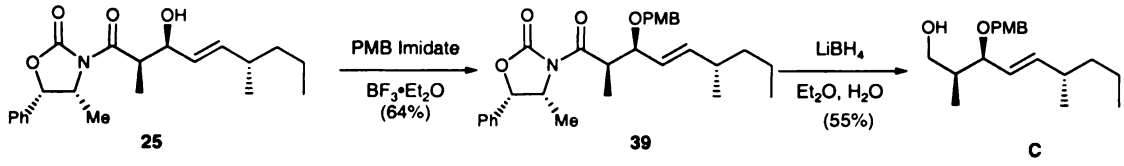
Scheme 23. TBS protection of **25** and Attempted Reduction



The protection of **25** with TBSOTf and 2,6-lutidine as a base proceeded smoothly at 0 °C to afford a nearly quantitative yield of the desired product (Scheme 23). After

protection as a TBS ether, the auxiliary was cleaved using the same $LiBH_4$ conditions used in the synthesis of **22**. This reaction afforded a mixture of products, including the desired alcohol (**37**). The major by-product is **38**, resulting from the reduction of the oxazolidinone ring instead of the amide of the side-chain. During the reaction, the hydride attacks the least hindered carbonyl, typically the amide carbonyl of the side-chain, however in this case the TBS protecting group may be too bulky, partially blocking the amide carbonyl and resulting in the mixture of products.

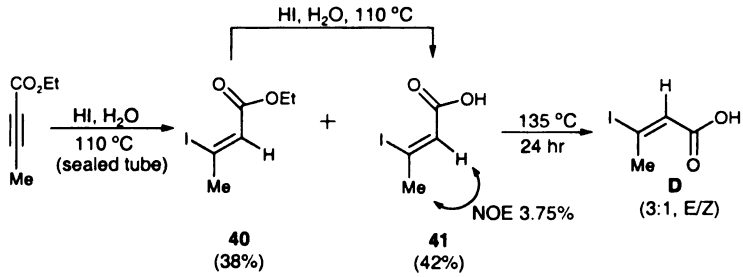
Scheme 24. PMB protection of 25 and Reduction of 39



The protection of **25** with *p*-methoxybenzyl trichloracetimidate under Lewis acid conditions affords the desired PMB ether in moderate yield.[32] Other Lewis acids, such as triflic acid, were tried in an attempt to increase the yield, but these stronger Lewis acids caused decomposition of the starting materials instead of increasing the yield of **39**. The reductive cleavage of **39** afforded the desired primary alcohol in moderate yield. The low yields cannot be attributed to the aforementioned regioselectivity issue, as the product from the attack of the oxazolidinone ring was not observed. Overall, the synthesis of fragment **C** involves a total of 10 steps from the readily available imidazolidinone auxiliary **30** with an overall yield of 8%.

2.4. The Synthesis of Fragment D

Scheme 25. Synthesis of Fragment **D**



Fragment **D** is a known compound,[33] readily available from the reaction of ethyl-2-butynoate and hydroiodic acid in a sealed tube (Scheme 25).[33a] The initial addition of HI occurs at 110 °C affording a 1:1 mixture of the *Z*-iodo ester (**40**) and *Z*-iodo acid (**41**). These two compounds were easily separated and the ester could be resubjected to the reaction conditions to undergo complete hydrolysis. The isolated *Z*-iodo acid was isomerized by heating to 135 °C, resulting in a thermodynamic mixture of 3:1 (*E*:*Z*) which was separated by careful flash chromatography to afford **D**. Although the experimental procedure for obtaining the above iodo acids was straightforward, the "cis/trans" nomenclature assignment in the Le Noble communication[33a] is confusing. Thus NOE interactions were measured to ensure correct product identification.

Chapter 3. First Generation Approach, Coupling and Elaboration of Sub-targets

The successful completion of sub-targets **A-D** allowed for the simultaneous investigation of multiple coupling strategies. In this way valuable information for determining the most efficient pathway for the final elaboration and coupling route to amphidinolide A could be rapidly ascertained.

3.1. Coupling of Fragments A and B

Fragments **A** and **B** were designed to be coupled via a chelation controlled addition of an organometallic derivative of **B** to the aldehyde moiety present in fragment **A**. Several organometallic species were tested including lithium, zinc, and magnesium. The Grignard reagent (magnesium) derived from fragment **B** proved to be the most successful and the pertinent results of this study are summarized herein.[34]

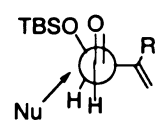
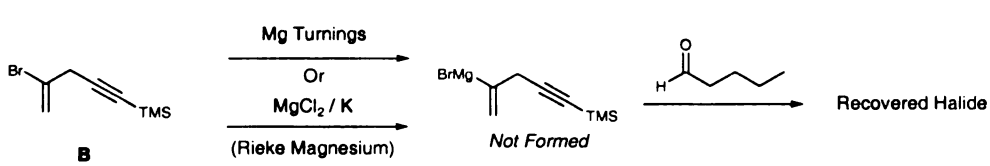


Figure 1. Felkin-Ahn Model

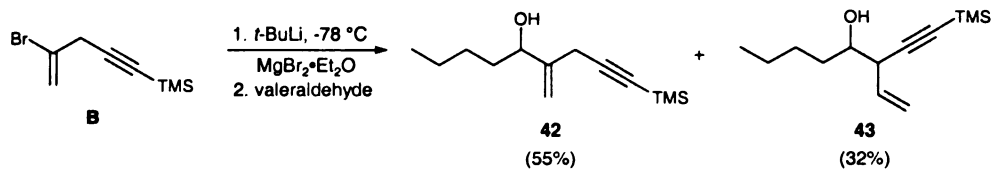
The TBS protected hydroxyl present in fragment **A** is unable to be utilized for chelation control, due to the electronic nature of the silyl ether. Fortunately, the desired relative stereochemistry is also predicted with the Felkin-Ahn model (Figure 1) for this addition reaction, *assuming* the alkene serves as the large group.[35] With this model we should be able to use fragment **A** without modification to achieve the desired stereochemistry.

Scheme 26. Attempted Grignard Formation



The first issue that must be addressed is the formation of an organometallic of fragment **B**. Since such a derivative is planned for the construction of both the **AB** and **CB** linkages it is essential to have a reliable method for generating such a species. Initial investigations into the formation of a Grignard reagent of **B** with commercial Mg turnings or Mg filings resulted in only recovered halide **B** (Scheme 26), indicating the Mg source was not active enough to form the Grignard reagent. The much more reactive Rieke magnesium was made by the reduction of $MgCl_2$ with potassium metal.[36] However, the use of Rieke magnesium also failed to afford the necessary Grignard of **B**, even with additives such as NaI, which has been used to facilitate the formation of Grignard reagents with difficult substrates. Since fragment **B** failed to afford a Grignard under traditional conditions, an alternative route to the organometallic derivatives needed to be investigated.

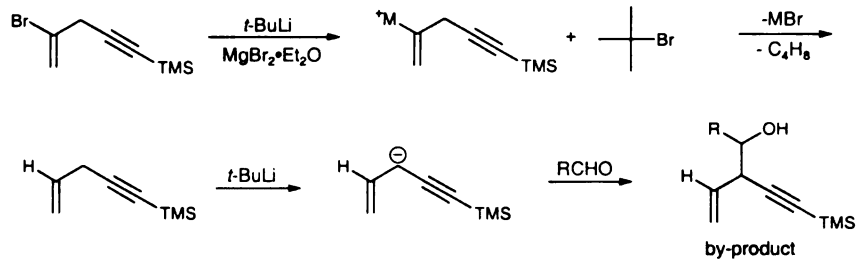
Scheme 27. Addition of Fragment **B** and Valeraldehyde



Although fragment **B** failed to metallate with Mg directly, the Grignard could be formed via a two-step process (Scheme 27). Addition of *t*-BuLi to fragment **B** afforded the halogen-lithium exchange product. Reaction with $MgBr_2 \cdot Et_2O$ then converts the lithium derivative, via transmetallation, to the desired Grignard. This intermediate was trapped with valeraldehyde resulting in the isolation of two products (85% combined yield). The byproduct **43** is derived from the proposed pathway illustrated in Scheme 28. Under the reaction conditions, the vinyl lithium derivative of fragment **B** acts as a base to deprotonate the *t*-butyl bromide formed during the reaction. The resulting alkene is then

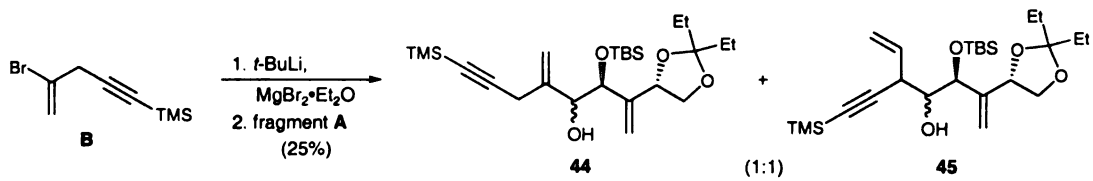
deprotonated in the allylic position resulting in the organometallic species responsible for **43**.

Scheme 28. Pathway for By-product (**43**) Formation



Although this two-step pathway was not fully optimized and resulted in substantial amounts of by-product, the protocol was applied in additions to **A** (Scheme 29). Two products were isolated, one from the vinyl addition and one from allyl addition. Both of these regioisomers consisted of diastereomeric mixtures. The lack of diastereoselectivity indicates the Felkin-Ahn model proposed in Figure 1 is not operating. After extensive experimentation aimed at improving these results it was determined the substrate (fragment **A**) needed to be modified to allow for the operation of a chelation-controlled model.

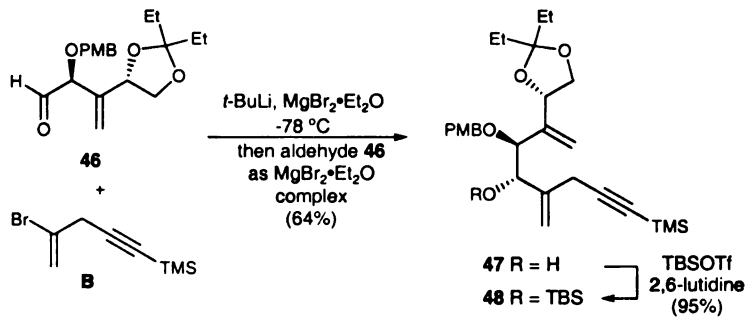
Scheme 29. Initial Coupling of Fragments **B** and **A**



Scheme 30 illustrates the culmination of the numerous modifications made to this coupling in order to achieve a diastereoselective reaction.[34] The TBS group was replaced with a *p*-methoxybenzyl (PMB) protective group. Unlike silyl ethers, benzyl ethers can undergo chelation. In order to eliminate the pathway for the formation of the allyl metal species of addition (Scheme 28) the metallation protocol was reversed. Thus fragment **B**

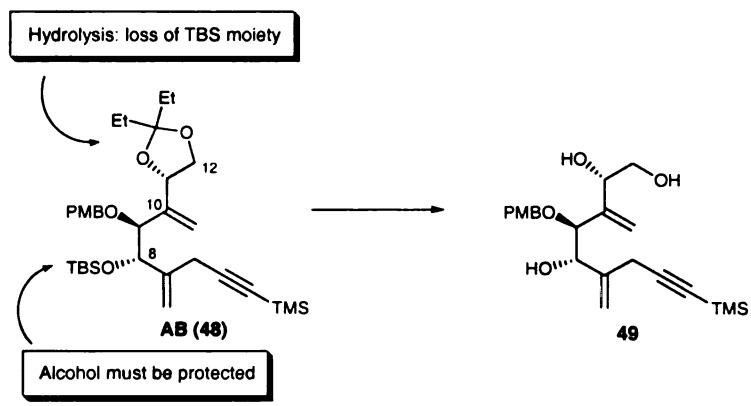
was added to a solution of *t*-BuLi. A stock solution of $MgBr_2 \cdot Et_2O$ (1.0 M in Et_2O/benzene (3:1)) was used to achieve the Grignard formation. This modified solvent system facilitates the dissolution of the magnesium salts at lower temperatures. Furthermore, the PMB modified fragment **A** (**46**)[17] was pre-chelated with the same stock solution of $MgBr_2 \cdot Et_2O$, before being added to the Grignard solution. This modified protocol successfully afforded the desired coupling product **47**, in 65% yield. Finally, TBS protection of the resultant secondary alcohol afforded **48** in high yield.

Scheme 30. Coupling of Fragment **B** and **46**



3.2. Elaboration of AB subunit:

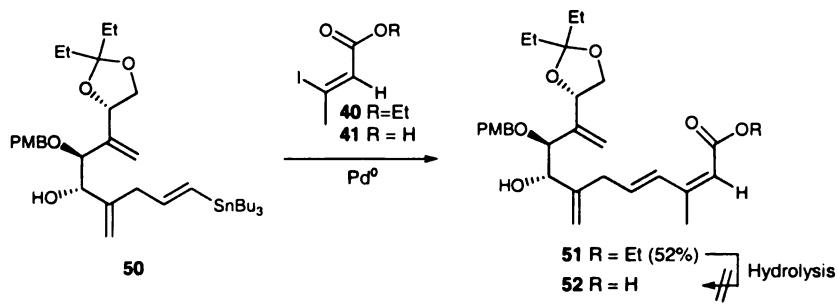
Scheme 31. Summary of **AB** Hydrolysis Results



With the successful formation of the **AB** subunit (**48**) the further elaboration of this fragment was investigated.[34] Scheme 31 summarizes the conclusions made after the attempted removal of the isopentylidene acetal. All attempts to hydrolyze the isopentylidene acetal in **AB** resulted in the loss of the TBS protective group and produced

the triol shown in Scheme 31. This C8 alcohol needed to remain protected for subsequent chemistry, such as the chelation controlled addition at C12 and the proposed macrolactonization. An attempt to change the protecting group on the C8 hydroxyl to a less labile PMB group resulted in very low yields and the resulting PMB ether could not be isolated cleanly. The problems associated with the protective group strategy indicated the need to completely reexamine the protection scheme for this fragment.

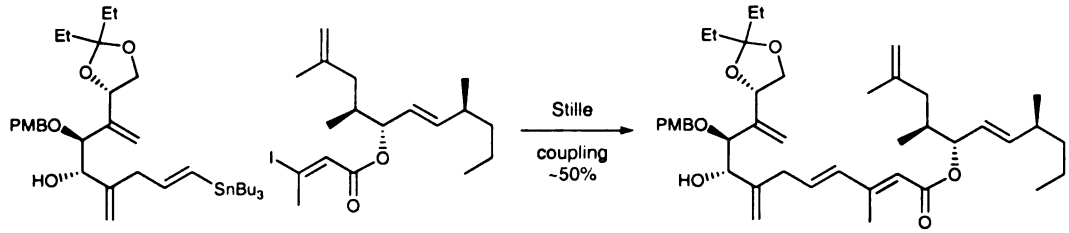
Scheme 32. Coupling and Attempted Hydrolysis of **AB** and **40**



Studies on the proposed Stille coupling were also conducted between the stannane derived from **AB** and *Z*-iodo acid (**41**) or *Z*-iodo ester (**40**) (Scheme 32). The *Z*-isomer was used instead of the *E*-isomer since both ester and acid forms of this isomer were readily formed during the synthesis of **D**. Thus coupling information could be obtained without "wasting" the *E*-isomer. After hydrostannation[17,37] to afford **50**, the Stille coupling with ethyl ester **40** was undertaken and afforded the desired cross-coupled product (**51**) in 52% yield. The free carboxylic acid derived from this substrate was needed for several reasons. First, a macrolactonization was planned to close the ring of amphidinolide A, requiring the free acid. Also, it was hoped that the carboxylic acid, or an easily obtained derivative thereof, would be a solid suitable for X-ray analysis to confirm the assignment of the stereocenters generated thus far. Unfortunately, attempts to hydrolyze ester (**51**) after coupling afforded a complex mixture of products and the

analogous *Z*-iodo-carboxylic acid (**40**) failed to afford the desired cross-coupled product (Scheme 32). In theory coupling fragment **AB** with **CD** could circumvent this problem. This hypothesis was successfully tested with an early model of the **CD** system (Scheme 33).

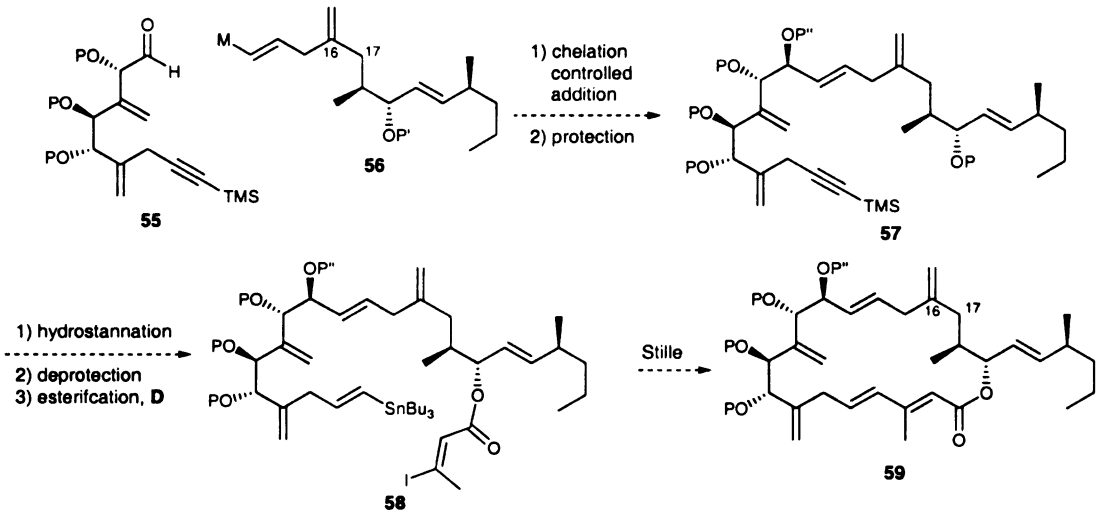
Scheme 33. Stille Coupling Model



50 **53** **54**

However, coupling fragments **D** and **C** would also force a change in the final ring closure step from a well-known macrolactonization protocol to one of the other bond disconnections proposed in the retrosynthesis. One possible route is outlined in Scheme 34. In this route, derivatives of fragments **AB** and **BC** would be coupled via a chelation controlled addition. Hydrostannation followed by esterification with **D** would afford an intermediate suitable for an intramolecular Stille coupling, which should proceed since the vinyl iodide is an ester, not a carboxylic acid.

Scheme 34. Proposed Alternative Coupling Route

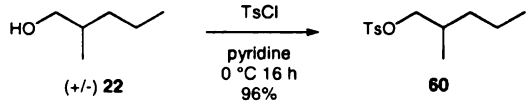


3.3. Coupling of Fragments C and B:

Be it the intramolecular Stille or any related approach we would likely have to join fragments **C** and **B** at C16-C17. Fragments **B** and **C** were designed to be coupled via a nucleophilic displacement of a tosylate derived from fragment **C** with an organometallic, such as a cuprate, derived from fragment **B**. Several other methods were also investigated in efforts for form the bond between what will be C16 and C17 in the final target (**1**).

3.3.1. Nucleophilic Displacement Route

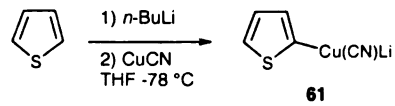
Scheme 35. Synthesis of Displacement Model **60**



Since it was not practical to perform the initial displacement tests with fragment **C**, a model compound was required. It was believed the tosylate of (+/-)-2-methyl pentanol (**22**) would adequately mimic the local sterics about the α methyl group of **C**. Commercially available racemic 2-methyl pentanol (**22**) was reacted with tosyl chloride

in pyridine solvent at 0 °C overnight to cleanly afford the desired tosylate (**60**) in multi-gram quantities (Scheme 35).[38]

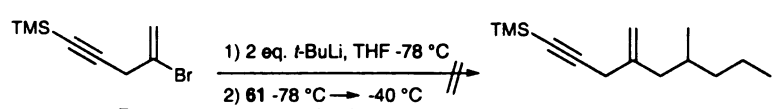
Scheme 36. Synthesis of Stock Soution of Thiophene Cuprate **61**



61

Initial displacements were to be from a CuCN based "higher order" cuprate. Although there is some debate as to the exact structure of these cuprates,[39] it is known that CuCN based cuprates are more reactive than their CuBr or CuI based counterparts. One drawback to the use of cuprates is the requirement for two equivalents of the organic compound being transferred, in our case fragment **B**, but only one of these groups will actually be used in the displacement and the second is lost. The net result is sacrificing one equivalent of fragment **B** for every equivalent that is used in the displacement. To avoid this Lipshutz and co-workers developed a method that uses thiophene as one of the ligands in a mixed cuprate.[40] The thiophene is nontransferable and acts as the sacrificial ligand during the displacement, allowing for the use of one equivalent of the desired transfer ligand (fragment **B**). A 1M stock solution of the precursor to these mixed cuprate was made per literature procedure and stored in a Sure-Seal® bottle (Scheme 36).[40]

Scheme 37. Attempted Mixed Cuprate Displacement of **60**

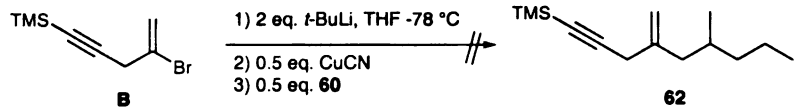


B **62**

Following Lipshutz's protocol for performing cuprate displacements,[40] fragment **B** was metallated at –78 °C by the addition of two equivalents of *t*-BuLi (Scheme 37). This solution was added via cannula to the thiophene cuprate (**61**) stock solution at –78

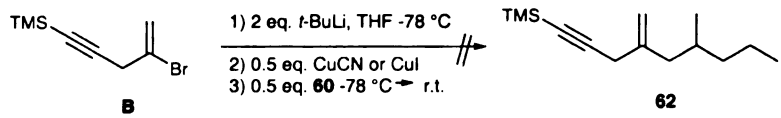
°C. The mixture was warmed to –40 °C for 30 minutes then recooled to –78 °C and the tosylate was added dropwise. The reaction was allowed to slowly warm to 0 °C for 2 hours then to room temperature overnight. After quenching and concentration of the reaction, GC/MS and ^{1}H NMR analysis did not indicate the presence of the desired compound. This reaction was repeated several times varying the rates of the various additions, but the desired product was never observed.

Scheme 38. Attempted Homo Cuprate Displacement of **60**



To see if the mixed cuprate was causing problems with the displacement, the homo-cuprate of fragment **B** was made by lithiating 2 equivalents of fragment **B** with *t*-BuLi and then adding this to a slurry of CuCN in THF. The solution was warmed slowly warmed to 0 °C for 5 minutes then recooled to –78 °C. The tosylate was then added dropwise and the mixture stirred overnight at –78 °C. A low temperature was chosen in case the cuprate was not stable at warmer temperature for extended periods of time. GC/MS analysis of the crude mixture did not indicate the presence of the desired product. Since the temperature may have been too low for the displacement to occur, the reaction was repeated and held at 0 °C for several hours before warming to room temperature overnight. Again GC/MS analysis of an aliquot did not show the desired coupling product. The mixture was then heated to 50 °C for 3 hours before quenching. Again, analysis of the crude mixture still did not reveal the desired product. Repeating this procedure with a ratio of 1.5:1 cuprate to tosylate also failed.

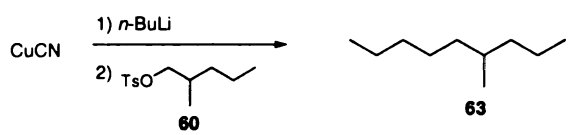
Scheme 39. Attempted Homo Cuprate Displacement of **60** II



B **62**

The above coupling studies were performed in concert with early studies on the **AB** coupling. In these early attempts, *t*-BuLi was added to a solution of fragment **B**, leading to a mixture of vinyl and allyl lithiated products (Scheme 28). However, this mixture should not compromise the results of the displacement studies. During these studies, GC/MS analysis did not show a mass peak corresponding to an addition product. The homo-cuprate reaction was repeated with the modified lithiation conditions (Scheme 39). Fragment **B** was added dropwise to a solution of *t*-BuLi, ensuring only vinyl lithiation. This solution was then added to a slurry of CuCN, followed by addition of tosylate **60**. After stirring overnight at room temperature the reaction was sampled and analyzed. The major peaks in the GC/MS were that of the tosylate and a mass peak corresponding to the protonated of the cuprate of **B**. In a further attempt at coupling, this revised protocol was repeated using CuI as a different copper source. Unfortunately, the use of CuI also failed to afford **62**.

Scheme 40. Butylcuprate Displacement of **60**

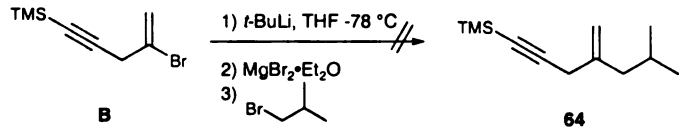


60 **63**

Given the failure of the cuprates formed from fragment **B**, an alternative cuprate was formed to determine if tosylate **60** was prone to displacement. Two equivalents of *n*-BuLi were added to a slurry of CuCN at –78 °C. Following a temperature protocol analogous to the previous displacement attempts (-78 °C – r.t. overnight). After workup, the crude mixture was analyzed by GC/MS, which indicated the consumption of tosylate

60 and formation of the desired 4-methyl nonane (**63**). Although the yield of this reaction was not quantified, we qualitatively proved that tosylate **60** could be displaced and that the previous displacement failures likely stemmed from a lack of reactivity of fragment **B.**

Scheme 41. Attempted Fragment **B** Grignard Displacement of Isobutyl Bromide

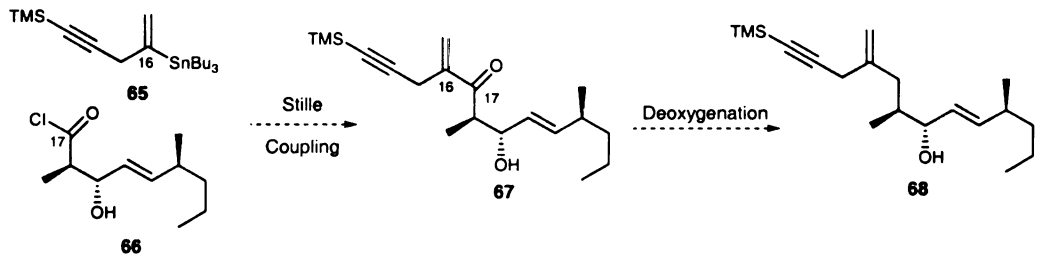


Because cuprates derived from fragment **B** were not reactive enough to displace tosylate **60**, an attempt was made to displace a primary bromide with the Grignard reagent derived from **B**. The Grignard reagent was formed by a procedure analogous to that used for the successful coupling of fragments **A** and **B**. Isobutyl bromide was added to the reaction and the mixture allowed to warm to room temperature while stirring overnight. None of the desired product was observed by GC/MS.

With the failure of the cuprates and Grignard reagents in the couplings described above and related couplings carried out by Lamont Terrell,[41] it was concluded that fragment **B** is unable to form a nucleophile of sufficient strength to complete the desired displacement.

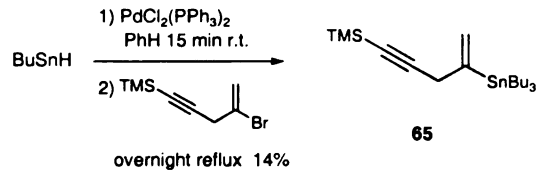
3.3.2. Stille Coupling Route:

Scheme 42. Proposed Stille Route to **68**



Another possible route to form the C16-C17 bond would involve a Stille coupling. Scheme 42 outlines this proposed route. We would convert the vinyl bromide of fragment **B** into a vinyl stannane by use of a palladium mediated halogen-tin exchange. The resulting vinyl stannane would then be subjected to a Stille coupling with an acyl chloride[42] derived from fragment **C**. Subsequent deoxygenation would remove the carbonyl and afford the desired product (**68**).

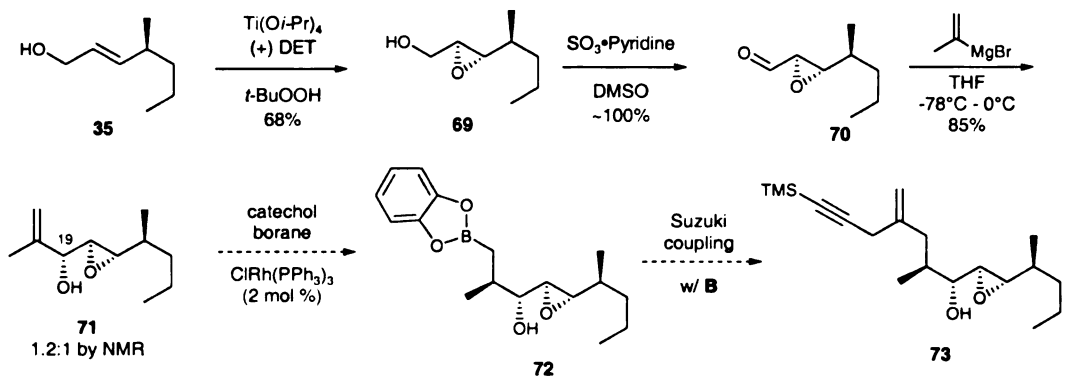
Scheme 43. Formation of Stannane **65**



The first compound needed to investigate this strategy was the vinyl tin dervative of fragment **B** (**65**). Palladium mediated bromine tin exchange could afford the desired vinyl stannane **65**.[43] While such a reaction has been demonstrated with aryl bromides, it has been successfully applied to few vinyl halides.[43c] Thus the reaction conditions in Scheme 15 were adapted from the aryl examples. First the $Bu_3SnSnBu_3$ was formed in situ by adding the Bu_3SnH to a solution of the Pd catalyst in benzene at room temperature (Scheme 43). Then fragment **B** was added and the reaction was refluxed overnight. The reaction was concentrated and chromatographed to afford the stannane in a disappointing 14% yield. Repeating this reaction with preformed hexabutylditin increased the yield to ca. 20%. Given these low yields and concern over exo olefin migration during the deoxygenation step this route was not pursued further.

3.3.3. Suzuki Coupling Route

Scheme 44. Proposed Suzuki Route to **73**

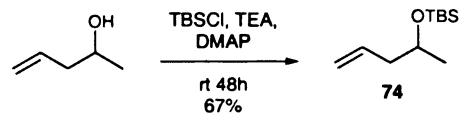


A Suzuki coupling could provide another possible means to couple fragments **B** and **C**.[44] For such a coupling, we needed to convert **C** into a suitable boron species. To achieve this the synthesis of "**C**" was changed significantly as shown in Scheme 44. Sharpless asymmetric epoxidation of **35** afforded epoxy alcohol **69** in moderate yield. Oxidation of **69** afforded aldehyde **70** and was followed by the addition of isopropenyl magnesium bromide to afford **71** as a 1.2:1 mixture of isomers.[45] The next step in the proposed synthesis was the rhodium catalyzed hydroboration of **71** with catechol borane. These hydroboration conditions have been known to afford a stereoselective hydroboration of similar olefins.[46] At this point in the synthesis there were two problems. First, the addition reaction afforded a mixture of epimers at what will be C19. Since the hydroboration relies on this stereocenter for chiral induction, only half of the material at this point was usable, the other half would have to be recycled or discarded. Secondly, while catechol borane is the only borane that would afford the desired stereochemistry at what would be C18 in the final target, the use of sp^3 catechol boranes in Suzuki couplings are troublesome and the conditions for such couplings are substrate dependant.[44] While another researcher worked on the stereochemistry and ratio of the addition reaction,[45] a

study was undertaken to find conditions that would couple fragment **B** with a catechol borane such as **72**.

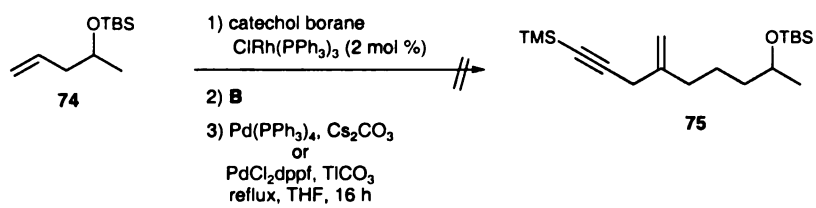
3.3.3a. Suzuki Coupling Studies with Fragment B

Scheme 45. Synthesis of **74**



Olefin **74** was chosen to be the initial substrate for the Suzuki study. TBS protection of the readily available 4-hydroxy-1-pentene afforded **74** in moderate yield after chromatography. Although **74** lacked the isopropenyl moiety and the hydroxyl is not α to the olefin, it was accessible in multi-gram quantities. Once a set of conditions was found to couple **B** and **74**, they could be modified to work with the actual system proposed in Scheme 44.

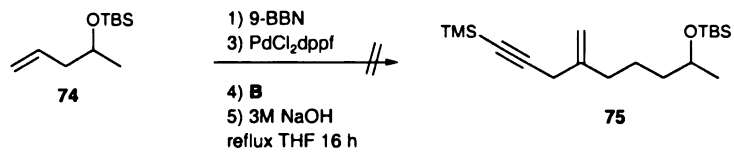
Scheme 46. Attempted sp^3-sp^2 Suzuki Coupling with **B**



In what became the general procedure used throughout this study catechol borane was added to olefin **74** using 2 mol % Wilkinson's catalyst (Scheme 46). After 6 hours **B** was added to the mixture followed by the palladium catalyst and finally the base. The reaction was then heated to reflux in an oil bath overnight (~16 hours). Use of $Pd(PPh_3)_4$ and $CsCO_3$ failed to afford any of the desired product **75**. Only **B** (60% recover) was isolated after purification of this reaction by flash chromatography. Application of Suzuki's recommended reagents, $PdCl_2$dppf and $TlCO_3$,[47] also failed to afford the cross-coupled product (**75**) as indicated by GC/MS analysis. To ensure the hydroboration was

not the issue, the reaction was repeated and after 6 hours a portion of the solution was removed and analyzed by ^{1}H NMR. The lack of olefin protons and other signals in the NMR suggested the hydroboration had indeed occurred. The Suzuki coupling with **B** appeared to be the problem.

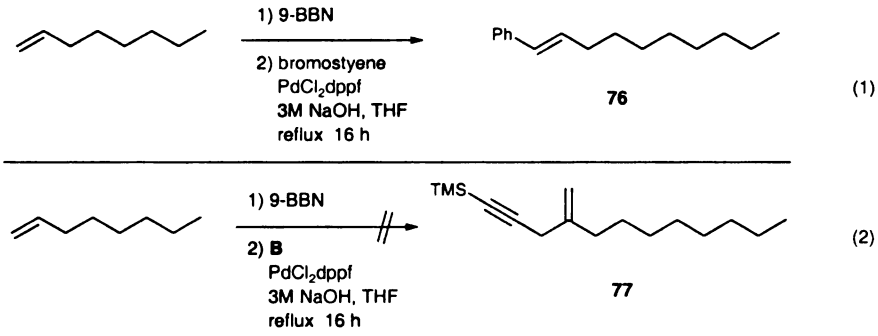
Scheme 47. Attempted Suzuki Coupling between 9-BBN-74 and B



74 75

9-BBN has been shown to be a better choice for performing Suzuki coupling with alkyl boron derivatives and the catalyst/base conditions are more general.[44] If **B** could not couple with a 9-BBN derivative of **74**, which is supposed to be the derivative of choice for alkyl couplings, then the likelihood of **B** coupling to a catechol derivative is very remote. Substrate **74** was hydroborated with 9-BBN in THF for 6 hours. This was followed by the addition of **B**, $PdCl_2dppf$, and 3M NaOH solution. The aqueous base was degassed to remove any dissolved oxygen that may shut down the reaction. The reaction was refluxed for 16 hours. GC/MS analysis of the crude reaction mixture did not indicate the presence of **75**, the desired cross-coupled product. As in the catechol case, the hydroboration was repeated and analyzed by ^{1}H NMR, which again suggested complete hydroboration.

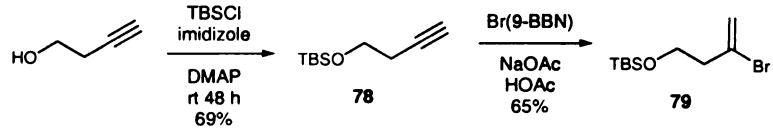
Scheme 48. Attempted Coupling of **B** and 9-BBN-octane



It was known that the 9-BBN hydroboration product of 1-octene can be coupled under the conditions shown in Scheme 48, reaction 1. This reaction was successfully repeated to qualitatively ensure the reaction was operating in our hands. Although similar conditions were used for the reaction in Scheme 47, the use of 1-octene was useful to determine if **74** was causing the problems and not fragment **B**. Application of these conditions to the coupling of 1-octene and fragment **B** (Scheme 48, reaction 2) failed to afford the desired coupling. GC/MS analysis afforded no evidence of **77** but did show the presence of unreacted **B**. With this experiment it was concluded that fragment **B** was very reluctant to undergo a Suzuki cross-coupling and thus it could not be used in the redesigned synthesis of **BC** (Scheme 44).

3.3.3b. Suzuki Coupling Studies with 79

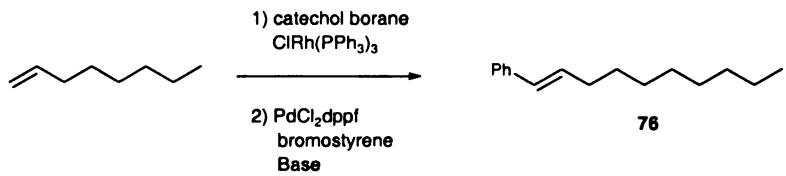
Scheme 49. Replacement for Fragment **B**



Since it was determined that fragment **B** would not work as a cross-coupling partner, a replacement was needed. The replacement needed to have a synthetic handle that could be modified to allow for the introduction of a vinyl moiety, such as a vinyl iodide. Vinyl bromide **79** has the functionality required to be useful to our synthetic

endeavor. The vinyl bromide would be used in a Suzuki coupling in place of fragment **B**, as outlined in Scheme 44. Commercially available 4-hydroxybutyne was protected as a TBS ether. Haloboronation with bromo-9-BBN effectively installed the bromide in the Markovnikov position.[48] Once coupled with fragment **C**, the TBS protected alcohol could be deprotected and oxidized. The resultant aldehyde could then be functionalized with a Wittig olefination, or a Takai reaction[49] to install the requisite olefin moiety for the coupling with **AB**.

Scheme 50. Survey of Bases for Suzuki Coupling

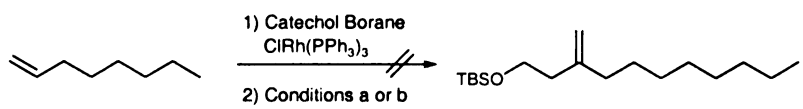


Entry	Hydroboration Time	Base	Solvent	Temp / Time	61 (GC/MS)
1	6 h	Tl_2CO_3	THF	Reflux / 48 h	Trace
2	16 h	0.5 M TlOH	PhH	50 °C / 48 h	Major Prod.
3	6 h	0.5 M TlOH	THF	50 °C / 48 h	None
4	6 h	$Ba(OH)_2$ / H_2O	THF	50 °C / 48 h	Complex Mix
5	6 h	KF / H_2O	THF	50 °C / 48 h	None

Before starting the coupling studies with **77**, a survey of bases for the Suzuki coupling were examined using the system 1-octene/bromostyrene system. Scheme 50 outlines the results of this survey. All reactions were run on 0.5 mmol scale, qualitatively monitored by GC/MS, and were typically unchanged after 16-20 hours of heating. Tl_2CO_3 (Entry 1)[47] afforded a trace amount of the desired product **76**. Entry 2 was unique in that it used benzene as the solvent, which slowed the hydroboration reaction (16 hours vs. 6 hours). The base for this reaction was 0.5 M TlOH,[47] which is no longer commercially available. A solution of TlOH was made by the hydrolysis of TlOEt in water to afford the desired TlOH solution.[50] Under these conditions the reaction went to completion and the major product by GC/MS was the desired coupling product **76**. Entry

3 employs the same TlOH conditions but in THF. The THF was used to achieve the hydroboration in 6 hours, however with this solvent the TlOH base was ineffective and afforded no product by GC/MS. $Ba(OH)_2$ (Entry 4) has been shown to be an effective base for aryl boronic acids and esters,[51] however on this system its use resulted in the formation of a complex mixture of signals on the GC/MS, none of which were of the desired product. This reaction was allowed to stir for 48 hours but no improvement was observed. Finally, KF, which has been known to accelerate Stille and Suzuki reactions, had no effect on the coupling in Entry 5.

Scheme 51. Attempted Synethsis of **80**



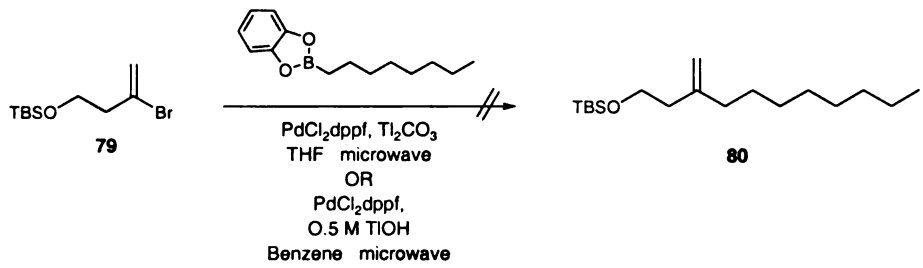
80

Conditions a) $PdCl_2$dppf, **79**, 0.5 M TlOH, Bezene, 50 °C 16 h
b) $PdCl_2$dppf, **79**, Tl_2CO_3, Bezene, 50 °C 16 h

Given that only TlOH and Tl_2CO_3 afforded any amount of product during the qualitative survey, these two bases were used in a Suzuki coupling with **79** (Scheme 51). Unfortunately, neither of these bases proved effective for the formation of **80**, which could not be detected by GC/MS. For the promising TlOH system only the hydrolysis products of the borane intermediate was observed along with unreacted vinyl bromide **79**. Based on these results, it was concluded that the catechol is not sufficiently active to be able to effect the coupling with either **79** or fragment **B**.

3.3.3c. Microwave Assisted Suzuki Couplings

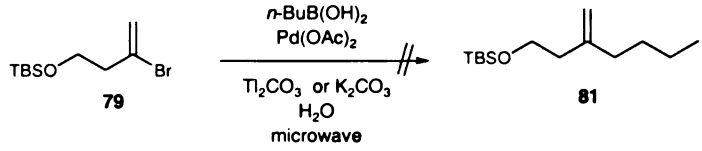
Scheme 52. Attempted Microwave Assisted Suzuki with boronic ester.



Recent literature reports detailed the use of microwave radiation from a standard household microwave (2.4 GHz) could promote the Suzuki coupling of aryl halide with aryl boronic acids in aqueous solutions.[52] Based on our experience with microwave assisted Stille reactions, the application of microwave acceleration to our coupling systems deserved further investigation.[53] It is known that alkylboronic acids are even worse substrates than catechol boronic esters. It remained to be determined if the microwave acceleration seen for the aryl bornic acids could be successfully translated to catechol boranes. As the microwave reactions were run in conical vials and on small scale it was more practical to isolate *n*-octylecatechol borane from the hydroboration of 1-octene in THF with Wilkinson's catalyst. After 6 hours the THF was removed and the product was purified by bulb-to-bulb distillation. Unfortunately, this product is unstable and needed to be used immediately or be redistilled prior to use. Combining the palladium catalyst, base, and 1.2 mL of degassed THF in a 2 mL conical vial assembled the microwave Suzuki reaction. The vial was purged with argon and the octylcatechol borane and vinyl bromide **79** were added via syringe. The sample was heated in the microwave. At some point between 10 and 15 minutes at 70 watts the reaction went dry. GC/MS analysis of a THF extract of the residue did not indicate any product formation. This reaction was repeated with 0.5 M TlOH. This reaction was assembled in the same

manner. The reaction was heated at 70 watts for 10 minutes. Sometime during the last 5 minutes the reaction vessel ruptured and the contents were lost. Repeated attempts to heat a mixture of benzene and water were met with the same explosive result. Since thallium is highly toxic the reaction was not repeated in fear of contaminating the microwave with thallium salts in the event of additional detonations.

Scheme 53. Attempted Microwave Assisted Suzuki Coupling



Although alkylboronic acids are typically worse substrates than catechol boronic esters, we decided to see if microwave acceleration would overcome this reactivity barrier and complete the coupling. As we had vinyl bromide **79** in hand it was a simple task to obtain some commercial butylboronic acid and try the coupling outlined in Scheme 53. Unfortunately, running the reaction with either K_2CO_3 (per reference 52) or Tl_2CO_3 under microwave heating at 70 watts for up to 15 minutes failed to give the Suzuki product (**81**).

At this point the Suzuki pathway was abandoned for several reasons. First, and most importantly none of the non-microwave conditions afforded coupling with either fragment **B** or its replacement **79**. Secondly, even though the microwave conditions were not vigorously pursued, the isomer ratio of intermediate **71** (Scheme 44, pg. 37) was never increased.[54] Thus limiting the attractiveness of this route.

3.4. Summary of Coupling and Elaboration Studies

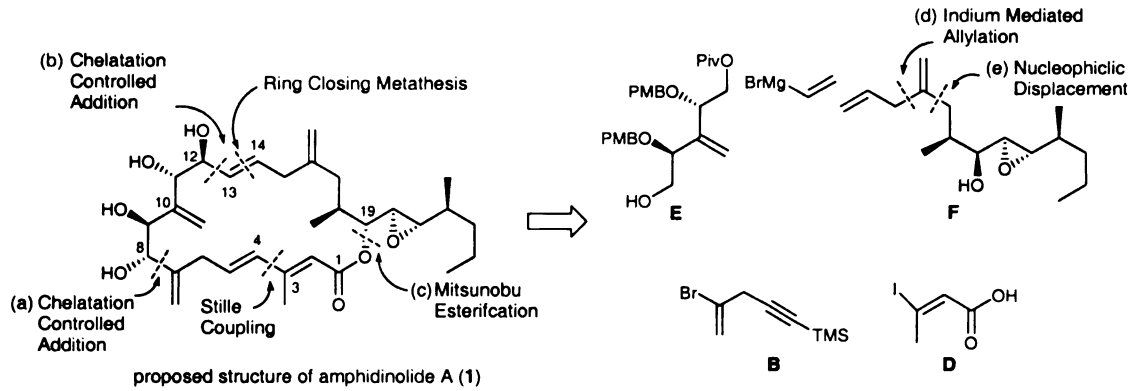
The results of these coupling and elaboration studies can be summarized by several key conclusions: a) the protection scheme for fragment **A** needed to be

reexamined, b) fragment **D** only undergoes the Stille coupling if it is an ester, and ethyl esters of fragment **D** do not hydrolyze, c) due to the previous restriction, the molecule cannot be closed with a macrolactonization, d) fragments **C** and **B** cannot be coupled by nucleophilic displacement or via cross-coupling indicating this portion of the molecule needs to be redesigned.

Chapter 4. Second Generation Approach

Based on conclusions gathered from the first generation coupling studies (Chapter 3), a second retrosynthesis was developed (Scheme 54). This redesign also afforded the opportunity for the evaluation of new organometallic methods, especially those involving organotin, -indium, -palladium, -ruthenium, and -copper chemistry. In addition to making advances in the area of these synthetic tactics, we also aimed to advance synthetic strategy via our synthesis; namely, we plan to close the macrocyclic ring via a highly selective ring closing metathesis[55] (RCM) to generate the C13-C14 alkene. Because of the failure to couple fragments **B** and **C**, we could not install the entire northern skipped diene as a single unit. We believed a stepwise approach to this moiety would be best. Use of commercially available lithium acetylide at the nucleophile to install a terminal alkyne in conjunction with an indium-mediated allylation to furnish a branched, skipped diene would afford the desired skipped diene. While the terminal olefin generated during this procedure would not be a useful synthetic handle for any of the coupling strategies previously discussed, it is an optimal synthetic handle for the RCM. Furthermore, with the knowledge garnered from the chelation controlled additions of fragments **A** and **B** we should be able to stereoselectively install a vinyl group at C12 of the tetraol region, affording the second terminal olefin. These two terminal olefins could then employed in the RCM. Given the broad array of alkene functionality present in amphidinolide A, use of RCM to close the ring at a late stage was not without risk. Of particular concern was the ability to control which alkenes underwent metathesis and the geometry of the resultant olefin. Thus a successful RCM-based approach would be a noteworthy application of this very important methodology and is detailed herein.[55]

Scheme 54. Second Generation Retrosynthesis

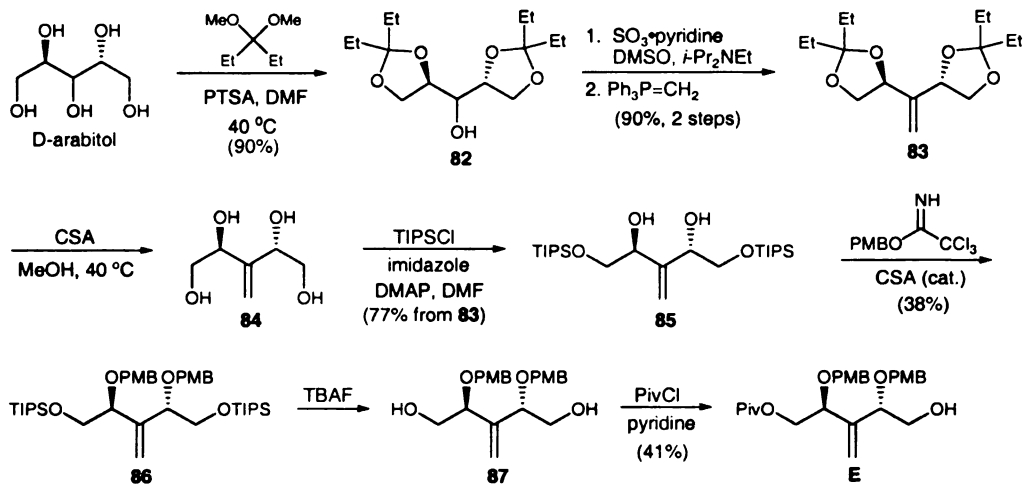


Scheme 54 outlines the second-generation retrosynthesis of amphidinolide A, breaking the molecule into five fragments: **B, D, E, F,** and vinyl-MgBr. As with the first generation retrosynthesis, (a-b) chelation controlled addition of the respective vinyl nucleophiles to aldehydes of D-arabitol derivative **E** would set the C8 and C12 stereocenters of the final target. Fragments **D** and **F** would be coupled by (c) a Mitsunobu esterification. The decision to invert C19 during the esterification was based on requirements for a stereocontrolled epoxidation of **F** (vide infra). Finally, the skipped diene portion of **F**, which previously was to be installed as a single unit (fragment **B**), is constructed stepwise by (d-e) indium-mediated allylation of a terminal alkyne.

4.1. Synthesis of Fragment E

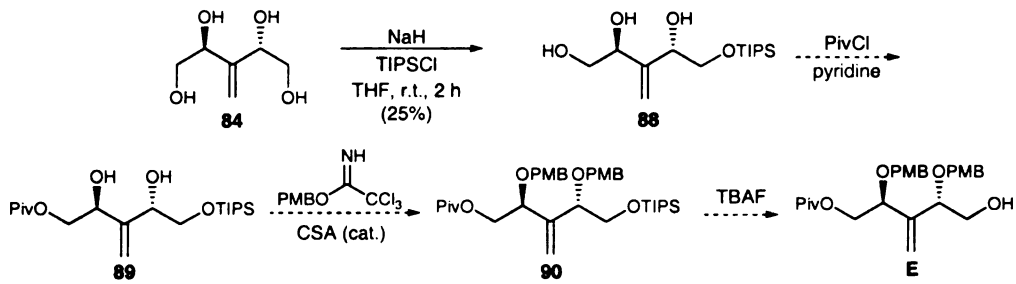
The redesign of fragment **A** not only allowed for implementation of a protecting strategy that was not susceptible to hydrolysis problems, but also allowed for the design of a shorter, high yielding reaction sequence (Scheme 55).[17]

Scheme 55. Preparation of Fragment E from D-Arabitol



The synthesis of **E** (Scheme 55)[17] began with the protection of D-arabitol as the bisisopentylidene acetal **82**. The remaining secondary alcohol was oxidized via a Doering-Parikh oxidation.[56] A subsequent Wittig reaction efficiently installed the *exo* olefin in **83** in a 90% yield over two steps. Hydrolysis of the bisisopentylidene acetals with CSA afforded **84**, which was not purified due to the water soluble nature of the tetraol. A selective protection of the primary alcohols as TIPS silyl ethers afforded **85** in high yield. The remaining secondary alcohols were protected as PMB ethers with *p*-methoxybenzyl tricholoracetimidate. Although this reaction afforded only 38% of the desired di-PMB product (**86**), the reaction also afforded 37% of mono-PMB product that can be converted into **87** by resubjection to the reaction conditions. Removal of the TIPS groups with TBAF afforded a C-2 symmetric diol, which was then monoprotected as a pivalate affording fragment **E**.

Scheme 56. Mono-Protection of Tetraol **84**



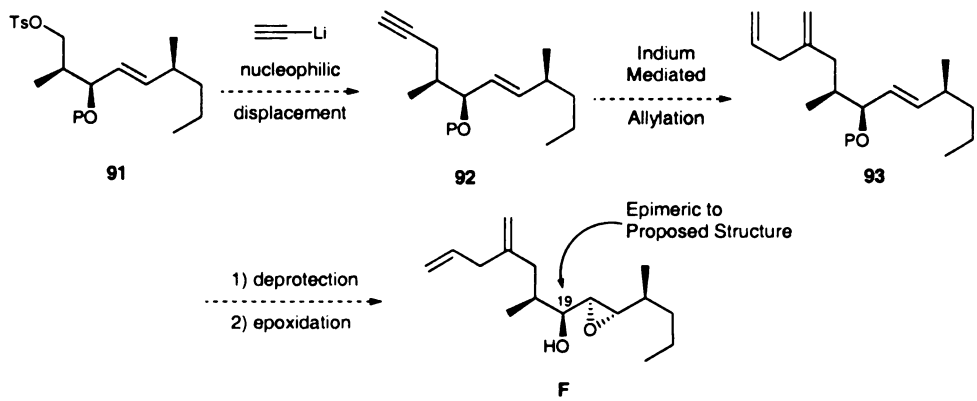
In an effort to further optimize the synthesis of fragment **E**, attempts were made to mono-protect tetraol **84** with TIPSCl (Scheme 56). While this route would not decrease the number of steps it would halve the amount of TIPSCl required, thus reducing cost. Applying conditions designed for the monoprotection of various 1,*n*-diols (Scheme 56), afforded only a 25% yield of the desired mono-protected product **88**.[57] The rest of the water-soluble tetraol was lost during the workup. In this procedure NaH is used to deprotonate one of the alcohols, this alkoxide then precipitates from solution preventing further deprotonation.[57] Once all of the alcohol is deprotonated (~2 hours) the TIPSCl is added to effect the protection. Since the tetraol was only sparing soluble in THF to begin with, it is possible the full equivalent of tetraol was not deprotonated. Further attempts to increase the yield of this reaction included using dioxane as the solvent and refluxing overnight to effect full deprotonation, but the yield from these reactions was not significantly higher. Thus loss of an extra equivalent of TIPSCl is preferred to the loss of 75% of the tetraol, and the overall route to **E** remained unchanged.

4.2. Synthesis of Fragment F

Among the key factors our second generation synthesis had to address was the installation of the upper skipped diene moiety. Due to the failure of coupling attempts in the first generation synthesis, we decided to construct this moiety using a stepwise

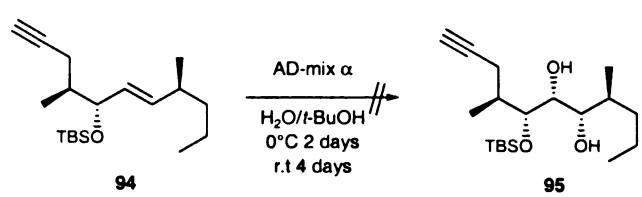
method. In theory the installation of a terminal alkyne by nucleophilic displacement, then an indium-mediated allylation would afford the skipped diene moiety (Scheme 57).

Scheme 57. Proposed Route to Fragment **F**



In choosing the most suitable starting point for introducing the skipped diene, we had to consider our plan for construction of the epoxide moiety. Originally, we planned to install the epoxide via a directed epoxidation, possibly vanadium mediated. While this remained a possible route, we felt it prudent to also investigate a more predictable method for the installation of the epoxide. A Sharpless asymmetric epoxidation (SAE)[13] would afford a highly predictable stereochemical outcome. Unfortunately, the SAE is *threo* selective when a chiral allylic alcohol is used.[13] The stereochemistry proposed for this portion of amphidinolide A is *erythro*. An SAE on a substrate with the proposed stereochemistry at C19 would result in a stereo mismatched case and afford poor diastereoselectivies.[13]

Scheme 58. Attempted Dihydroxylation of **95**



One way to overcome the stereochemical restraints of the SAE would be to use an asymmetric dihydroxylation, which is not as sensitive to existing chirality (Scheme 58).[58] The resulting diol would then be converted into a halohydrin and subsequently to the desired epoxide.[59] Using the mnemonics developed by Sharpless for the prediction of the dihydroxylation, the AD mix α would install the desired stereochemistry. AD mix α was combined with protected allylic alcohol **94**[60] in a mixture of water and *t*-BuOH. The AD mix used had more ligand and osmium than the standard mix in order to ensure that existing chirality would not interfere.[59] Unfortunately, this reaction did not afford the desired dihydroxylated product (**95**) even after reacting for 6 days.

Because the failure of the dihydroxylation and other epoxidation routes that were simultaneously investigated[61] we decided to make the necessary design changes to allow for the SAE to proceed in a stereo matched case. To avoid the stereo mismatch during the SAE, the stereocenter at C19 would need to be epimeric to that found in the natural product (Scheme 57). The needed C19 stereochemistry along with the appropriate C18 methyl stereochemistry could be established by an auxiliary driven anti-aldol condensation. The stereochemistry at C19 could ultimately be corrected by a Mitsunobu esterifcation with fragment **D**. Two auxiliary systems were examined to find an efficient route to the desired anti-aldol product.

4.2.1. Heathcock Modification to Evans Aldol Methodology

Heathcock demonstrated that by modifying protocols and reagents, the same oxazolidinone auxiliaries used to facilitate *syn*-aldol reactions, such as the one used for the synthesis of fragment **C**, could afford a stereoselective *anti*-aldol reaction.[62] The effectiveness of this protocol is based on the transition state illustrated in Figure 2.

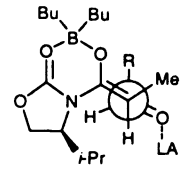
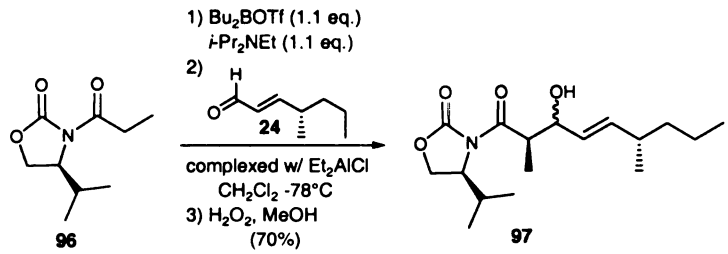


Figure 2. Transition state for Heathcock Aldol

Unlike the closed 6-membered transition state for the standard Evans' aldol, the Heathcock modification proceeds though an open transition state. In the Evans case, the boron used for the enolization is also used as a Lewis acid to activate the aldehyde for the aldol. However, in the Heathcock case, the boron remains complexed to the oxazolidinone carbonyl, leading to the open transition state, and a second Lewis acid is used to activate the aldehyde. Provided the Lewis acid is sufficiently bulky, the aldehyde should take the orientation shown in Figure 2 and lead to an anti-aldol product.

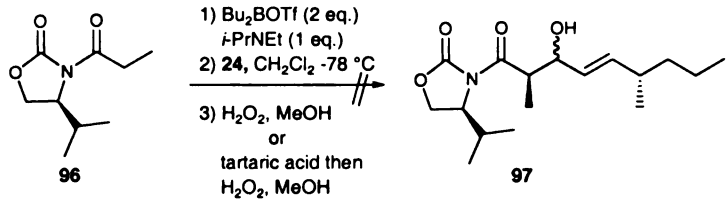
Scheme 59. Heathcock Anti-aldol with Et_2AlCl



Acylated auxiliary **96**, which was prepared following literature procedures,[19] was enolized with dibutylboron triflate and diisopropyl ethyl amine at -78 °C (Scheme 59). To that solution, aldehyde **24** was added as a precomplexed solution with Et_2AlCl (2.2 equivalents). After stirring overnight and workup per standard procedures,[62] **97** was isolated in 70% yield as a 1:1 mixture of diastereomers (determined by HPLC, 10% mass recovery). This was disappointing since there did not seem to be sufficient bias for the orientation of the aldehyde in this system. Also, while the diastereomeric mixture was separable via HPLC, it eluted as a single spot under various flash chromatography

conditions. This along with the low mass recovery made isolation of purified samples in preparative quantities difficult.

Scheme 60. Heathcock Anti-aldol with Bu_2BOTf

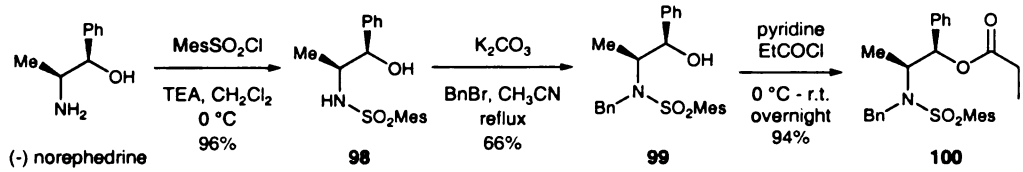


In hopes that a different Lewis acid might provide the necessary bias for a diastereoselective process, we attempted to use dibutylboron triflate as both the Lewis acid and the enolization reagent (Scheme 60). In this protocol, two equivalents of dibutylboron triflate were used but only one equivalent of base. This ratio allows the extra equivalent of boron triflate to act as the Lewis acid.[63] Unfortunately, these conditions failed to afford the desired product as judged by TLC or ^1H NMR. After several attempts at improving this reaction, including the use of the literature recommended tartaric acid workup protocol, no viable improvement was seen with either Lewis acid.[62] Even though the desired isomer was present in the mixture, it was determined that the separation problem associated with this aldol system and the poor levels of diastereoselectivity made this approach unworkable.

4.2.2. Abiko-Masamune Anti-Aldol System

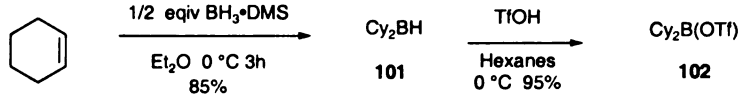
Unlike Heathcock's method which in effect forces an anti-aldol reaction, Abiko and Masamune developed an auxiliary for the express purpose of performing anti-aldol reactions.[64] With this system, they were able to achieve >90% yields and excellent diasteroselectivity (98:2 anti:syn) with various aldehydes.

Scheme 61. Synthesis of Abiko-Masamune Auxiliary



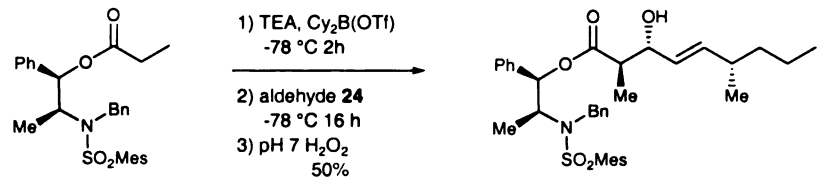
Scheme 61 illustrates the synthesis of the Abiko-Masamune auxiliary. Treating (1R, 2S)-(-)-norephedrine with mesitylsulfonyl chloride in the presence of triethylamine affords **98** in excellent yield and purity. *N*-Benzylation afforded **99** in moderate yield after chromatographic purification. Finally, the auxiliary was completed by acylating the alcohol to afford ester **100**.

Scheme 62. Synthesis of Dicyclohexylboron Triflate



The Abiko-Masamune protocol requires dicyclohexylboron triflate to form the boron enolate, but this reagent is not commercially available. Following procedures described by Brown[65] (Scheme 62), dicyclohexyl boron triflate was synthesized via hydroboration of cyclohexene with one half equivalent of borane-dimethylsulfide complex to afford the dicyclohexylborane **101** in 85% yield. The product was dried at 0° to r.t. overnight under vacuum. After dissolving **101** in hexanes, triflic acid was added dropwise.[65a] The 0 °C solution was concentrated under vacuum, and the yield was calculated (95%). It was crucial that this concentration step was done cold and rapidly; as the more concentrated the solution the faster triflate **102** decomposes. Rapid addition of fresh hexanes afforded the desired stock 1 M solution of **102**, which had a shelf life of 1-2 months before decomposition was noticable.

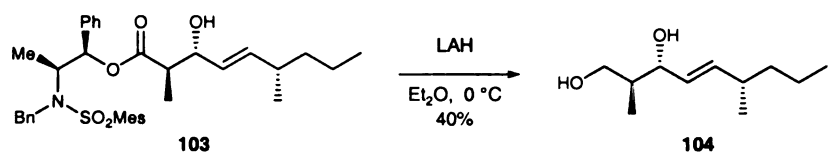
Scheme 63. Synthesis of Anti-aldol **103**



100 **103**

With all the components in hand, the anti-aldol protocol was applied to our system (Scheme 63). Typical oxidative workup and careful flash chromatography afforded the desired anti-aldol product in 50% yield. HPLC analysis of this material showed the product ratio was 91:9:6 (desired anti:opposite anti:syn).

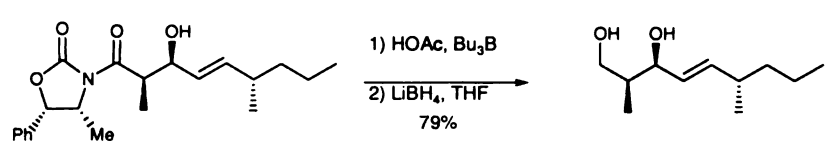
Scheme 64. Synthesis of Diol **104**



103 **104**

To further support our assignment, a small amount of material was manipulated in order to compare it to the analogous syn-diol. Using known conditions[64] LAH was able to successfully remove the auxiliary without first protecting the free alcohol. The ability to use LAH indicated that unlike the Evans aldol systems these particular aldol products are robust enough to withstand basic conditions. That said, the low 40% yield may be attributed to retro aldol or just a consequence of the unoptimized reaction conditions.

Scheme 65. Synthesis of Diol **105**

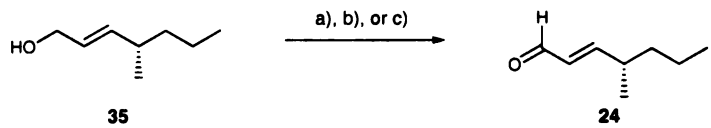


25 **105**

To obtain a sample of the diol from the syn methodology, a modified $LiBH_4$ reductive cleavage was performed on **25** (Scheme 65). Using an Evans' method for the temporary protection the free alcohol with tributylborane and acetic acid, the successful

reductive cleavage occured without retro aldol complications.[20b] Subsequent oxidative workup removed all of the boron from the compound to afford diol **105** in good yield. Comparison of the spectroscopic data for **104** and **105** confirmed the molecules were indeed diastereomers of each other. Thus given the predictive literature precedent,[64] we were reasonably confident of our stereochemical assignment. Of course, an X-ray crystal structure to unequivocally confirm the stereochemistry would be welcome.

Scheme 66. CMD Oxidation of **24**



35 **24**

a) CMD 15 equiv., CH_2Cl_2, r.t. 8 h >95%
b) CMD 10 equiv., CH_2Cl_2, r.t. 16 h >95%
c) CMD 5 equiv., 4 Å M.S., CH_2Cl_2, r.t 16 h > 95%

For the anti-aldol in Scheme 63, **24** was made using a Dess-Martin oxidation (Scheme 21, pg. 20). This reaction was clean, with the exception of a small amount of polar by-product, and was used crude in the syn aldol reactions. For the anti-aldol reactions the aldehyde had to be purified by silica gel chromatography to remove the by-product. Without this purification the yield of the aldol reaction was <50% and significant amounts of aldehyde were lost upon purification, even when the column was buffered with 1% TEA. An efficient oxidation that did not require purification should alleviate this problem. Thus an alternative to the Dess-Martin periodane was sought.

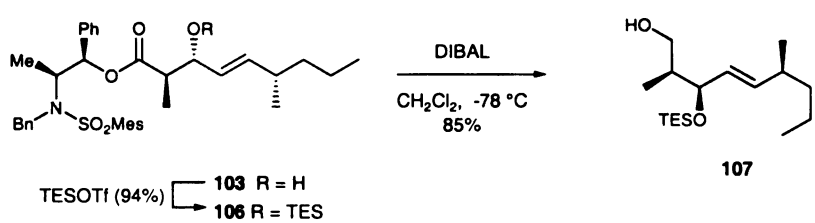
Chemically treated MnO_2 has been shown to be a successful oxidant for allylic and benzylic alcohols.[66] The use of MnO_2 is not new to the oxidation of allylic alcohols. However, commercially available MnO_2 can vary in activity from excellent to unreactive and usually requires activation by azeotropic removal of water from freshly prepared manganese dioxide.[67] Chemical Manganese Dioxide (CMD) is commercially available

from Wako Chemical of Japan and according to the literature does not suffer from the same variable activity of traditional MnO_2. Furthermore it can be purchased at a fraction of the cost, as CMD is manufactured on large scale for the alkaline battery industry.[66] One possible problem with CMD was that, to the best of our knowledge, there were no instances of using this acidic oxidant on epimerizable chiral alcohols such as **35**. Initially a small-scale reaction was performed to confirm that **24**, could be formed with no loss of optical activity. The workup for this reaction is very simple, consisting of a vacuum filtration to remove the heterogeneous CMD oxidant, rinsing the filter cake with diethyl either, and concentration the combined organic filtrates to afford the product. No chromatography is required. Aldehyde **24** generated using this method has been used in the subsequent anti-aldol reactions with the result of increasing the yield to an average of 65%.

4.2.3. Final Elaboration of Fragment F:

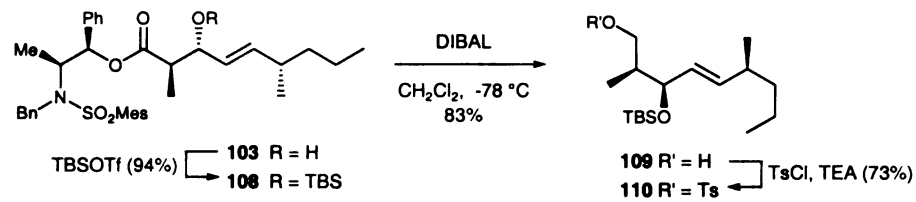
With a successful albeit moderately yielding aldol in hand, the final elaboration of fragment **F** could commence. With the Evans auxiliaries (Chapter 2), it was difficult to find a way to protect the aldol moiety that did not introduce steric complications during cleavage of the auxiliary. While the current auxiliary system may not contain the same structural elements, it could be problematic if the protective group was too bulky to allow the clean reduction of the ester.

Scheme 67. TES Protection and DIBAL Reduction of **103**



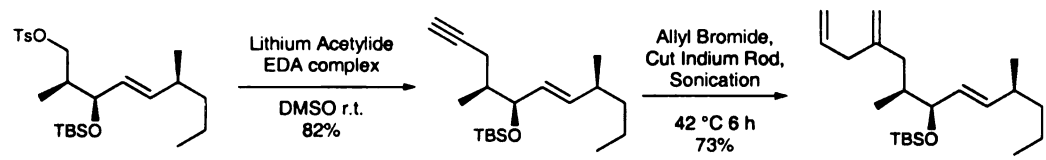
Similar anti aldol products of the Abiko-Masamune auxiliary were effectively protected with a triethylsilyl (TES) group and cleaved with DIBAL.[68] Application of these conditions to our system (Scheme 67) afforded the desired primary alcohol **107** in high yield. However, when **107** was carried forward though tosylation and nucleophilic displacement by others in our laboratory it was found that the TES group was not stable under the displacement conditions and did not afford the desired displacement product.[54]

Scheme 68. TBS Protection and DIBAL Reduction of **103**



To counter this issue, a more robust protecting group was needed. Scheme 68 illustrates the protection of aldol adduct **103** as a TBS silyl ether in high yield. Fortunately, reduction with DIBAL cleanly affords the desired primary alcohol **109**. As with the previous DIBAL reduction, moderate amounts of auxiliary **99** could be recycled for subsequent aldols. Treatment of **109** with tosyl chloride, TEA, and DMAP afforded the primary tosylate (**110**) in 73% yield.

Scheme 69. Stepwise Construction of Skipped Diene

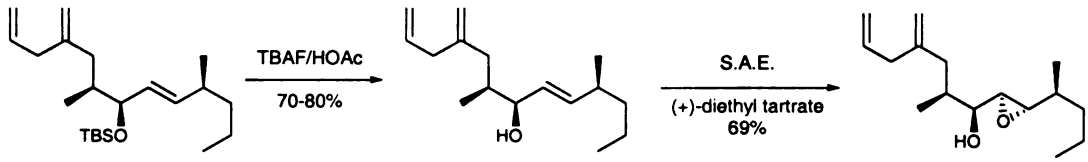


110 111 112

With tosylate **110** in hand, the last 5 carbons of fragment **F** could be constructed in a stepwise fashion (Scheme 69). The first step was the displacement of the primary tosylate **110** with lithium acetylide ethylene diamine complex. Initially, this displacement proceeded with very low (<40%) yields. After considerable modifications

to the reaction protocol it was found that neat addition of tosylate **110** to a 2M lithium acetylide complex in DMSO,[69] followed by stirring overnight at room temperature afforded the desired terminal alkyne **111** in 82% yield.[60] The last three carbons of fragment **F** were installed via indium mediated Markovnikov addition of an allyl group to the terminal alkyne **111**.[70] This reaction proceeded efficiently under sonication to afford skipped diene **112**. Also it was found that freshly cut indium rod gave better results than other indium metal sources (shot, dust, etc.). Thus, with this two step process, we were able to install the final carbons of fragment **F** and one of the monosubstituted alkenes to be used later in the RCM.

Scheme 70. Deprotection and Sharpless Epoxidation of **112**

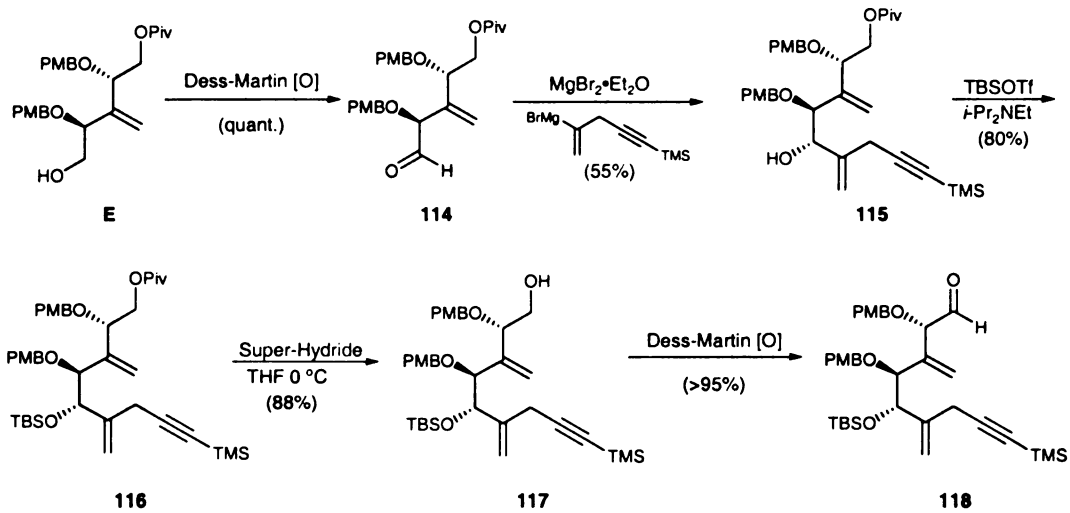


The TBS protecting group of **112** was removed with TBAF buffered with half of an equivalent of acetic acid (Scheme 70). This reaction was slow and typically did not go to completion, but the starting material could be easily recovered and resubjected to the reaction conditions. Attempts to drive the reaction by not using the buffer resulted in a complex mixture of products, none of which were the desired allylic alcohol **113**. The subsequent Sharpless asymmetric epoxidation proceeded in a stereomatched case to install the epoxide with excellent diasteroselectivity to afford fragment **F** as the only observable isomer.

4.3. Coupling and Elaboration of Fragments

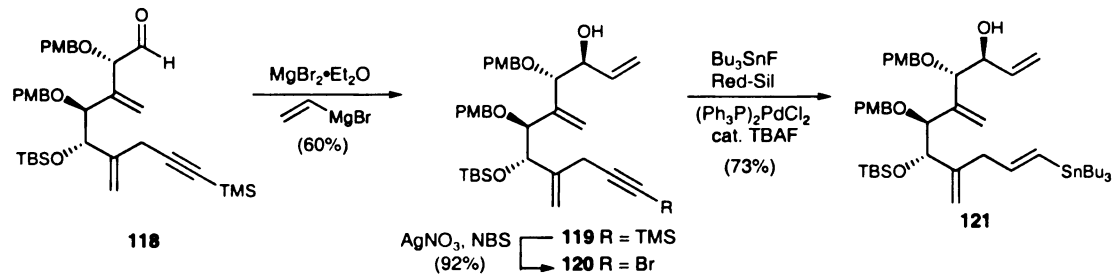
With all five fragments in hand (**B** and **D** were previously described), the coupling and elaboration of these fragments could commence. The first coupling to be explored was that of fragments **E** and **B**, and was based on the successful synthesis of **AB**.

Scheme 71: Coupling of Fragments **E** and **B**



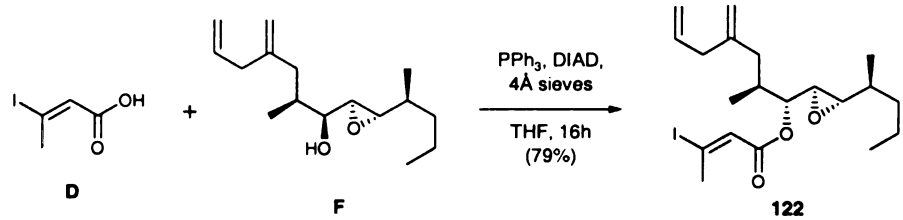
Dess-Martin oxidation of **E** afforded the pseudosymmetric aldehyde **114**. This intermediate afforded the option to initially install either the commercially available vinyl-MgBr or fragment **B**. In theory, it is preferable to install the vinyl-MgBr first and our synthetic material late in the synthesis. However, in practice, chelation controlled addition of the Grignard reagent derived from **B** proved best, affording **115** as a single diastereomer. In contrast, the addition of vinyl-MgBr to the same aldehyde gave a mixture of products. The resultant secondary alcohol from the addition of **B** was protected as a TBS ether. Reduction of the pivalate with Super-Hydride® afforded **117**. Oxidation of the primary alcohol with the Dess-Martin periodane afforded **118**.

Scheme 72. Preparation of Vinylstannane **121**



Chelation controlled addition of vinyl-MgBr to **118** proved reasonably effective, affording a 7:1 mixture of epimers at what will become C12 in the final target. Because placement of a bromide at the terminal position of an alkyne provides a good regiocontrol handle[71] for Pd^0 mediated hydrostannations, the acetylinc TMS group was exchanged for a bromide by reaction with NBS in the presence of silver nitrate to afford **120**. The Bu_3SnH for the hydrostannations was generated in situ[37] from Bu_3SnF, catalytic TBAF, and Red-Sil (silane capped silica gel).[72] Compared to the direct employment of Bu_3SnH, the in situ method afforded **121** in superior yield and geometric purity. Furthermore, all spent reagents were salts, which could be removed by passage though a plug of silica gel, minimizing destannylation by silica gel.[73]

Scheme 73. Mitsunobu Esterification of Fragment **F**

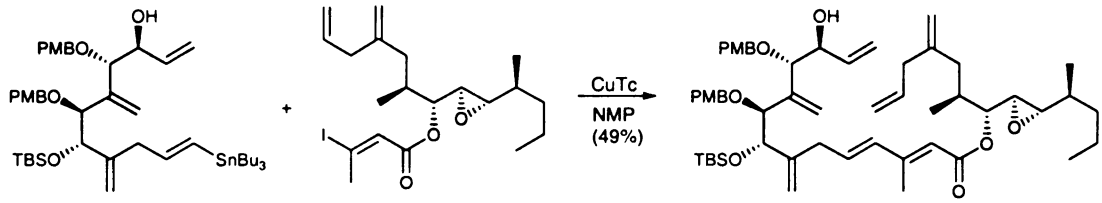


The Mitsunobu esterification of iodo acid **D** and fragment **F** initially proved inefficient affording only 70% conversion.[60] This is likely due to the low nucleophilicity of the conjugated iodo acid. Fortunately, the addition of 4Å molecular sieves helped to drive the reaction to completion, and leading to a 79% yield of the desired ester (Scheme

73). This coupling completes the right half of the molecule and sets the C19 stereocenter to what is proposed for the final target, **1**.[74]

4.4. Final Coupling and Elaboration

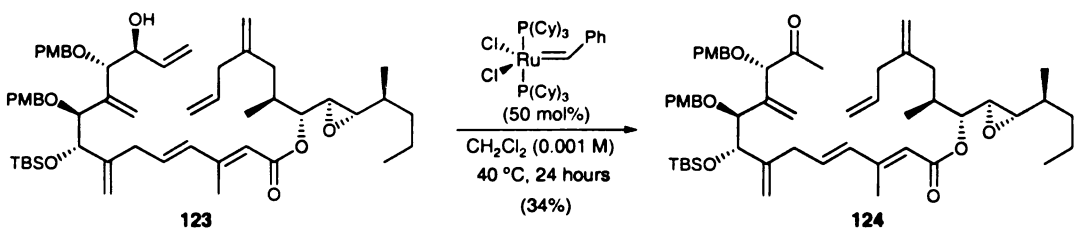
Scheme 74. Stille Coupling of **121** and **122**



121 **122** **123**

With the two halves, **121** and **122**, of amphidinolide A complete, we were now ready to investigate the final intermolecular union. Standard Stille coupling conditions (Pd_2dba_3, $AsPh_3$, NMP, 45 °C, 18 hours) worked fine, affording **123** in 60% yield. However, it was found that by utilizing stoichiometric amounts of Liebsekind's Cu(I) thiophene carboxylate (CuTc), the reaction afforded **123** with the same yield, but in only 30 minutes.

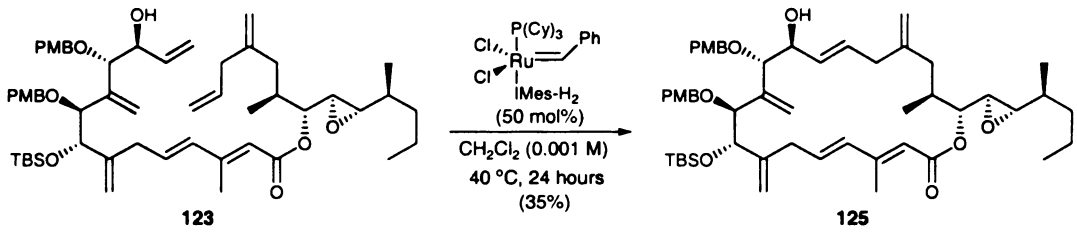
Scheme 75. Initial RCM of **123**



123 **124**

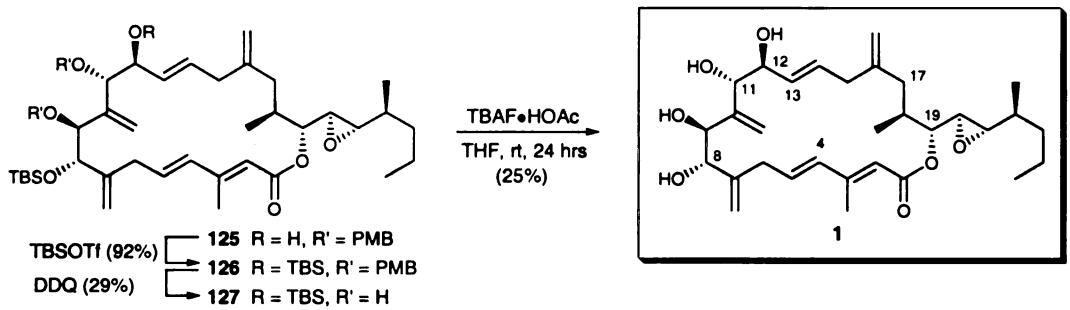
Following isolation of diene **123**, the key RCM reaction was investigated (Scheme 75). Initially, Grubbs' first generation RCM catalyst was used under the premise that it would selectively react with the monosubstituted olefins. When **123** was subjected to the RCM conditions, only the truncated[75] ketone product **124** and starting material were recovered. All attempts to modify the reaction conditions[17] (solvent, temperature, chelating agent additives, etc.) failed to afford the desired macrocycle.

Scheme 76. RCM of **123** with Imidazolium Catalyst



Fortunately, use of the imidazolium based catalyst system eliminated the truncation problem (Scheme 76), affording the desired macrocycle **125**.[55b] Though metathesis occurred in only moderate (35%) yield, no other RCM products were detected and only the *E* isomer of the C13-C14 alkene was observed. The analysis of the spectral data of **125** was complicated because it exists as a mixture of conformers.[76] Variable temperature NMR proved the molecule exists as a mixture of conformers and has the C13-C14 *E* alkene geometry.

Scheme 77. Final Deprotection



With the ring system closed, all that remained to complete the total synthesis of **1** was the removal of the protecting groups. Attempts at removing the PMB groups from **125** resulted in the formation of PMB-derived acetals with the C12 hydroxyl. To prevent this, the C12 hydroxyl was first protected as a TBS ether (Scheme 77), followed by removal of the PMB groups by buffered DDQ oxidation, affording **127**.[76] The two TBS groups were then removed with TBAF buffered with acetic acid to afford the proposed structure of amphidinolide A (**1**).

Unfortunately, when the spectral data of **1** was compared to the data available for the natural product there were significant discrepancies. First, the optical rotation of our synthetic material (-56) differed in both sign and magnitude from the natural product (+46). Major discrepancies were also seen in the ^{1}H NMR data primarily, in the chemical shifts of protons at C4, C8, C9, C11, C13, C17, and C19.

Assigning the structure of **1** based on spectral data alone is difficult at best. The difference between the synthetic and natural product could be the result of a several factors. While it is possible that a trace contaminant could be interfering with the NMR data causing the shifts, this is unlikely since the magnitude and more importantly the sign of the optical rotation do not match the natural product. Also, while we do have strong literature precedent and spectroscopic evidence for our structural assignments, the difference between the synthetic and natural products could be the result of a misassignment made during our synthesis or during isolation of the natural material.[77] Therefore, we set out to (a) confirm the structure of our material by single crystal analysis of advanced intermediates and (b) synthetically explore the possibility that Kobayashi misinterpreted his spectral data.

4.5. Synthesis of Analogs

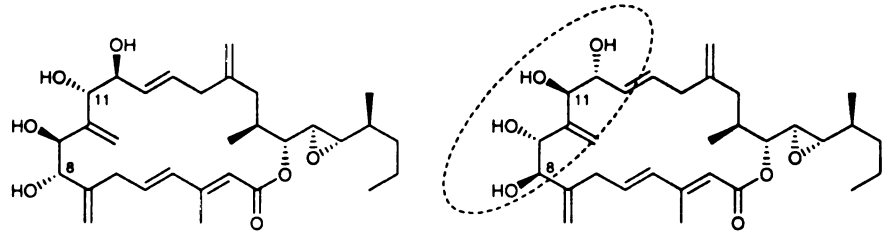
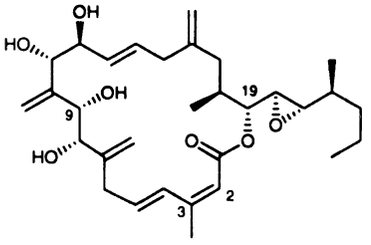


Figure 3. Possible Structure of Natural Amphidinolide A

Because the two stereochemical containing regions of **1** (C8-C12 and C18-C22) are separated in the molecule, we hypothesized Kobayashi's original correlation between these two halves may have been in error. We constructed **128**, which is epimeric to **1** at C8, C9, C11, and C12. The route used for the synthesis of **128** was identical to the approach to **1**, except that L-arabitol was used instead of the D sugar.[17] If Kobayashi's correlation between the two halves of the molecule was in error **128** would either be natural amphidinolide A or its enatiomer. In either case the NMR data should correlate and the optical rotation should be identical or differ only in sign. In fact, ^{1}H NMR and optical rotation data both did not agree with Kobayashi's data, indicating **128** is also a diastereomer of the natural product.



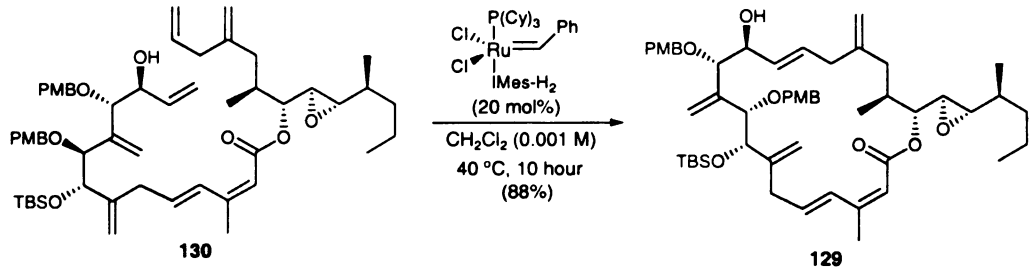
129

Figure 4. "Z amphidinolide A"

Another analog generated during the course of developing the synthesis of **1** was "C2-C3 *Z*-amphidinolide A" (**129**). This analog was also constructed by the same route, only changing the geometry of fragment **D**.[17] While ^{1}H NMR analysis clearly indicated that **129** is a diastereomer of the natural product, it proved an interesting exercise with regards to the RCM step as illustrated in Scheme 78. Whereas the *E* analogs only proceeded with ~35% with a 50% catalyst load, the *Z* analog proceeded with 88% yield with a 20% catalyst load. The synthesis of **129** highlights the potential of an RCM approach to polyene macrocycles. However, it also illustrates that further study is needed

to correlate the diene structure and/or conformation with the efficiency at which the RCM proceeds.[78]

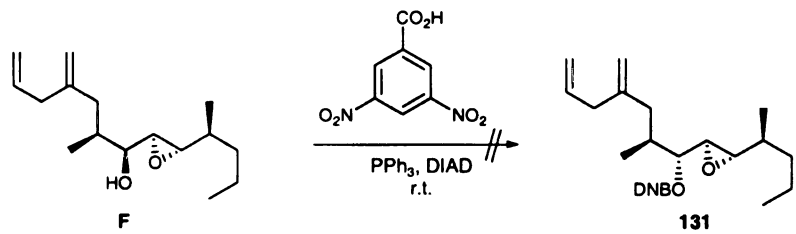
Scheme 78. RCM of *Z* Analog



4.6. Synthesis of Substrates for X-ray Analysis

While the above analogs were made to test the validity of the proposed structure, several attempts were made to synthesize a crystalline derivative of fragment **F**. An X-ray structure would substantiate the stereochemical assignments. The first derivative investigated was a 3,5-dinitrobenzoate (DNB) ester. An ester was chosen because a Mitsunobu esterification could be used with 3,5-dintirobenzoic acid. This would implement the same inversion during the derivative formation as took place during the coupling of fragments **D** and **F** (Scheme 73), thus allowing for the inversion stereochemical result to be confirmed.

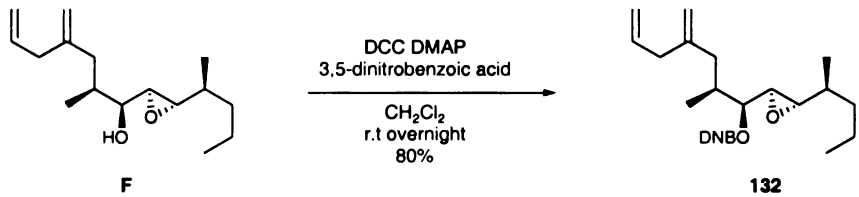
Scheme 79. Attempted Synthesis of DNB Ester **131**



Application of esterification conditions used similar to those used for the coupling of **D** and **F** failed to afford the desired product after 16 hours at room temperature. Since 3,5-dinitrobenzoic acid is deactivated like fragment **D** (see page 62), it was expected the

reaction may be sluggish and may not go to completion. The reaction was repeated with stirring for 6 days. Upon workup and analysis none of the desired product could be detected. It appears that the combination of fragment **F** and the 3,5-dintirobenzoic acid is not amenable to the Mitsunobu protocol.

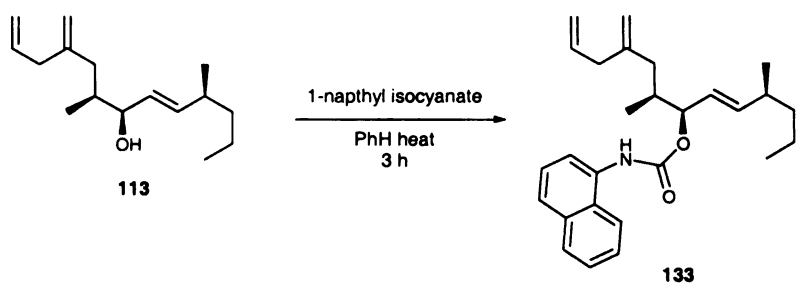
Scheme 80. DCC Route to **132**



F **132**

Although the Mitsunobu protocol failed to afford the desired ester **131**, it was hoped that a 3,5-dinitrobenozate would provide a crystalline derivative. To that end, a DCC/DMAP coupling of 3,5-dinitrobenzoic acid and fragment **F** afforded derivative **132**. While this derivative would not provide information concerning the Mitsunobu esterification it would still confirm the other stereochemical assignments. Unfortunately **132** is a low melting solid which only solidified after being placed under vacuum and frozen. Numerous attempts to crystallize that material from various solvents (ethyl acetate, benzene, ethanol, carbon tetrachloride, etc.) and solvent systems proved fruitless.

Scheme 81. Synthesis of Carbamate **133**



113 **133**

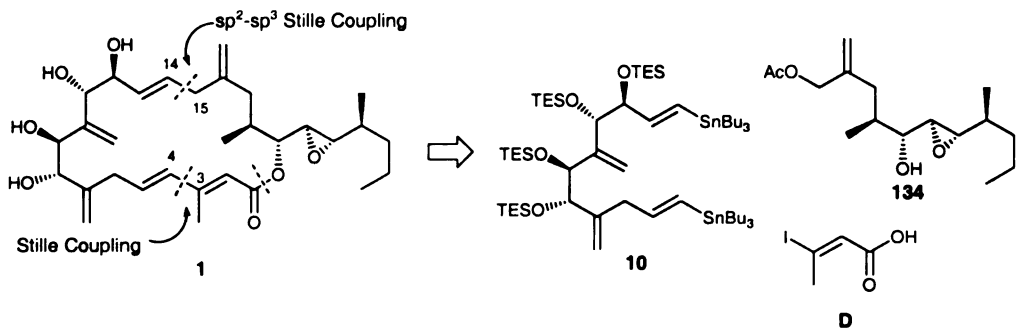
In another attempt to form a crystalline derivative. Alcohol **113** was heated in the presence of 1-napthyl isocyanate for 3 hours in benzene.[79] It was hoped that this functionality would sufficiently order the system to create a crystalline solid. Upon

workup and purification by flash chromatography, the derivative **133** was isolated. After several weeks in the freezer the once oily material had solidified, however there were no obvious crystals in the solid mass that had formed. Repeated attempts to recrystallize this material failed to afford suitable crystals.

4.7. Comparison to Pattenden Synthesis

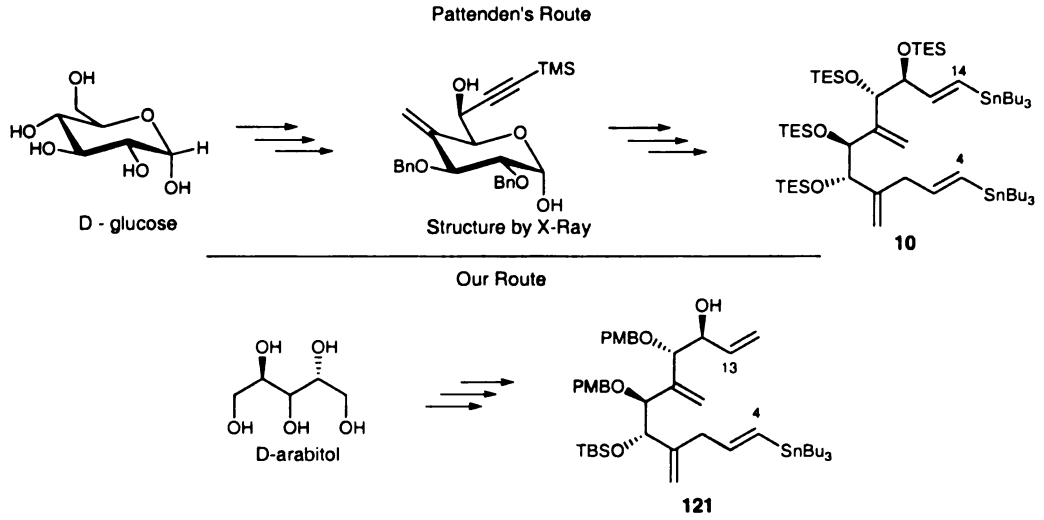
After the failure of the above attempts to generate a derivative for single crystal analysis, more elaborate derivations were being planned to allow for the introduction of multiple ester and/or carbamate functionalities. Before those studies began, Pattenden and Lam published their total synthesis of the presumed structure of amphidinolide A.[11]

Scheme 82. Pattenden's Retrosynthesis of 1



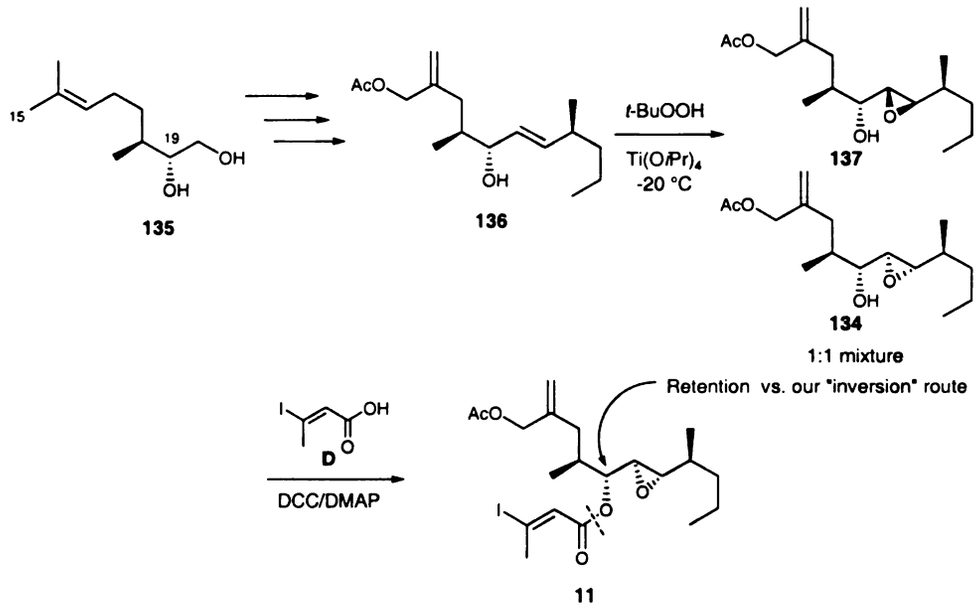
While Pattenden's route differed from our own in many areas, there were similarities between the two routes. In particular, Pattenden utilizes a Stille coupling between C3 and C4 to construct the lower conjugated diene moiety. The vinyl iodide partner for the Stille coupling comes from the same subunit in both synthetic routes, fragment **D**. Our two routes differ in several regards including the final ring-closing step. Whereas our route utilizes an RCM between C13 and C14, Pattenden closes the ring with his own sp^2-sp^3 coupling method.[10a]

Scheme 83. Comparison of routes to tetraol portion of 1



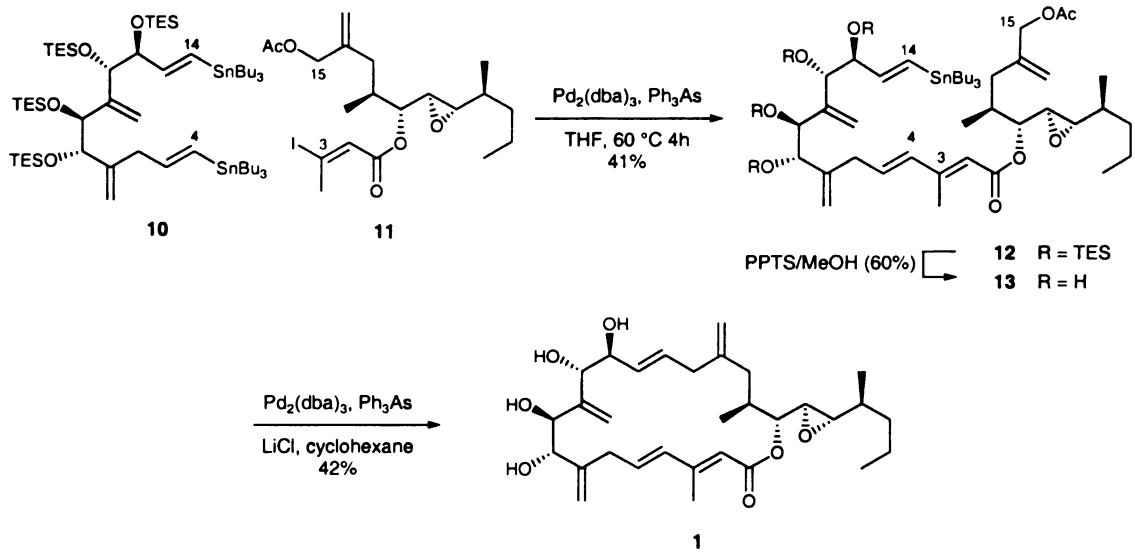
A comparison of the routes toward the tetraol portion of the molecule shows the common feature of using a sugar as the chiral starting material for the tetraol. However, Pattenden started from D-glucose and after several steps installed the TMS acetylene group via a chelation controlled addition to what will become C12 in the final target. Pattenden was able to obtain a single crystal analysis of this product to confirm the stereochemistry at these hydroxyl groups. In terms of protective group strategy, we used two protecting groups (PMB and TBS) while Pattenden used only TES groups to protect all 4 hydroxyls. Pattenden's protecting group strategy proved to be a superior choice when these groups had to be removed.

Scheme 84. Summary of Pattenden's route to Right Half of 1



In our route to the right half of **1,** we began from the sidechain moiety and worked inward to what eventually became the upper skipped diene of **1**. Pattenden started from the known diol **135**, which represents the C15-C20 portion of **1**. The rest of the sidechain was constructed outward and after several manipulations afforded **136** which is analogous to our fragment **F.** In contract to our controlled introduction of the epoxide, Pattenden used a non-stereoselective epoxidation to afford a 1:1 mixture of **134** and **137**. Since the stereochemistry required for one is the *erythro*, it is possible they originally used a Sharpless asymmetric epoxidation and that resulted in a poor mixture of diastereomers. Fortunately, these diastereomers were separable. Thus after taking a 50% loss in material, carbodimide coupling with iodo-acid **D** afforded the completed right half of the molecule (**11**).

Scheme 85. Pattenden's Synthesis of 1



With both halves of the final target in hand, Pattenden coupled the two subunits via a standard sp^2-sp^2 Stille coupling between C3 and C4 (Scheme 85). At this point they were able to remove the TES protecting groups under acidic conditions. Finally, the macrocycle was closed with a Stille like sp^2-sp^3 coupling between C14 and C15 affording **1**.

When Pattenden and co-workers compared their spectral and optical data Kobayashi's data for the natural product it did not match. Pattenden's conclusion was that **1** is a diastereomer of the natural product. They also completed the synthesis of an analog of **1** that had the opposite stereochemistry at the C20-C21 epoxide, using the **134** isomer from the epoxidation. This analog also did not match the data for the natural product.

Comparison of Pattenden's spectral and optical data with our own material confirmed both groups made the same structure. Pattenden's route sufficiently differs from our own approach in that (a) their synthesis of the tetraol region starts with D-glucose and employs different protective groups (b) their esterification does not invert

C19, (c) they close the macrocycle via Pattenden's sp^2-sp^3 coupling method. Because of these differences the probability of a common erroneous step corrupting the spectral and optical data in exactly the same manner is negligible. Thus, despite the lack of crystallographic data, the two independent routes to **1** affirmed both group's assignment of their synthetic materials as being identical to the proposed amphidinolide A, and confirms the proposed structure of amphidinolide A needs to be revised.

Chapter 5. Synthesis of Tetra-Ortho Substituted Biaryls

Numerous cross-couplings were studied during the total synthesis of proposed structure of amphidinolide A (**1**). The experience gained during these studies resulted in a collaboration with Sue Masten (MSU Department of Civil and Environmental Engineering) and her research on Polyaromatic hydrocarbons (PAHs). PAHs are produced during the combustion of fossil fuels and also exist in many petroleum waste products. Due to years of improper disposal, PAH contamination has become a major environmental concern in the soil and groundwater systems. Removal of these compounds during remediation of waste sites has become a priority as most are classified as either carcinogenic or potentially carcinogenic.[80] One technology which has been developed for the removal of PAHs, such as pyrene, is to use ozone to chemically degrade[80a] pyrene to afford compounds which are more amenable to biodegradation than the hydrophobic parent compound. Such remediation methods are typically monitored for completion by the disappearance of the PAH. Unfortunately, as determined by Masten and co-workers determined that initial degradation products from ozonolysis are in fact more toxic than the parent PAH. This increased toxicity is further complicated because ozonolysis under aqueous conditions affords a complex mixture of products.

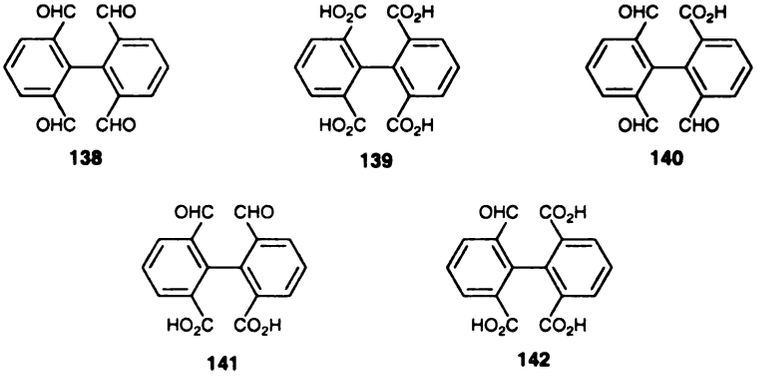


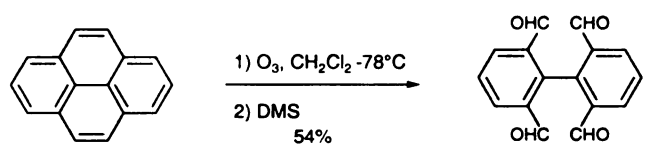
Figure 5. Tetra-Ortho Substituted Biaryls

Masten and her group have exposed pyrene to ozonolysis in acetonitrile/H_2O, which afforded a complex mixture of products. They were able to identify many of the compounds by a combination of HPLC and mass spectroscopy, but were unable to obtain samples of sufficient purity for use in their toxicological studies. A better understanding of the individual degradation products would allow for the development of better remediation techniques and for developing improved monitoring techniques that will indicate when the system has been rendered nontoxic. While many compounds were identified from the Masten reaction mixture, the five tetra-*ortho*-substituted biphenyls shown in Figure 5 were of particular interest. Aside from providing material for toxicological studies, a synthetic route to **140-142** via a cross coupling to form the biaryl linkage would be useful. At the time this project began there were no synthetically useful methods for generating tetra-ortho substituted biaryls via a cross coupling. If a protocol could be developed to access these unsymmetrical functionalized tetra-ortho substituted biaryls, it would have applications in other areas of organic synthesis.

5.1. Symmetrical Tetra–Ortho Substituted Biaryls 138 and 139

Both the tetraaldehye (**138**)[81] and tetracaboxylic acid (**139**)[82] have been previously reported, however their preparations were poorly described and lacked characterization data. As such, modified procedures were developed and the compounds fully characterized to ensure the fidelity of the toxicological studies.

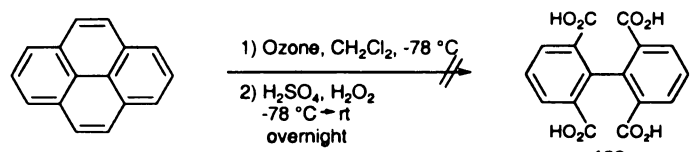
Scheme 86. Synthesis of Biphenyl-2,2',6,6'-tetracarbaldehyde (**138**)



Pyrene **138**

Compound **138** was synthesized by ozonolysis of pyrene followed by reductive workup with dimethyl sulfide (Scheme 86). Flash chromatography afforded the desired product in 54% yield and an analytical sample was afforded by recrystallization from water. All spectral and microanalysis data were found to be in accord with the desired product.

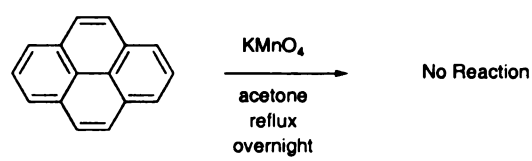
Scheme 87. Attempted Synthesis of Biphenyl-2,2',6,6'-tetracarboxylic Acid (**139**)



139

Scheme 87 shows an attempt at a known literature preparation of tetracarboxylic acid **139**. In this procedure the ozonolysis of pyrene was followed by an acidic oxidative workup.[82a] However, this reaction failed to afford the desired product. Product data from this report are limited, consisting of a decomposition temperature (>400 °C), and recrystallization solvent. Our attempt to reproduce this reaction gave a product that did not recrystallize from hot water and melted below 200 °C.

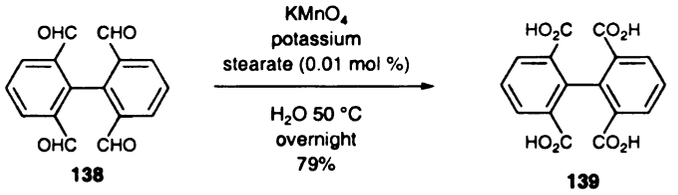
Scheme 88. Attempted $KMnO_4$ Oxidation of Pyrene



It has also been shown in the literature that permanganate can be used to oxidize double bonds similar to that found **139**.[83] However, application of $KMnO_4$ in refluxing acetone (Scheme 88) failed to form **139**, affording only unreacted pyrene. Since these two methods failed to afford the desired product it was determined the best route would

be a two-step procedure, first generating tetra-aldehyde **138** and then oxidizing this compound with permanganate to the tetra-acid.

Scheme 89. $KMnO_4$ oxidation of **138**

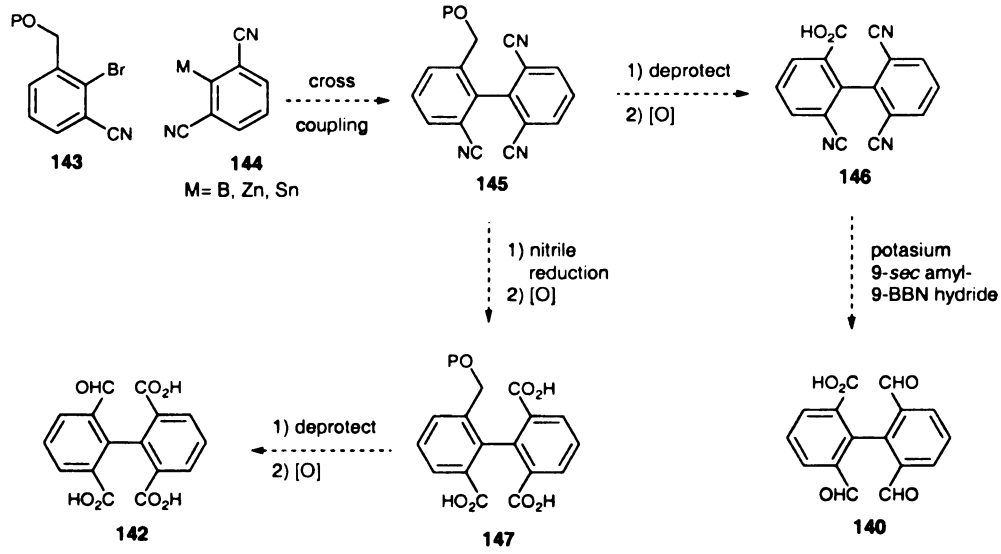


138 **139**

The tetra-aldehyde was formed using the reductive ozonolysis conditions previously described. Application of a permanganate oxidation in the presence of a surfactant afforded the desired product in 79% yield.[84] Elemental analysis and direct probe mass spectroscopy indicated the desired molecular formula. The UV spectrum was red shifted by 20 nm possibly indicating that the molecule was isolated as a salt.[82b] This was proven not to be the case as the use of acidic ethanol as the solvent did not change the spectrum. Also the NMR of this compound matched a report concerning the synthesis of the molecule via a Ruthenium based oxidation route.[82c] The tetraaldehyde (**138**) and tetracarboxylic acid (**139**) were given to the Masten group for toxicological testing and use in their experiments as standards for identification of these compounds. With the completion of the symmetrical biaryls attention was turned to the synthesis of the other three required biaryls.

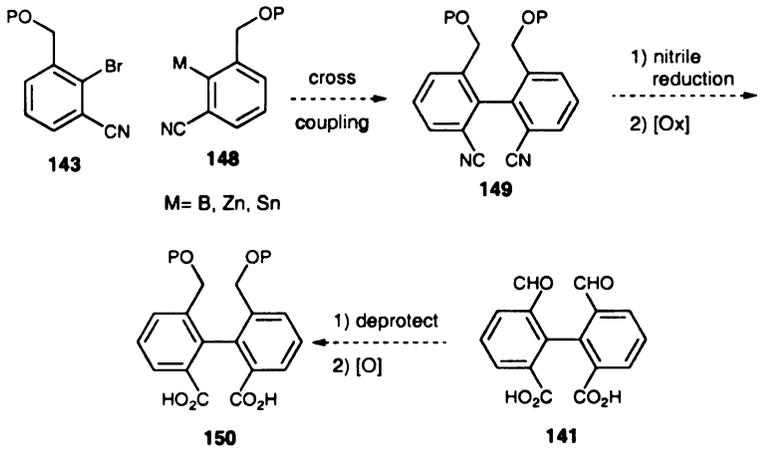
5.2. Aryl Nitrile Route to 140-142

Scheme 90. Proposed Synthesis of **140** and **142**



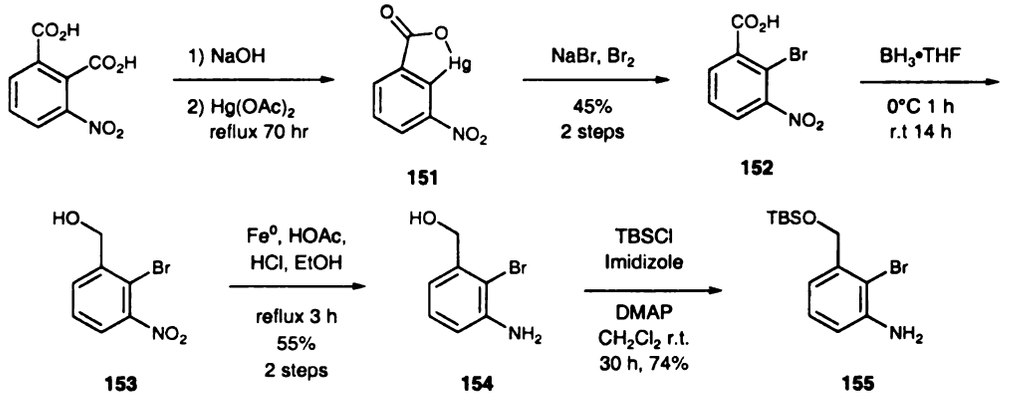
Our initial route to **140** and **142** is outlined in Scheme 90. The key step in this synthesis was the cross-coupling of subunits **143** and **144.** These two subunits were designed to have 2 different synthetic handles, a protected benzylic alcohol and nitrile groups that are masked aldehydes. Since the cross-coupling of such stericly hindered substrates was unknown, the cross-coupling could be via a Stille coupling (M=Sn), a Suzuki (M=Boron), or a Negishi reaction (M=Zn). Once a successful coupling protocol was developed, deprotection of the benzylic alcohol in **145** followed by oxidation to the carboxylic acid would afford **146**. Use of potassium 9-sec-amyl-9-BBN hydride would then reduce the aromatic nitriles in the presence of a carboxylic acid to afford **140**.[85] Returning to the common intermediate **145**, the reduction of the three nitrile moieties followed by oxidation to the tricarboxylic would afford **147**. Finally deprotection and oxidation to the aldehyde would afford **142**.

Scheme 91. Proposed Synthesis of **141**



Our route to **141**, outlined in Scheme 91, is very similar to the route for **140** and **142**. Cross-coupling between **143** and **148**, which would be derived from **143** by halogen metal exchange, would afford intermediate **149**. Because both coupling partners have the same substitution pattern, a homo coupling of either **143** or **148** would also afford **149**. Reduction of the nitriles would be followed by the oxidation to the dicarboxylic acid **150**. Finally deprotection the benzylic alcohols and oxidation would afford the final target, **141**.

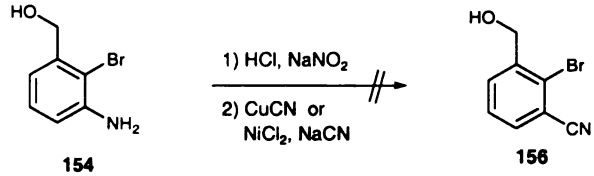
Scheme 92. Synthesis of **155**



The routes proposed for **140-142** each require the common cross-coupling partner **143**. Though not a known compound, it was believed that a Sandmeyer reaction on the known[86] 3-amino-2-bromo benzyl alcohol **154** would install the desired nitrile.

Following a literature procedure[87] for the synthesis of **152,** the nitro benzoic acid was afforded in a modest 45% yield from commercially available 3-nitropthalic acid. Borane THF complex efficiently reduced the benzoic acid to afford **153.**[86] Crude **153** was reduced with Fe^0 under acidic conditions to afford the desired amino alcohol **154.**[86] Finally protection of alcohol **154** as a TBS silyl either afforded **155.** While **155** was not the target (as a TBS group will not survive the acidic Sandmeyer conditions) it was a fully characterized compound in the literature and this could be used to confirm our synthesis.[86]

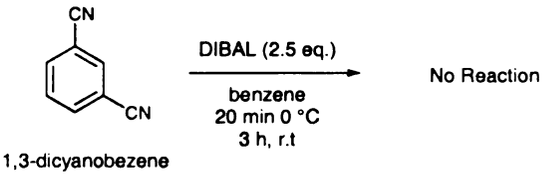
Scheme 93. Attempted Sandmeyer Reaction with **154**



154 **156**

With **154** in hand, numerous attempts were made to install the nitrile group (Scheme 93). In all cases the diazonium formation was performed with HCl and sodium nitrite. This was followed by the addition of CuCN, which should have installed the desired nitrile group.[88] Unfortunately this only resulted in the loss of the starting material and a complex mixture of compounds. Several more attempts at the Sandmeyer were made. All of the reagents were replaced and/or purified at various stages but to no avail. Changing the source of metal nitrile to $NiCl_2$ and sodium cyanide also did not afford the desired product.[89] With the Sandmeyer reaction failing to install the necessary nitrile group, an alternative pathway needed to be investigated.

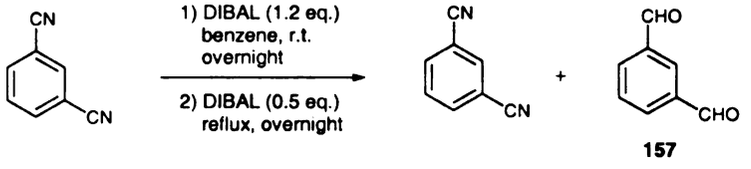
Scheme 94. Attempted Mono-reduction of 1,3-Dicyanobenzene



1,3-dicyanobezene

Since the nitrile group could not be installed with the bromine and hydroxymethyl groups already present, a route was devised where the nitrile would be present from the beginning of the synthesis. This route required the mono-reduction of a 2-bromo-1,3-dicyano benzene to install an aldehyde, which could then be reduced the alcohol to afford **154**. To test the viability of the mono-reduction 1,3-dicyanobenzene was subjected to DIBAL reduction in benzene. At room temperature there was no reaction observed after 16 hours (Scheme 94).

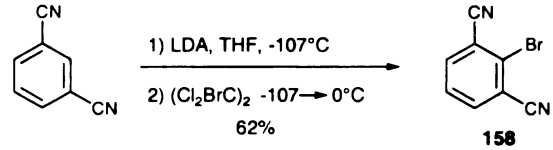
Scheme 95. Attempted Mono-reduction of 1,3-Dicyanobenzene II



157

The reaction was repeated with 1.2 equivalents of DIBAL at room temperature overnight, and once again no reaction was observed. Another 0.5 equivalents of DIBAL were added and the reaction heated to reflux for ~16 hours. With heating there was a reaction, however by both GC/MS and crude ^{1}H NMR the only product observed other than recovered starting material was a small amount of dialdehyde **157**. Since no mono-reduced product was detected, it was likely the mono-reduced product was more reactive than the starting 1,3-dicyanobenzene, thus it reduced to the dialdehyde without the mono-reduced product accumulating.

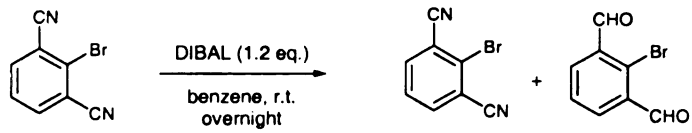
Scheme 96. Synthesis of **158**



158

In an effort to perturb the system in favor the production of the mono-reduced, bromide **158** was made by ortholithiation (Scheme 96).[90] LDA was freshly prepared from diisopropyl amine and *n*-BuLi. After cooling the LDA solution to –107 °C (isooctane/liquid nitrogen bath) a solution of 1,3-dicyanobenzene was added dropwise. This was followed 30 minutes later by the addition of a solution of $(Cl_2BrC)_2$. The reaction was then allowed to slowly warm to room temperature, and after workup and isolation afforded **158** in 62% yield.

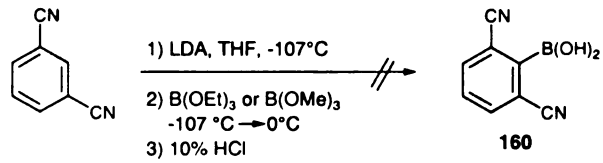
Scheme 97. Attempted Mono-reduction of **158**



158 **158** **159**

With bromide **158** in hand, the reduction was repeated using 1.2 equivalents of DIBAL and stirred overnight. Unlike the 1,3-dicyanobenzene case, **158** did show some product formation at room temperature. Unfortunately, GC/MS analysis indicated only starting material and doubly reduced product (**159**).

Scheme 98. Attempted Synthesis of Boronic Acid **160**.

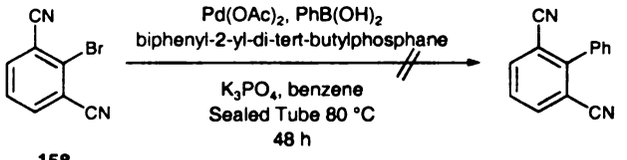


160

Since we had no viable route to the proposed coupling partner **143** a redesign of the route was required. This conclusion was furthered by our failure to make boronic acid **160** (Scheme 98). In this reaction 1,3-dicyanobenzene was ortholithiated at the 2

position and then quenched by the addition of either triethyl or trimethyl borate. Acid workup should have freed the boronic acid. However, the reaction afforded only a complex mixture of products of which appreciable amounts of starting 1,3-dicyano benzene was present. Since the LDA protocol worked on past substrates (**158**), it was believed that this position is too hindered for either triethyoxyborate or trimethoxyborate to be successfully captured. As a related capture with tributyltin chloride also seemed unlikely, it appeared that forming either metal species for a Suzuki or Stille coupling would not be possible. This precluded 1,3-dicyanobezene from being used as the nucleophile in either cross-coupling methodology.

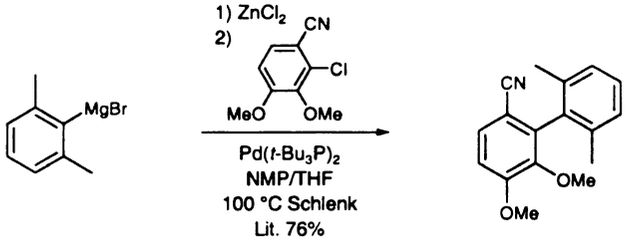
Scheme 99. Attempted Suzuki Coupling with **158**



Although it was apparent that we could not generate a nucleophile (metal species) of 1,3-dicyanobenzene for use in one of the cross-coupling methods, it remained to be seen if **158** could be used as an electrophile. After a survey of the literature to determine the cross-coupling protocol which has the highest chance for success, it was determined a Suzuki coupling was the likeliest candidate.[91] Recent literature suggests that the best catalyst systems available for Suzuki couplings, would be Buchwald's ligand system (biphenyl-2-yl-di-*tert*-butylphosphane/K_3PO_4).[91b] Several attempts were made to couple **158** with commercially available phenyl boronic acid (Scheme 99). The reactions were run in sealed tubes that were purged to preclude oxygen, which is known to interfere with Suzuki couplings. Unfortunately, GC/MS analysis of the crude reaction mixture did not indicate the presence of the desired coupling product, but only a considerable amount of

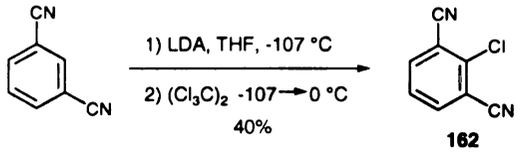
unreacted starting material. Repeating the reaction at 115 °C afforded similar results, with no coupling product detected at either 24 or 48 hours.

Scheme 100. Fu's Tetra-ortho Substituted Biaryls Synthesis[92]



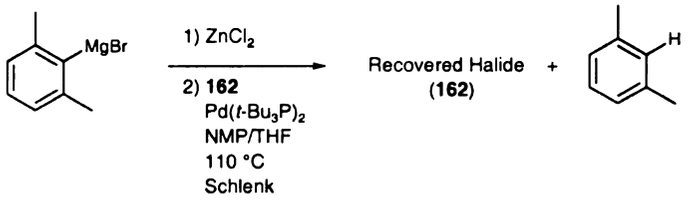
As we were about to abandon the synthetic routes proposed in Scheme 90 and Scheme 91, Fu published a paper on Negishi couplings of aryl chlorides and aryl Zn species.[92] What made this system so appealing was that Fu was able to construct a tetra-ortho substituted biaryl with a nitrile group in the ortho position (Scheme 100). Also this reaction used the less active aryl chloride, so it appeared to be a powerful method worth exploring.

Scheme 101. Synthesis of **162**



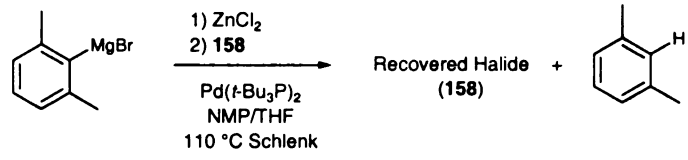
As Fu's reaction protocol utilizes aryl chlorides, the 2,6-cyanochlorobenzene **162** was made via the same ortho-lithiation method used for the synthesis of the corresponding bromide **158**. After recrystallization, chloride **162** was isolated in 40% yield.

Scheme 102. Attempted Negishi Coupling With **162**



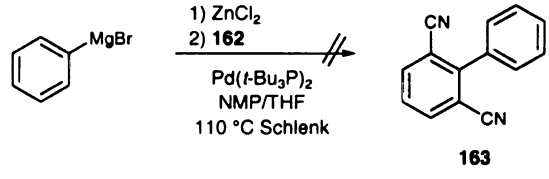
The requisite Zn species was made from the reaction of 2,6-dimethylphenyl magnesium bromide and commercially available $ZnCl_2$ in an argon purged Schlenk tube. Then *N*-methylpyrolidnone (NMP) was added followed by the addition of neat **162** via the Teflon valved sidearm. The Schlenk tube was purged for 10 minutes then sealed and placed in a 110 °C oil bath. After 20 hours, an aliquot was removed via syringe and analyzed by GC/MS. This analysis indicated only the presence of the starting halide and *m*-xylene from the protonation of Zn species. This reaction was repeated several times with lab prepared catalyst, in situ generated catalyst ($Pd_2(dba)_3$/ P(*t*-Bu)$_3$), or commercial catalyst.[93] Each time the reaction was monitored and showed no formation of the desired product over a period of several days.

Scheme 103. Attempted Negishi Coupling with **158**



In hopes that bromide **158** would be more reactive than chloride **162**, the reaction was repeated using **158**. These experiments also failed to deliver the desired product.

Scheme 104. Attempted Synthesis of **163**



163

It is possible that a system with two cyano groups and two methyl groups is too stericly hindered to undergo Negishi coupling. Although, Fu did form a single tetra-ortho substituted molecule, the full steric limits of this reaction were unclear. To test if it was the combined steric bulk stopping the reaction or if it was just that dicyano species are not amenable to the coupling, the Negishi coupling shown in Scheme 104 was attempted.

This reaction was identical to previous attempts and utilized the commercially prepared catalyst. After 24 hours the GC/MS showed predominantly unreacted starting material and biphenyl from the homo coupling of the unhindered Zn species.

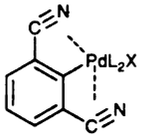
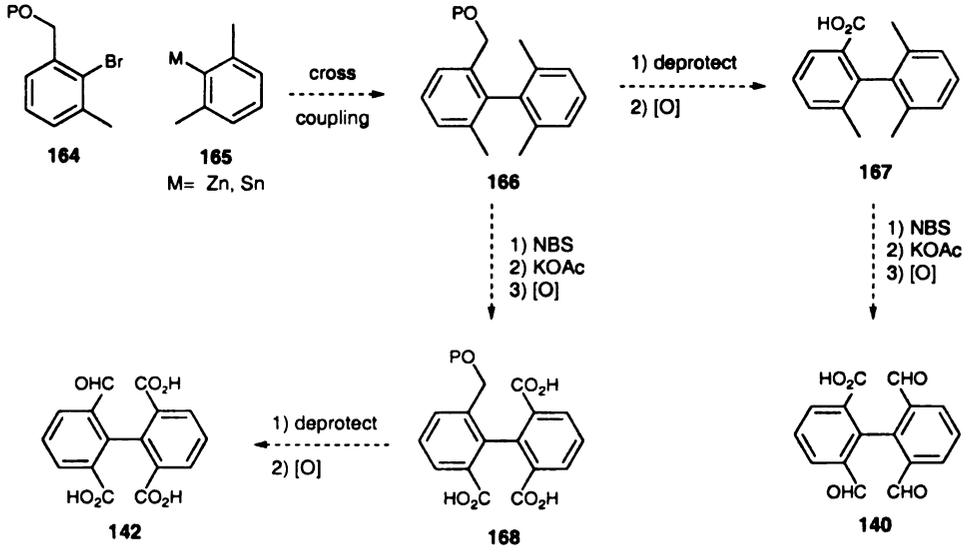


Figure 6. Possible Palladium Complex

Since electrophiles, **158** and **162**, failed to afford the desired coupling products it may be that the electronics of the dicyano system are not amenable to the catalytic cycle. Either the palladium cannot insert into the system or once the Pd inserts it is stabilized by the coordination of the two cyano groups (Figure 6) and does not undergo transmetallation. In either case these substrates were not amenable to either the Suzuki reaction or the promising Fu conditions for the Negishi reaction. Coupled with the failure of the Sandmeyer reaction to afford the intermediate **t1** the entire strategy to this projected had to be redesigned.

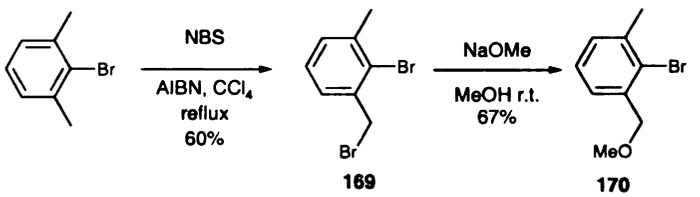
5.3. Second Generation Route to 140-142

Scheme 105. Redesigned route to **140** and **142**



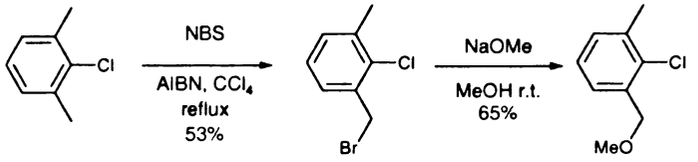
Since the cyano groups were problematic, the second-generation route to biaryls compounds went for much simpler synthetic handles, methyl groups. The use of methyl groups should not adversely affect the electronics of the coupling system, nor should they coordinate to palladium and interfere with the transmeallation step of the cross-coupling (Figure 6). In this route the desymmetrized 2-bromo-*m*-xylene derivative **164** would be coupled with the either the 2,6-dimethylphenyl Zn species used in the previous Negishi couplings, or a analogously prepared trialkyl tin derivative for a Stille coupling. Once coupled to afford **166**, the benzyl alcohol would be deprotected and oxidized to carboxylic acid **167**. NBS would then brominate the three remaining methyl groups. After acetate displacement of the bromides and hydrolysis, the resulting triol would be oxidized to afford **140**. Along an analogous pathway the same **166** intermediate could be brominated. Displacement and hydrolysis would be followed by oxidation to the tricarboxylic acid **168**. Subsequent deprotection and oxidation of the remaining alcohol would afford **142**.

Scheme 106. Synthesis of Aryl Bromide **170**



To gain quick access to a set of compounds for investigating the revised coupling strategy, a simple starting halide was chosen. Following a literature preparation, 2-bromo-*m*-xylene was brominated using a NBS free-radical bromination in carbon tetrachloride.[94] The benzylic bromide was then displaced with sodium methoxide to afford the desired oxygenated *m*-xylene derivative in good yield (Scheme 106).

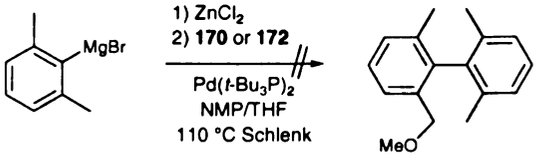
Scheme 107. Synthesis of Aryl Chloride **172**



171 **172**

As the aryl chloride should be the best electrophile with the Fu cross-coupling conditions,[92] the same procedures used for the synthesis **170** were followed to afford the requisite aryl chloride **172** (Scheme 107). With the aryl halides **170** and **172** in hand the proposed Negishi coupling was attempted.

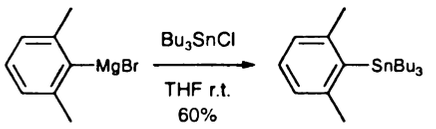
Scheme 108. Attempted Synthesis of **173** via Negishi Coupling



173

Unfortunately, neither bromide **170** nor chloride **172** afforded the desired cross-coupling product when reacted with 2,6-dimethylphenyl zinc chloride in the presence of commercial catalyst (Scheme 108). These reactions were monitored by GC/MS at 16 hours and 36 hours, showing only starting halide and *m*-xylene. Personal communications with Adam Littke, who was in Fu's laboratory at the time, suggested that the Negishi coupling may not be a viable solution for tetra-ortho substituted cross couplings. Rather it was noted that a Stille reaction with the Fu catalyst system proved most efficient at affording 2,2',4,6,6'-pentamethyl biphenyl.

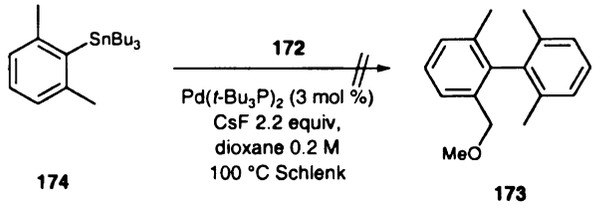
Scheme 109. Synthesis of Aryl Stannane **174**



174

To examine the Stille coupling route to the biaryls, the aryl stannane **174** was made by adding tributyltin chloride to a solution of 2,6-dimethylphenyl magnesium bromide. After stirring the reaction for 2 hours, workup and flash chromatography afforded **174** in 60% yield.

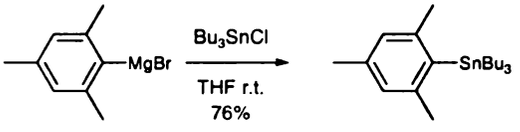
Scheme 110. Attempted Stille Coupling Between **174** and **172**



174 **173**

With both coupling partners in hand a Stille coupling between the two was attempted (Scheme 110). Aryl chloride **172** and stannane **174** were combined in 5 mL of distilled dioxane (0.2 M) in a Schlenk tube under argon. Then unpurified CsF (2.2 equiv.) was added followed by the addition of 3 mol % $Pd(t\text{-}Bu_3P)_2$. The reaction was purged with argon, sealed and placed in a preheated 100 °C oil bath. After 48 hours the reaction was sampled and GC analysis showed none of the desired coupling product. The only peaks detected were unreacted halide, a small amount of unreacted stannane, and a significant amount of *m*-xylene, from proteodestannylation.

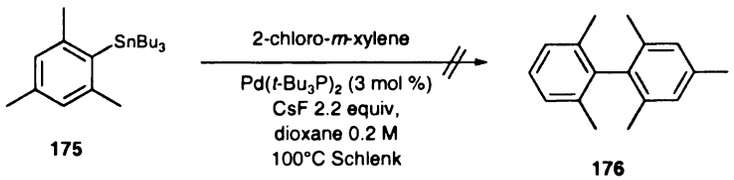
Scheme 111. Synthesis of Stannane **175**



175

In order to test if the reaction conditions were viable, a known reaction was repeated. The requisite 2,4,6-trimethylphenyl stannane was made by reacting tributyltin chloride with 2,4,6-trimethylphenyl magnesium bromide and afforded **175** in 76% yield after flash chromatography.

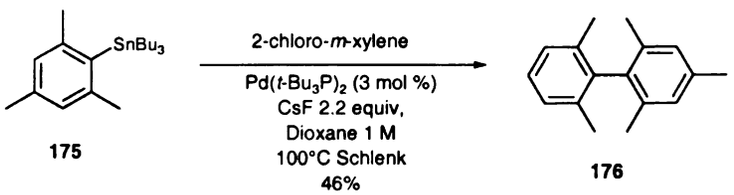
Scheme 112. Attempted Synthesis of **176**



175 **176**

With this new stannane in hand the reaction shown in Scheme 112 was attempted using the same procedure used for the previous Stille coupling. After 48 hours the reaction was analyzed by GC/MS and was found not to contain any of the desired product and was mainly unreacted aryl chloride and 1,3,5-trimethylbenzene, from proteodestannylation. Since there was no reaction except for the destannylation of **175** there was likely something wrong with the reaction conditions being applied.

Scheme 113. Synthesis of **176**

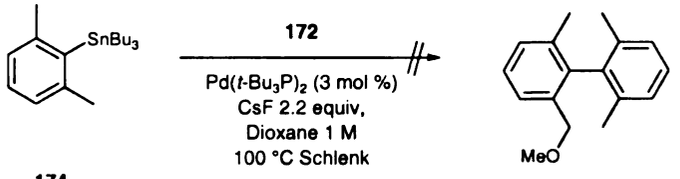


175 **176**

Further communication with Littke resulted in a detailed experimental for the application of their Stille protocol to the synthesis of **176**. From these experimental details there were three problems with our conditions. First, the Fu group used anhydrous dioxane purchased from Aldrich Chemical Co. in Sure-Seal® bottles. Secondly, they ground and dried the CsF under vacuum at 100 °C for several hours. These first two differences probably accounted for the large amount of proteodesannylation that occurred during the reaction. Finally, and probably most importantly, we arbitrarily chose a concentration of 0.2 M, however this was a factor of five more dilute than those used by the Fu group which used a concentration of 1.0 M.[95] Application these new conditions (Scheme 113) showed appreciable amounts of the desired coupled product and very little

proteodestannylated product after 15 hours. However the reaction was not complete as both unreacted halide and stannane were also observed. An additional 3 mol % of $Pd_2(dba)_3$ and 6 mol % $(t\text{-}Bu)_3P$ was added by syringe in the minimal amount of solvent. After an additional 24 hours, the reaction had proceeded further, as the ratio of starting materials to product changed, however it still was not complete. The reaction was worked up and purified by flash chromatography to afford the desired cross-coupled material **176** in 46% yield.

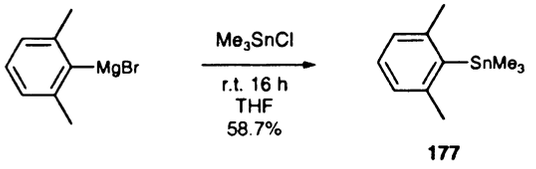
Scheme 114. Attempted **173** via Tributyl Stannane **174**



174 **173**

Although the known reaction did not go to completion and did not afford the reported yield (89%), it was working and so these conditions were applied to our biaryl system (Scheme 114).[96] To guard against aventious oxygen, on all further attempts the Schlenk tube was thoroughly evacuated and purged to several times to minimize the amount of oxygen in the system. Unfortunately, these modified conditions did not afford the desired cross-coupling. No *m*-xylene was detected by GC/MS, indicating that proteodestannylation was not shutting down the reaction as before. Thus it appears as though a methoxy substitution on one of the methyl groups shuts down the cross-coupling. It is possible that methoxy group on **172** combined with the steric bulk of the tributylstannane prevents transmetallation from occurring and thus the cross-coupling.

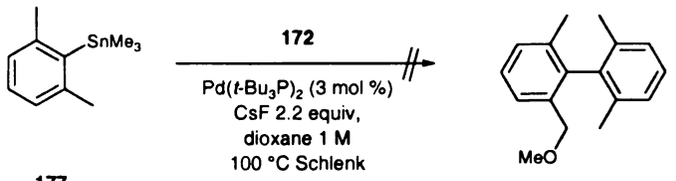
Scheme 115. Synthesis of Trimethyl Stannane **177**



177

In hopes that the smaller trimethyltin group would minimize the steric hinderance and allow the reaction to proceed, trimethylstannane **177** was made using the same procedure as the previous aryl stannanes. This stannane was purified by bulb-to-bulb distillation to afford the desired stannane in 58% yield.

Scheme 116. Attempted Synthesis of **173** via Trimethyl Stannane **177**



177 **173**

With the trimethyl stannane in hand the coupling protocol was repeated as before (Scheme 116). Again the reaction did not afford the desired product nor did it afford any significant amounts of proteodestannylation product, even after 48 hours. It was apparent that the Fu coupling protocol works with four methyl groups in the ortho position, but was shut down when there was substitution, even as small as a methoxy, on one of the four methyl groups. Given that Fu's group has found the Stille reaction to be the most amenable to stericly congested biaryls cross-coupling[95] and the results of these cross-coupling attempts, a viable cross coupling route to functionalized tetra-ortho substituted biaryls remains elusive.

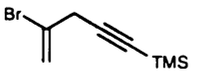
Importantly, Masten's research was not overly hindered by the unavailability compounds **140-142**. Their toxicology studies of the compounds we provided (**138**, **139**), found the tetraaldehyde to be the main cause of the toxicity after the Masten ozone

treatment. The tetracarboxylic acid was found to be non-toxic.[97] As non-toxic oxidation products are the goal of their remediation method, studies are ongoing into modifying their conditions (temperature, pH, water level, etc.) to achieve efficient conversion of pyrene to the tetra acid and thus maximize the effectiveness of this remediation method.

Experimental Details

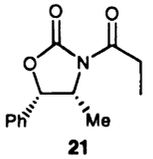
Materials and Methods

All air or moisture sensitive reactions were carried out in oven- or flame-dried glassware under a 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. Melting points were determined on a Thomas-Hoover Apparatus, uncorrected. 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 $CDCl_3$ (δ = 7.24 ppm for ^{1}H NMR or δ = 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.).



B

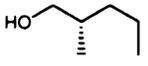
Preparation of fragment B: To a cold (0 °C) solution of EtMgBr (11 mL, 33 mmol, 3.0M Et_2O) was added dropwise (~45 minutes) a solution of trimethylsilylacetylene (4.2 mL, 30 mmol) in THF (45 mL). After stirring for an additional 10 minutes at 0 °C, the reaction was immersed into a preheated oil bath (55 °C), and stirred for 1 hour and then recooled to 0 °C. The septum was removed and CuI (0.11 g, 0.60 mmol) was added quickly. 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 (5% EtOAc/hexanes) to afford 6.02 g (93%) of fragment **B** as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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].



21

Preparation of 21: A flask was charged with **26** (0.55g, 3.1 mmol) in 5.7 mL dry THF. The flask was capped with a septum and purged with N_2 gas and cooled to -78 °C. Then *n*-butyllithium (1.6M in hexanes, 2.1 mL, 3.36 mmol) was added slowly via syringe. The

mixture was allowed to stir for 20 min. Propionyl chloride (0.33 mL, 3.38 mmol) was then added via syringe and the mixture was allowed to warm to 0 °C and stir for 3 h. Following this reaction time, the reaction was quenched by the addition of 1M aqueous K_2CO_3 (2.5 mL). The THF was removed in vacuo and the reaction mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were washed with saturated aqueous K_2CO_3 (2 x 2.5 mL) and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by Kugelrohr distillation (0.5 torr, 210-220 °C) to yield 0.52 g of **21** as a viscous colorless oil. $[\alpha]_D^{20}$ +31.5 (c = 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.65 (d, J = 7.2 Hz, 1 H), 4.75 (p, J = 6.9 Hz, 1 H), 2.94 (m, 2 H), 1.16 (t, J = 7.5 Hz, 3 H), 0.85 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 153.09, 133.30, 128.72, 128.67, 125.59, 78.99, 54.72, 29.26, 14.55, 8.24. Product data was in agreement with reported literature.[20]



22

Preparation of 22 via LAH reduction of 28: A three-neck flask was fitted with a thermometer, dropping funnel and septa. The flask was charged with a solution of **28** (1.90 g, 6.9 mmol) in dry THF (20 mL) and cooled to -78 °C. LAH (0.262 g, 6.90 mmol) in 10 mL of THF was then added dropwise via the addition funnel. The rate was such to maintain the internal temperature below -65 °C. The reaction was allowed to stir at -78 °C for 1 h, then was allowed to warm to -20 °C over a period of 2 h. The reaction was quenched by the dropwise addition of 1:9 water:THF solution (5 mL). Then 2 mL of 2M NaOH followed by 2 mL water. The mixture was stirred vigorously for 10 min. Then 10 mL hexanes and 2 g $MgSO_4$ was added. The mixture was filtered through Celite 503.

The filter cake was washed with diethyl ether. The solution was then distilled under aspirator pressure to remove the ether and hexanes. Then 10 mL 1:1 diethyl ether:pentane was added to the residue and a precipitate formed which was the chiral auxiliary **26**. The mixture was cooled in an ice bath and the supernatant was decanted. The precipitate was then washed with more 1:1 diethyl ether:pentane solution. The combined supernatants were distilled by short path distillation under aspirator pressure. First the pentane and ether was removed then the product came over at ~51 °C affording **22** as a colorless liquid (0.12 g, 17% yield). For spectroscopic data see below.

Preparation of 22 via $LiBH_4$ reduction of 28: Water (0.16 mL, 0.27 mmol) was added to a solution of **28** (2.32 g, 8.4 mmol) in diethyl ether (100 mL). The solution was cooled to 0 °C in an ice bath. THF (4 mL) was then added followed by $LiBH_4$ (0.20 g, 9.27 mmol) as a solid in 4 portions. Clouding and gas evolution was observed. The reaction was warmed to room temperature and monitored by TLC. After 3 h no more consumption of starting material was observed and the reaction was quenched by the addition of 1M aq. NaOH. The mixture was then stirred until both layers were clear. The mixture was poured into ether/water and the layers separated. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuum. The resulting residue was chromatographed on silica gel (1:3 EtOAc: hexanes +1% TEA) to afford **22** as a colorless liquid (0.60 g, 70.5%). For spectroscopic data see below.

Preparation of 22 via lipase resolution (method 1): Chloroacetate **29** was combined with pH 7 buffer (10 mL) and water (90 mL) in a 3-neck round bottom. The flask was fitted with a mechanical stirrer, pH probe, septa, and syringe filled with 1M NaOH mounted on a syringe pump connected to a Cole-Palmer pH controller. The pH of the

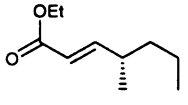
solution was corrected to 7.5 and Amano PS lipase (80 mg) was added and immediately the addition of NaOH started. The reaction was monitored by GC until the reaction reached 50% completion. Et_2O was added and the layers separated. The aqueous phase was extracted with Et_2O (2x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil. Chromatography (30% ethyl acetate in hexanes) afforded 1.21 g (85%) 2-methylpentanol enriched in the desired (S) isomer $[\alpha]_{578}^{20}$ -1.0 (c = 0.765, $CHCl_3$) (7.8% ee) and 2.2 g of the chloroacetate which upon spontification (NaOH/MeOH overnight) afforded 2-methylpentanol (**22**) enriched in the (R) enantiomer $[\alpha]_{578}^{20}$ +2.5 (c = 1.25, $CHCl_3$). For spectroscopic data see below.

Preparation of 22 via lipase resolution (method 2): Chloroacetate **29** was combined with pH 7 buffer (125 mL) and water (125 mL) in a 3-neck round bottom. The flask was outfitted as before and the mixture was cooled to 5 °C. The pH of the solution was corrected to 7.5 and Amano PS lipase (40 mg) was added and immediately the addition of NaOH started. The reaction was monitored by GC until the reaction reached 33% completion. Et_2O was added and the layers separated. The aqueous phase was extracted with Et_2O (2x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil. Chromatography (30% ethyl acetate in hexanes) afforded 2-methylpentanol (**22**) enriched in the desired (S) isomer $[\alpha]_{578}^{20}$ -1.3 (c = 1.515, $CHCl_3$) (10 % ee). For spectroscopic data see below.

Preparation of 22 via lipase resolution (method 3): Chloroacetate **29** was combined with pH 7 buffer (125 mL) and water (125 mL) in a 3-neck round bottom. The flask was as before and the mixture cooled to 5 °C. The pH of the solution was corrected to 7.0 and Amano PS lipase (40 mg) was added and immediately the addition of NaOH started.

The reaction was monitored by GC until the reaction reached 20% completion. Et_2O was added and the layers separated. The aqueous phase was extracted with Et_2O (2x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford an oil. Chromatography (30% ethyl acetate in hexanes) afforded 2-methylpentanol (**22**) enriched in the desired (S) isomer $[\alpha]_{578}^{20}$-4.0 (c = 1.94, $CHCl_3$) (28.5% ee). For spectroscopic data see below.

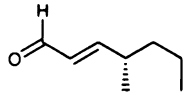
Preparation of 22 via $LiBH_4$ reduction of (33): Water (0.08 mL, 5.2 mmol) was added to a solution of **33** (1.4 g, 4.8 mmol) in diethyl ether (50 mL). The solution was cooled to 0 °C in and ice bath. Then $LiBH_4$ (5.28 mmol, 1M in THF) was dropwise. Clouding and gas evolution was observed. The reaction was warmed to room temperature over 3 h. The reaction was quenched by the addition of 1M aq. NaOH and then the mixture was stirred until both layers were clear. The mixture was poured into ether/water and the layers separated. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuum. The resulting residue was chromatographed (1:3 EtOAc: hexanes +1% TEA) on silica gel to afford the **22** as a colorless liquid (0.40 g, 85%). $[\alpha]_{578}^{20}$ -13 (c = 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (qd, J = 8.0, 5.7 Hz, 2 H), 1.60 (m, 1 H), 1.28 (m, 4 H), 1.08 (m, 1 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.8, 35.4, 34.5, 20.0, 16.5, 14.3. The product data is in agreement with reported literature.[18]



23

Preparation of 23: A solution containing oxalyl chloride (8.0 mL, 11.72 g, 95.35 mmol) in CH_2Cl_2 (250 mL) was cooled to -78 °C. Then a solution of DMSO (13.52 mL, 14.8 g,

190.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After 15 minutes, a solution of **22** (8.12 g, 79.46 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After an additional 20 minutes $^iPr_2NEt$ (96.88 mL, 71.9 mmol) was added. After another 20 minutes ethyl (triphenylphosphoronylidene) acetate (71.52 g, 119.19 mmol) was added. The reaction was allowed to warm to room temperature overnight. The solvent was removed in vacuum and the flask was filled with diethyl ether. After stirring for several hours the solution was filtered through a pad of silica gel in a fritted funnel. The filter cake was washed with diethyl ether (~ 500 mL). The ether was removed in vacuum and the product was isolated via flash chromatography (5% EtOAc/hexanes) to afford **23** as a clear liquid (10.95 g, 80%). $[\alpha]_D^{20}$ +28.5 (c = 1.775, $CHCl_3$); IR (neat) 2963, 1722, 1653, 1224; ^1H NMR (300 MHz, $CDCl_3$) δ 6.8 (ABq, J = 15.6 Hz, 7.9 Hz, 1 H), 5.7 (ABq, J = 15.6 Hz, 1.1 Hz, 1 H), 4.1 (q, J = 7.1 Hz, 2 H), 2.2 (m, 1 H), 1.3 (m, 3 H), 1.2 (m, 6 H), 0.8 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 154.7, 119.5, 60.0, 38.1, 36.2, 20.3, 19.4, 14.3, 14.0; HRMS (EI) *m/z* 170.1307 [$(M)^+$; calcd. for $C_{10}H_{18}O_2$: 170.1307].



24

Preparation of 24 (Swern Oxidation): To a -78 °C solution of oxalyl chloride (0.5 g, 3.93 mmol) in CH_2Cl_2 (15 mL) was added DMSO (0.69 g, 7.8 mmol) dropwise. After 10 minutes a solution of **35** (0.42 g, 3.27 mmol) in CH_2Cl_2 (4 mL, 2 mL rinse) was added dropwise. After an additional 20 minutes *i*-Pr_2NEt (2.82 mL, 16.35 mmol) was added and the solution allowed to warm to room temperature. The solution was poured into a 50% brine solution and the layers were separated. The aqueous layer was extracted with 2 x 10 mL CH_2Cl_2. The combined organic layers were washed with brine and dried over

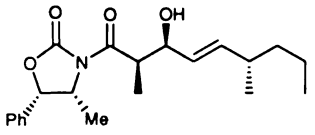
$MgSO_4$. Silica gel chromatography(5% EtOAc/hexanes) afforded 0.30 g (72%) of **24** as a slightly yellow oil. For spectroscopic data see below.

Preparation of 24 (Dess-Martin oxidation): Alcohol **35** (13.1 mmol, 1.68 g) and Dess-Martin Periodane[98] (14.4 mmol, 6.1g) were combined in a flask with CH_2Cl_2 (160 mL) and allowed to stir at r.t. for 2 h. The reaction was diluted with ether (300 mL) and quenched by the addition of 1:1 aq. sat. $NaHCO_3$:10% Na_2SO_3 (150 mL). The mixture was allowed to stir for 60 min. The layers were separated and the organic layer was washed with water and brine. The combined Et_2O layers were dried over $MgSO_4$ and concentrated to yield **24** (1.65 g, 100%) as a yellow oil, which was used without further purification. For spectroscopic data see below.

Preparation of 24 (SO_3 pyridine oxidation): A solution of **35** (1.50 mg, 11.7 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C and diisopropylethylamine (12.2 mL, 70.2 mmol) was added followed by DMSO (15 mL). Then a solution of SO_3•pyridine complex (5.58 g, 35.1 mmol) in DMSO (18 mL) was added. The reaction was warmed to r.t. and stirred for 30 min. The reaction was quenched by the addition of NH_4Cl (40 mL, aq. sat.) The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 5% EtOAc/Hex TEA buffered) afforded the desired product **24** (1.22 g, 83%). For spectroscopic data see below.

Preparation of 24 (CMD oxidation): To a solution of allylic alcohol **35** (4.38 g, 34.2 mmol) in CH_2Cl_2 (250 mL) was added chemical manganese dioxide (CMD, Wako Chemical Co., Japan) (32 g, 374 mmol) in one portion. After stirring 20 h, the reaction was filtered through celite. The filter cake was washed thoroughly with Et_2O. The combined filtrates were concentrated to afford 4.1 g (95%) of **24** as a colorless liquid.

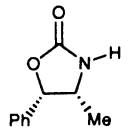
$[\alpha]_D^{20}$ +28, (c = 0.85, $CHCl_3$); IR (neat) 2932, 1738, 1687, 1458, 1373, 1240; ^1H NMR (300 MHz, $CDCl_3$) δ 9.4 (d, J = 7.7 Hz, 1 H), 6.7 (ABq, J = 15.6 Hz, 7.4 Hz, 1 H),), 6.0 (ABq, J = 15.6 Hz, 7.9 Hz, 1 H), 2.4 (p, J = 6.6 Hz, 1 H), 1.0 (m, 6 H), 0.8 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.32, 164.27, 131.17, 37.98, 36.68, 20.22, 19.07, 13.96; HRMS (EI) *m/z* 126.1041 [$(M)^+$; calc. for $C_8H_{14}O$, 126.1045]



25

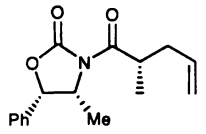
Preparation of 25 (method 1): To a –78 °C soln of **21** (0.36g, 1.58 mmol) in CH_2Cl_2 (10 mL) was added di-*n*-butylboryl triflate (1.9 mL,1.6M in THF, 1.89 mmol) dropwise via syringe pump. After 5 min triethylamine (0.33 mL, 1.95 mmol) was added dropwise via syringe pump. The reaction temperature was maintained at –78 °C for 30 min., then warmed to 0°C slowly and maintained for 1 h. The solution was re-cooled to –78 °C and **24** (0.2 g, 1.58 mmol) in CH_2Cl_2 was added dropwise. The reaction was held at -78 °C for 45 min and then allowed to rise to 0 °C for 1 h. The reaction was quenched by the addition of pH 7 phosphate buffer. Then MeOH (10 mL) was added followed by 15 mL 30% H_2O_2 in 30 mL MeOH. The resulting mixture was stirred at 0 °C for 1 h. The solvents were removed in vacuo and 30 mL 10% $NaHCO_3$ was added. The solution was extracted with CH_2Cl_2 (3x50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to yield an oil. Silica gel chromatography (1:6 EtOAc:pet. ether) afforded the desired product **25** (53 mg, 10% yield) as a very viscous yellow oil. For spectroscopic data see below.

Preparation of 25 (method 2): To a –78 °C soln. of **21** (0.42g, 1.80 mmol) in CH_2Cl_2 (15 mL) was added di-*n*-butylboryl triflate (3.6mL, 1.6M in THF, 3.60 mmol) dropwise via syringe pump. After 5 min freshly distilled triethylamine (0.75 mL, 5.4 mmol) was added dropwise via syringe pump. The reaction temperature was maintained at –78 °C for 30 min., then warmed to 0 °C slowly and maintained for 1 h. The solution was re-cooled to –78 °C and **24** (0.25 g, 1.98 mmol) in CH_2Cl_2 was added dropwise. The reaction was held at –78 °C overnight, then allowed to rise to 0 °C. The reaction was quenched by the addition of pH 7 phosphate buffer. Then MeOH (10 mL) was added followed by 15 mL 30% H_2O_2 in 30 mL MeOH. The resulting mixture was stirred at 0 °C for 1 h. The solvents were removed in vacuum and 30 mL 10% $NaHCO_3$ was added and the solution was extracted with CH_2Cl_2 (3x50 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Silica gel chromatography (1:5 EtOAc:hexanes) afforded the desired product **25** (360 mg, 67% yield) as a colorless oil. $[\alpha]_D^{20}$ +18.5 (c = 0.465, $CHCl_3$); IR ($CDCl_3$) 3537, 3155, 3020, 2961, 1782, 1697, 1458 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.66 (d, J = 7.8 Hz, 1 H), 5.65 (ddd, J = 15.9, 7.8 , 1.2 Hz, 1 H), 5.4 (ddd, J = 15.3 , 6.9 , 0.9 Hz, 1 H), 4.78 (p, J = 6.7 Hz, 1 H), 4.4 (m, 1 H), 3.8 (dd, J = 3.6, 7.2 Hz, 1 H), 2.76 (d, J = 3.0 Hz, 1 H), 2.15 (m, 1 H), 1.25 (m, 4 H), 1.19 (d, J = 6.9 Hz, 3 H), 0.9 (d, J = 6.3 Hz, 3 H), 0.8 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ176.5, 152.7, 139.1, 133.0, 128.8, 128.7, 127.0, 125.6, 78.9, 72.7, 54.8, 42.8, 39.0, 36.1, 20.5, 20.4, 14.3, 14.1, 10.9; HRMS (EI) *m/z* 359.2088 [$(M)^+$; calcd. for $C_{21}H_{29}NO_4$, 359.2097].



26

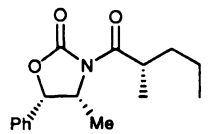
Preparation of 26: A mixture of (1S,2R)-(+)-norephedrine (5.68 g, 37.62 mmol), diphenyl carbonate (11.43 g, 82.7 mmol), and K_2CO_3 (8.86 g, 41.4 mmol) was heated to 110 °C for 6 h. The mixture was then cooled to 60 °C upon which methanol (25 mL) was added and the mixture was heated to reflux for 0.5 h. After adding water (30 mL) to dissolve the K_2CO_3, the methanol was removed in vacuo. The solution was extracted with dichloromethane (3 x 100 mL). The combined extracts were washed with 2M aqueous sodium hydroxide (2 x 100 mL), 1M aqueous hydrochloric acid (2 x 100mL), and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 6.0 g (90%) of **26** as a light brown crystalline solid. mp 111-115 °C; $[\alpha]_D^{20}$ +149.2 (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.5 (s, 1 H), 5.70 (d, *J* = 7.9 Hz, 1 H) 4.18 (p, *J* = 6.5 Hz, 1 H), 0.79 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.78, 134.86, 128.38, 128.41, 125.86, 80.96, 52.37, 17.42. Product data was in agreement with reported literature.[20]



27

Preparation of 27: NaHMDS (18.6 mL of a 1M in THF soln, 18.6 mmol) was cooled to –78 °C. A solution of **21** (3.33 g, 14.2 mmol) in THF (30 mL) was added dropwise via a syringe pump (1 mL/min). After 25 min, allyl bromide (3.67 mL, 42.6 mmol) was added dropwise via syringe pump (0.2 ml/min). The resulting solution was stirred at -78 °C to -60 °C for 16 h. The reaction was quenched by the addition of aq. sat. NH_4Cl (10 mL).

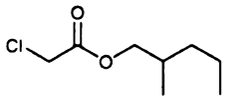
The THF was removed in vacuo. The residue was diluted with 50 mL Et_2O and washed successively with 30 mL each of H_2O, aq. sat. $NaHSO_3$, H_2O, aq. sat. $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield **27** (3.87 g, 92%) as light yellow crystals. mp. 67 °C (lit 67-69 °C); $[\alpha]_D^{20}$ +51.2 (*c* = 2.175, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.80 (m, 1 H), 5.62 (d, *J* = 7.4 Hz, 1 H), 5.05 (m, 2 H), 4.75 (p, *J* = 7.1 Hz, 1 H), 3.85 (sextet, *J* = 6.8 Hz, 1 H), 2.5 (p, *J* = 7.1 Hz, 1 H) 2.2 (p, *J* = 7.1 Hz, 1 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 152.7, 135.2, 133.4, 128.7, 128.7, 125.6, 117.1, 78.7, 54.8, 37.9, 37.1, 16.5, 14.6. Product data was in agreement with reported literature.[20]



28

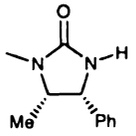
Preparation of 28: Approximately 10 mol % Pd/C (10%) was added to a solution of **27** (0.50 g 1.83 mmol) in ethyl acetate (~125 mL). The flask was evacuated via aspirator and then charged with H_2 via balloon. The process was repeated 3 times to sufficiently purge the sample. Then reaction was allowed to stir overnight with the balloon being recharged after several hours. Filtration through Celite 503 and concentration afforded 0.50 g (100%) of **28** as an oil, which solidified upon cooling. mp. 52-55 °C; $[\alpha]_D^{20}$ +48.7 (*c* 0.82, $CHCl_3$); IR (neat) 2968, 1772, 1456, 1340, 1196, 960, 632. ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.6 (d, *J* = 7.4 Hz, 1 H), 4.7 (p, *J* = 6.5 Hz, 1 H), 3.7 (q, *J* = 6.5 Hz, 1 H), 1.69 (m, 1 H), 1.3 (m, 3 H), 1.1(d, *J* = 6.8 Hz, 3 H), 0.9 (t, *J* = 7.2 Hz, 3 H), 0.8(d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.19, 152.7, 133.45, 128.7,

128.68, 125.64, 78.68, 54.80, 37.33, 35.91, 20.2, 16.87, 14.58, 14.06; HRMS (EI) *m/z* 275.1515 [$(M)^+$; calcd. for $C_{16}H_{21}NO_3$: 275.1521].



29

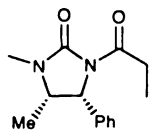
Preparation of 29: Racemic 2-methylpentanol **22** (25g, 244 mmol), chloroacetyl chloride (20.38 g, 269 mmol), and DMAP (0.112 g, 1 mmol) were combined in a round bottom flask containing CH_2Cl_2 (110 mL). The reaction was refluxed for 6 h, before being cooled and washed with water. The organic phase was dried over $MgSO_4$ and concentrated affording 42 g (96%) of chloroacetate **29**, which was used without further purification. IR (neat) 2961, 2876, 1759, 1309, 1184, 790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 2 H), 4.01 (dd, *J* = 10.8, 6.0 Hz, 1 H), 3.90 (dd, *J* = 10.8, 6.8 Hz, 1 H), 1.8 (m, 1 H), ca. 1.2 (m, 4 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.84 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 70.69, 40.83, 35.27, 32.11, 19.77, 16.57, 14.07; HRMS (CI) *m/z* 179.0847 [$(M + H)^+$; calcd. for $C_8H_{16}ClO_2$, 179.0839].



30

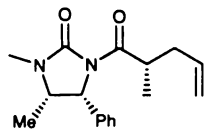
Preparation of 30: (-)-Ephedrine hydrochloride (50 g, 247.8 mmol) and urea (45g, 750 mmol) was heated for 30 min at 176 °C. The mixture was then heated to 210 °C for 1 hour. The mixture was cooled and quenched with water. The solid was filtered and washed thoroughly with HCl (5% aq) and water. Recrystalization from 95% ethanol afforded **30** (28 g, 50%) as a white solid. mp 174-177 °C (lit. 177 °C). $[\alpha]_D^{20}$ -45 (*c* = 0.97, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 4.7 (d, *J* = 8.4 Hz, 1 H), 4.6 (br s, 1 H), 3.8 (dq, *J* = 9.0, 6.3 Hz, 1 H), 2.7 (s, 3 H), 0.73 (d, *J* = 6.6, 3 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 162.4, 138.1, 128.5, 128.0, 127.2, 58.2, 57.5, 28.2, 14.3. The product data is in agreement with reported literature.[26b]



31

Preparation of 31: To a 0 °C solution of **30** (52.5 g, 278.2 mmol) in THF (1.5 L) was added *n*-BuLi (292.1 mmol, 1.6M in hexanes) rapidly but still dropwise. The solution was stirred for 30 minutes. Propionyl chloride (25 mL, 330 mmol) was then added and the resulting solution was allowed to stir at 0 °C for 1 h. The reaction was quenched with $NaHCO_3$ (aq. sat.) The THF was removed *in vacuo* and CH_2Cl_2 (400 mL) was added and the layers separated. The organic layer was washed with brine and dried over $MgSO_4$. Concentration of the organic layer afforded **31** (62.8 g, 92%) as a white solid. mp 103-106 °C (lit. 107 °C); $[\alpha]_D^{20}$ -43.6 (c = 1.45, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.2 (d, J = 6.3 Hz, 1 H), 3.8 (dq, J = 9.0, 7.0 Hz, 1 H), 2.9 (q, J = 7.0 Hz, 2 H), 2.7 (s, 3 H), 1.0 (t, J = 7.0, 3 H), 0.75 (d, J = 6.6, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ173.5, 155.9, 136.7, 128.4, 127.9, 126.8, 59.2, 53.9, 29.3, 28.1, 14.8, 8.5. The product data is in agreement with reported literature.[26b]

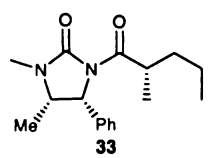


32

Preparation of 32 (method 1): NaHMDS (12.1 mL of a 1M in THF soln, 12.1 mmol) was cooled to –78 °C. A solution of **31** (2.0 g, 8.1 mmol) in THF (20 mL) was added dropwise via a syringe pump. After 25 min, allyl bromide (2.08 mL, 45.2 mmol) was added dropwise via syringe pump. The resulting solution was stirred at –78 °C for 16 h.

The reaction was quenched by the addition of aq. sat. NH_4Cl (10 mL). The THF was removed in vacuo. The residue was diluted with 100 mL Et_2O and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (1:3 EtOAc:hexanes) afforded 1.5 g (64%) of **32** as a waxy solid. For spectroscopic data see below.

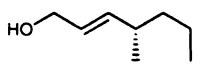
Preparation of 32 (method 2): NaHMDS (215 mL, 1M in THF, 215 mmol) was cooled to –78 °C. A solution of **31** (44.1 g, 179.1 mmol) in THF (500 mL) precooled to near -30 °C was added dropwise via cannula. After 25 min, allyl bromide (46.3 mL, 537.3 mmol) was added dropwise via syringe pump. The resulting solution was stirred at –78 °C for 16 h. The reaction was quenched by the addition of aq. sat. NH_4Cl (10 mL). The THF was removed *in vacuo*. The residue was diluted with CH_2Cl_2 (300 mL) and washed with water, $NaHCO_3$ (sat), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield **32** (52.7 g, 100%) as waxy solid. $[\alpha]_D^{20}$ -50.3 (c = 0.55, $CHCl_3$), IR (neat) 2976, 1730, 1684, 1456, 1387, 1311, 1203, 974, 758, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.6 (m, 1 H) 5.2 (d, J = 8.7 Hz, 1 H), 4.9 (m, 2 H), 3.9 (m, 1 H), 3.8 (m, 1 H), 2.7 (s, 3 H), 2.0 (m, 1 H), 2.3 (m, 1 H) 1.0 (d, J = 6.9 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 155.5, 136.6, 135.6, 128.3, 127.8, 126.9, 116.5, 59.2, 53.6, 37.9, 37.1, 28.1, 16.1, 14.9; HRMS (FAB) *m/z* 287.1758 [$(M + H)^+$; calcd. for $C_{17}H_{23}N_2O_2$, 287.1760].



33

Preparation of 33: Approximately 10 mol % Pd/C (10 %) was added to a solution of **32** (1.50 g, 5.2 mmol) in ethyl acetate (100 mL). The flask was evacuated via aspirator and

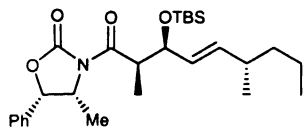
then charged with H_2 via balloon. The process was repeated 3 times to sufficiently purge the sample. Then reaction was allowed to stir overnight with the balloon being recharged after several hours. Filtration through Celite 503 and concentration (hi vac) afforded 1.4 g (95%) of **33** as a white solid. mp 70-71 °C; $[\alpha]_D^{20}$ -37° (*c* = 0.295, $CHCl_3$); IR (neat) 2959, 1728, 1682, 1387, 1224 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 5.2 (d, *J* = 9.0 1 H), 3.8 (m, 2 H), 2.7 (s, 3 H), 1.6 (m, 1 H), 1.2 (m, 3 H), 1.0 (d, *J* = 6.9 Hz, 3 H), 0.79 (t, *J* = 7.2, 3 H), 0.75 (d, *J* = 6.6, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 155.6, 136.8, 128.3, 127.8, 126.8, 59.2, 53.5, 37.2, 35.9, 28.1, 19.9, 16.6, 14.9, 13.9; HRMS (EI) *m/z* 288.1828 [$(M)^+$; calcd. for $C_{17}H_{24}N_2O_2$, 288.1838].



35

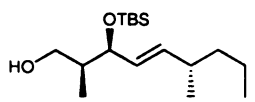
Preparation of 35: To a solution of **23** (5.95 g, 2.58 mmol) in CH_2Cl_2 (180 mL) was added DIBAL (1.0M in hexane, 87.3 mL, 87.3 mmol) dropwise. The mixture was allowed to stir at -78 °C for 3 h. The reaction was quenched by the addition of 4 mL water. Then a potassium sodium tartrate solution (200 mL) was added and the mixture was allowed to stir overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (150 mL). The combined organic layers were washed with Rochelle's salt solution, and dried over $MgSO_4$, and concentrated. The crude mixture was purifed with a plug of silica gel (Et_2O eluant) to afford 3.61 g (80%) of **35** as a colorless oil. $[\alpha]_D^{20}$ +23.6 (*c* = 2.06, $CHCl_3$); IR (neat) 2961, 1456, 1379, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55-5.65 (m, 2 H), 4.06-4.12 (m, 2 H), 2.04-2.22 (m, 1 H), 1.43, (s, 1 H), 1.20-1.34 (m, 4 H), 0.97 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 139.3, 126.9, 63.8, 39.0, 36.0, 20.3 (2), 14.0; HRMS (EI) *m/z* 127.1123 [(M - H)$^+$; calcd. for $C_8H_{15}O$, 127.1123.

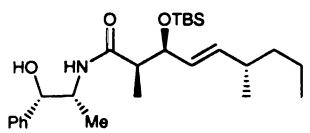


36

Preparation of 36: To a 0 °C solution of **25** (112 mg, 0.31 mmol) in CH_2Cl_2 (6 mL) was added 2,6 lutadine (0.1 mL 0.77 mmol) followed by dropwise addtion of TBSOTf (0.1 mL, 0.465 mmol). After 6 hours, the reaction was quenched by the addtion of water (5 mL) and CH_2Cl_2 (5 mL). The layers were separted and the organic phase was washed with $NaHCO_3$ (4 mL). Subsequent dring over $MgSO_4$, concentration, and silica gel chromotography (1-10% EtOAc/hexanes) afforded 146 mg **36** as a colorless oil (146 mg). $[\alpha]_D^{20}$ +4.9 (*c* = 0.75, $CHCl_3$); IR (neat) 2957, 1784, 1701, 1340, 1194, 837, 775 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3) δ 7.2 (m, 5 H), 5.6 (d, *J* = 4.5 Hz, 1 H), 5.4 (m, 2 H), 4.6 (p, *J* = 6.9 Hz, 1 H), 4.2 (t, *J* = 6.3 Hz, 1 H), 3.9 (p, *J* = 6.9 Hz, 1 H), 2.1 (m, 1 H), 1.2 (m, 4 H), 1.1 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.86 (m, 6 H), 0.87 (s, 9 H), 0.0 (d, *J* = 6.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.7, 138.3, 133.2, 129.0, 128.6, 125.5, 78.7, 75.2, 44.5, 39.0, 35.9, 31.5, 25.7, 22.6, 20.6, 20.3, 18.1, 14.3, 14.1, 12.5, -4.3, -5.1. HRMS (EI) *m/z* 416.2256 [(M - Bu)$^+$, calcd. for $C_{23}H_{34}O_4NSi$, 416.2257].



37



38

Preparation of 37 and 38: Water (11 μL, 0.61 mmol) was added to a solution of **36** (146 mg, 0.31mmol) in diethyl ether (10 mL). The resulting solution was cooled to 0 °C with an ice bath. $LiBH_4$ (200 μL, 2M in THF, 0.4 mmol) was then added dropwise.

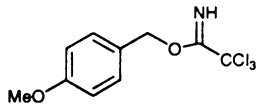
Clouding and gas evolution was observed. The reaction was warmed to room temperature. After 4 h, the reaction was quenched by the addition of 1M aq. NaOH and then the mixture was stirred until both layers were clear. The mixture was then poured into ether/water and the layers separated. The aqueous phase was extracted with diethyl ether (2 x 20 mL). The combinded organics were washed with brine, dried over magnesium sulfate, and concentrated in vacuum. Silica gel chromatography (10-20% EtOAc/hexanes) afforded 35 mg (33%) **37** and 80 mg (57%) of **38** both of which were oils.

For **37**: $[\alpha]_D^{20}$ +13.5 (*c* = 1.00, $CHCl_3$); IR (neat) 3364, 2957, 2858, 1471, 1253, 1033, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.3 (m, 2 H), 4.1 (m, 1 H), 3.6 (m, 1 H), 3.4 (m, 1 H), 3.0 (m, 1 H), 2.1 (m, 1 H), 1.9 (m, 1 H), 1.2 (m, 4 H), 0.95 (d, *J* = 6.4 Hz, 3 H), 0.87 (3 H), 0.86 (s, 9 H), 0.73 (d, *J* = 6.9 Hz, 3 H), 0.04 (s, 3 H); 0.0 (s, 3 H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 127.0, 77.8, 65.9, 40.8, 39.0, 36.1, 25.7, 20.7, 20.4, 18.1, 14.1, 12.6, -4.3, -5.1; HRMS (EI) *m/z* 241.1988 [(M - $C_3H_7O)^+$, calcd. for $C_{14}H_{29}OSi$, 241.1988].

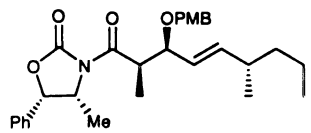
.

For **38**: $[\alpha]_D^{20}$ +48.4 (*c* = 0.465, $CHCl_3$); IR (neat) 3400, 3346, 2959, 2858, 1645, 1568, 1456, 1255, 1064, 837, 777, 734, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 6.61 (d, *J* = 7.5 Hz, 1 H), 5.50 (dd, *J* = 15.4, 7.5 Hz, 1 H), 5.30 (dd, *J* = 15.4, 7.5 Hz, 1 H), 4.85 (d, *J* = 3.0 Hz, 1 H), 4.21 (m, 1 H), 4.15 (m, 1 H), 2.48 (m, 1 H), 2.34 (m, 1 H), 1.2 (m, 4 H), 1.22 (d, *J* = 7.0 Hz, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.84 (s, 9 H), 0.84 (3 H), 0.04 (s, 3 H), 0.0 (s 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.4, 141.0, 140.1, 128.1, 127.4, 126.8, 126.4, 76.4, 76.3, 51.3, 46.7, 39.0, 36.0, 25.8,

20.4, 20.3, 18.0, 14.5, 14.2, 12.8, -4.1, -4.9; HRMS (CI) *m/z* 446.3084 [(M - H)$^+$, calcd. for $C_{26}H_{44}NO_3Si$, 446.3090].



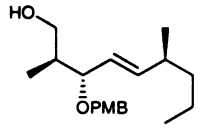
Preparation of *p*-methoxybenzyl trichloracetimidate: Sodium Hydride (0.90 g, 3.61 mmol) was suspended in Et_2O (10 mL) and a solution of *p*-methoxylbenzyl alcohol (5.0 g, 36.1 mmol) in Et_2O (20 mL) was added dropwise. After 20 min the solution was clear. At that time the mixture was cooled to 0 °C with an ice bath. Trichloroacetonitrile (1.44 mL, 36.1 mmol) was added dropwise. The reaction was allowed to warm to 20 °C over 60 min. The reaction was concentrated and pentane (10 mL) containing 0.3 mL anhydrous MeOH. After vigorous stirring and shaking and filtration, the combined pentane/MeOH and pentane washings were concentrated to yield a yellow/red liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.3 (ABq, *J* = 136.2, 8.79 Hz, 4 H), 5.25 (s, 2 H), 3.79 (s, 3 H). The product data is in agreement with reported literature.[32]



39

Preparation of 39: A solution of **25** (510 mg, 1.41 mmol) and *p*-methoxybenzyltrichloroacetimidate (480 mg, 1.7 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to –78 °C. BF_3•etherate (14 μL, cat.) was added using a GC solvent rinse injection technique. After 30 min the solution was warmed to r.t. and quenched by adding a 2:1 diethyl ether/water mixture (50 mL). The layers were separated and the organic phase washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford an oil. Silica gel chromatography (1:5 EtOAc/hexanes) afforded 450 mg (65%) of **39** as

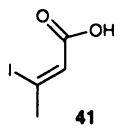
an oil. $[\alpha]_D^{20}$ +12 (*c* 0.20, $CHCl_3$); IR (neat) 2924, 1780, 1701, 1456, 1246, 1033, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; 7.4 (m, 3 H), 7.2 (d, *J* = 8.4 Hz, 4 H), 6.8 (d, *J* = 8.4 Hz, 2 H), 5.5 (dd, *J* = 15.6, 7.5 Hz, 1 H), 5.3 (dd, *J* = 15.6, 8.1 Hz, 1 H), 5.1 (d, *J* = 6.9 Hz, 1 H), 4.5 (m, 2 H), 4.2 (d, *J* = 12 Hz, 1 H), 4.1 (p, *J* = 6.6 Hz, 1 H), 3.9 (t, *J* = 7.0 Hz, 1 H), 3.7, (s, 3 H), 2.2 (m, 1 H), 1.3 (m, 4 H), 1.1 (d, *J* = 6.9 Hz, 3 H), 1.0 (d, *J* = 6.9 Hz, 3 H), 0.89 (t, *J* = 6.3, 3 H), 0.82 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 159.0, 152.9, 141.88, 133.2, 130.7, 129.6, 128.5, 125.5, 113.6, 80.0, 78.6, 69.3, 55.3, 55.2, 42.4, 39.1, 36.3, 20.7, 20.5, 14.3, 14.2, 12.1. HRMS (FAB^+) *m/z* 480.2764 [$(M + H)^+$; calcd. for $C_{27}H_{38}NO_5$, 480.2764].



C

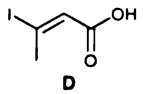
Preparation of Fragment C: Water (2.5 μL, 0.142 mmol) was added to a solution of **39** (70 mg, 0.14 mmol) in diethyl ether (5 mL). The solution was cooled to 0 °C by an ice bath. $LiBH_4$ (70 μL, 2M in THF, 0.142 mmol) was then added dropwise. Clouding and gas evolution was observed. The reaction was warmed to room temperature. After 3 h the reaction was quenched by the addition of 1M aq. NaOH and then the mixture was stirred until both layers were clear. The mixture was poured into ether/water and the layers separated. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuum. The resulting residue was chromatographed (30% EtOAc/hexanes) on silica gel to afford 24 mg (55%) as an oil. $[\alpha]_D^{20}$ +60 (*c* = 0.11, $CHCl_3$) IR ($CDCl_3$) 3449, 2860, 1612, 1383, 1352, 1111, 978, 843, ^1H NMR (300 MHz, $CDCl_3$) δ; 7.2 (d, *J* = 8.0 Hz, 2 H), 6.8 (d, *J* = 8.4 Hz, 2 H), 5.5 (dd, *J* = 15.6, 7.5 Hz, 1

H), 5.3 (dd, J = 15.6, 8.1 Hz, 1 H), 4.5 (d, J = 11.4 Hz, 1 H), 4.2 (d, J = 11.6 Hz, 1 H), 3.7 (m, 1 H), 3.7 (s, 3 H), 3.6 (t, J = 8.1 Hz, 1 H), 3.4 (m, 1 H), 2.6 (s, 1 H), 2.2 (m, 1 H), 2.0, (m, 1 H), 1.3 (m, 4 H), 0.98 (d, J = 6.9 Hz, 3 H), 0.89 (t, J = 6.6 Hz, 3 H), 0.84 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 142.1, 130.4, 129.3, 125.1, 113.8, 83.3, 69.5, 65.9, 55.2, 39.6, 39.1, 36.5, 20.8, 20.5, 14.1, 12.5; HRMS (EI) *m/z* 306.2197 [$(M)^+$; calcd. for $C_{19}H_{30}O_3$, 306.2194].



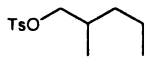
41

Preparation of 40 and 41: 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 41 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 **40**. Resubjection of the ethyl ester to the reaction conditions afforded the desired (Z)-β-iodo acid **41** quantitatively. mp = 107-109 °C (lit. 113 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.54 (s, 1 H), 6.34 (s, 1 H), 2.75 (s, 3 H). There is a 3.75% NOE between 6.34 and 2.75. The product data is in agreement with the reported literature.[33]



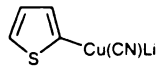
D

Preparation of Fragment D: The (Z)-β-iodo acid **41** was heated to 135 °C in a sealed tube for 24 hours. From ^{1}H 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 (25% EtOAc/hexanes +1% MeOH) the two isomers were separated. mp = 64-65 °C (lit. 66 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.54 (s, 1 H), 6.35 (s, 1 H), 2.76 (s, 3 H); There is a 0.3% NOE between 6.35 and 2.76. The product data is in agreement with the reported literature.[33]



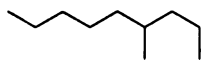
60

Preparation of 60: To a 0 °C solution of racemic 2-methyl pentanol **22** (2.0 g, 19.5 mmol) in dry pyridine (40 mL) was added *p*-toluenesulfonyl chloride (5.24 g, 27.3 mmol). The mixture was stirred at 0 °C overnight. The reaction was then diluted with diethyl ether and quenched with water. The layers were separated and the organic layer was washed with aq. sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to afford 4.99 g (96%) of **60** as a light yellow oil. The crude material was of sufficient purity as to not require further purification. IR (CDCl3) 2963, 2874, 1599, 1468, 1359, 1176, 1097, 968. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7 (d, *J* = 8.1 Hz, 2 H), 7.3 (d, *J* = 7.8 Hz, 2 H), 3.7 (m, 2 H), 2.4 (s, 3 H), 1.7 (m, 1 H), 1.3-1.0 (m, 4 H), 0.85, 0.79 (overlapping d and t, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 133.1, 129.7, 127.8, 75.1, 34.87, 32.5, 21.5, 19.6, 16.3, 14.0. The product data is in agreement with reported literature.[99]



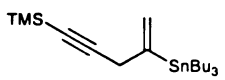
61

Preparation of 61 stock solution:[40] To a solution of thiophene (0.82 mL, 10.2 mmol) in THF (10 mL) at –78 °C was added *n*-BuLi (7.87 mL, 1.27M in hexanes) and stirred for 15 minutes. The reaction mixture was warmed to –20 °C over 30 minutes. This solution was transferred via canula to a –78 °C slurry of CuCN (0.896 g, 10.0 mmol) in THF (10 mL) with a wash of THF (10 mL). The solution was warmed to –40 °C to afford a light tan solution. This solution was diluted with THF (61 mL) and stored in an Aldrich Sure-Seal as a 0.1M solution of the cuprate **61**.



62

Preparation of 62: To a –78 °C slurry of CuCN (0.17 g, 1.95 mmol) in dry THF (20 mL) was added dropwise *n*-BuLi (2.43 mL, 1.6M in hexanes, 3.90 mmol). The solution was warmed slowly to 0 °C over 5 minutes and then recooled to –78 °C and tosylate **24** (0.250 g, 0.97 mmol) in THF (1 mL) was added slowly. The mixture was allowed to warm to room temperature overnight. The reaction was quenched with aqueous NH_4Cl (0.5 mL) and then diluted with water (5 mL)/Et_2O (10 mL). The layers were separated and the organic layer was dried over $MgSO_4$ and concentrated in vacuo to afford a yellow oil. By GC/MS analysis only 2 products were formed, the desired 4-methylnonane mass peak and a by-product from the displaced tosylate.

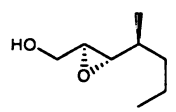


65

Preparation of 65 (method 1): The $PdCl_2(PPh_3)_2$ (9 mg) was dissolved in dry benzene (10 mL). Slowly Bu_3SnH (0.587 mL, 2 mmol) was added via syringe and the reaction

was allowed to stir for 15 minutes. Then **B** (217 mg, 1 mmol) was added via syringe and the reaction was allowed to stir for 1 hr at room temperature. There was no visible change via TLC (eluant: hexanes) so the reaction was heated to reflux. After 3 h a small change in TLC indicated the reaction was proceeding. The reaction was allowed to reflux overnight. The reaction was cooled and the concentrated. Silica gel chromatography (hexanes) afforded 63 mg of **65** (14.8%) as an oil. For spectroscopic data see below.

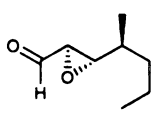
Preparation of 65 (method 2): The $PdCl_2(PPh_3)_2$ (5 mg) was dissolved in dry benzene (10 mL). Hexabutyl ditin (0.46 mmol) was added via syringe. TBAI (127 mg, 0.46 mmol) was then added. Then **B** (100 mg, 0.46 mmol) was added via syringe and the reaction was allowed to reflux overnight. The reaction was cooled and concentrated. Silica gel chromatography (hexanes) afforded product 50 mg (28%) of **65**. IR (neat) 2959, 2856, 2174, 1585, 1250, 844; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (d, J = 2 Hz, 1 H), 5.2 (d, J = 2 Hz, 1 H), 3.1 (s, 2 H), ca. 1.2 (m, 12 H), 0.9 (m, 15 H), 0.1 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 126.2, 104.7, 87.19, 3135, 29.2, 27.4, 13.7, 9.8, 0.17; HRMS (EI) *m/z* 371.1215 [(M - Bu)$^+$; calcd. for $C_{16}H_{31}SiSn$, 371.1219].



69

Preparation of 69: To a –30 °C solution of titanium isoproxide (1.25 mL, 4.6 mmol) in CH_2Cl_2 (10 mL) containing 4 Å sieves was added dropwise a solution of diethyl tartrate (0.75 mL, 4.3 mmol) in CH_2Cl_2 (3 mL). After 20 min, the allylic alcohol **35** (0.506, 3.94 mmol) in CH_2Cl_2 (7 mL) was added over 1 h via syring pump. *t*-Butyl hydrogen peroxide was then added dropwise and the reaction was allowed to stir at –23 °C for 24 h.

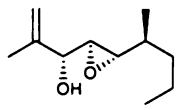
The reaction was quenched by the addition of Na_2SO_3 (aq. sat., 3 mL), Na_2SO_4 (aq. sat., 3 mL), and diethyl ether (9 mL). After stirring at room temperature overnight the reaction was filtered through celite and washed with ether until the precipitate turned from a gel to a solid. The solid was returned to the reaction flask, ethyl acetate (15 mL), was added and the solution was heated to boil for several minutes. The hot solution was filtered through the same celite pad followed by a hot ethyl acetate (15 mL) wash. The filtrate was washed with 15 mL of 50% KOH, brine and dried over $MgSO_4$. The organics were concentrated and silica gel chromatography (33% EtOAc/hexanes) afforded 385 mg (68%) of **69** as a colorless oil. $[\alpha]_D^{20}$ -24.0 (c = 3.24, $CHCl_3$); IR (neat) 3422, 2961, 1458, 1376, 1070, 893 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.9, (m, 1 H), 3.6 (m, 1 H), 2.9 (dd, J = 4.8, 2.4 Hz, 1 H), 2.7 (dd, J = 7.2, 2.4 Hz, 1 H), 1.7 (br. s, 1 H), 1.15-1.55 (m, 5 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.90 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.87, 60.59, 57.01, 36.63, 35.00, 19.95, 15.74, 14.2; HRMS (EI) m/z 145.1229 [$(M + H)^+$; calcd. for $C_8H_{17}O_2$, 145.1228].



70

Preparation of 70: To a 0 °C solution of **69** (0.20 g, 1.38 mmol) in CH_2Cl_2 (14 mL) was added i-Pr_2NEt (1.44 mL, 8.28 mmol), DMSO (3.0 mL), and SO_3•pyridine complex (0.66 g, 4.14 mmol) in DMSO (1.3 mL). The reaction was warmed to room temperature and stirred for 30 min, before being quenched with aq. sat. NH_4Cl (20 mL) and diluted with Et_2O (40 mL). The layers were separated and the organic layer was washed with brine (2 x 10 mL). The organics were concentrated to afford 0.2 g (100%) of **70** as a yellow oil.

This crude product was immediately used in the next reaction without further purification.



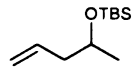
71 / *iso*-71

Preparation of 71: To a –78 °C solution of **70** (1.96 g, 138 mmol) was added *iso*-propenyl magnesium bromide (3.30 mL, 0.5M in THF) dropwise. The solution was allowed to warm slowly to 0 °C over 1 h and allowed to stir an additional 1 h. The reaction was quenched by the addition of NH_4Cl (aq. sat., 1 mL) at 0 °C. The mixture was warmed to room temperature and diluted with water/ether. The layers were separated and the aqueous phase was extracted with ether (2 x 5 mL). The combined organics were washed with brine, dried over $MgSO_4$ and concentrated to afford an oil. Silica gel chromatography (100 % hexanes – 25% EtOAc/hexanes) afforded **71** (138 mg), *iso*-**71** (49.1 mg) and a mixture of the two (65 mg) with a total combined yeild of 85%.

For **71**: $[\alpha]_D^{20}$ -22 (c = 0.15, $CHCl_3$); IR (neat) 3449, 2961, 1716, 1653, 1456, 1379, 1242 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (m, 1 H), 4.94 (m, 1 H), 3.86 (d, J = 5.1 Hz, 1 H), 2.84 (dd, J = 5.1, 2.4 Hz, 1 H), 2.75 (dd, J = 7.2, 2.4 Hz, 1 H), 2.1 (br s, 1 H), 1.80 (s, 3 H), 1.6-1.2 (m, 5 H), 1.0-0.8 (m, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 112.1, 74.9, 61.5, 58.5, 36.7, 35.1, 20.0, 18.9, 15.7, 14.2; HRMS (EI) *m/z* 185.1542 [$(M + H)^+$; calcd. for $C_{11}H_{21}O_2$, 185.1541].

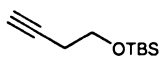
For *iso*-**71**: $[\alpha]_D^{20}$ +5.1 (c = 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (m, 1 H), 4.96 (m, 1 H), 4.27 (d, J = 2.7 Hz, 1 H), 2.9-2.8 (m, 2 H), 1.79 (s, 3 H), 1.6-1.2 (m, 5 H), 1.0-0.8 (m, 6 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 112.9, 72.3, 58.6, 58.6, 36.7, 35.1,

20.0, 18.2, 15.8, 14.2; HRMS (EI) *m/z* 185.1542 [(M + H)$^+$; calcd. for $C_{11}H_{21}O_2$, 185.1541].



74

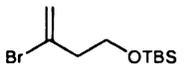
Preparation of 74: To a solution of 4-pentene-2-ol (4.5 g, 52.2 mmol) in CH_2Cl_2 (225 mL) was added TBSCl (8.653 g, 57.4 mmol), TEA (7.98 mL, 57.4 mmol), and DMAP (0.663 g, 5.22 mmol). The reaction was stirred for 48 h. The reaction was then quenched with aq. sat. NH_4Cl (25 mL) and diluted with ether. The layers were separated and the organic layer was washed with KOH (2 x 25 mL, 50%) and brine, dried over $MgSO_4$ and concentrated. Silica gel chromotography (1% – 25% EtOAc/hexanes) afforded 6.9 g (67%) of **78** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (m, 1 H), 5.05 (m, 2 H), 3.8 (m, 1 H), 2.15 (m, 2 H), 1.1 (d, *J* = 6 Hz, 3 H), 0.86 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 116.5, 68.6, 44.3, 25.8, 23.4, 18.2, -4.5, -4.7. The product data is in agreement with reported literature.[100]



78

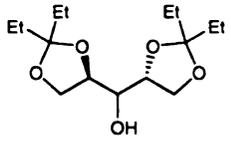
Preparation of 78: To a solution of 3-butyne-1-ol (3.0 g, 42.8 mmol) in CH_2Cl_2 (125 mL) was added TBSCl (7.08 g, 56.5 mmol), imidizole (5.83 mL, 85.6 mmol), and DMAP (0.5 g, 0.43 mmol). The reaction was stirred for 48 h. The reaction with aq. sat. NH_4Cl (25 mL) and diluted with ether. The layers were separated and the organic layer was washed with KOH (2 x 25 mL, 50%) and brine. Dried over $MgSO_4$ and concentrated afforded 7.6 g (69%) of **78** as a colorless liquid which was pure enough by NMR to proceed to next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.7 (t, *J* = 7.2 Hz, 2 H), 2.3 (td, *J* = 6.9, 2.4 Hz, 2 H), 1.9 (t, *J* = 2.4 Hz, 1 H), 0.87 (s, 9 H),

0.0 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.5, 69.3, 61.7, 25.8, 22.8, 18.3, -5.3. The product data is in agreement with reported literature.[101]



79

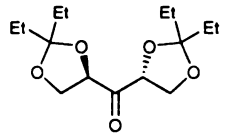
Preparation of 79: To neat **78** (7.6 g, 41.2 mmol) was added *B*-bromo-9-BBN (61.8 mL, 1.0M in CH_2Cl_2, 61.8 mmol). The solution was stirred for 1.25 h at room temperature. NaOAc (5.07 g, 6.18 mmol) was then added, followed immediately by HOAc (31 mL) to hydrolyze the boron adduct. After 45 min, the solution was diluted with hexanes (300 mL), washed with water (250 mL), $NaHCO_3$ (aq. sat. 2 x 250 mL), and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford a translucent oil. Silica gel chromatography (1% – 5% EtOAc/hexanes) afforded **79** (7.02 g, 65 %) as a colorless oil. IR (neat) 2957, 2930, 2858, 1631, 1471, 1388, 1361, 1255, 1105, 837, 777, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.6 (d, J = 1.2 Hz, 1 H), 5.4 (d, J = 1.8 Hz, 1 H), 3.7 (t, J = 6.3 Hz, 2 H), 2.4 (td, J = 6.3, 1.5 Hz, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 118.4, 60.8, 44.8, 25.8, 18.3, -5.3. The product data is in agreement with reported literature.[102]



82

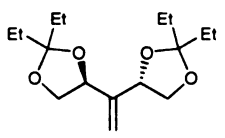
Preparation of 82: To a 40 °C slurry of D-arabitol (15 g, 99 mmol) in DMF (15 mL) containing CSA (0.70 g, 3.0 mmol) was added 3,3-dimethoxypentane (29.0 g, 217 mmol) dropwise (~40 minutes). After stirring for an additional 5.5 hours, the reaction was quenched with Et_3N (0.45 mL) and then concentrated 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 **82** as a clear oil. The crude material was used without purification in the next step.



82a

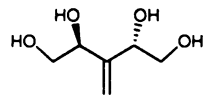
Preparation of 82a: To a solution of alcohol **82** (1.0 g, 3.5 mmol) in CH_2Cl_2 (35 mL) were added DMSO (2.46 mL, 34.7 mmol), *i*-Pr_2NEt (3.62 mL, 20.8 mmol) and SO_3•pyridine (1.65 g, 10.4 mmol). After stirring at room temperature for 90 minutes, the reaction was quenched with a saturated aqueous 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 phases wer 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 (10% EtOAc/hexanes) afforded 0.68 g (68%) of ketone **82a** as a clear oil. $[\alpha]_D^{20}$ +62.4 (c = 0.66, $CHCl_3$); IR (neat): 2975, 2944, 2884, 1736, 1464, 1360, 1262, 1201, 1173, 1082, 1061, 912, 799 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.82 (t, J = 7.69 Hz, 2 H), 4.31 (t, J = 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 (EI) *m/z* 257.1390 [(M - Et)$^+$; calcd. For $C_{15}H_{26}O_5$, 257.1389].



83

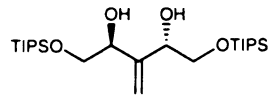
Preparation of 83: To a cold (0 °C) mixture of methyltriphenylphosphonium bromide (1.35 g, 3.77 mmol) in THF (5 mL) was added NaHMDS (3.5 mL, 1.0M THF, 3.5 mmol)

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 **82a** (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 phases were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to give an oil. Purification by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 0.196 g (99%) of alkene **83** as a clear oil. IR (neat): 2975, 2942, 2882, 1464, 1356, 1271, 1198, 1173, 1132, 1080, 1059, 1040, 920 cm^{-1}; $[\alpha]_{589}^{20}$ +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, 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 (EI) *m/z* 255.1599 [(M - Et)$^+$; calcd. For $C_{16}H_{28}O_4$, 255.1596].



84

Preparation of 84: To a solution of bisisopentylidene acetal **83** (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 tetraol **84** as a yellow oil. The crude material was used without purification in the next step.

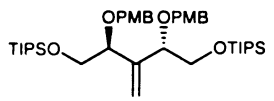


85

Preparation of 85: To a solution of crude tetraol **84** 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, was 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 9.54 g of a yellow oil. Purification by flash chromatography on silica gel (10-50% EtOAc/hexanes) afforded 6.3 g (77% yield, 2 steps) of TIPS disilylated tetraol **85** as a clear oil and 1.04 g (19% yield, 2 steps) of TIPS monosilylated tetra-ol **88** as a white solid.

For **85**: $[\alpha]_D^{20}$ +16.1 (c = 1.6, $CHCl_3$); IR (neat) 3385, 2945, 1464, 1064, 883, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.2 (br s, 2 H), 4.25 (m, 2 H), 3.6 (m, 2 H), 2.9 (br s, OH), 1.0 (m, 42 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 113.4, 73.4, 67.2, 17.9, 11.8; LRMS *m/z* 273 $(M\text{-}(TIPS\text{-}OCH_2))^+$.

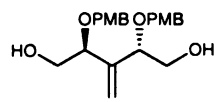
For **88**: mp. 53-55 °C; $[\alpha]_D^{20}$ +18.5 (c = 2.1, $CHCl_3$); IR (neat) 3424, 2945, 1464, 1115, 883, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.2 (m, 2 H), 4.3 (m, 2 H), 3.7 (m, 4 H), 1.0 (m, 24 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 114.1, 73.6, 73.4, 67.2, 65.8, 17.8, 11.7; LRMS *m/z* 273 $(M\text{-}CH_3O)^+$.



86

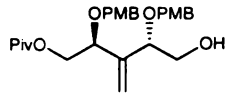
Preparation of 86: To a solution of **85** (2.30 g, 4.99 mmol) in cyclohexane/CH_2Cl_2 (3:1) (44 mL) were added PMB-imidate (5.64 g, 20 mmol) and CSA (0.12 g, 0.50 mmol). The

reaction flask was immersed into a preheated oil bath (~40 °C). After stirring for 24 hours, additional CSA (60 mg, 0.25 mmol) and PMB-imidate (2.8 g, 10 mmol) 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 (5% EtOAc/hexanes) afforded 1.35 g (38%) of fully protected **86** as a clear oil and 1.06 g (37%) of the mono-protected PMB-ether derivative.



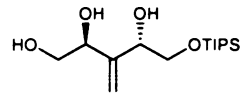
87

Preparation of 87: To a solution of **86** (5.97 g, 8.51 mmol) in THF (90 mL) was added TBAF (19 mL, 1.0M 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.



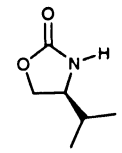
E

Preparation of Fragment E: To a cold (0 °C) solution of diol **87** (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 (35-75% EtOAc/hexanes) afforded 0.68 g (47%) of alcohol **E** as a clear oil and 0.33 g (28%) of recovered diol **86**. For **E**: $[\alpha]_D^{20}$ +91.3 (c = 1.095, $CHCl_3$); IR (neat): 3492, 2965, 2872, 2838, 1728, 1613, 1588, 1514, 1646, 1399, 1364, 1302, 1285, 1250, 1173, 1139, 1073, 1036, 927, 820 cm^{-1}; ^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.



88

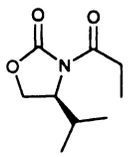
Preparation of 88: To flask charged with pentane washed NaH (50 mg, 2.1 mmol) was added tetraol **84** (260 mg, 1.75 mmol) in THF (4 mL). After stirring at room temperature for 2 hours, TIPSCl (0.37 mL, 1.75 mmol) was added was added and the solution stirred at room temperature overnight. The mixture was diluted with diethyl ether and washed with brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (50% EtOAc/hexanes) afforded 113 mg (25%) of **88** as a white solid. mp. 53-55 °C; $[\alpha]_D^{20}$ +18.5 (c = 2.1, $CHCl_3$); IR (neat) 3424, 2945, 1464, 1115, 883, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.2 (m, 2 H), 4.3 (m, 2 H), 3.7 (m, 4 H), 1.0 (m, 24 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 114.1, 73.6, 73.4, 67.2, 65.8, 17.8, 11.7; LRMS m/z 273 $(M\text{-}CH_3O)^+$.



(4S)-4-isopropyl-2-oxazolidinone

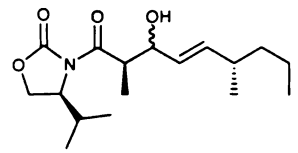
Preparation of (4S)-4-isopropyl-2-oxazolidinone: (S)-Valinol (61 mmol, 6.29 g), freshly distilled diethyl carbonate (61.1 mmol, 8.12 mL), and K_2CO_3 (61 mmol, 8.43 g) were combined in a round bottom flask fitted with a short vigeroix column fitted with a short path stillhead at the top. The mixture was heated to internal reaction temperature of ~126 °C until approx. 120 mmol of ethanol was collected (~6.5 hrs). The mixture was cooled to room temperature and diethyl ether (150 mL) was added. This mixture was filtered to remove K_2CO_3 and concentrated to afford the (4S)-4-isopropyl-2-oxazolidinone (6.7g, 85%) with no further purification necessary. $[\alpha]_D^{20}$ +14.9 (c =

7.21, $CHCl_3$), IR ($CDCl_3$) 3263, 2981, 2916, 2876, 1751, 1479, 1408, 1246, 1091, 1051, 1012, 935, 769, 713. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.1 (br. s, 1 H), 4.4 (t, *J* = 9.0 Hz, 1 H), 4.2 (dd, *J* = 9.0, 6.3 Hz, 1 H), 3.5 (dt, *J* = 8.6, 6.3 Hz, 1 H), 1.6 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H),0.88 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.66, 68.44, 58.22, 32.49, 17.72, 17.43. The product data is in agreement with reported literature.[20]



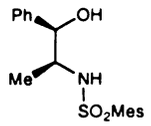
96

Preparation of 96: To a –78 °C solution of (4S)-4-isopropyl-2-oxazolidinone (51.1 mmol, 6.6 g) in THF (250 mL) was added *n*-BuLi (35.1 mL, 1.6M in hexanes, 56.2 mmol) slowly. After 30 min propionyl chloride was added in one portion and the reaction stirred for 3 h at 0 °C. The reaction was quenched with 1M aq. K_2CO_3. The THF was removed via rotovap and the resultant suspension was extracted with CH_2Cl_2 (3 x 200 mL). The combined organics were washed with aq. sat K_2CO_3, dried, and concentrated. Bulb to bulb distillation (0.1 torr) afforded **96** (7.07g, 75.8%) as a colorless oil. mp 64-68 °C (lit. 71-75 °C); $[\alpha]_D^{20}$ +87.2 (*c* = 1.38, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.4 (m, 1 H), 4.2 (m, 2 H), 2.8 (m, 2 H), 2.3 (m, 1 H), 1.2 (d, *J* = 7.6 Hz, 3 H), 0.85 (d, *J* = 7.14 Hz, 3 H), 0.80 (d, *J* = 7.14 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 154.0, 63.2, 58.2, 28.9, 28.2, 17.8, 14.4, 8.2. The product data is in agreement with reported literature.[20]



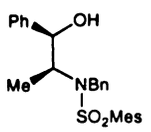
97
(1:1 mix)

Preparation of 97: To a 0 °C solution of **96** (10.1 mmol, 1.87 g) in CH_2Cl_2 (20 mL) was added Bu_2BOTf (12.1 mmol, 12.1 mL, 1M in CH_2Cl_2) followed by slow addition of *i*-Pr_2NEt (11.6 mmol, 2.0 mL). The reaction was stirred for 45 min and then cooled to –78 °C. The solution was added slowly via cannula to a –78 °C solution of **24** (13.1 mmol, 1.65 g) and Et_2AlCl (26.2 mmol, 26.2 mL, 1M in CH_2Cl_2) in CH_2Cl_2 (18 mL). The reaction was stirred overnight at –78 °C. A 5:1 solution of MeOH/30% H_2O_2 (30 mL) was then added and the reaction stirred for 10 min, before being warmed to 0 °C and stirred an additional 1 hour. The solvent was removed via rotovap and the solution was extracted with ether (3 x 50 mL). The combined organics were washed with dilute $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. Chromatography (25% EtOAc/hexanes w/ 1% TEA) afforded **97** (2.17 g, 70%) as a mixture of isomers as determined by ^1H and ^{13}C NMR. Spectral data for mixture: IR (neat) 3505, 2963, 1782, 1703, 1458, 1387, 1205, 1120, 972, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.6 (m, 2 H), 5.4 (m, 2 H), 4.4 (m, 4H), 4.2 (m, 4 H), 3.9 (m, 2 H), 2.6 (d, *J* = 2.7 Hz, 1 H), 2.5 (d, *J* = 7.1 Hz, 1 H), 2.35 (m, 2 H), 2.30 (m, 2 H), 1.2 (m, 8 H), 1.1 (d, *J* = 7.6 Hz, 6 H), 0.9 (m, 24 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 175.8, 154.1, 154.0, 140.2, 139.1, 128.4, 126.9, 122.0, 76.0, 73.1, 63.3, 63.2, 58.7, 58.5, 43.2, 42.7, 39.1, 39.0, 36.2, 36.1, 28.5, 28.4, 20.4, 20.36, 20.34, 20.33, 17.9, 14.7, 14.6, 14.4, 14.1, 14.0, 10.9; HRMS (ESI) *m/z* 350.1750 [$(M+K)^+$, calcd. for $C_{17}H_{29}KNO_4$, 350.1734].



98

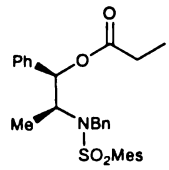
Preparation of 98: To a 0 °C solution of (1S,2R)-(-)norephedrine (6.0 g, 39.6 mmol) in CH_2Cl_2 (15.2 mL) was added triethylamine (6.65 mL, 47.52 mmol). To this solution was added mesityl sulfonyl chloride (8.66g, 39.6 mmol) in one portion. The reaction was stirred at 0 °C for 45 minutes then warmed to r.t. for 1 h 40 min. The reaction was diluted with ethyl ether (200 mL) and washed with water, 1M HCl, $NaHCO_3$ (aq. sat.), and brine. The organics were dried over $MgSO_4$ and concentrated to afford 12.5 g (96%) of **98** as a white solid. $[\alpha]_D^{20}$ -12.6 (c = 1.955, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H), 6.95 (s, 2 H), 4.81 (d, J = 8.8 Hz, 1 H), 4.5 (t, J = 3.8 Hz, 1 H), 3.5 (m, 1 H), 2.7 (s, 6 H), 2.55 (d, J = 4 Hz, 1 H), 2.3 (s, 3 H), 0.85 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 140.2, 138.8, 134.3, 132.0, 128.4, 127.7, 126.0, 75.6, 54.5, 22.9, 20.8, 14.6. The product data is in agreement with reported literature.[64]



99

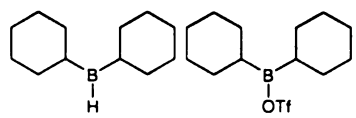
Preparation of 99: To a solution of **98** (7.0 g, 20.9 mmol) in acetonitrile (80 mL) was added benzyl bromide (2.98 mL, 25.08 mmol) and potassium carbonate (4.33 g, 31.35 mmol). The reaction was heated at reflux for 7 h. The reaction was then cooled to r.t. and filtered through a bed of celite. The filter cake was washed with ethyl ether (20 mL). The combined filtrates were concentrated via rotovap and chromatographed on silica (300 g, 10% - 20% EtOAc/hexanes) to afford 8.86 g (66%) of **99**. mp 125-126 °C (lit. 123-124 °C); $[\alpha]_D^{20}$ -7.0 (c = 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 8

H), 7.1 (d, J = 7.6 Hz, 2 H), 6.9 (s, 2 H), 4.99 (s, 1 H), 4.75 (B of ABq, J = 16 Hz, 1 H), 4.5 (A of ABq, J = 16 Hz, 1 H), 3.8 (m, 1 H), 2.6 (s, 6 H), 2.3 (s, 3 H), 2.1 (d, J = 3.3 Hz, 1 H), 1.0 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 142.1, 140.1, 138.6, 133.4, 132.1, 128.6, 128.1, 127.7, 127.4, 127.2, 125.5, 76.6, 59.7, 49.1, 23.0, 20.9, 9.8. The product data is in agreement with reported literature.[64]



100

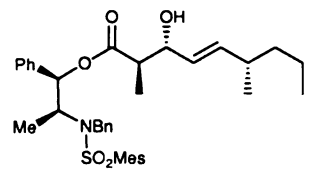
Preparation of 100: To a 0 °C solution of **99** (5.6 g, 13.2 mmol) was added pyridine (1.4 mL, 17.12 mmol) followed by dropwise addition of EtCOCl (1.37 mL, 15.8 mmol). The reaction was allowed to warm to r.t. overnight. The reaction was then diluted with ether and washed with water, 1M HCl, $NaHCO_3$ (aq. sat.), and brine. The organics were dried over $MgSO_4$ and concentrated to afford 5.9 g (94%) **100** as a white solid. mp 147-148 °C (lit. 147-148 °C); $[\alpha]_D^{20}$ +10.1 (c = 2.9, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-7.4 (m, 8 H), 6.9 (m, 2 H), 6.8 (s, 2 H), 5.8 (d, J = 3.8 Hz, 1 H), 4.7 (ABq, J = 17 Hz, 2 H), 4.0 (m, 1 H), 2.5 (s, 6 H), 2.3 (s, 3 H), 2.2 (m, 2 H), 1.1 (d, J = 6.6 Hz, 3 H), 1.0 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 142.5, 140.2, 138.7, 138.6, 133.2, 132.14, 128.39, 128.35, 127.8, 127.3, 127.1, 125.8, 77.9, 56.7, 48.1, 27.4, 23.0, 20.8, 12.6, 8.8. The product data is in agreement with reported literature.[64]



101 **102**

Preparation of 102 via 101:[65] To a 0 °C solution of cyclohexene (20.5 mL, 200 mmol) in ether (100 mL) was added borane-DMS complex (50 mL, 2M in THF, 100 mmol)

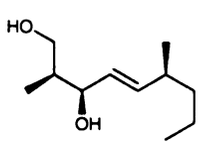
dropwise. The reaction was stirred at 0 °C for 2 h and then allowed to settle for 1 h. The solvent was removed with a cannula and then 50 mL of ether was added. The reaction was stirred, then allowed to resettle. The solvent was removed via cannula and then the reaction was placed under high vacumn at 0 °C overnight affording **101** (15.9 g, 85%) as a white solid. Dry hexanes (150 mL) were added to a flask containing **101** (15.9 g) and stirred for 1 h at 0 °C to dissolve as much **101** as possible. Triflic acid (11.6 g, 84.8 mmol) was added dropwise over an hour and the reaction stirred for 3 h at 0 °C. The reaction was then allowed to settle for 1 h. Contrary to the literature, no yellow layer formed. The bulk of the solvent was removed via aspirator vacuum, then the concentrate was quickly concentrated to driness under high vacuum. The compound started to yellow and the mass of product **102** was taken (26 g, 95%) and then the solution was recooled to 0 °C and dry hexanes (80 mL) were added and the resulting 1M solution was transferred to a Sure-Seal™ bottle for storage.



103

Preparation of 103: To a –78 °C solution of **100** (9.36 g, 19.5 mmol) in CH_2Cl_2 (200 mL) was added freshly distilled TEA (7.59 mL, 54.6 mmol). This mixture was then added dropwise, via cannula, to a –78 °C solution of Cy_2BOTf (47.6 mL, 0.9M in hexanes, 42.9 mmol) in CH_2Cl_2 (70 mL). The reaction was allowed to stir for 2 h at –78 °C. A solution of aldehyde **24** (3.2 g, 25.3 mmol) in CH_2Cl_2 (15 mL) was then added via syringe pump over 1 h. The cold bath was packed with dry ice, a cryocool was set for –60 °C, and the reaction was allowed to stir overnight (~16 h) at this temperature. The

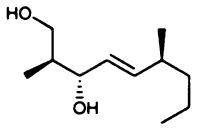
reaction was quenched by the addition of pH 7 buffer (80 mL). This was followed by the addition of cold MeOH (200 mL) and 30% H_2O_2 (22 mL). The reaction was placed in an ice /water bath and allowed to warm to 0 °C. The reaction was maintaned at 0 °C for 8 h, before being allowed to warm to room temperature overnight. The solvent was removed via rotovap (to remove methanol for extraction purposes). The residue was dissolved in CH_2Cl_2 (200 mL) washed with $NaHCO_3$ (aq. sat.). The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford a viscous, colorless oil. Flash chromatography (10-15% EtOAc/Hexanes, Silica Gel) afforded 7.0 g (59%) of **103** as a viscous oil. $[\alpha]_D^{20}$ +26.1 (*c* = 1.8, $CHCl_3$), IR(neat) 3500, 2959, 2936, 1741, 1604, 1496, 1456, 1323, 1153, 1014, 860, 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.2 (m, 8 H), 6.95 (s, 2 H), 6.9 (m, 2 H), 5.8 (d, *J* = 4.4 Hz, 1 H), 5.5 (dd, *J* = 15.3, 7.7 Hz, 1 H), 5.35 (dd, *J* = 16, 7.7 Hz, 1 H), 4.8 (B of ABq, *J* = 16.4 Hz, 1 H), 4.55 (A of ABq, *J* = 16.4 Hz, 1 H), 4.1 (m, 2 H), 2.5 (s, 6 H), 2.28 (s, 3 H), 2.1 (m, 2 H), 1.25 (m, 4 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 1.05 (d, *J* = 7.6 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 142.5, 141.8, 140.3, 138.7, 138.3, 133.5, 132.1, 128.4, 128.3, 127.9, 127.8, 127.7, 127.2, 125.8 78.2, 75.0, 56.8, 48.2, 45.8, 38.9, 36.2, 22.9, 20.8, 20.4, 20.3, 14.1, 14.0, 13.5; HRMS (FAB) *m/z* 644.2839 [(M + K)$^+$, calcd. for $C_{36}H_{47}KNO_5S$, 644.2812]



104

Preparation of 104: To a 0 °C solution of **103** (450 mg, 0.74 mmol) in THF (10 mL) was added $LiAlH_4$ (73 mg, 1.9 mmol). The reaction was stirred for 1 h at 0 °C, then $Na_2SO_4 \bullet 10\ H_2O$ (~2 g) was added slowly. The resulting mixture was allowed to warm

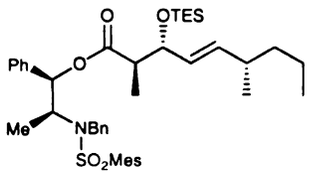
to room temperature and stirred for 2 h. The reaction was filtered through celite 503 and the precipitate was washed with diethyl either. The combined organics were concentrated. Chromatography (50% EtOAc/hexanes) afforded the desired product **104** (54 mg, 40%) as a colorless oil. $[\alpha]_D^{20}$ +31.1 (*c* = 2.70, $CHCl_3$); IR (neat) 3331, 2959, 2850, 1668, 14456, 1379, 1022, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42 (m, 2 H), 3.87 (t, *J* = 7.69 Hz, 1 H), 3.6 (m, 3 H), 3.35 (br s, 1 H), 2.1 (m, 1 H), 1.7 (m, 1 H), 1.2 (m, 4 H), 0.9 (d, *J* = 6.6 Hz, 3 H), 0.85 (t, *J* = 6.5 Hz, 3 H), 0.8 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 129.7, 79.2, 67.7, 40.2, 39.0, 36.2, 20.5, 20.4, 14.0, 13.6; HRMS (CI) *m/z* 185.1536 [$(M - H)^+$, calcd. for $C_{11}H_{21}O_2$, 185.1542].



105

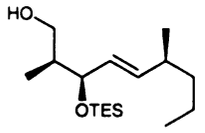
Preparation of 105: To a solution of **25** (1.54 g, 4.28 mmol) in THF (20 mL) was added acetic acid (0.365 mL, 6.42 mL), followed by the dropwise addition of Bu_3B (4.7 mL, 1M in THF, 4.7 mmol). The resulting mixture was stirred at r.t. for 1.5 h. The reaction was then cooled to 0 °C and $LiBH_4$ (4.28 mL, 2M in THF, 8.56 mmol) was added dropwise. The reaction was stirred at 0 °C for 1.5 h. MeOH (15 mL), pH 7 Buffer (9 mL) were then added followed by the slow addition of 30% H_2O_2 (8.5 mL). The reaction was stirred for 1 hr at r.t., volatile solvents were removed and the reaction was extracted with CH_2Cl_2 (5 x 15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (50% EtOAc/hexanes) afforded 618 mg (78%) of **105** as an oil. $[\alpha]_D^{20}$ +15.6 (*c* = 1.9, $CHCl_3$), IR (neat) 3360, 2959, 2874, 1728, 1458, 1379, 1288, 1032, 972 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.5 (m, 2 H), 4.2 (m, 1 H), 3.6 (m, 2 H), 2.4 (br s, 2 H), 2.1 (m, 1 H), 1.9 (m, 1 H), 1.2 (m, 4 H), 0.96 (d, *J*

= 6.9 Hz, 3 H), 0.86 (t, J = 6.9 Hz, 3 H), 0.84 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 127.8, 76.1, 66.2, 39.8, 39.0, 36.2, 20.5, 20.3, 14.1, 11.5; HRMS (EI) m/z 185.1540 [(M - H)$^+$, calcd. for $C_{11}H_{21}O_2$, 185.1541].



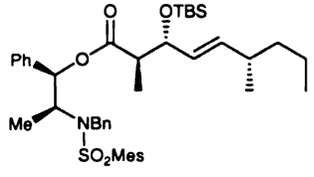
106

Preparation of 106: To a solution of **104** (7.16 g, 11.8 mmol) was in CH_2Cl_2 (125 mL) was added 2,6-lutidine (1.644 mL, 14.12 mmol). TESOTf (3.2 mL, 14.12 mmol) was then added dropwise. The reaction was almost complete after 5 minutes (TLC). The reaction was diluted with ether after 20 minutes. The ethereal solution was washed twice with 1M $KHCO_3$ followed by brine. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography on silica gel (10% EtOAc/hexane) afforded the desired product **106** as a colorless thick oil (8.0 g, 94%). $[\alpha]_D^{20}$ +29.6 (c = 0.34); IR (neat) 3034, 29.59, 2876, 1747, 1604, 1458, 1327, 1240, 1153, 974, 012, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.0-7.4 (m, 8 H), 6.9 (s, 2 H), 6.7 (d, J = 7.1 Hz, 2 H), 5.7 (d, J = 4.3 Hz, 1 H), 5.4 (dd, J = 15.3, 7.6 Hz, 1 H), 5.2 (dd, J = 15.9, 7.6 Hz, 1 H), 4.9 (ABq, J = 16.48, 1 H), 4.5 (ABq, J = 16.48, 1 H), 4.2 (t, J = 7.6 Hz, 1 H), 4.0 (m, 1 H), 2.5 (t, J = 7.1 Hz, 1 H), 2.49 (s, 6 H), 2.3 (s, 3 H), 2.05 (m, 1 H), 1.25 (m, 4 H), 1.1 (d, J = 6.5 Hz, 3 H), 0.9 (m, 18 H), 0.55 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 142.3, 140.3, 139.5, 138.7, 138.4, 133.2, 132.1, 128.4, 128.3, 128.2, 128.14, 127.7, 127.1, 126.1, 77.6, 75.7, 56.7, 48.2, 47.1, 39.0, 36.1, 22.8, 20.8, 20.4, 20.1, 14.2, 14.0, 13.3, 6.7 , 4.9; HRMS (FAB) m/z 758.3651 [(M + K)$^+$, calcd. for $C_{42}H_{61}KNO_5SSi$, 758.3677]



107

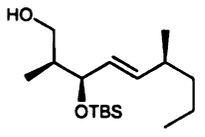
Preparation of 107: To a –78 °C solution of **106** (8.0 g, 11.1 mmol) in CH_2Cl_2 (~200 mL) was added DIBAL (27.75 mL, 1M in hexanes, 27.75 mmol) slowly by syringe. The reaction was stirred for 1 h then quenched by the addition of Rochelle's salt. The resulting mixture was stirred and allowed to warm to r.t. overnight. The layers were separated and the organic layer was washed with Rochelle's salt and brine. The combined aqueous layers were back extracted with CH_2Cl_2 (2 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography (250 g silica, 10 % EtOAc/hexanes + 1% TEA pack) afforded the desired product **107** as a thick colorless oil (2.8 g, 85 % yield). $[\alpha]_{365}^{20}$ +9.4 (c = 0.47, $CHCl_3$); IR (neat) 3424, 2959, 1458, 1379, 1238, 1097, 798, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.4 (m, 2 H), 4.0 (m, 1 H), 3.6 (m, 2 H), 3.2 (s, 1 H), 2.15 (m, 1 H), 1.7 (m, 1 H), 1.25 (m, 4 H), 0.9 (m, 18 H), 0.6 (q, J = 8.2 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 130.2, 80.5, 67.0, 41.1, 39.1, 36.2, 20.4, 20.2. 14.0, 13.9, 6.6, 5.0; HRMS (EI) *m/z* 271.2090 [$(M - Et)^+$, calcd. for $C_{15}H_{31}O_2Si$, 271.2093].



108

Preparation of 108: To a solution of **103** (2.0 g, 3.2 mmol) was in CH_2Cl_2 (100 mL) was added 2,6-lutidine (0.46 mL, 3.9 mmol). TBSOTf (0.74 mL, 3.9 mmol) was then added dropwise. The reaction was quenched by diluting with ether after 1.5 h. The ethereal solution was washed twice with 1M $KHCO_3$ followed by brine. The organic

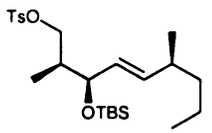
layer was dried over $MgSO_4$ and concentrated. Chromatography on silica gel (10% EtOAc/hexane) afforded the desired product **108** as a highly viscous oil (2.15 g, 94%). $[\alpha]_D^{20}$ +20 (c = 0.255, $CHCl_3$) IR (neat) 2959 , 2932, 2858 , 1743 , 1604 , 1454 , 1327 , 1250 , 1155 , 974 , 910 , 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.0-7.4 (m, 8 H), 6.85 (s, 2 H), 6.7 (d, J = 7.1 Hz, 2 H), 5.65 (d, J = 5.4 Hz, 1 H), 5.38 (dd, J = 15.38, 7.69 Hz, 1 H), 5.20 (dd, J = 15.38, 7.69 Hz, 1 H), 4.8 (Abq, J = 16.48 Hz, 1 H), 4.41 (Abq, J = 16.48 Hz, 1 H), 4.2 (t, J = 7.4 Hz, 1 H), 4.1 (p, J = 6.4 Hz, 1 H), 2.5 (t, J = 7.1 Hz, 1 H), 2.41 (s, 6 H), 2.3 (s, 3 H), 2.05 (m, 1 H), 1.2 (m, 4 H), 1.12 (d, J = 6.5 Hz, 3 H), 0.9 (m, 6 H), 0.8 (s, 12 H), 0.0 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 142.4, 140.3, 139.4, 138.6, 138.3, 133.1, 132.1, 131.7, 128.4, 128.16, 128.14, 127.7, 127.2, 126.3, 77.6, 75.4, 56.7, 48.1, 46.9, 39.0, 36.1, 25.9, 22.8, 20.8, 20.4, 20.2, 18.1, 14.4, 14.0, 13.0, -4.1, -4.6; HRMS (FAB) m/z 758.3698 [$(M + K)^+$, calcd. for $C_{42}H_{61}KNO_5SSi$, 758.3677].



109

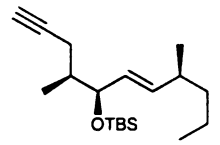
Preparation of 109: To a –78 °C solution of **108** (2.0 g, 2.77 mmol) in CH_2Cl_2 (~100 mL) was added DIBAL (6.92 mL, 1M in hexanes, 6.92 mmol) slowly by syringe. The reaction was stirred for 2 h then quenched by the addition of Rochelle's salt. The reaction was allowed to warm to r.t. and stir overnight. The layers were separated and the organic layer was washed with Rochelle's salt and brine. The combined aqueous layers were back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Chromatography (silica, 10 % EtOAc/hexanes + 1% TEA) afforded 689 mg (83%) of **109** as a colorless oil. $[\alpha]_D^{20}$ -8 (c = 0.245, $CHCl_3$); IR (neat) 3370, 2959, 2800, 1465, 1301, 1251, 1060, 974, 835 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 5.34 (m, 2 H), 3.96 (t, *J* = 6.5 Hz, 1 H), 3.68 (m, 1 H), 3.5 (m, 1 H), 2.11 (m, 1 H), 1.67 (m, 1 H), 1.2 (m, 4 H), 0.95 (d, *J* = 6.5 Hz, 3 H), 0.88 (m, 15 H), 0.05 (d, *J* = 12.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 130.12, 79.9, 66.3, 41.0, 39.0, 36.2, 25.8, 20.4, 20.3, 17.9, 14.1, 14.0, -3.7, -4.8; HRMS (CI) *m/z* 241.1990 [(M - $C_3H_7O)^+$, calcd. for $C_{14}H_{29}OSi$, 241.1988].



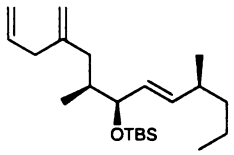
110

Preparation of 110: To a 0 °C solution of **109** (1.75 g, 5.8 mmol) in CH_2Cl_2 (50mL) was added TEA (1.61 mL, 11.6 mmol) followed by *p*-toluenesufonyl chloride (1.32g, 6.96 mmol) and DMAP (61 mg, 0.5 mmol). The reaction was stirred at 0 °C for 20 min, then allowed to warm to r.t. and stir overnight. The reaction was diluted with 150 mL CH_2Cl_2 and washed with 5% HCl (2x), aq. sat. $NaHCO_3$, and brine. The organics were dried over $MgSO_4$, fithered, and concentrated. Chromatography (15% Et_2O/hexanes) afforded the desired product **110** (1.8 g, 68% yield) as a colorless oil. $[\alpha]_D^{20}$ +0.9 (*c* = 0.94, $CHCl_3$); IR (neat) 2959, 2858, 1457, 1367, 1179, 972, 777, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.3 (d, *J* = 8.2 Hz, 2 H) 5.3 (dd, *J* = 15.38, 7.69 Hz, 1 H), 5.15 (dd, *J* = 15.38, 7.69 Hz, 1 H), 3.9 (m, 3 H), 2.41 (s, 3 H), 2.05 (m, 1 H), 1.8 (m, 1 H), 1.2 (m, 4 H), 0.9 (d, *J* = 6.5 Hz, 3 H), 0.8 (m, 15 H), -0.05 (d, *J* = 2.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.0, 133.0, 129.8, 129.0, 127.9, 75.0, 72.6, 39.6, 39.0, 36.2, 25.7, 21.6, 20.4, 20.3, 18.0, 14.0, 13.1, -3.8, -5.0; HRMS (EI) *m/z* 397.1871 [(M - Bu)$^+$; calcd. for $C_{20}H_{33}O_4SSi$, 236.2139].



111

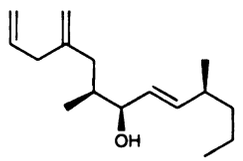
Preparation of 111: Lithium acetylide ethylene diamine complex (962 mg, 10.4 mmol) was weighed out in a glove bag. The solid was added quickly to DMSO (5 mL) and resulting solution was stirred vigorously for 5 min. Then neat tosylate **110** (1.9 g, 4.18 mmol) was added dropwise. The reaction was stirred overnight and at which time it appeared complete by TLC. The mixture was diluted with diethyl ether and carefully quenched with 10% HCl. The mixture was washed with 10% HCl and $NaHCO_3$ (aq. sat.). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography afforded 882 mg (76%) of **111** as a colorless oil. $[\alpha]_D^{20}$ +10.3 (c = 1.56, $CHCl_3$); IR (neat) 3316, 2959, 1482, 1251, 1062, 837, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (d, *J* = 7.5, 15.4 Hz, 1 H), 5.25 (d, *J* = 7.5, 15.4 Hz, 1 H), 3.9 (t, *J* = 7.0 Hz, 1 H), 2.27 (m, 1 H), 2.12 (m, 2 H), 1.95 (s, 1 H), 1.70 (m, 1 H), 1.25 (m, 4 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.85 (12 H), 0.02 (s, 3 H), -0.01 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 131.8, 129.7, 76.8, 69.0, 39.3, 39.1, 36.3, 25.9, 21.7, 20.6, 20.5, 18.2, 15.4, 14.2, -3.8, -4.7; HRMS (CI) *m/z* 307.2458 [$(M - H)^+$; calcd. for $C_{19}H_{35}OSi$, 307.2457].



112

Preparation of 112: To a solution of **111** (638 mg, 2.06 mmol) in THF (2.0 mL) was added indium rod (472 mg, 4.13 mmol, cut into small peices) and allyl bromide (1.5 mL, 16.48 mmol). The flask was purged with N_2 and fitted with a N_2 filled balloon. The

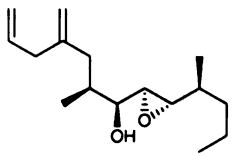
reaction was sonicated without temperature control for 6 hours. The reaction was quenched by diluting with diethyl ether (75 mL), washed with 10% HCl, $NaHCO_3$, dried over $MgSO_4$, and concentrated. Silica gel chromatography (hexanes) afforded the desired product **112** (529 mg, 73%) as a colorless oil. $[\alpha]_D^{20}$ +17.2 (c = 1.0, $CHCl_3$); IR (neat) 2959, 1482, 1255, 1062, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.8 (m, 1 H), 5.3 (m, 2 H), 5.05 (d, J = 7.6 Hz, 1 H), 5.0 (s, 1 H), 4.75 (d, J = 13.7 Hz, 2 H), 3.8 (m, 1 H), 2.70 (d, J = 7.1 Hz, 2 H), 2.25 (m, 1 H), 2.05 (m, 1 H), 1.7 (m, 2 H), 1.2 (m, 4 H), 0.9 (d, J = 6.5 Hz, 3 H), 0.8 (m, 12 H), 0.77 (d, J = 6.6 Hz, 3 H), 0.0 (d, J = 7.7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 137.8, 136.5, 129.5, 116.0, 111.4, 77.6, 40.3, 39.4, 39.2, 37.5, 36.3, 25.9, 20.6, 20.5, 18.5, 14.9, 14.1, -3.9, -4.8; HRMS (CI) *m/z* 351.3064 [$(M - H)^+$, calcd. for $C_{22}H_{41}OSi$, 351.3083].



113

Preparation of 113: To a solution of **112** (467 mg, 1.3 mmol) in THF (10 mL) was added acetic acid (141 mg, 2.34 mmol) and TBAF (2.6 mL, 1M in THF, 2.6 mmol). The mixture was stirred at room temperature overnight. An addition quantity of TBAF (2 mL) was added and the mixture heated in a 40 °C oil bath for 5 hours. The mixture was cooled to room temperature, diluted with diethyl ether, and washed with 10% HCl and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Chromatography (silica gel, 10% diethyl ether/hexanes) afforded 150 mg (50%) of **113** and starting material (101 mg, 22% recovery) both of which were oils. Resubjecting the recovered material to the reaction conditions afforded an additional 61 mg of productto

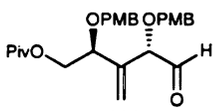
give a total of 211 mg (69%) of **113**. $[\alpha]_D^{20}$ +12.8 (c 0.50, $CHCl_3$); IR (neat) 3441, 2961, 1724, 1456, 1377, 972 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 5.93-5.72 (m, 1 H), 5.35-5.60 (m, 2 H), 5.01-5.17 (m, 2 H), 4.81 (d, *J* = 11.54 Hz, 2 H), 3.82-3.99 (m, 1 H), 2.67-2.83 (m, 2 H), 2.08-2.35 (m, 2 H), 1.71-1.94 (m, 2 H), 1.61 (br s, 1 H), 1.14-1.40 (m, 4 H), 0.99 (d, *J* = 7.14 Hz, 3 H), 0.70-0.95 (m, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ 146.6, 139.5, 136.3, 128.5, 116.1, 111.7, 77.2, 40.4, 39.6, 39.1, 36.5, 36.4, 20.7, 20.5, 14.9, 14.1; HRMS (EI) *m/z* 236.2140 [$(M)^+$, calcd. for $C_{16}H_{28}O$, 236.2139].



F

Preparation of Fragment F: Molecular sieves (4 Å) were added to a round bottom flask that was then flame dried and cooled under inert atmosphere. The flask was charged with CH_2Cl_2 (30 mL) and Ti(*i*-PrO)$_4$ (124 mg, 0.67 mmol) was then added. The temperature was lowered to –30 °C before (+)-diethyl *L*-tartrate (150 mg, 0.73 mmol) in CH_2Cl_2 (4 mL) was added dropwise. Then solution of **113** (160 mg, 0.67 mmol) in CH_2Cl_2 (4 mL) was added dropwise over 10 min followed by *t*-BuOOH (314 μL, 4.2M in toluene, 1.3 mmol). The reaction placed in a –23 °C bath and stirred for 24 hours before being quenched with saturated aqeious solutions of Na_2SO_3 (1 mL) Na_2SO_4 (1 mL). The reaction mixture was diluted with 10 mL diethyl ether warmed to r.t. and stirred for overnight. The mixture was filtered through celite and the filter cake washed with diethyl ether until the precipitate became granular. The yellow paste was scraped from the filter aid and placed back into the reaction flask. Ethyl acetate (10 mL) was added and the mixture was heated to a boil for 5 minutes. The mixture was then filtered through the

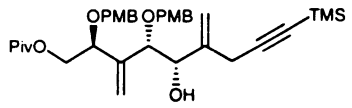
same filter aide and the filter cake was washed with hot ethyl acetate (5 mL). The filtrate was washed with brine, dried over MgSO4, filtered, and concentrated. Chromatography (silica gel, 10% EtOAc/ hexanes) afforded 117 mg (69%) of **F** as a colorless oil. $[\alpha]_D^{20}$ +14.3 (c = 2.8, $CHCl_3$); IR (neat) 3445, 2928, 1728, 1641, 1458, 1379, 1288, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73-5.93 (m, 1 H), 5.01-5.16 (m, 2 H), 4.84 (d, J = 9.89 Hz, 2 H), 3.69 (br s, 1 H), 2.82-2.92 (m, 2 H), 2.77 (d, J = 6.59 Hz, 2 H), 2.33-2.47 (m, 1 H), 1.83-1.99 (m, 3 H), 1.67 (br s, 1 H), 1.20-1.59 (m, 4 H), 0.83-1.00 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 136.3, 116.3, 112.2, 72.0, 59.5, 57.9, 40.3, 39.1, 36.7, 35.2, 34.6, 20.0, 15.9, 15.0, 14.2; HRMS (EI) *m/z* 253.2165 [$(M+H)^+$, calcd. for $C_{16}H_{29}O_2$, 253.2168].



114

Preparation of 114: To a stirred solution of Dess-Martin periodinane[98] (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 **E** (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 **114** as a yellow oil. $[\alpha]_D^{20}$ +50.1 (c = 0.685, $CHCl_3$); IR (neat): 2963, 2870, 2837, 1730, 1613, 1514, 1464, 1397, 1366, 1283, 1250, 1173, 1157, 1078, 1034, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (d, J = 1.65 Hz, 1 H), 7.23 (d, J = 8.79 Hz,

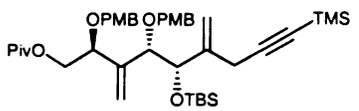
2 H), 7.19 (d, J = 8.79 Hz, 2 H), 6.85 (d, J = 8.79 Hz, 2 H), 6.83 (d, J = 8.79 Hz, 2 H), 5.51 (s, 1 H), 5.48 (s, 1 H), 4.57 (ABq, J = 11.54 Hz, 1 H), 4.44 (s, 1 H), 4.38 (ABq, J = 11.54 Hz, 1 H), 4.13 – 4.22 (m, 3 H), 4.06 – 4.12 (m, 2 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 1.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.1, 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.



115

Preparation of 115: t-BuLi (2.85 mL, 1.7M 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, 1.0M 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 **114** (0.76 g, 1.62 mmol) in CH_2Cl_2 (8 mL) was added $MgBr_2 \bullet Et_2O$ (1.60 mL, 1.0M 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 (25% EtOAc/hexanes) afforded 0.57 g (58%) of alcohol **115** as a yellow oil. $[\alpha]_D^{20}$ +72.3 (c = 0.495, $CHCl_3$); IR (neat): 3382, 2961, 2917, 2885, 2178, 1727, 1653,

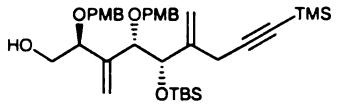
1617, 1514, 1458, 1250, 1154, 1036, 843, 760 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.39 Hz, 2 H), 7.19 (d, *J* = 8.39 Hz, 2 H), 6.85 (d, *J* = 8.39 Hz, 2 H), 6.84 (d, *J* = 8.39 Hz, 2 H), 5.57 (s, 1 H), 5.48 (s, 1 H), 5.36 (s, 1 H), 5.19 (s, 3 H), 4.53 (ABq, *J* = 10.99 Hz, 1 H), 4.51 (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, 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_3)$^+$; calcd for $C_{35}H_{52}O_7SiN$, 626.3501].



116

Preparation of 116: To a cold (0 °C) solution of alcohol **115** (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 (10% EtOAc/hexanes) to give 1.07 g (81%) of TBS-silylated alcohol **116** as a clear oil. $[\alpha]_D^{20}$ +19.8 (*c* = 0.57, $CHCl_3$); IR (neat): 2955, 2858, 2174, 1720, 1613, 1587, 1514, 1464, 1362, 1302, 1157, 1099, 862,

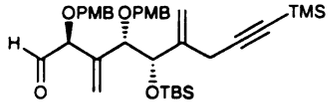
841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.79 Hz, 4 H), 6.89 (d, *J* = 8.24 Hz, 4 H), 5.57 (s, 1 H), 5.41 (s, 1 H), 5.33 (d, *J* = 1.65 Hz, 1 H), 5.16 (s, 1 H), 4.56 (ABq, *J* = 11.54 Hz, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.46 (d, *J* = 4.94 Hz, 1 H), 4.35 (ABq, *J* = 10.99 Hz, 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 [$(M + H)^+$; calcd for $C_{41}H_{63}O_7Si_2$, 723.4112].



117

Preparation of 117: To a cold (0 °C) solution of Piv-ester **116** (1.07 g, 1.48 mmol) in THF (12 mL) was added dropwise (~3 minutes) Super-Hydride® (3.11 mL, 1.0M 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), 0.5M 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 (25% EtOAc/hexanes) to give 0.83 g (88 %) of alcohol **117** as a clear oil. $[\alpha]_D^{20}$ +26.3 (*c* = 0.51, $CHCl_3$); IR (neat): 3455, 2957, 2932, 2897, 2859, 2176, 1613, 1514, 1464, 1302, 1250, 1173, 1096, 1063, 1038, 841, 777, 760 cm^{-1}; ^1H

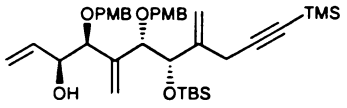
NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.79 Hz, 2 H), 7.22 (d, *J* = 8.79 Hz, 2 H), 6.86 (d, *J* = 8.79 Hz, 2 H), 6.84 (d, *J* = 8.79 Hz, 2 H), 5.47 (s, 1 H), 5.35 (s, 1 H), 5.29 (s, 1 H), 5.11 (s, 1 H), 4.55 (ABq, *J* = 10.99 Hz, 1 H), 4.50 (ABq, *J* = 12.09 Hz, 1 H), 4.40 (d, *J* = 5.49 Hz, 1 H), 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].



118

Preparation of 118: To a stirred solution of Dess-Martin periodinane[98] (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 **117** (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 **118** as a yellow oil. $[\alpha]_D^{20}$ -55.2° (*c* = 0.545, $CHCl_3$);IR ($CHCl_3$): 2955, 2857, 2174, 1730, 1613, 1588, 1514, 1464, 1362, 1304, 1101, 1003, 910, 862, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.33 (d, *J* = 2.75 Hz, 1 H), 7.24 (d, *J* = 8.79 Hz, 2

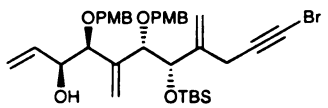
H), 7.20 (d, J = 8.79 Hz, 2 H), 6.86 (d, J = 8.79 Hz, 2 H), 6.83 (d, J = 8.79 Hz, 2 H), 5.52 (s, 1 H), 5.41 (s, 1 H), 5.26 (s, 1 H), 5.05 (s, 1 H), 4.52 (ABq, J = 11.54 Hz, 1 H), 4.42 (ABq, J = 11.54 Hz, 1 H), 4.42 – 4.32 (m, 3 H), 4.18 (ABq, J = 10.99 Hz, 1 H), 3.91 (d, J = 5.49 Hz, 1 H), 3.79 (s, 3 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.



119

Preparation of 119: To a cold (0 °C) solution of crude aldehyde **118** (0.74 g, 1.2 mmol) in a $Et_2O/PhH/CH_2Cl_2$ (3:1:1) solution (18 mL) was added $MgBr_2 \bullet Et_2O$ (1.3 mL, 1.0M Et_2O/PhH (3:1), 1.3 mmol). After stirring for 6 minutes, vinyl magnesium bromide (2.3 mL, 1.0M 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 (10% EtOAc/hexanes) to give 0.45 g (58%) of alcohol **119** as a clear oil. $[\alpha]_D^{20}$ +6.8 (c = 0.575, $CHCl_3$); IR (neat): 3552, 2958, 2932, 2900, 2858, 2176, 1614, 1514, 1464, 1362, 1303, 1250, 1173, 1091, 1037, 921, 841, 779, 760 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.39 Hz,

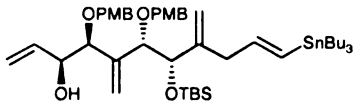
2 H), 7.22 (d, J = 8.39 Hz, 2 H), 6.86 (d, J = 8.39 Hz, 4 H), 5.90 (ddd, J = 17.23, 10.16, 5.30 Hz, 1 H), 5.50 (s, 1 H), 5.42 (s, 1 H), 5.33 (s, 1 H), 5.31 (m, 1 H), 5.18 (s, 1 H), 5.15 (m, 1 H), 4.55 (ABq, J = 11.49 Hz, 1 H), 4.54 (ABq, J = 11.05 Hz, 1 H), 4.50 (d, J = 4.86 Hz, 1 H), 4.35 (ABq, J = 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, 104.4, 86.8, 82.1, 80.5, 77.2, 73.5, 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].



120

Preparation of 120: TMS-alkyne **119** (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 (10% EtOAc/hexanes) afforded 0.28 g (92%) of 1-bromo-alkyne **120** as a clear oil. ^{1}H 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

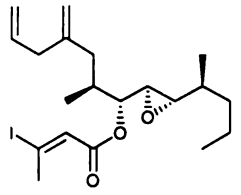
Hz, 1 H), 4.31 (ABq, J = 11.93 Hz, 1 H), 4.23 (ABq, J = 11.05 Hz, 1 H), 4.02 (m, 2 H), 3.92 (d, J = 4.86 Hz, 1 H), 3.79 (s, 6 H), 3.17 (ABq, J = 19.44 Hz, 1 H), 3.04 (ABq, J = 19.44 Hz, 1 H), 2.45 (br s, OH), 0.85 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 159.1, 142.9, 142.8, 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].



121

Preparation of 121: 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 **120** (0.167 g, 0.248 mmol) in Et_2O (0.5 mL) and a drop of TBAF (1.0M 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 (10-15% EtOAc/hexanes) to give 0.16 g (73%) of E-vinyl stannane **121** as a clear oil. $[\alpha]_D^{20}$ +3.6° (c = 0.555, $CHCl_3$); IR (neat): 2955, 2928, 2855, 1613, 1514, 1464, 1361, 1302, 1250, 1173, 1084, 1040, 920, 835, 777 cm^{-1}; ^{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

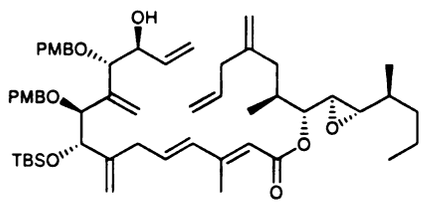
H), 3.79 (s, 6 H), 3.0 (m, 2 H), 2.39 (d, J = 5.74 Hz, 1 H), 1.50 (m, 6 H), 1.30 (m, 6 H), 0.87 (m, 24 H), -0.01 (s, 3 H), -0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 159.1, 147.2, 146.6, 143.2, 138.3, 130.7, 130.6, 130.2, 129.3, 129.0, 116.0, 114.2, 113.7, 113.7, 113.1, 81.9, 80.8, 78.0, 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 $C_{43}H_{67}O_6Si^{116}Sn$, 823.3726].



122

Preparation of 122: To a 0 °C solution of Ph_3P (613 mg, 2.34 mmol) in THF(10 mL) was added 4 Å MS followed by DIAD (473 mg, 2.34 mmol). After 2 minutes, large amounts of white precipitate formed. To this milky suspension was quickly added a premixed solution of epoxide **F** (295 mg, 1.17 mmol) and fragment **D** (496 mg, 2.34 mmol) in THF (5 mL). Shortly after the addition the solution turned clear. The reaction was stirred at 0 °C for 30 minutes before the white precipitate returned. The reaction was stirred overnight at room temperature. The reaction was then diluted with diethyl ether and washed with 1M HCl, water, and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (1% EtOAc/hexanes) afforded 484 mg (71%) of **122** and 20 mg (16%) recovered **F**, both as colorless oils. $[\alpha]_D^{20}$ -19.5 (c = 1.46, $CHCl_3$); IR (neat) 2963, 1718, 1616, 1332, 1178, 1074 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66-6.74 (m, 1 H), 5.71- 5.91 (m, 1 H), 4.98-5.14 (m, 2 H), 4.87 (s, 1 H), 4.78 (s, 1 H), 4.62 (dd, J = 5.1, 6.9 Hz, 1 H), 3.01 (s, 3 H), 2.89 (dd, J = 2.1, 6.9 Hz, 1 H), 2.68-2.78 (m, 2 H), 2.65 (dd, J = 5.1, 7.2 Hz, 1 H), 2.30 (dd, J = 8.7, 13.8 Hz, 1 H), 1.98-2.14 (m, 1

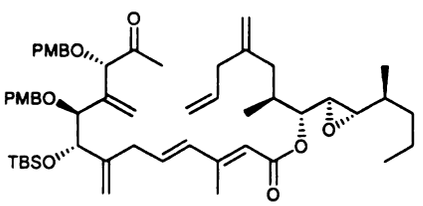
H), 1.85 (dd, J = 6.9, 13.8 Hz, 1 H), 1.22-1.57 (m, 5 H), 0.86-1.03 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 144.9, 136.0, 131.0, 121.3, 116.4, 112.9, 61.6, 56.7, 54.1, 40.2, 39.1, 36.6, 35.2, 33.5, 31.1, 19.9, 15.8, 14.9, 14.2; HRMS (CI) *m/z* 447.1395 [(M + H)$^+$, calcd. for $C_{20}H_{32}IO_3$. 447.1398].



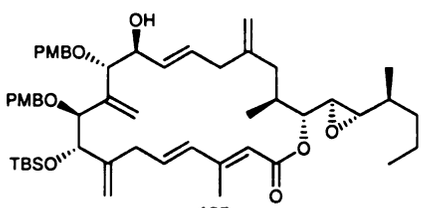
123

Preparation of 123: To a cold (0 °C) solution of (E)-vinyl iodide **122** (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 **121** (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 (10-15% EtOAc/hexanes) to give 0.17 g (62%) of diene **123** as a light yellow oil. $[\alpha]_D^{20}$ -2° (c = 0.70, $CHCl_3$); IR (neat): 3513, 3077, 2959, 2930, 1715, 1636, 1613, 1588, 1514, 1464, 1381, 1302, 1248, 1173, 1150, 1074, 1036, 914, 835, 779 cm^{-1}; ^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 (125 MHz, $CDCl_3$) δ 166.3, 159.2, 152.9, 146.7, 145.3, 143.2, 138.3, 138.2, 136.3, 136.2, 135.5, 134.8, 130.7, 130.5, 130.4, 129.3, 129.2, 129.1, 129.0, 117.8, 116.5, 116.2, 114.3, 113.7, 113.2, 112.7, 81.9, 80.8, 80.7, 78.4, 77.8, 75.9, 73.5, 73.3, 71.6, 70.8, 70.7, 61.5, 57.0, 55.3, 40.3, 39.3, 37.1, 36.6, 35.3, 33.7, 25.9, 20.0, 18.3, 15.8, 15.0, 14.2, 14.0, -5.0, -5.1; HRMS (FAB) *m/z* 913.5652 [(M + H)$^+$; calcd for $C_{55}H_{81}O_9Si$, 913.5650].



124



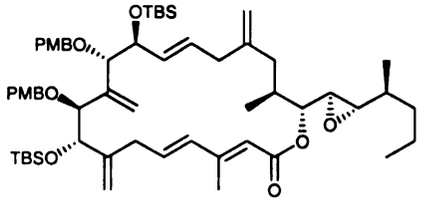
125

Attempted Preparation of 125 (First generation Grubbs catalyst): To a gently refluxing solution of diene **123** (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 (10% EtOAc/hexanes) to give 8.7 mg (34%) of truncated ketone **124** as an

oil and 6 mg (23%) of the recovered diene. For **124**: IR (neat): 2957, 2930, 2857, 1715, 1636, 1613, 1514, 1464, 1389, 1358, 1302, 1250, 1173, 1150, 1074, 1038, 912, 835, 777 cm^{-1}; ^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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 166.4, 159.4, 159.1, 153.0, 146.8, 145.3, 141.8, 136.2, 135.4, 134.8, 130.5, 129.7, 129.3, 129.2, 117.7, 116.4, 114.7, 113.9, 113.6, 112.6, 86.1, 80.9, 78.1, 75.8, 71.5, 70.9, 65.8, 61.5, 57.0, 55.3, 40.3, 39.3, 36.4, 35.8, 35.3, 33.7, 29.7, 25.9, 23.9, 20.0, 18.3, 15.8, 15.2, 15.0, 14.2, 14.0, -5.0, -5.1; HRMS (FAB) *m/z* 899.58 [(M + H)$^+$; calcd for $C_{54}H_{79}O_9Si$, 899.55].

Preparation of 125 (imidazolium based catalyst): To a gently refluxing solution of diene **123** (20 mg, 0.022 mmol) in CH_2Cl_2 (20 mL) was added dropwise (~8 hours) a solution of $PhHC{=}Ru(PCy_3)(IMes\text{-}H_2)Cl_2$ (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 (10% EtOAc/hexanes) afforded 7 mg (36%) of macrocycle

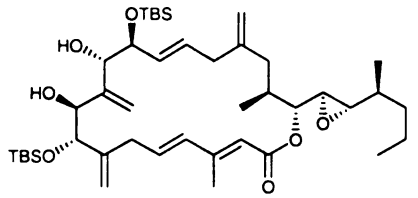
125. IR (neat): 3515, 2957, 2930, 2857, 1709, 1636, 1613, 1514, 1464, 1381, 1302, 1248, 1173, 1154, 1074, 1038, 909, 835, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) most diagnostic peaks (two conformers)[76] δ 7.29 (d, *J* = 8.84 Hz, 1 H), 7.21 (d, *J* = 8.39 Hz, 1 H), 7.11 (d, *J* = 8.39 Hz, 2 H), 6.86 (d, *J* = 8.84 Hz, 1 H), 6.83 (d, *J* = 8.84 Hz, 1 H), 6.81 (d, *J* = 8.39 Hz, 1 H), 6.80 (d, *J* = 8.84 Hz, 1 H), 5.93 (m, 1 H), 5.85 (d, *J* = 15.91 Hz, 1 H), 5.64 (s, 1 H), 5.56 (d, *J* = 5.30 Hz, 1 H), 5.41 (br s, 1 H), 5.09 (s, 1 H), 5.05 (m, 1 H), 5.02 (s, 1 H), 4.96 (br s, 1 H), 4.82 (s, 1 H), 4.73 (s, 1 H), 4.64 (ABq, *J* = 11.93 Hz, 1 H), 4.60 (ABq, *J* = 11.05 Hz, 1 H), 4.53 (ABq, *J* = 11.05 Hz, 1 H), 4.48 (ABq, *J* = 11.93 Hz, 1 H), 4.44 (dd, *J* = 3.53, 7.51 Hz, 1 H), 4.38 (ABq, *J* = 11.93 Hz, 1 H), 4.33 (m, 1 H), 4.19 (d, *J* = 7.51 Hz, 1 H), 4.07 (ABq, *J* = 11.93 Hz, 1 H), 3.80 (s, 3 H), 3.78 (m, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.76 (s, 3 H), 3.55 (d, *J* = 7.07 Hz, 1 H), 3.42 (s, 1 H), 3.02 (dABq, *J* = 8.84, 14.58 Hz, 1 H), 2.93 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.82 (dABq, *J* = 6.19, 14.58 Hz, 1 H), 2.71 (m, 1 H), 2.69 (dd, *J* = 2.21, 7.51 Hz, 1 H), 2.49 (m, 1 H), 2.46 (dABq, *J* = 3.98, 13.25 Hz, 1 H), 1.94 (s, 3 H), 1.84 (d, *J* = 7.95 Hz, 1 H), 1.00 (d, *J* = 7.07 Hz, 3 H), 0.97 (d, *J* = 6.63 Hz, 3 H), 0.08 (s, 3 H), 0.06 (s, 3 H), 0.03 (s, 3 H), -0.01 (s, 3 H); HRMS (FAB) *m/z* 907.5197 [(M + Na)$^+$; calcd for $C_{53}H_{76}O_9SiNa$, 907.5156].



126

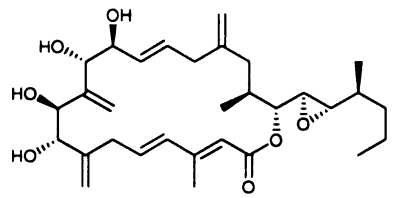
Preparation of 126: To a cold (0 °C) solution of alcohol **125** (0.021 g, 0.024 mmol) in CH_2Cl_2 (0.6 mL) were added 2,6-lutidine (6 drops) and TBSOTf (6 drops). After stirring for 7.5 hours, additional 2,6-lutidine (3 drops) and TBSOTf (3 drops) were added. After stirring an additional 60 minutes, 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 (10% EtOAc/hexanes) afforded 21 mg (90%) of fully protected macrocycle **125** as a clear oil. IR (neat): 2957, 2928, 2857, 1709, 1614, 1514, 1464, 1389, 1360, 1302, 1248, 1173, 1152, 1082, 1038, 914, 835, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (mixture of conformers)[76] 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), 3.80 (s, 3H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.75 (s, 3 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 (FAB) *m/z* 999.60 [$(M + H)^+$; calcd for $C_{59}H_{91}O_9Si_2$, 999.62].



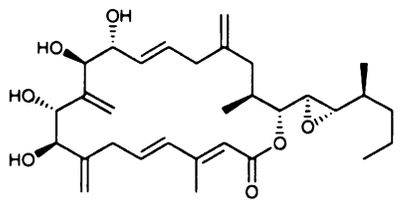
127

Preparation of 127: To a solution of PMB-ether **126** (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 (10% EtOAc/hexanes) to give 4.6 mg (52%) of diol **127** as a clear oil. IR (neat): 3567, 2965, 2928, 2857, 1707, 1636, 1603, 1464, 1379, 1262, 1154, 1098, 1030, 905, 801; ^{1}H 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, 4 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); HRMS (FAB) *m/z* 759.34 [(M + H)$^+$; calcd for $C_{43}H_{75}O_7Si_2$, 759.50].



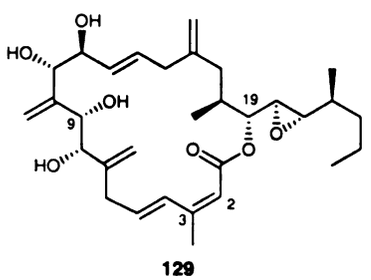
1

Preparation of 1: To a solution of disilylated macrocycle **127** (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, 0.1M 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 (25% EtOAc/hexanes, 1% MeOH] and eluted with EtOAc/hexanes (1:3) to give 0.3 mg (25%) of presumed amphidinolide A (**1**) as a white solid. $[\alpha]_D^{20}$ -56 (c = 0.18, $CHCl_3$); IR (neat) 1711, 1638, 1608, 1462, 1246, 1236, 1151, 970, 904, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.18 (d, J = 15.63 Hz, 1 H), 6.06 (ddd, J = 4.40, 10.25, 15.14 Hz, 1 H), 5.77 (s, 1 H), 5.74 (m, 1 H), 5.57 (s, 1 H), 5.56 (s, 1 H), 5.35 (s, 1 H), 5.26 (dd, J = 3.42, 15.14 Hz, 1 H), 5.21 (s, 1 H), 4.85 (s, 1 H), 4.76 (s, 1 H), 4.52 (dd, J = 3.91, 6.84 Hz, 1 H), 4.28 (d, J = 2.44 Hz, 1H), 4.22 (s, 1 H), 4.20 (m, 1 H), 3.83 (br s, 1 H), 3.20 (dABq, J = 3.91, 15.63 Hz, 1 H), 3.09 (dABq, J = 10.25, 14.65 Hz, 1 H), 2.90 (dd, J = 2.44, 7.32 Hz, 1 H), 2.74 (dABq, J = 4.88, 14.16 Hz, 1 H), 2.68 (dd, J = 2.44, 7.32 Hz, 1 H), 2.65 (m, 1 H), 2.52 (dd, J = 3.91, 12.70 Hz, 1 H), 2.27 (d, J = 1.47 Hz, 3 H), 2.12 (m, 1 H), 1.76 (dd, J = 10.74, 12.70 Hz, 1 H), 1.50 – 1.20 (m, 5 H), 0.97 (d, J = 4.40 Hz, 3 H), 0.96 (d, J = 4.40 Hz, 3 H), 0.89 (t, J = 7.07 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 152.0, 146.8, 145.4, 144.1, 136.4, 134.8, 131.2, 130.5, 119.4, 115.4, 114.8, 113.6, 77.6, 73.9, 72.9, 71.3, 70.0, 61.3, 54.4, 38.5, 38.5, 36.8, 36.7, 35.4, 33.5, 20.0, 16.0, 16.0, 14.2, 13.8; HRMS (FAB) m/z 553.3115 [$(M + Na)^+$; calcd. for $C_{31}H_{46}O_7Na$, 553.3141].



128

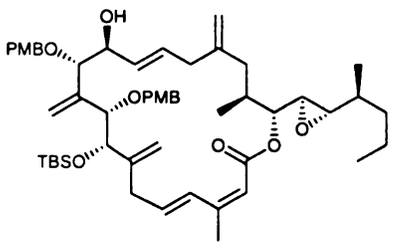
Spectral and optical data for 8,9,11,12-epi-"amphidinolide A" (128): $[\alpha]_D^{20}$ -89 (*c* = 0.11,$CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 6.14 (d, *J* = 15.64 Hz, 1 H), 6.06 (dt, *J* = 15.38, 6.66 Hz, 1 H), 5.80 (s, 1 H), 5.67 (dt, *J* = 14.10, 6.41 Hz, 1 H), 5.46 (s, 1 H), 5.37 (s, 1 H), 5.36 (dd, *J* = 4.61, 15.38 Hz, 1 H), 5.30 (s, 1 H), 5.18 (s, 1 H), 4.83 (s, 1 H), 4.75 (s, 1 H), 4.58 (dd, *J* = 3.33, 6.92 Hz, 1 H), 4.37 (d, *J* = 4.61 Hz, 1 H), 4.16 (t, *J* = 4.36 Hz, 1 H), 4.09 (d, *J* = 4.61 Hz, 1 H), 3.88 (d, *J* = 3.33 Hz, 1 H), 3.19 (dABq, *J* = 6.66, 14.35 Hz, 1 H), 2.96 (dABq, *J* = 7.18, 14.10 Hz, 1 H), 2.90 (dd, *J* = 2.05, 6.66 Hz, 1 H), 2.71 (dABq, *J* = 6.66, 14.10 Hz, 1 H), 2.66 (dd, *J* = 2.06, 7.69 Hz, 1 H), 2.61 (dABq, *J* = 7.95, 14.10 Hz, 1 H), 2.41 (dd, *J* = 3.59, 14.10 Hz, 1 H), 2.23 (s, 3 H), 2.2 – 0.9 (complex series of signals, 26 H; due in part to the small sample size, **128** was not isolated in pristine form. Both water and grease are present in the ^1H NMR spectrum making the assignment of this series of signals difficult); HRMS (ESI-MS) *m/z* 531.3315 [$(M + H)^+$, calcd for $C_{31}H_{47}O_7$, 531.3322].



129

Spectral and optical data for 2,3-Z-"amphidinolide A" (129): $[\alpha]_D^{20}$ +19 (*c* = 0.11, $CHCl_3$); ^1H 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),

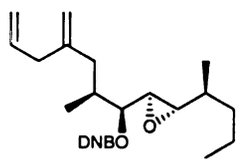
5.35 (s, 1 H), 5.13 (s, 1 H), 4.87 (s, 1 H), 4.73 (s, 1 H), 4.64 (dd, J = 3.09, 6.63 Hz, 1 H), 4.24 (br s, 1 H), 4.14 (br s, 1 H), 4.12 (br s, 1 H), 4.04 (br s, 1 H), 3.09 (dABq, J = 15.02, 5.74 Hz, 1 H), 2.94 (d, J = 8.39 Hz, 1 H), 2.91 (dd, J = 6.63. 2.21 Hz, 1 H), 2.82 (dABq, 14.58, 6.19 Hz, 1 H), 2.63 (m, 3 H), 2.25 (m, 1 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 (FAB) *m/z* 553.3115 [(M + Na)$^+$, calcd for $C_{31}H_{46}O_7Na$ 553.3141.



130a

Preparation of 130a: To a gently refluxing solution of diene **130** (26 mg, 0.029 mmol) in CH_2Cl_2 (26 mL) was added dropwise (~2 hours) a solution of PhHC=Ru(PCy_3)(IMes-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 (10% EtOAc/hexanes) afforded 22 mg (88%) of macrocycle **130a**. $[\alpha]_D^{20}$ +37.5 (c = 0.557, $CHCl_3$); IR (neat): 3515, 2957, 2930, 2857, 1709, 1636, 1613, 1514, 1464, 1381, 1302, 1248, 1173, 1154, 1074, 1038, 909, 835, 777 cm^{-1}; ^{1}H 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, 2 H), 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

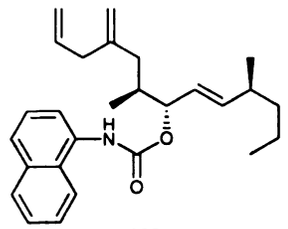
Hz, 1 H), 4.20 (ABq, J = 11.49 Hz, 1 H), 4.19 (d, J = 6.19 Hz, 1 H), 3.96 (br s, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.78 (m, 1 H), 3.69 (br s, 1 H), 3.07 (dABq, J = 7.51, 15.91 Hz, 1 H), 2.96 (dABq, J = 6.19, 15.46 Hz, 1 H), 2.90 (dd, J = 2.21, 6.63 Hz, 1 H), 2.78 (dABq, J = 6.19, 14.58 Hz, 1 H), 2.64 (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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 159.2, 158.8, 150.6, 146.3, 145.6, 144.2, 136.2, 132.6, 131.2, 130.5, 129.4, 129.2, 128.8, 116.6, 115.1, 114.3, 113.7, 113.5 (2), 112.1, 82.4, 78.4, 76.4, 71.8, 71.7, 70.1, 65.8, 61.3, 56.5, 55.2 (2), 39.9, 37.9, 37.0, 36.7, 35.3, 33.4, 25.9, 21.0, 20.0, 18.3, 15.9, 15.2, 14.2, -4.6, -4.8; HRMS (FAB) *m/z* 907.5197[(M + Na)$^+$; calcd for $C_{53}H_{76}O_9SiNa$, 907.5156].



132

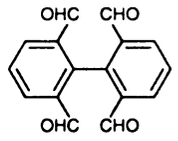
Preparation of 132: To a solution of **F** (10 mg, 0.04 mmol) in dry CH_2Cl_2 (5 mL) was added 3,5-dinitrobenzoic acid (13 mg, 0.07 mmol) and DMAP (2 mg, 0.012 mmol). DCC (0.07 mL, 1M in CH_2Cl_2, 0.07 mmol) was then added and the reaction stirred overnight. The mixture was diluted with diethyl ether, washed with HCl (1M), dried over $MgSO_4$, filtered, and concentrated. Chromatography (1.5 g silica gel, 10% EtOAc/hexanes) afforded the 14.3 mg (80%) of **132** as a light yellow oil. $[\alpha]_D^{20}$ -12.6 (c = 1.955, $CHCl_3$); IR (neat) 3103, 2961, 1736, 1549, 1344, 1271, 1167, 912, 731; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.2 (t, J = 2.2 Hz, 1 H), 9.0 (d, J = 2.2 Hz, 2 H), 5.76 (m, 1 H), 5.0 (m, 2 H), 4.9 (t, J = 6.1 Hz, 1 H), 4.83 (d, J = 11 Hz, 2 H), 2.95 (dd, J = 2.9, 6.2 Hz, 1 H),

2.78 (m, 3 H), 2.39 (dd, J = 4.8, 14.1 Hz, 1 H), 2.2 (m, 1 H), 2.0 (dd, J = 9.7, 14.1 Hz, 1 H) 1.3 (m, 5 H), 1.08 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H), 0.85 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 148.8, 144.8, 136.0, 133.7, 129.4, 122.5, 116.5, 113.1, 79.4, 61.4, 54.9, 40.3, 39.1, 36.6, 35.2, 33.8, 20.0, 15.8, 15.3, 14.2. HRMS (CI) *m/z* 446.2050 [$(M)^+$, calcd. for $C_{23}H_{30}N_2O_7$, 446.2053].



133

Preparation of 133: Allylic alcohol **113** (50 mg, 0.21 mmol) was combined with naphtyl isocyanate (33.8 mg, 0.26 mmol). After heating to 70 °C for 3 hours, the reaction was cooled to room temperature. Petrolium ether (2 mL) was added and the mixture heated to boiling for 2 minutes. The hot solution was filtered though a cotton plug and the solvent was removed to afford 48 mg (56%) of **133** as a low melting (<39 °C) white solid. $[\alpha]_D^{20}$ +27.5 (c = 1.31, $CHCl_3$); IR (neat) 3316, 3072, 2957, 1701, 1539, 1496, 1211 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4-7.8 (m, 7 H), 6.85 (s, 1 H), 5.80 (m, 1 H), 5.65 (dd, J = 7.9, 15.4 Hz, 1 H), 5.40 (dd, J = 7.9, 15.4 Hz, 1 H), 5.18 (t, J = 6.2 Hz, 1 H), 5.05 (m, 2 H), 4.84 (s, 1 H), 4.79 (s, 1 H), 2.8 (s, 2 H), 2.0-2.25 (m, 3 H), 1.80 (dd, J = 9.2, 13.7 Hz, 1 H), 1.3 (m, 4 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 3 H), 0.88 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 145.9, 141.6, 136.3, 134.1, 132.7, 128.6, 126.0, 125.8, 125.7, 124.8, 123.9, 120.5, 116.1, 112.0, 79.8, 40.4, 39.4, 39.0, 36.4, 34.9, 20.4, 20.35, 14.9, 14.0; HRMS (ESI) *m/z* 406.2760 [$(M+H)^+$, calcd. for $C_{27}H_{36}NO_2$, 406.2746].

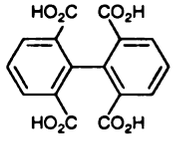


138

Preparation of 138: Pyrene was dissolved in a 2:1 CH_2Cl_2/MeOH solution. TEA (1 mL) was added. The solution was purged with nitrogen for 15 min and cooled to –78 °C. Ozone was then bubbled through the solution for 1.5 h at which time the solution was greenish-blue. Nitrogen was then bubbled through the solution for 15 min, then dimethylsulfide (7 mL) was added dropwise and the solution was slowly warmed up to r.t. overnight. The solvent was removed and the residue dissolved in EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and filtered. Norit–A charcoal was added to the filtrate and the mixture was heated to a boil to decolorize. The solution was filtered and concentrated. Silica gel chromatography (50% EtOAc/hexanes) afforded **138** (2.1g, 54%). An analytical sample was recrystallized from water. mp 155-156 °C (lit. 162-163). IR (KBr) 3373, 3076, 2831, 2737, 1695, 1572, 1450, 1383, 1238, 1159, 958, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 4 H) 8.28 (d, J = 8.1 Hz, 4 H), 7.89 (t, J = 8.1 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 135.6 (2), 135.5, 129.7.

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.23; H, 3.98.

The product data is in agreement with reported literature.[81]



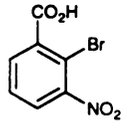
139

Preparation of 139: To a solution of **138** (3.7 mmol, 1.0 g) in water (20 mL) was added potassium stearate (0.0004 mmol, 0.130 g) and $KMnO_4$ (11.1 mmol, 1.75 g). The

reaction was heated to 50 °C overnight and was then cooled to room temperature and filtered through a pad of NaCl. The filtrate was acidified to pH 2.5, filtered, and dried (3 azeotropes with benzene followed by overnight on high vacuum) to afford the desired product **139** (950 mg, 79%) as a light brown solid. IR (KBr) 2997, 1684, 1583, 1464, 1404, 1267, 929, 761, 684, 534 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.2 (s, ~4 H), 7.9 (dd, J = 7.69, 3.3 Hz, 4 H), 7.50 (td, J = 7.69, 3.3 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3 ,142.1, 132.2, 131.6, 126.4; λ_{max} = 292 nm (EtOH); LRMS (direct probe EI) m/z 330 $(M)^+$.

Anal. Calcd for $C_{16}H_{10}O_8$: C, 58.19; H, 3.05. Found: C, 58.10; H, 3.10.

The product data, with the exception of λ_{max}, is in agreement with reported literature.[82]

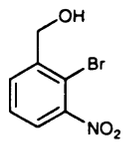


152

Preparation of 152: To a warm solution of sodium hydroxide (18.9 g, 0.472 mol) in water (190 mL) was added 3-nitropthalic acid (50 g, 0.237 mol). $Hg(OAc)_2$ (83.1 g, 0.261 mol) was dissolved in water (170 mL) and acetic acid (12 mL) (contrary to the literature no filtration appeared necessary). The two solutions above were combined in a 1L flask equipped with a condenser and then slowly heated to 170 °C and held at that temperature for 70 hours. The reaction was tested for completion by connecting a tygon tube to the top of the condenser and placing the free end into a flask of water to test for bubbles of CO_2. As the reaction cooled the product settled to the bottom and the supernatant liquid was filtered off. The product in the reaction flask was stirred with 3 x100 mL portions of water to facilitate breaking up the resultant mass before being transfered to the aforementioned fritted filter. The product was air dried for at least 30

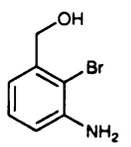
min then the vacuum was broken and 100 mL 100% ethanol was added and the product was broken up with a glass rod. The product, anhydro-2-hydroxymercuri-3-nitrobenzoic acid, was then air-dried.

In a 2L 3-neck flask fitted with a condenser and mechanical stirred, sodium hydroxide (31.2 g, 0.78 mol) was dissolved in water (950 mL) and heated to a low boil. The product from the above procedure was added slowly to the boiling solution. Concentrated HCl (63 mL) was added slowly followed by acetic acid (18.7 mL) and the reaction allowed to cool with constant stirring to afford a thick precipitate. A solution of bromine (32 mL), NaBr (64.4 g), and water (95 mL) was then added rapidly through a bent glass funnel along the mechanical stirrer shaft taking care that the solution is not so hot as to cause the bromine to boil out before being incorporated into the mixture. After the bromine was added, the reaction was heated to a boil for 5-10 minutes. The solution was then made basic by the addition of sodium hydroxide (12 g) and filtered through a gravity filter. The filtrate was acidified to Congo red by the addition of conc. HCl. The precipitated product was collected in a fritted filter and air-dried. The product was purified by recyrstallization from ethanol/water and vacuum drying to afford 28 g (48% 2-steps) of the **152** as an off white solid. ^{1}H NMR (300 MHz, $CDCl_3$/DMSO-d_6) δ 7.47 (dd, J = 1.65, 7.69 Hz, 1 H), 7.37 (dd, J = 1.65, 7.69 Hz, 1 H), 7.14 (t, J = 7.69 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$/ DMSO-d_6) δ 165.7, 150.9, 135.8, 132.5, 127.5, 125.2, 110.9. The product data is in agreement with reported literature.[87]



153

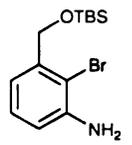
Preparation of 153: A 100 mL pear flask was charged with 2-bromo-3-nitro-benzoic acid (**152**) (1.1g, 4.5 mmol). Dry THF (10 mL) was then added and then the solution was cooled to 0 °C. BH_3·THF complex (9.2 mL, 1M in THF, 9.2 mmol) was added dropwise. The reaction was stirred at 0 °C for 1 h, then at r.t overnight. Water (10 mL) was added slowly followed by K_2CO_3 (0.25 g). The reaction was extracted with ether (4 x 10 mL). The combined organic layers were dried and concentrated to afford the crude product in quantitative yield as a white solid. This material is used without purification in the next step.



154

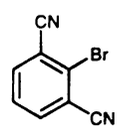
Preparation of 154: Crude **153** (0.9g, 4.6 mmol) was suspended in acetic acid (10 mL). Concentrated HCl (0.15 mL), ethanol (10 mL), and iron powder (1.1 g, 19.7 mmol) were added. The reaction was fitted with a reflux condenser and after a nitrogen purge was refluxed (ca. 113 °C) for 3 h. The reaction was neutralized with sodium carbonate (ca. pH 7). The mixture was extracted with ethyl acetate (4 x 17 mL). The combined extracts were washed with sat. $NaHCO_3$, dried, and concentrated to afford a yellow solid. Flash chromatography (50 g silica gel, 25% EtOAc/hexanes) afforded the 0.5 g (55% from 2-bromo-3-nitro-benzoic acid) of **154** as a white solid. mp. 115-117 °C (lit. 113-115 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.6, (s, 2 H), 4.1 (br s, 2 H), 6.77 (d, J = 7.6 Hz, 1 H), 6.85

(d, J = 6.5 Hz, 1 H), 7.1 (t, J = 7.6 Hz, 1 H). The product data is in agreement with reported literature.[86]



155

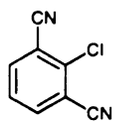
Preparation of 155: To a solution of **154** (200mg, 0.99 mmol) in CH_2Cl_2 (5 mL) was added TBSCl (165 mg, 1.1 mmol), imidizole (134 mg, 1.98 mmol) and a few crystals of DMAP. The reaction was fitted with an N_2 filled balloon and allowed to stir for 30 h. The solvent was removed and the crude material was dissolved in ether (50 mL) and washed with 1M $KHCO_3$ (2 x 15 mL), dried, and concentrated. Chromatography (20% EtOAc/exanes) afforded 230 mg (74%) of **155** as a white semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (t, J = 7.6 Hz, 1 H), 7.0 (d, J = 6.6 Hz, 1 H), 6.71, (d, J = 7.7 Hz, 1 H), 4.76 (s, 2 H), 4.1 (br s, 2 H), 1.1 (s, 9 H), 0.19 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.9, 127.6, 117.0, 114.1, 107.9, 65.0, 25.9, 18.3, -5.3. The product data is in agreement with reported literature.[86]



158

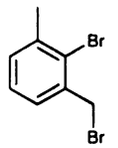
Preparation of 158: To a 0 °C solution of diisopropyl amine (1.15 mL, 8.2 mmol) in THF (40 mL) was added *n*-BuLi (5.1 mL, 1.6M in hexane, 8.2mmol) dropwise. The mixture was allowed to stir at 0 °C for 30 min and was then cooled to –107 °C (isooctane/liq. N_2). A solution of 1,3-dicyanobenzene (1.0 g, 7.8 mmol) in THF (20 mL) was then added via syringe pump over 0.5 h. After 30 min of stirring at –107 °C a solution of 1,2-dibromo-tetrachloroethane (2.67 g, 8.2 mmol) in THF (10 mL) was added

dropwise and the resulting solution was allowed to slowly warm to room temperature. The solvent was removed from the dark solution and brine (50 mL) was added. The mixture was extracted with CH_2Cl_2 (50 mL). The organic layer was dried and concentrated. Silica Gel chromatography (25% EtOAc/hexanes) afforded the 1.0 g (62%) as a white solid. mp. 188-188.5 °C (lit 190-191 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6 (t, J = 7.6 Hz, 1 H), 7.8 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 128.8, 128.4, 118.1, 115.6. The product data is in agreement with reported literature.[103]



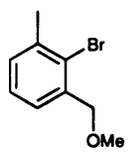
162

Preparation of 162: To a 0 °C solution of diisopropyl amine (2.28 mL, 16.4 mmol) in THF (80 mL) was added *n*-BuLi (10.8 mL, 1.6M in hexane, 16.4 mmol) dropwise. The mixture was allowed to stir at 0 °C for 30 min and was then cooled to –107 °C (isooctane/ liq. N_2). A solution of 1,3-dicyanobenzene (2.0 g, 15.6 mmol) in THF (40 mL) was then added via syringe pump over 0.5 h. After 30 min of stirring at –107 °C a solution of hexachloroethane (4.0 g, 17.2 mmol) in THF was added dropwise and the solution allowed to slowly warm to room temperature. The solvent was removed from the dark solution and brine (50 mL) was added. The mixture was extracted with CH_2Cl_2 (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Recyrstallization (dichloromethane-pentane) of the crude mixture afforded 1.0 g (40%) of **162** as a white solid. mp. 154-155 °C (lit. 154-156); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.69 Hz, 2 H), 7.53 (t, J = 7.69 Hz, 1 H); ^{13}C NMR (125 MHz, CDCl3) δ 139.8, 137.43, 127.79, 115.5, 114.16. The product data is in agreement with reported literature.[103]



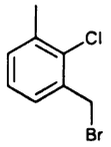
169

Preparation of 169: To a solution of NBS (0.96 g, 5.4 mmol) in CCl_4 (12 mL) was added 2-bromo-*m*-xylene (0.7 mL, 5.4 mmol) and AIBN (42 mg, 0.26 mmol). After refluxing for 3 h, the solution was cooled to room temperature and filtered through a pad of celite. The pad was washed with CCl_4 (3 mL). The solvent was removed to afford a light yellow oil. Purification by flash chromatography on silica gel (hexanes) afforded 866 mg (60.7%) of **169** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 3 H), 4.6 (s, 2 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 137.2, 130.9, 128.6, 127.2, 127.0, 34.6, 23.7. The product data is in agreement with reported literature.[94]



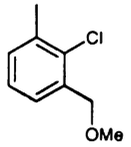
170

Preparation of 170: Sodium metal (88.4 mg, 3.85 mmol) was added piecewise to MeOH (3 mL) at 0 °C. After the metal had fully reacted, this solution was added via pipette to a 0 °C solution of **169** (849 mg, 3.21 mmol) in MeOH (12.5 mL). The reaction was stirred at 0 °C for 20 minutes then allowed to stir overnight at room temperature. The reaction was quenched by slow addition of NH_4Cl (aq. sat. 1 mL). The solvent was removed via rotovap and the residue dissolved in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 460 mg (67%) of **170** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 3 H), 4.5 (s, 2 H), 3.45 (s, 3 H), 2.48 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 138.3, 137.8, 129.7, 126.8, 126.2, 74.5, 58.6, 23.4.



171

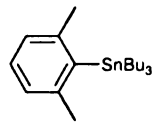
Preparation of 171: To a solution of NBS (2.52 g, 14.2 mmol) in CCl_4 (30 mL) was added 2-chloro-*m*-xylene (2.0 g, 14.2 mmol) and AIBN (115 mg, 0.7 mmol). After refluxing for 3 h, the solution was cooled to room temperature and filtered through a pad of celite. The pad was washed with CCl_4 (5 mL). The solvent was removed to afford a light yellow oil. Purification by flash chromatography on silica gel (hexanes) afforded 1.67 g (54%) of **171** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 3 H), 4.6 (s, 2 H), 2.4 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 135.4, 134.4, 131.2, 128.7, 126.5, 31.4, 20.5. The product data is in agreement with reported literature.[104]



172

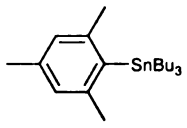
Preparation of 172: Sodium metal (182 mg, 7.9 mmol) was added piecewise to MeOH (6 mL) at 0 °C. After the metal had fully reacted, this solution was added via pipette to a 0 °C solution of **171** (1.45 g, 6.62 mmol) in MeOH (20 mL). The reaction was stirred at 0 °C for 20 minutes then allowed to stir overnight at room temperature. The reaction was quenched by slow addition of NH_4Cl (aq. sat. 3 mL). The solvent was removed via rotovap and the residue dissolved in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 1.12 g (65%) of **172** as a colorless liquid. IR (neat) 2926, 1454, 1371, 1196, 1120, 1045, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 3 H), 4.6 (s, 2 H), 3. 5

(s, 3 H), 2.4 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 136.2, 132.9, 129.9, 126.3, 126.2, 72.1, 58.5, 20.2; HRMS (EI) *m/z* 170.0495 [$(M)^+$; calcd. for $C_9H_{11}ClO$, 170.0498].



174

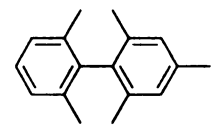
Preparation of 174: To a solution of 2,6-dimethylphenyl magnesium bromide (10 mL, 1.0M in THF, 10 mmol) was added dropwise a solution of Bu_3SnCl (3.25g, 10 mmol) in THF (10 mL). The heat generated by the reaction was controlled by occasionally placing it in an ice bath. The reaction was allowed to stir at room temperature for 2.5 hours. The reaction was quenched by the addition of NH_4Cl (aq. sat.). The solvent was removed via rotovap and the residue dissolved in Et_2O, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 2.38 g (60%) of the stannane **174** as a colorless oil. IR (neat) 3049, 2957, 1458, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.0-7.3 (m, 3 H), 2.46 (s, 6 H), 1.6 (m, 6 H), 1.4 (m, 6 H), 1.19 (m, 6 H), 0.95 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.3, 128.1, 126.5, 29.1, 27.4, 25.7, 13.6, 12.5. HRMS (EI) *m/z* 339.1133 [$(M\text{-}Bu)^+$; calcd. for $C_{16}H_{27}Sn$, 339.1137].



175

Preparation of 175: To a solution of 2,4,6-trimethylphenyl magnesium bromide (5 mL, 1.0M in THF, 5 mmol) was added dropwise a solution of Bu_3SnCl (1.63 g, 5 mmol) in THF (10 mL). The heat generated by the reaction was not controlled. The reaction was allowed to stir at room temperature overnight. The reaction was quenched by the

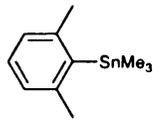
addition of NH_4Cl (aq. sat.). The solvent was removed via rotovap and the residue dissolved in Et_2O, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 1.6 g (78%) of the stannane **175** as a colorless oil contaminated with small amount of 1,3,5-trimethylbenzene (< 3% by GC/MS). ^1H NMR (300 MHz, $CDCl_3$) δ 6.9 (s, 2 H), 2.42 (s, 6 H), 2.32 (s, 3 H), 1.57 (m, 6 H), 1.4 (m, 6 H), 1.14 (m, 6 H), 0.95 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 138.2, 137.8, 127.6, 29.17, 27.44, 25.5, 20.9, 13.6, 12.4. This product has been reported in the literature,[96] however spectral data was not availible for comparison.



176

Preparation of 176: An argon purged modified Schlenk tube was charged with 5 mL dioxane, stannane **175** (324 mg, 0.789 mmol), 2-chloro-*m*-xylene (0.1 mL, 0.755 mmol), dried CsF (257 mg, 1.69 mmol), and Pd(*t*-$Bu_3P)_2$ catalyst (13.4 mg, 0.02 mmol). The stopper was replaced and the tube purged thoroughly with argon before being sealed and placed in a 105 °C oil bath for 15 hours. GC/MS analysis of the crude mixture showed some coupling had occurred, but the reaction was not yet complete. Pd_2dba_3 (10 mg) and *t*-Bu_3P (13 mg in 0.1 mL THF) were added and the reaction heated for an additional 24 hours. The mixture was diluted with EtOAc and filtered through a pad of celite. The filter pad was washed with EtOAc (10 mL x 3) and the combined filtrates were concentrated. Purification by flash chromatography on silica gel (hexanes) afforded 79 mg (46%) of the biaryl **176**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.1-7.2 (m, 3 H), 6.9 (s, 2 H), 2.38 (s, 3 H), 1.94 (s, 6 H), 1.90 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 136.9,

136.1, 135.6, 135.2, 128.2, 127.3, 126.6, 21.1, 19.9, 19.7. The product data is in agreement with reported literature.[96]



177

Preparation of 177: To a solution of 2,6-dimethylphenyl magnesium bromide (10 mL, 1.0M in THF, 10 mmol) was added dropwise a solution of Me_3SnCl in THF (10 mL, 1.0M in THF, 10 mmol). The reaction was allowed to stir at room temperature for 16 hours. The reaction was quenched by the addition of NH_4Cl (aq. sat.). The solvent was removed via rotovap and the residue dissolved in CH_2Cl_2, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. Purification by bulb to bulb distillation at reduced pressure (1 torr) afforded 1.58 g (58.7%) of the stannane **177** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.1 (t, J = 7.5 Hz, 1 H), 6.9 (d, J = 7.5 Hz, 2 H), 2.4 (s, 6 H), 0.35 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 141.8, 128.5, 126.7, 25.67, -5.16. The product data is in agreement with reported literature.[105]

REFERENCES AND NOTES

1. Review: Ishibashi, M.; Kobayashi, J. *Heterocycles*, **1997**, *44*, 543–572.

2. Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134-142.

3. Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1455-1456.

4. (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. (d) Kissel, W. S. also completed the synthesis of amphidinolide R, Personal Communication, July 2002.

5. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Yamasu, T. Sasaki, T.; Hirata, Y. *Tetraheron Lett.* **1986**, *27*, 5755–5758.

6. (a) Terrell, L. R.; Ward, J. S., III; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 3097–3100. (b) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III *Org. Lett.* **2002**, *4*, 2841-2844.

7. O'Connor S. J.; Williard P. G. *Tetrahedron Lett.* **1989**, *30*, 4637–4640.

8. Kobayashi, J.; Ishibashi, M.; Hirota, H. *J. Nat. Prod.* **1991**, *54*, 1435-1439.

9. Yu, Y.; Williard, P. G. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society, San Deigo, CA; American chemical Socicety: Washington DC. 2001; ORGN 580.

10. (a) Boden, C.; Pattenden, G. *Synlett* **1994**, 181–182. (b) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 703–706.

11. Lam, H. W.; Pattenden, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 508-511.

12. (a) Schmid, C. R.; Bryant, J. D.; Dowlatzadah, 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. Commun.* **1991**, *21*, 151–154.

13. Pfenninger, A. *Synthesis* **1986**, 89-116.

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

15. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *113*, 7277-7287.

16. Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282-2291.

17. For details of the development and optimization of this protocol/compound see: Terrell, L. R. Ph.D. Dissertation, *Michigan State University*, 2001.

18. (a) Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1994**, 1153-1160. (b) Abiko, A.; Masamune, S. *Tetraherdon Lett.* **1996**, *37*, 1081-1084. (c) Desrut, M.; Kergomard, A; Renard, M. F.; Veschambre, H. *Tetrahedron* **1981**, *37*, 3825-3829. (d) The *R* enatiomer was also made via an Evans' chiral auxillary approach: Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032-5036.

19. Evans, D. A.; Matre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830-1835.

20. (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739. (b) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 6260-6268. (c) Mathre, D. J. Ph.D. Dissertation, *California Institute of Technology*, 1985.

21. Penning, T. D.; Djurić, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307-312.

22. Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608-1633.

23. Schwartz, S.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1-9.

24. Kalaritis, P.; Regenye, R. W. *Org. Synth.* **1990**, *69*, 10-18.

25. Clark, W. M.; Bender, C. *J. Org. Chem.* **1998**, *63*, 6732-6734.

26. (a) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131-1134. (b) Drewes, S. E.; Malissar, D. G. S.; Roos, G. H. P. *Chem. Ber.* **1993**, *126*, 2663-2673.

27. Evans, D. A. in *Asymmetric Synthesis* (ed.: J.D. Morrison), Academic Press, U.S.A., **1984**, Vol. 3, part B, pp. 2-110.

28. Cardillo, G.; Orena, M. Romero, M.; Sandri, S. *Tetrahedron* **1989**, *45*, 1501-1508.

29. Ireland, R. E.; Norbeck, D.W. *J. Org. Chem.* **1985**, *50*, 2198-2000.

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

31. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129. (b) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J.M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290-5313.

32. Nakajimia, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139-4142.

33. (a) Le Noble, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3897-3899. (b) Thibonnet, J.; Launay, V.; Abarbri, M.; Duchêne, A.; Parrain, J. *Tetrahedron Lett.* **1998**, *39*, 4277-4280.

34. For a detailed account of the coupling and hydrolysis studies of the **AB** subunit see: Terrell, L. R. Ph.D. Dissertation, *Michigan State University*, 2001.

35. Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191-1224.

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. Maleczka, R. E., Jr.; Terrell, L. R.; Clark, D. H.; Whitehead, S. L.; Gallagher, W. P.; Terstiege, I. *J. Org. Chem.* **1999**, *64*, 5958-5965.

38. Mori, K.; Murata, N. *Liebigs Ann. Chem.* **1994**, 1153-1160.

39. Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 79-81.

40. Lipshutz, B. H.; Koerner, M.; Parker, D. A. Tetrahedron Lett. 1985, 28, 945-948.

41. Terrell, L. R. unpublished results.

42. Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634-4642.

43. (a) Benaglia, M.; Toyota, S.; Woods, C. R.; Siegel, J. S. *Tetrahedron Lett.* **1997**, *38*, 4737-4740. (b) Kosugi, M.; Shimizu, K.; Ohtani, A.; Migita, T. *Chem. Lett.* **1981**, 829-830. (c) Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49-58.

44. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

45. The stereochemistry of these two isomers was determined by Geng, F. Ph.D. Dissertation, *Michigan State University*, 2001.

46. Burgess,K.; Ohlmeyer, M. J.; *Chem. Rev.* **1991**, *91*, 1179-1191.

47. Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405-1408.

48. Protocol adapted from analogous BPS protected compound: Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198-11199.

49. Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268-1270.

50. Crookes, W. *J. Chem. Soc.* **1864**, 112-153.

51. Watanabe, T.; Miyaura, M.; Suzuki, A. *Synlett* **1992**, 207-210.

52. Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885-3890.

53. Maleczka, R. E., Jr.; Lavis, J. M.; Clark, D. H., Gallagher, W.P. *Org. Lett.* **2000**, *2*, 3655-3658.

54. Geng, F. Unpublished results.

55. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (b) Trnka, T. M. Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.

56. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *113*, 7277-7287.

57. McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.

58. Kolb, H. C.; Van Niewenhze, M. S; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.

59. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515.

60. For details of the development and optimization of this protocol/compound see: Geng, F. Ph.D. Dissertation, *Michigan State University*, 2001.

61. For altenative epoxidations attempts see reference 60.

62. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747-5750.

63. (a) Heathcock, C. H.; Hansen, M. M.; Danda, H. *J. Org. Chem.* **1990**, *55*, 173-181. (b)Raimundo, B. C.; Heathcock, C. H. *Synlett* **1995**, *12*, 1213-1214.

64. (a) Abiko, A.; Liu, J.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586-2587. (b) Abiko, A. *Org. Synth.* **2002**, *79*, 109-115. (c) Abiko, A. *Org. Synth.* **2002**, *79*, 116-124.

65. (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499-504. (b) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147-153.

66. Aoyama, T.; Sonoda, N.; Yamauchi, M.; Toriyama, K.; Anazai, M.; Ando, A.; Shioiri, T. *Synlett* **1998**, 35-36.

67. Goldman, I. M. *J. Org. Chem.* **1969**, *34*, 1979-1981.

68. Yokokawa, F.; Fujiwara, H.; Shioiri, T. *Tetrahedron* **2000**, *56*, 1759-1775.

69. It was determined that this solution needed to be exactly 2M lithium acetylide in DMSO. Significant deviations from this concentration lead to a dramatic decrease in yield.

70. (a) Ranu, B. C.; Majee, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1225-1226. (b) Klaps, E.; Schmid, W. *J. Org. Chem.* **1999**, *64*, 7537-7546.

71. (a) Zhang, H .X; Guibé, F.; Balavoine, G.; *J. Org. Chem.* **1990**, **55**, 1857-1867. (b) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin 1* **1996**, 2417-2419.

72. Reed-Mundell, J. J.; Nadkarni, D. V; Kunz, J. M., Jr.; Fry, C. W.; Fry, J. L. *Chem. Mater.* **1995**, *7*, 1655-1660.

73. Use of premade Bu_3SnH in analogous systems results in formation of $(Bu_3Sn)_2$ dimer, which makes isolation of the desired product more difficult.

74. (a) Diastereomers using the analogous syn route were also used to confirm the differences in stereochemistry at C19: Geng, F. Ph.D. Dissertation, *Michigan State University*, 2001. (b) NOSEY and other advanced NMR techniques were applied to confirm the relative stereochemistry of this half of (**1**) and also confirmed that no Payne rearrangement occurred during the course of the esterification.

75. Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123-1125.

76. The interpretation of NMR data for compounds **125** and **126** (Scheme 76, pg. 63) was complicated because each compound exists as a mixture of conformers. Upon removal of the PMB protective groups the mixture of conformers was eliminated and the data interpretation simplified.

77. Comparisons to the natural product are complicated by the existence of only a TLC sample of natural amphidinolide A. Kobayashi, J., Hokkaido University, personal communication, 2000.

78. Conformer search and modeling of the RCM precursors using MMF94 and/or PM3 semi-empirical levels of theory were inconclusive in determining a reason for the difference in reactivity.

79. Berkowitz, W. F.; Wilson, P. J. *J. Org. Chem.* **1991**, *56*, 3097-3102.

80. (a) Upham, B. L.; Yao, I. J.; Trosko, J. E.; Masten, S. J. *Environ. Sci. Technol.* **1995**, *29*, 2923-2928. (b) Upham, B. L.; Masten, S. J.; Lockwood, B. R.; Trosko, J. E. *Fundam. Appl. Toxicol.* **1994**, *23*, 47-475.

81. (a) Fieser, L. F.; Novello, F. C. *J. Am. Chem. Soc.* **1940**, *62*, 1855-1859. (b) Agarwal, S. C.; Van Duuren, B. L. *J. Org. Chem.* **1975**, *40*, 2307-2310.

82. (a) Vollman, H.; Becker, H.; Corell, M.; Streeck, H. *Justus Liebigs Ann. Chem* **1937**, 1-159. (b).Yakobson, G. G.; Vlasov, V. M.; Vorozhtsov, N. N. *Dokl. Chem. Engl. Transl.* **1966**, *169*, 762-764. (c) Pryor, K. E.; Shipps, G. W., Jr.; Skyler, D. A.; Rebek, J., Jr. *Tetrahedron* **1998**, *54*, 4107-4124.

83. Farley, C. P.; Eliel, E. L. *J. Am. Chem. Soc.* **1956**, 3477-3484.

84. (a) Jursic, B. *Can. J. Chem.* **1989**, 67, 1381-1383. (b) The actual surfactant recommendation from this report was sodium stearate, but the potassium salt proved just as effective.

85. Cha, J.S.; Yoon, M.S. *Tetrahedron Lett.* **1989**, *30*, 3677-3680.

86. Sotomayor, N.; Vicente, T.; Dominguez, E.; Lete, E.; Villa, M. J. *Tetrahedron* **1994**, *50*, 2207-2218.

87. (a) Whitmore, F. C.; Culhane, P. J.; Neher, H.T. *Org. Synth. Coll. Vol. 1*, 56-58. (b) Culhane, P.J. *Org. Synth. Coll. Vol. 1*, 125-127.

88. Clarke, H. T.; Read, R. R. *Org. Synth. Coll. Vol. 1*, 514-516.

89. Dann, O.; Char, H.; Fleischmann, P.; Fricke, H. *Liebigs Ann. Chem.* **1986**, 438-455.

90. Krizan, T. D.; Martin, J. C. *J. Org. Chem* **1982**, *47*, 2681-2682.

91. (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360-1370

92. Dai, C.; Fu, G. *J. Am. Chem. Soc.* **2001**, *123*, 2719-2724.

93. Purchased from Strem Chemical.

94. (a) Gorth, F. C.; Rucker, M.; Eckhardt, M.; Bruckner, R. *Eur. J. Org. Chem.* **2000**, 2605-2611. (b) Miyano, S.; Fukushima, H.; Inagawa, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 3285-3286.

95. Personal communication with A. Littke, *Massachusetts Institute of Technology*, 2001.

96. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343-6348.

97. (a) Paper in preparation for *Environmental Science & Technology*. b) Ph.D. Dissertation in preparation, Stephanie Luster-Teasley, Michigan State University, 2002.

98. Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141-152.

99. Macomber, R. S. *J. Am. Chem. Soc.* **1970**, *92*, 7101-7106.

100. Kalivretenos, A.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2883-2894.

101. Mitchell, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 291-296.

102. Magnus, P.; Quagliato, D. *J. Org. Chem.* **1985**, *50*, 1621-1626.

103. Gorvin, J. H. *J. Chem. Res. M.* **1992**, 1831-1851.

104. Zhang, J. T.; Dai, W.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 8125-8132.

105. Schaeffer, C.D., Jr.; Zukerman, J. J. *J. Organomet. Chem.* **1975**, *99*, 407-420.