SEMISYNTHESIS OF AMPHOTERICIN B AND ITS DERIVATIVES VIA ITERATIVE CROSS-COUPLING

BY

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DISSERTATION

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ABSTRACT

Despite almost 40 years of investigation, the mechanism of action of amphotericin B (AmB), a potent but toxic antimycotic, has eluded the scientific community. The leading hypothesis involves insertion into the lipid bilayer of fungal cells followed by self-assembly into ion permeable channels that disrupt the transmembrane electrochemical gradient and induce cell death. This self-assembly into a protein-like ion channel complex puts AmB outside the paradigm of most chemotherapeutic agents which operate via the inhibition of protein targets. In this way, AmB also represents an outstanding prototype for small molecules that replicate the function of protein ion channels whose deficiency underlies currently incurable human diseases. Understanding the mechanism of this unique natural product at an atomistic level would also further enable the synthesis of antifungal derivatives with a better therapeutic index. However, due to the challenges present in the synthesis of this complex natural product and its derivatives, structure/function data are limited.

The study of AmB would be greatly aided by the development of a modular and flexible total synthesis of this complex small molecule and its derivatives. Toward this end, we developed a strategy for the synthesis of polyene natural products via the iterative Suzuki-Miyaura cross-coupling of bifunctional polyenyl MIDA boronate building blocks. This methodology was taken on to complete efficient total syntheses of all-*trans*-retinal, β-parinaric acid, and one half of AmB.

In order to validate this iterative cross-coupling methodology as an effective endgame strategy, we proceeded with a semisynthesis of AmB. Degradation of the natural product allowed access to an excellent model for an advanced intermediate in the proposed total synthesis. The iterative cross-coupling strategy then proved effective in converting this intermediate into the final product, validating the endgame strategy of the total synthesis. This same methodology was then applied to the semisynthesis of an AmB derivative lacking the C35 hydroxyl group. The completion of this synthesis required the development of a protecting group strategy that was robust to various chemical transformations, but also able to be cleaved under mild conditions such that the sensitive structure of the derivative could survive.

The lessons learned from the synthesis of C35 deoxy AmB have informed the synthetic strategies currently under investigation towards a total synthesis of the natural product and will hopefully lead to the rapid synthesis of other mechanistically informative derivatives. With a

solid understanding of the molecular underpinnings of the mechanism of action of AmB, we stand to enable the synthesis of derivatives with a better therapeutic index. Additionally, amphotericin B may serve as a prototype for the development of a new class of pharmaceuticals that can serve as substitutes for defective protein-based ion channels, thus operating as molecular scale prosthetics.

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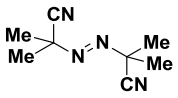
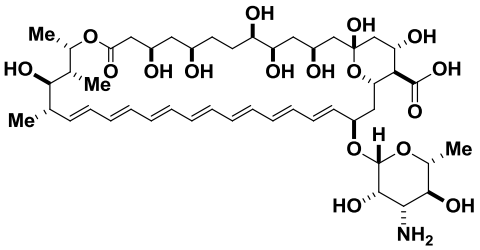
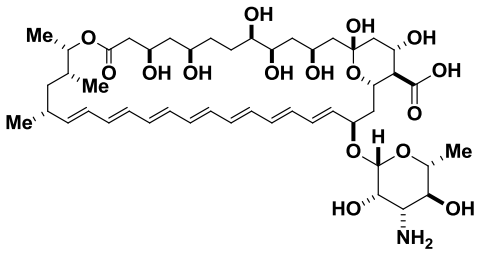
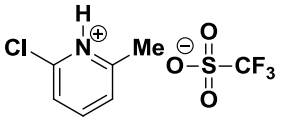
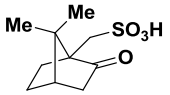
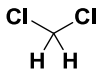
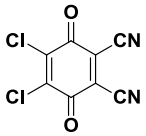
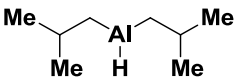
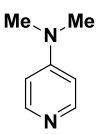
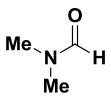
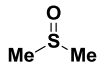
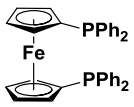
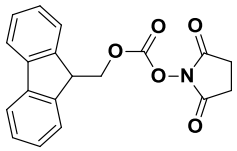
AIBN	2,2’-azobis(2-methylpropionitrile)	
AmB	amphotericin B	
C35deOAmB	C35-deoxy amphotericin B	
CMPT	2-chloro-6-methyl-pyridinium triflate	
CSA	(±)-10-camphorsulfonic acid	
DCM	dichloromethane	
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone	
DIBAL	diisobutylaluminum hydride	
DMAP	4-(dimethylamino)-pyridine	
DMF	dimethyl formamide	

DMSO	dimethyl sulfoxide	
dppf	1,1’-bis(diphenylphosphino)ferrocene	
FMOC-OSu	9-fluorenylmethyl *N*-succinimidyl carbonate	
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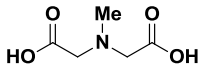
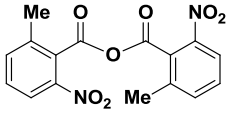
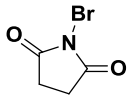
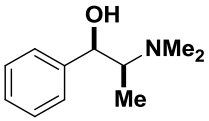
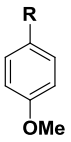
MIDA	*N*-methyliminodiacetic acid	
MNBA	2-methyl-6-nitrobenzoic anhydride	
NBS	*N*-bromosuccinimide	
(-)-NME	*N*-methyl-ephedrine	
PMP	*p*-methoxyphenyl	
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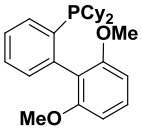
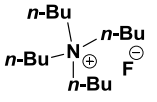
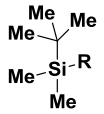
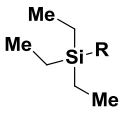
S-Phos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl	
TBAF	tetra-*n*-butylammonium fluoride	

TBS	*t*-butyldimethylsilyl	
TES	triethylsilyl	
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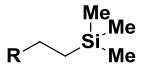
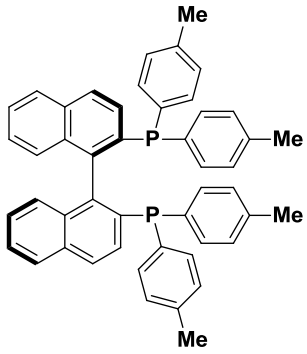
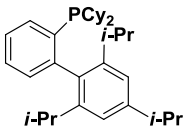
TMSE	2-(trimethylsilyl)ethyl	
(+)-Tol-BINAP	(*R*)-(+)-2,2’-Bis(di-*p*-tolylphosphino)-1,1’-binapthyl	
X-Phos	2-dicyclohexylphophino-2’,4’,6’-triisopropylbiphenyl	

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CHAPTER 1

INTRODUCTION

1-1 AMPHOTERICIN B AS A LAST LINE OF DEFENSE

Amphotericin B (AmB, **1.1**, Figure 1.1) is a prototypical natural product that can form membrane-permeabilizing ion channels in living eukaryotic cells.[1] The proper function of such cells is normally dependent on protein ion channels that regulate the transmembrane electrochemical gradient. However, there is a class of diseases that stem from the lack of properly functioning protein ion channels, such as cystic fibrosis, that cannot be treated with the normal paradigm of a small molecule binding to a protein target. An advanced understanding of how AmB interacts with living systems thus stands to enable efforts to develop small molecules that serve as surrogates for these deficient or dysfunctional protein ion channels that underlie currently incurable human diseases.[2,3,4]

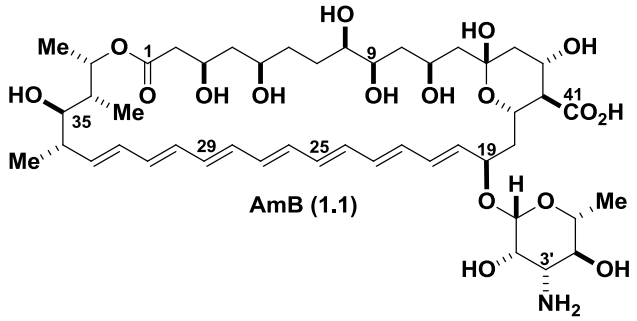


Figure 1.1. Chemical Structure and numbering system of AmB.

In addition, as the population with immunodeficiency has expanded over the past three decades, systemic fungal infections have emerged as one of the leading causes of human morbidity and mortality worldwide. Between the years 1979 and 2000 alone, the annual number of cases of sepsis caused by fungal organisms increased by 207%.[5] In fact, *Candida* species remain the fourth most common cause of hospital-acquired bloodstream infection and 40% of those cases result in death of the patient.[6] In addition to its mortality rate, the economic cost of fungal infections is also extremely high. It was estimated that in 1998 the United States spent $2.6 billion on systemic fungal infections.[7] Many of these problems have arisen because resistance to most currently available antifungal agents is becoming increasingly common. In

contrast, AmB has remained the last line of defense in the treatment of these invasive infections for over 50 years.

AmB was first isolated by Gold and coworkers in 1955 from a culture of *Streptomyces nodosus*[8] and was approved by the FDA for clinical use in the treatment of systemic fungal infections only two years later. AmB belongs to a larger class of antifungal natural products known as the polyene macrolides and in 1970, over a decade after its first clinical use, it became the first of its class to be fully structurally characterized.[9,10] This natural product has enjoyed over 5 decades of continuous clinical use in the treatment of systemic fungal infections and despite this incredibly extended period of time, there have been remarkably few documented cases of resistance to this drug.[11] Albeit refractory to resistance, the challenge associated with the broad spectrum application of AmB to invasive mycoses is not associated with its antifungal effectiveness, but its toxicity. At therapeutic doses, it is known to be extremely nephrotoxic and can cause cardiac arrhythmias as well as hemolytic anemia. In one study comparing AmB to caspofungin, an alternative antifungal agent, 32% of patients treated with AmB had moderate to severe infusion-related side effects as compared to 0.9% with caspofungin.[12] Due to this extensive toxicity, in many cases an effective dose of AmB cannot be tolerated by the patient and this has led to the high mortality rate in these types of infections. While the therapeutic index has been marginally improved by the introduction of lipid-based delivery methods,[13] the development of a less toxic derivative of AmB has been limited by the lack of understanding of its mechanism of action.

1-2 CLASSIC MODEL OF AMPHOTERICIN B'S MECHANISM OF ACTION

The current leading model of AmB's mechanism of action involves insertion into the lipid bilayer of fungal cells followed by self-assembly into ion-permeable channels that disrupt the transmembrane electrochemical gradient and induce cell death.[14,15] This hypothesis originates as early as the 1960s when it was observed that AmB had membrane permeabilizing activity.[15,16] Further evidence for the channel mechanism of action was obtained by Ermishkin and coworkers in 1976.[1] Through use of planar lipid bilayers, they were able to observe single AmB ion channel conductance. Additionally, these ion channels had characteristics of gating and ion selectivity that are similar to protein ion channels.

The size and nature of AmB ion channel were further studied by looking at the membrane permeability of small non-ionic solutes.[16b] There was found to be a strong correlation between hydrodynamic radius and permeability through the ion channel. Small solutes such as urea and glycerol were able to permeate readily in the presence of AmB whereas larger molecules, such as glucose, remained relatively impermeable. Based on this data, in particular the low permeability of glucose, Andreoli and coworkers predicted that AmB formed channels of a defined size between 7 and 10 angstroms (Å) in diameter.

These observations led to the now classic "barrel-stave" model for AmB action.[17] Despite the existence of this model for over 35 years, the exact nature of this self-assembled complex is still poorly understood. However, based upon experimental[1,18] and computational[19] studies, AmB is predicted to self-assemble into an octameric complex giving a pore with an interior diameter of about 8 Å (Figure 1.2). In this model the AmB molecules are aligned such that the hydrophilic polyol units line the water filled interior of the pore while the hydrophobic polyene units interact with the non-polar chains of the phospholipids. In addition to the hydrophobic effects, the classic model predicts that there are two rings of stabilization. The first ring of stabilization is thought to be a salt bridge between the C41 carboxylate and the C3´ amine. A second proposed interaction is a hydrogen bond between the C8 and C9 hydroxyl groups at the interior of the pore. Additionally, in some models the mycosamine appendage, specifically the C3' amine[20] and the C2' hydroxyl group[21] have been proposed to form a hydrogen bonding interaction with the β-hydroxyl group in sterols. In other models, the sterols do not form direct contacts with AmB but instead modify the global membrane properties in a manner that is conducive with channel assembly.[22] Finally, it has been proposed that the C35 hydroxyl group may be critical for forming transmembrane pores in the lipid bilayer. Specifically, AmB is roughly half the length of a lipid bilayer and hydrogen bonding between C35 hydroxyl groups may be critical for the dimerization of AmB to form a membrane-spanning complex (Figure 1.2C).[23,24]

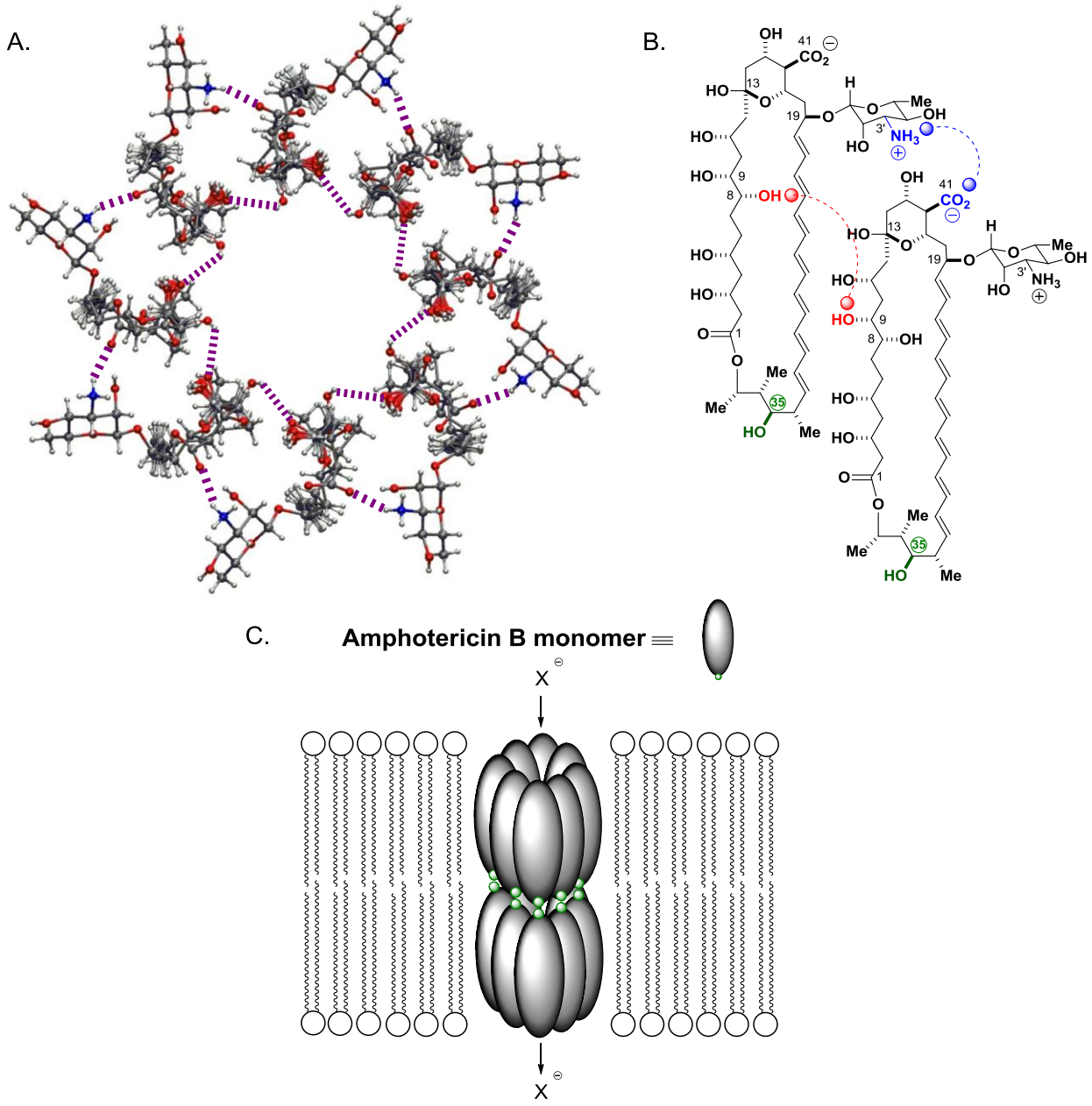


Figure 1.2. (A) The barrel stave model for AmB with the polyol pointing in to form a hydrophilic pore and the polyene pointing out towards the hydrophobic lipid bilayer. (B) The proposed C41 carboxylate /C3' amine salt bridge and C8 alcohol/C9 alcohol hydrogen bonding interaction. (C) The tail-to-tail dimer of AmB pores stabilized by C35 hydroxyl group hydrogen bonding.

Adapted with permission from Palacios, D.S.; Anderson, T.M.; Burke, M.D. *J. Am. Chem. Soc.* **2007**, *129*, 13804-13805. Copyright 2007 American Chemical Society.

This self-assembly into a protein-like ion channel complex puts AmB outside the paradigm of most chemotherapeutic agents which operate via the inhibition of protein targets. A potential outcome of understanding AmB's ion channel formation is that this small molecule

could serve as a prototype for the development of a new class of pharmaceuticals that can act as substitutes for defective protein-based ion channels, thus operating as molecular scale prosthetics. This strategy has the potential to treat diseases caused by deficiencies in ion channel function, which to date, remain outside the reach of modern medicine. However, such a goal cannot be achieved without a molecular understanding of its mechanism of action.

1-3 DELETION STRATEGY FOR UNDERSTANDING THE MECHANISM OF ACTION

While the channel model of AmB action described above is widely accepted, there is very little experimental evidence to confirm its accuracy. In fact, work from the Burke group demonstrated that the C41 carboxylate, proposed to be critical for the salt bridge ring of stabilization, is not necessary for potent antifungal activity.[3] In a degradative synthesis from the natural product, Palacios et al. were able to synthesize derivatives missing the C41 carboxylate, the mycosamine, and both functionalities. The derivatives were tested against two strains of yeast, *Saccharomyces cerevisiae* and *Candida albicans*, and as predicted, the mycosamine was found to be critical for antifungal activity. However, the derivative lacking the C41 carboxylate was equipotent to the natural product, bringing into question the importance of the salt bridge in the classical barrel-stave model. To confirm that this activity was not caused by a change in the shape of AmB, NMR studies were done confirming that these modifications had not changed the conformation of the macrolactone core. Many earlier studies had attempted to understand the role of these two functional groups via covalent modification of the acid and the amine.[25] It is difficult to draw conclusions about the importance of the functional groups from these studies given that it is known that the self-assembly of small molecules, such as AmB, can be sensitive to steric encumbrance.[26] However, by simply deleting the functional groups in question, the importance of the C41 carboxylate in antifungal activity was discernable without the added complication of steric perturbation.

These functionally deficient derivatives were then taken on into more in-depth biophysical studies to understand the role of the mycosamine in the antifungal activity of AmB. In particular, is had long been recognized that lipid bilayers containing sterols are uniquely vulnerable to permeabilization by AmB, but it had not been clear if this was an effect of sterol-mediated global membrane properties[22] or due to direct sterol binding.[20,21] Through isothermal calorimetry studies with the functionally deficient derivatives, Palacios et al. demonstrated that

AmB directly binds membrane-embedded ergosterol in a manner that requires the presence of the mycosamine.[2] Deletion of this appendage yielded a derivative, amphoteronilide B, that cannot bind ergosterol, is unable to form channels, and has no antifungal activity.

This work further revealed that this functional group deletion-based approach is a powerful way to illuminate the molecular underpinnings of AmB function.[2,3,24] It is interesting to note that an analogous strategy, known as alanine scanning, has been widely used in the protein sciences as a systematic method to understand the role of important residues.[27] It is our goal to use this method as a general strategy to understand the role of protic functional groups in biologically active small molecules, in particular, AmB. By systematically deleting each of the alcohols on the AmB skeleton, essentially performing a "methylene scan," we hope to gain an atomistic understanding of AmB's mechanism of action. In order to be able to take on such a strategy, many of the derivatives will need to be accessed through total synthesis, meaning that the challenges of synthesizing AmB will need to be addressed.

1-4 SYNTHETIC STUDIES

The challenge of making AmB has drawn the interest of many synthetic chemists due to its structural complexity and interesting biological activity. Since the 1980s, more than a dozen synthetic groups have worked on the total synthesis of this natural product including Masamune,[28] McGarvey,[29] Carreira,[24,30] and Solladié,[31] but to date, the only completed total synthesis was achieved by Nicolaou and coworkers in 1987.[32,33] Nicolaou's retrosynthesis of AmB begins with the disconnection of the mycosamine to get back to the macrolactone core (Figure 1.3).[32] The aglycone was then divided into two components **1.3** and **1.4** via a Horner-Wadsworth-Emmons (HWE) macrolactonization transform and an esterification transform. These two molecules were then further disconnected into five key building blocks via a HWE transform as well as several steps in between. Building blocks **1.5** and **1.9** were both made from (+)-diethyltartrate and **1.6** and **1.7** were accessed from carbohydrate starting materials as well as through Sharpless asymmetric epoxidation chemistry.[32b] In the forward direction this strategy proved to be effective in accessing the protected form of amphoteronilide B.[32c] One of the main challenges in completing the total synthesis was the final attachment of the mycosamine. Use of anchimeric assistance by the neighboring C2' acetate ensured the proper β-glycosyl linkage, however, this step had low conversion and competitive formation of the orthoester resulting from

attack on the acetoxonium carbon.[32d] After its attachment the stereochemistry of the C2' hydroxyl group was then inverted to match the natural product.

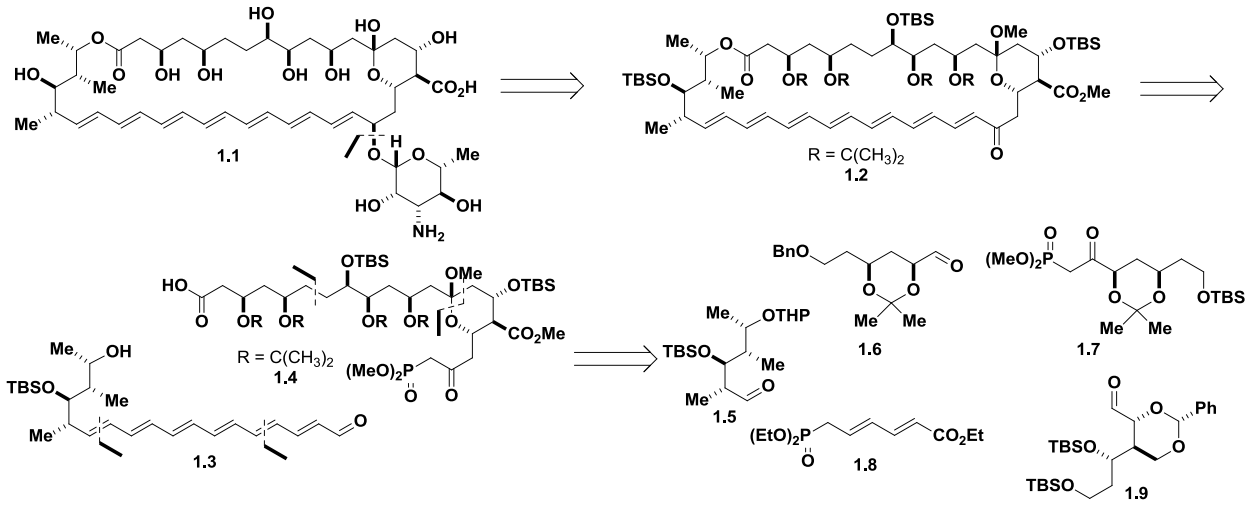


Figure 1.3. Nicolaou's retrosynthesis of AmB.

Carreira and coworkers utilized a similar HWE-based macrolactonization strategy followed by mycosamine attachment in the synthesis of C35-deoxy AmB methyl ester.[24,34] In the context of this synthesis the Carreira group made several important synthetic advances. In earlier syntheses of the polyol subunit, the stereochemistry was largely determined by use of chiral pool starting materials or the Sharpless asymmetric epoxidation. The Carreira group recognized that the repeating 1,3-diol motif could, instead, be accessed from δ-hydroxy-β-keto esters derived from a vinylogous Mukaiyama aldol reaction (Figure 1.4).[30a] With this in mind, they set out to develop a catalytic, enantioselective method for aldol additions that relied on the recursive generation of chiral enolates rather than Lewis acid activation of the aldehyde.[35] It was found that a Tol-BINAP·CuF_2 complex generated *in situ* promoted an aldol addition of dienolate **1.15** to a broad range of aldehydes in up to 98% yield and 97.5:2.5 e.r (Scheme 1.1).[36] In particular, furfural was an excellent substrate proceeding in 95% yield and e.r. = 97:3. **1.13** and *ent*-**1.13** were then used in the synthesis of **1.11** and **1.12**, respectively.

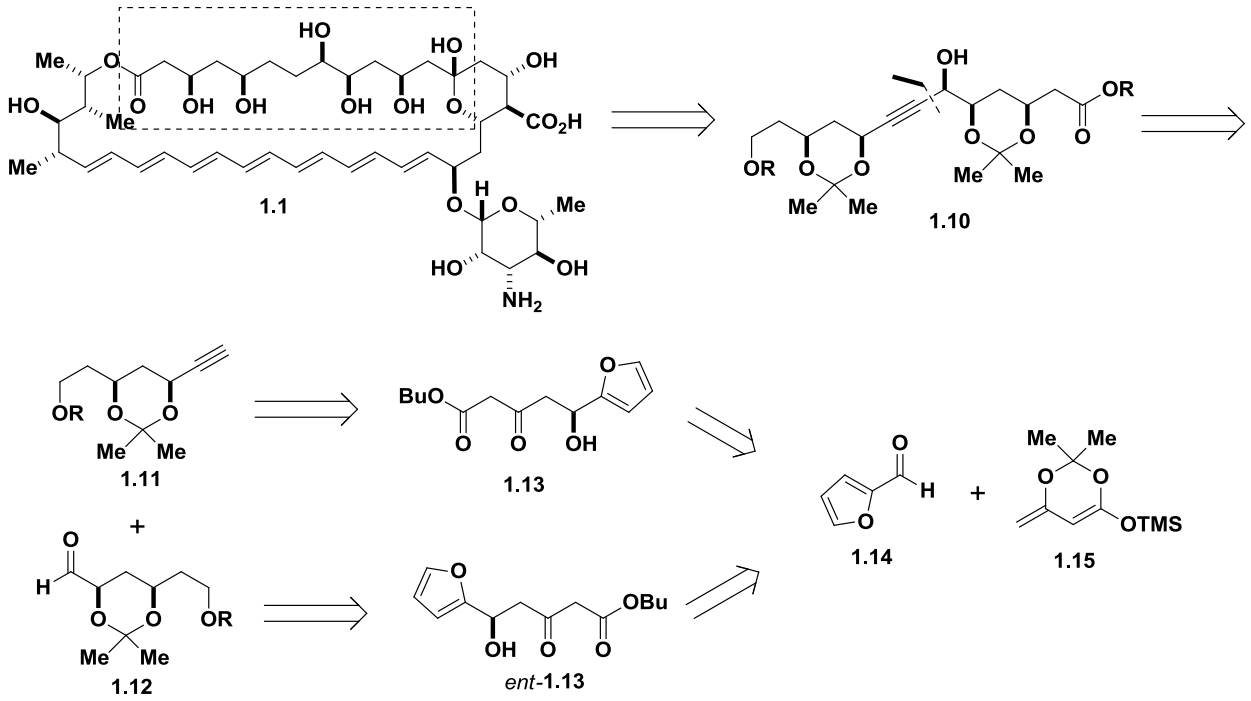
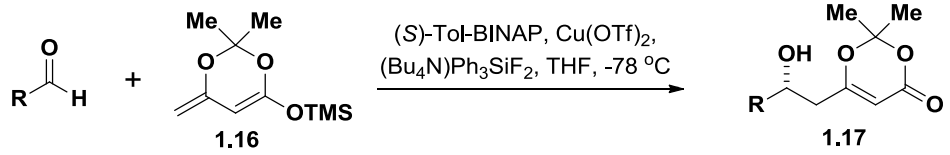
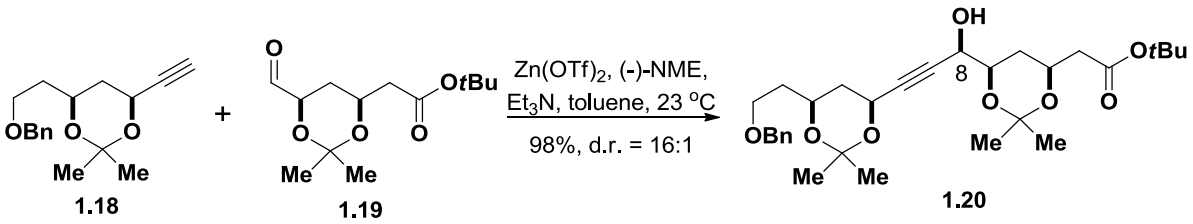


Figure 1.4. Carreira's retrosynthesis of the polyol fragment of AmB. Both **1.11** and **1.12** come from asymmetric dienolate (**1.15**) aldol addition to furfural (**1.14**).



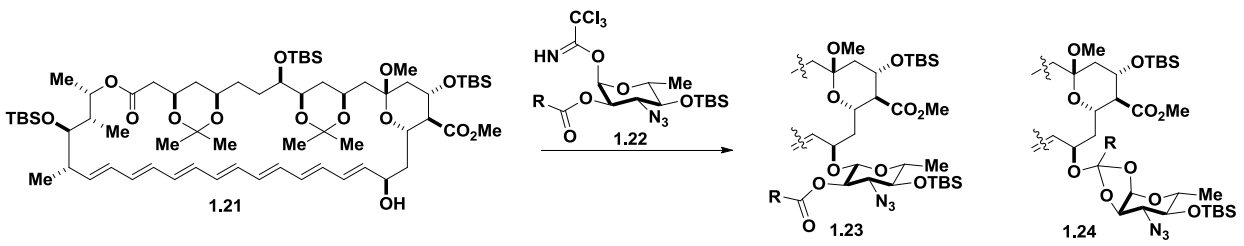
Scheme 1.1. General scheme for Carreira's catalytic, asymmetric vinylogous Mukaiyama aldol reaction.

In moving forward with their synthesis, **1.18** and **1.19** needed to be connected through an addition of the alkyne to the aldehyde. However, coupling of lithiated **1.18** to **1.19** produced the undesired (*S*)-C8 epimer of **1.20** as the major product.[24a] The Carreira group had previously developed an asymmetric zinc acetylide addition to aldehydes to generate a wide variety of enatioenriched propargylic alcohols in up to 99% yield and e.r. = 99.5:0.5.[37] The formation of **1.20** allowed them to test if this methodology could overcome substrate bias in a complex system. Treatment of **1.18** with $Zn(OTf)_2$, (-)-*N*-methyl-ephedrine ((-)-NME), Et_3N, and aldehyde **1.19** produced **1.20** in 98% yield and d.r. = 16:1 (Scheme 1.2).[24a]



Scheme 1.2. Carreira's asymmetric zinc acetylide addition for the synthesis of AmB's polyol subunit.

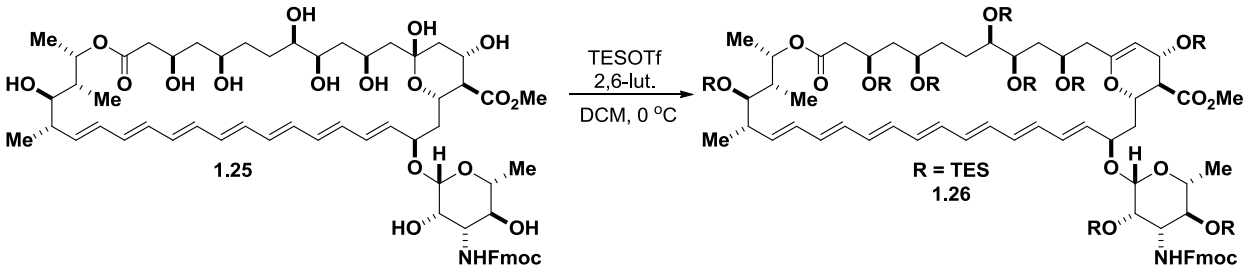
In addition to their novel synthesis of the polyol, the Carreira group was able to better address the challenge of the glycosidation in their synthesis. They hypothesized that by using a bulky, but electron pore acyl protecting group on C2' that they could drive conversion and disfavor orthoester formation.[24b] In a head-to-head comparison on suitably protected amphoteronilide B (**1.21**), the acetate gave 4% yield of desired product **1.23** with 12% orthoester **1.24** formation and 75% recovered starting material (Scheme 1.3). Use of the bulkier group 2-chloroisobutyrate improved the reaction to give 27% of desired product with only 11% orthoester and 57% recovered starting material. Finally, switching the acid activator from pyridinium *para*-toluenesulfonate (PPTS) to 2-chloro-6-methyl-pyridinium triflate (CMPT) gave complete conversion and a 43% yield of desired product. These conditions translated to their C35-deoxygenated derivative to give a 45% yield.[38] Using this material they were able to access C35-deoxy AmB methyl ester. Challenges with the deprotection of the methyl ester due to the sensitivity of AmB derivatives lacking protic functional groups prohibited the synthesis of the singly modified derivative. Despite this challenge, the synthesis of this derivative inspired the development of new methodology including a catalytic, enantioselective Mukaiyama aldol reaction, an asymmetric zinc acetylide addition to aldehydes, and an improved glycosidation reaction.



R	Activator	1.23	1.24	1.21
Me	PPTS	4%	12%	75%
$CCl(CH_3)_2$	PPTS	27%	11%	57%
$CCl(CH_3)_2$	CMPT	43%	23%	--

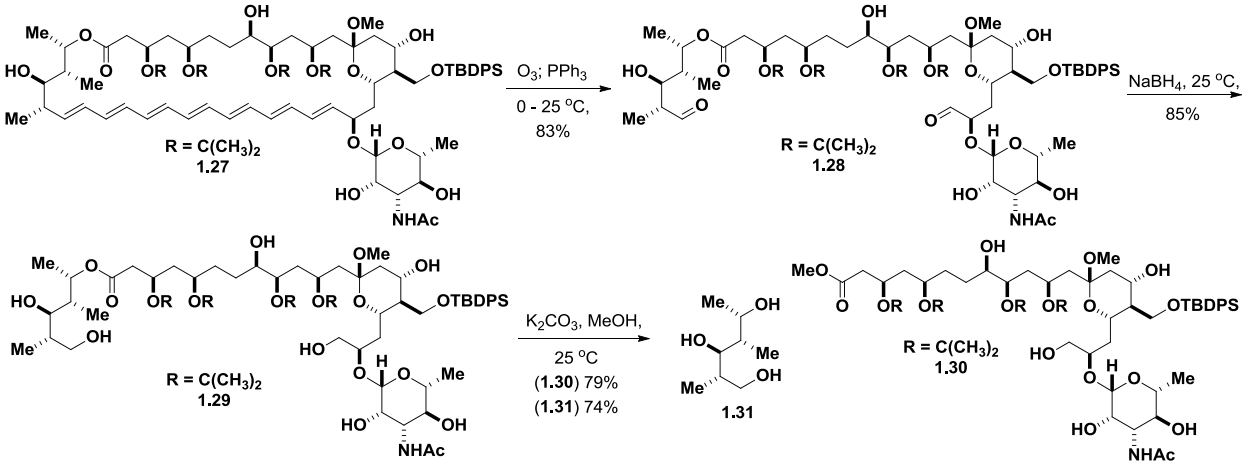
Scheme 1.3. The optimization of the glycosidation of suitably protected amphoteronilide B. Carreira's use of the 2-chloro-2-methylpropanoic ester decreased the amount of undesired orthoester formation. Also, switching the activator from PPTS to CMPT allowed for complete conversion of starting material **1.21**.

While the total synthesis of AmB has allowed for the development of new methodology and the synthesis of a deoxygenated derivative, it is not the only route to accessing derivatives of this small molecule. Top-down degradative syntheses as well as hybrid top-down/bottom-up syntheses have the potential to access derivatives in a much more efficient manner. Along these lines, Nicolaou,[39] Masamune,[40] and researchers at SmithKline Beecham[41] have looked at the chemistry of the natural product via degradation studies. Both Nicolaou and Masamune found that the oxidative conditions of *N*-bromosuccinimide (NBS) and 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), respectively, could cleave the mycosamine to form a heptaenone. Additionally, chemists at SmithKline Beecham explored a range of protecting groups to give optimal working characteristics to the natural product. AmB, in its fully deprotected form, is difficult to work with due to its lack of solubility in most organic solvents. They found that use of a 9-fluorenylmethoxycarbonyl (Fmoc) protecting group on the C3' amine made the compound easier to work with and it was easy to deprotect under mild conditions that are compatible with AmB's sensitive core. Also, in trying to silylate the free hydroxyl groups, it was found that the hemiketal at C13 can eliminate to form dihydropyran **1.26** when treated with triethylsilyl trifluoromethane sulfonate (TESOTf) in polar solvents like dichloromethane (DCM) (Scheme 1.4).[41]

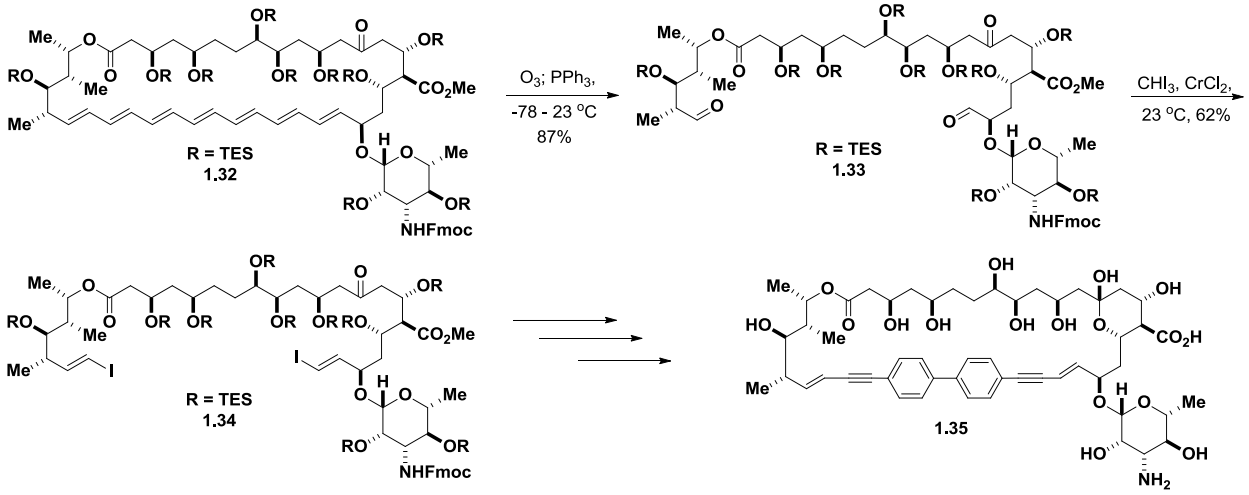


Scheme 1.4. SmithKline Beecham's TES protection of AmB. Use of the polar solvent DCM with TESOTf caused elimination of the hemiketal to form dihydropyran **1.26**.

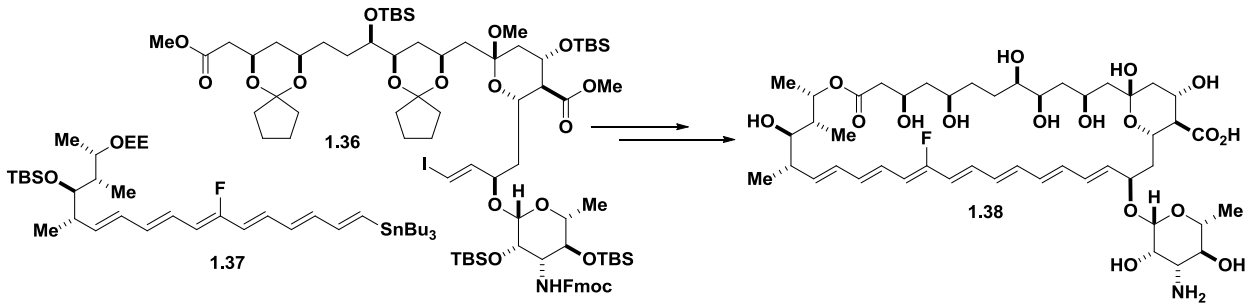
In addition to the deglycosidation studies, Nicolaou and coworkers also explored the chemistry of the macrolactone.[39] After suitable protection to access **1.27**, it was found that ozonolysis could effectively cleave the polyene section of the molecule and after reduction give the free alcohols (**1.29**, Scheme 1.5). The western half of the molecule could subsequently be cleaved with methanolysis. In the synthesis of a derivative with a rigid, non-polyene core (**1.35**), Rychnovsky and coworkers used a similar oxidative cleavage of the polyene with a PPh_3 workup to give the bisaldehyde of AmB (Scheme 1.6).[42] Subsequent Takai olefination allowed access to a bisvinyliodide derivative of AmB. A similar degradation/Takai olefination sequence was employed by Murata and coworkers in the synthesis of an AmB derivative having a fluorine at C28 in the polyene (Scheme 1.7).[43] Stille coupling of fragments **1.36** and **1.37** followed by macrolactonization and deprotection yielded the targeted AmB derivative (**1.38**).



Scheme 1.5. Nicolaou's degradation of AmB.



Scheme 1.6. Rychnovsky's hybrid synthesis of an AmB derivative with a rigid non-polyene core.



Scheme 1.7. Murata's semisynthesis of fluorine labeled **1.38**.

1-5 ITERATIVE CROSS-COUPLING STRATEGY

Even with the strides that have been made in the synthesis and degradation of AmB, there are still clear challenges in making a full class of deoxygenated derivatives in order to elucidate its mechanism of action. For example, Nicolaou's route to AmB, while a classic in total synthesis, is quite long (>100 steps, 47 steps in the longest linear sequence), making it less favorable for making derivatives. Additionally, the hybrid routes of Rychnovsky and Murata, while very useful for modifying the C21-C40 section of the macrolactone, do not allow for derivatization of the C1-C20 fragment or the mycosamine. Therefore, overcoming these challenges with a modular and efficient synthesis would enable access to AmB derivatives in quantities suitable for testing. We envisioned that the simplest way to disconnect the molecule was through a series of Suzuki-Miyaura (SM) transforms and a macrolactonization transform giving four key building blocks (Figure 1.5). Such a strategy would allow for all of the functionality and oxidation states to be preinstalled in the building blocks and then one mild reaction, the SM reaction, could bring them all together. This would also allow for deoxygenated

derivatives to be accessed by modifying only the building block containing the functional group. For such a strategy to work we needed to use a protecting group for boron that would allow for iterative cross-coupling of bifunctional building blocks, but could be removed under mild conditions.

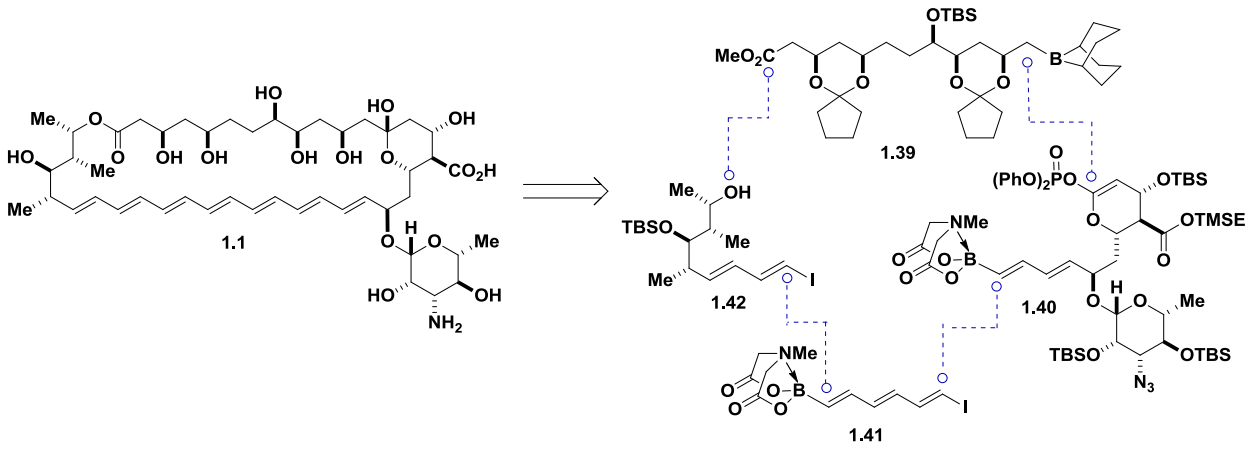


Figure 1.5. Our proposed retrosynthesis of AmB via iterative cross-coupling.

In 2007, Gillis et al. reported the development of a protecting group for boronic acids known as *N*-methyliminodiacetic acid, or MIDA.[44] Earlier data suggested that a free and Lewis acidic boron p-orbital is necessary for the transmetallation of boronic acids.[45,46] Gillis et al. found that the trivalent ligand, MIDA, is capable of complexing to boronic acids, rehybridizing them to sp^3 MIDA boronates and effectively removing the p-orbital (Figure 1.6). These B-protected haloboronic acids are able to selectively cross couple at the halide under anhydrous SM coupling conditions then subsequent mild deprotection with NaOH reveals the free boronic acid for further chemistry. Analogous to iterative peptide coupling, this has allowed for the synthesis of small molecules from building blocks having all of the required functional groups pre-installed in the correct oxidation states and with the desired stereochemical relationships. They can then be sequentially linked via iterative application of one mild reaction.[44,47]

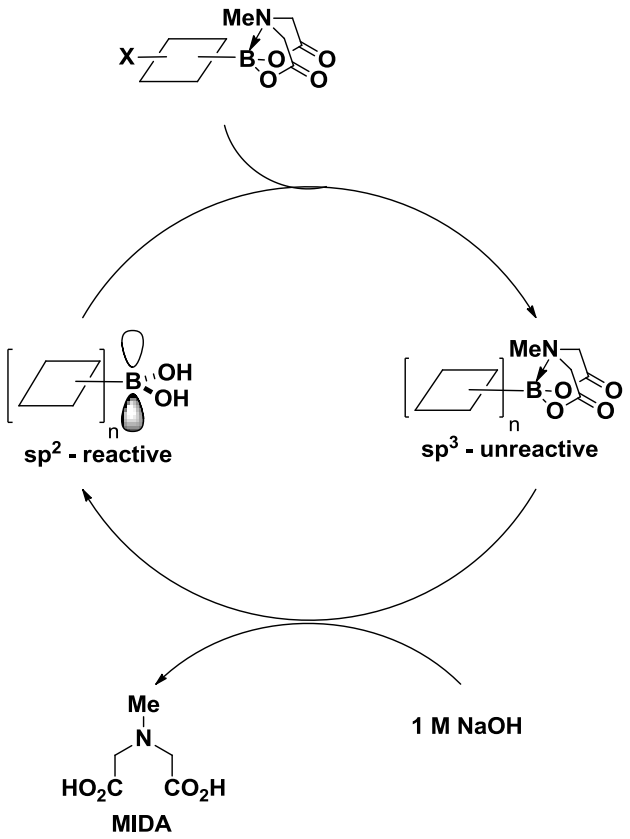


Figure 1.6. Iterative Suzuki-Miyaura cross-coupling of B-protected haloboronic acids. The MIDA protecting group allows for selective cross-coupling of the halide terminus, then mild basic deprotection reveals the reactive boronic acid for iteration.

1-6 SUMMARY

AmB is the archetype for small molecule-based ion channels. Its ability to form discrete ion channels in eukaryotic cells suggests that small molecules may possess untapped potential to replicate the functions of protein ion channels that are deficient in a wide range of currently incurable human diseases. Additionally, it is a clinically vital antifungal agent, however its high toxicity has limited its effective use. The development of a small molecule surrogate for protein ion channels and/or a derivative with a better therapeutic index would be greatly aided by a molecular understanding of AmB's mechanism of action. Given the success of the deletion strategy in understanding the role of the mycosamine and the C41 carboxylate, we propose systematically deleting each of the protic functional groups on AmB and studying the biological and biophysical properties. In order for such a strategy to be possible we need to develop a modular, flexible, and mild synthesis of AmB that would be compatible with the synthesis of derivatives. The following thesis describes the expansion of the MIDA boronate methodology to the synthesis of polyene natural products and a semisynthesis of AmB. Additionally, this

chemistry was successfully employed in a semisynthesis that accessed the targeted deoxygenated derivative C35-deoxy AmB. The lessons learned from this synthesis stand to assist in the development of a general platform to access all of the deoxygenated derivatives of AmB.

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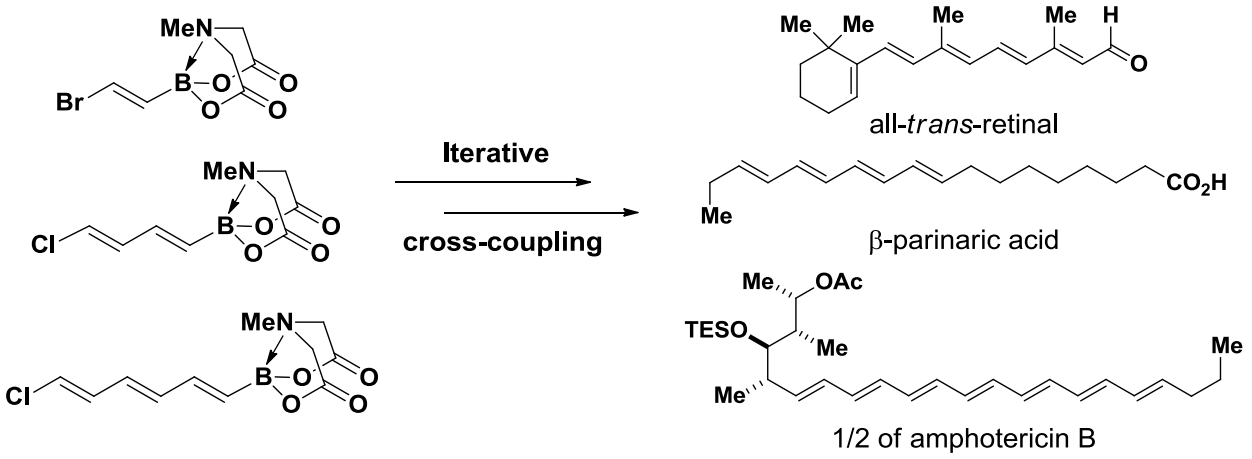
CHAPTER 2

SYNTHESIS OF POLYENE NATURAL PRODUCTS VIA ITERATIVE CROSS-COUPLING

Polyenes are a common structural motif in natural products, but the sensitivity of the conjugated framework complicates the preparation of these molecules. This chapter describes the discovery of bench-stable and highly versatile B-protected haloalkenylboronic acid building blocks that enabled the synthesis of polyenes via iterative Suzuki-Miyaura cross-coupling. In contrast to their boronic acid equivalents, the intermediate polyenylboronate esters are remarkably stable to both column purification and storage. Moreover, the reactive boronic acids can be cleanly liberated using very mild aqueous base. This methodology has facilitated the simple, efficient, and modular total syntheses of all-*trans*-retinal, β-parinaric acid, and the heptaenyl portion of the amphotericin B skeleton, which at the time of its completion was the longest polyene synthesized by the Suzuki-Miyaura reaction. We additionally demonstrated the first selective cross-coupling with a differentially ligated diboron reagent and the first cross-couplings between polyenyl chlorides and vinylboronic acids. These new building blocks can enable the efficient synthesis of polyene natural products and their derivatives. Suk Joong Lee contributed to the work presented in this chapter by performing the experiments described in schemes 2.1 and 2.7. James Paek completed the synthesis described in scheme 2.6. Portions of this chapter were adapted from Lee, S.J.; Gray, K.C.; Paek, J.S.; Burke, M.D. *J. Am. Chem. Soc.* **2008**, *130*, 466-468. Copyright 2008 American Chemical Society.



2-1 BACKGROUND

Most biologically active small molecules exert their effects via the perturbation of macromolecular targets.[1] There are a few, however, that operate via higher-order mechanisms that lie outside this paradigm. The class of "polyene natural products"[2] is particularly rich with examples. Perhaps most notable is the antifungal heptaene macrolide AmB, which self-assembles into a membrane-spanning channel complex with functional properties reminiscent of protein-based ion channels.[3,4] Other polyenes are known to provide structural support for cell membranes,[5] transduce solar energy into mechanical energy,[6] serve as pigments for efficient light harvesting[7] and/or species-specific coloration,[8] act as fluorescent probes,[9] and/or quench reactive oxygen species.[10] The existence of these natural prototypes suggests that the potential for small molecules to perform useful functions in living systems likely extends far beyond that which is currently utilized. Unfettered synthetic access to these compounds and their derivatives is paramount for realizing this potential.

The synthesis of polyenes is made challenging by the sensitivity of conjugated double bond frameworks to light, oxygen, and many common synthetic reagents, especially protic and Lewis acids. Controlling stereochemistry during the formation of each double bond is also a critical issue. Syntheses based on palladium-mediated cross-coupling are attractive due to the mild, nonacidic, and stereospecific nature of these methods.[11,12] Among these, the Suzuki-Miyaura (SM) reaction[11d] stands out due to its use of nontoxic boronic acid reagents and well precedented functional group compatibility. However, polyenylboronic acids are notoriously unstable,[13] which precludes their general utilization. Gillis et al. in 2007 developed a simple and flexible strategy for making small molecules involving the iterative cross-coupling of haloboronic acids protected as the corresponding pyramidalized *N*-methyliminodiacetic acid (MIDA, **2.5**, Scheme 1) adducts.[14] This chapter reports a novel collection of B-protected haloalkenylboronic acid building blocks **2.1**, **2.2**, and **2.3** (Figure 2.1) that are strikingly stable to purification and storage and highly selective toward a wide range of cross-coupling reactions. This stability is maintained in the resulting polyenyl MIDA boronate ester intermediates, thereby enabling the simple, efficient, and modular construction of a variety of polyene natural products with higher-order functions.

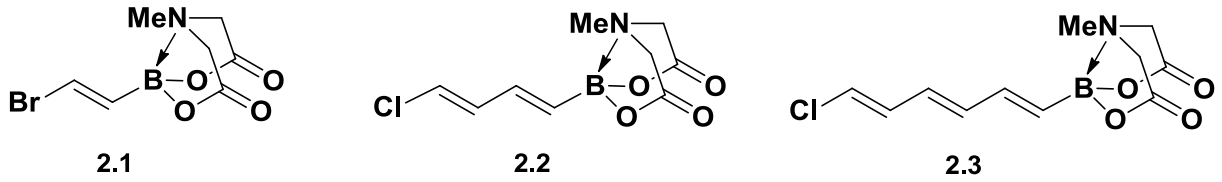


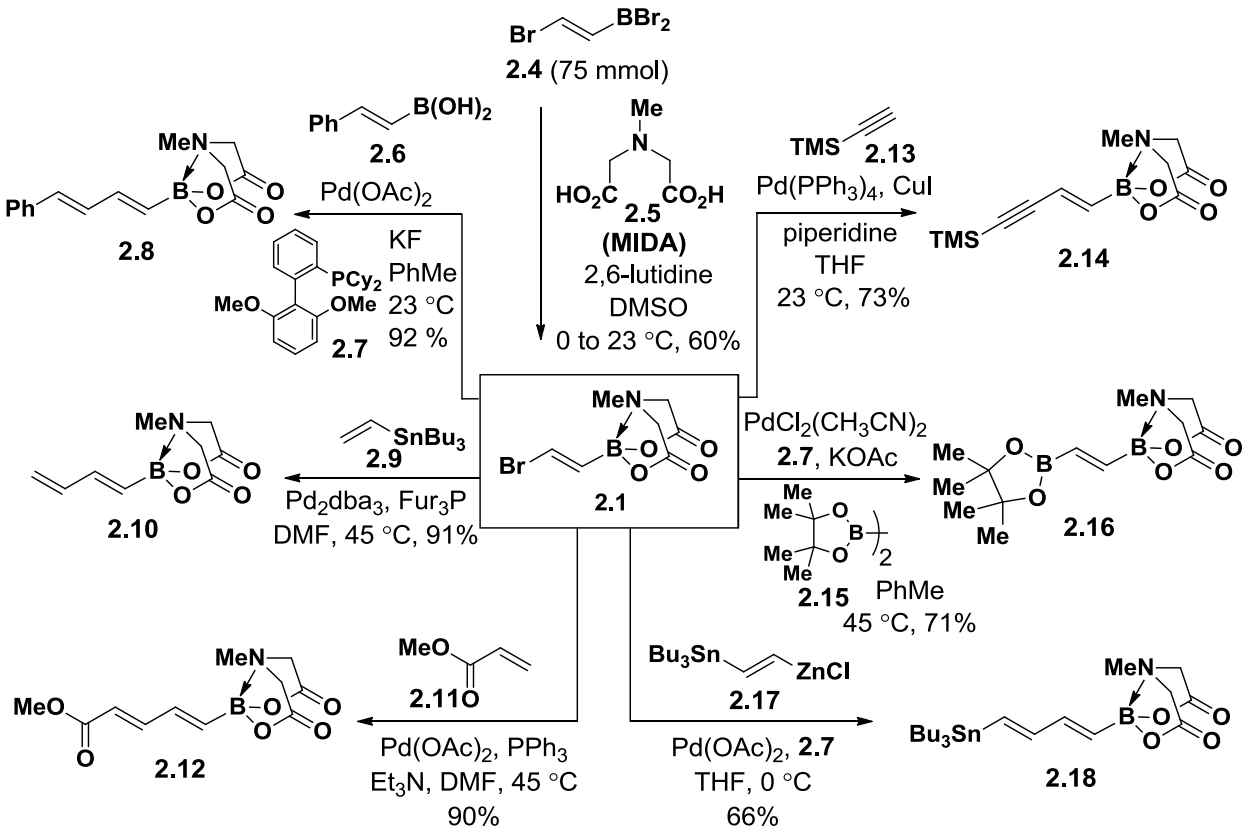
Figure 2.1. Chemical structure of bifunctional polyene building blocks **2.1**-**2.3**.

2-2 POLYENE BUILDING BLOCKS

The first targeted building block containing a single double bond (**2.1**) was prepared via complexation of (*E*)-(2-bromoethenyl)-dibromoborane **2.4**[15] with MIDA (Scheme 2.1). This reaction was performed on >20 g scale (75 mmol) to yield the desired bifunctional olefin **2.1** as a crystalline, free-flowing solid. X-ray analysis confirmed unambiguously the pyramidalized nature of the boron center. Remarkably, this densely functionalized alkene is stable to silica gel chromatography and storage for at least 1.5 years on the benchtop under air.

Moreover, **2.1** was found to be a very versatile cross-coupling partner (Scheme 2.1). For example, the sp^3-hybridized boronate ester terminus was inert to Buchwald's anhydrous SM conditions,[16] thus enabling a selective cross-coupling with (*E*)-styrenylboronic acid **2.6** to provide dienyl boronate **2.8** in excellent yield.[17,18] A Stille coupling between **2.1** and vinyl stannane **2.9** was similarly efficient, yielding butadienyl boronate **2.10**. Finally, a Heck coupling with methyl acrylate **2.11** yielded the unsaturated methyl ester **2.12** as a single regio- and stereoisomer.

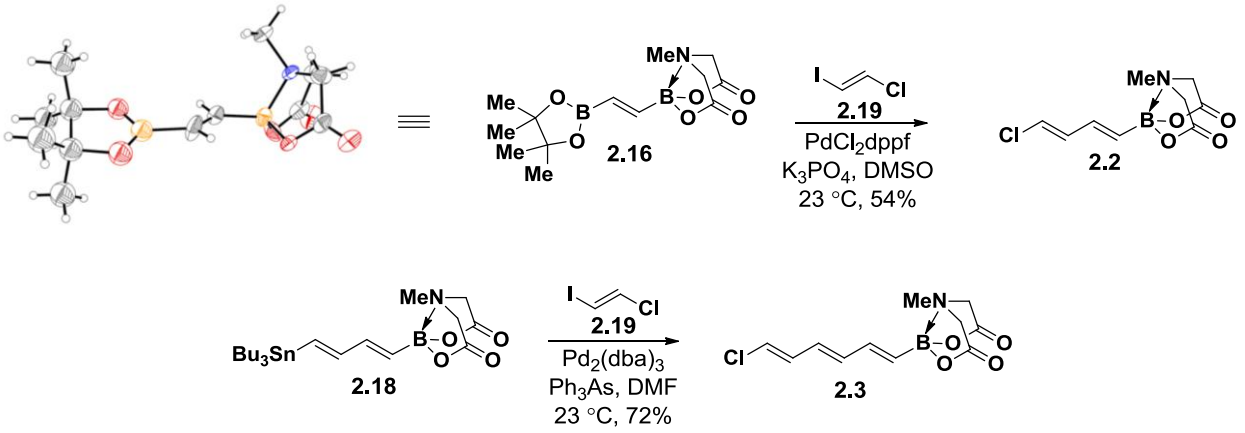
A series of novel bismetalated lynchpin-type reagents[12] were also created. Specifically, Sonogashira coupling between **2.1** and TMS acetylene **2.13** generated hetero-bismetalated enyne **2.14**. Although Miyaura borylations[19] with (*E*)-1,2-disubstituted vinyl halides are challenging,[19b] we found that ligand **2.7**[19c] enabled the smooth conversion of **2.1** into the novel bisborylated olefin **2.16** (an X-ray structure of **2.16** is shown in Scheme 2.2). Like **2.1**, **2.16** is a column and shelf stable crystalline solid (stable under air for at least 1.5 years). Finally, Negishi cross-coupling between **2.1** and the heterobismetalated vinyl zinc reagent **2.17**[12d] yielded lynchpin **2.18** in a novel triply metal selective (Zn vs Sn and B) reaction. Use of Buchwald ligand **2.7** was required to get complete conversion of **2.1** at the low temperature of 0 °C required to keep Negishi reagent **2.17** transiently stable. In contrast, $Pd(PPh_3)_4$ was able to provide some product, however it gave low and irreproducible conversion.



Scheme 2.1. Utility of building block **2.1** in making polyene building blocks through selective palladium-catalyzed reactions at the bromide terminus. Building blocks **2.14**, **2.16**, and **2.18** can serve as lynchpin-type reagents.

With the goal of developing robust, shelf-stable building blocks for polyene synthesis, we designed di- and trienyl halides **2.2** and **2.3** as the corresponding vinyl chlorides.[20] A direct route to the targeted dienyl chloride **2.2** was envisioned via a concomitant metal- and halogen selective SM cross-coupling between bisborylated olefin **2.16** and (*E*)-1-chloro-2-iodoethylene **2.19**[21] (Scheme 2.2). Due to the absence of a boron p-orbital,[14a] we hypothesized that the sp^3-hybridized MIDA boronate terminus of **2.16** would be unreactive relative to the sp^2-hybridized pinacolboronic ester. In fact, as shown in scheme 2.2, single-crystal X-ray diffraction analysis confirmed the distinct hybridization states of the two boron termini of **2.16**, and a halogen- and boron-selective cross-coupling with **2.19** yielded the targeted bifunctional diene **2.2** as a column- and shelf-stable crystalline solid. This novel type of selective cross-coupling with a differentially ligated diboron reagent has since proven to be generally useful.[22,23]

The final targeted polyene building block containing three double bonds (**2.3**) was prepared via another metal-[12i] and halogen-selective cross-coupling between bisfunctionalized reagents **2.18** and **2.3** (Scheme 2.2). Despite containing a potentially sensitive triene moiety, **2.3** is also both column- and shelf-stable.



Scheme 2.2. Synthesis of bifunctional building blocks **2.2** and **2.3**. The crystal structure of **2.16** is shown to its left. The crystal structure shows that the pincol boronic ester terminus is sp^2-hybridized while the MIDA boronate is sp^3-hybridized. This allows for boron selective cross-coupling of the pinacol boronic ester terminus.

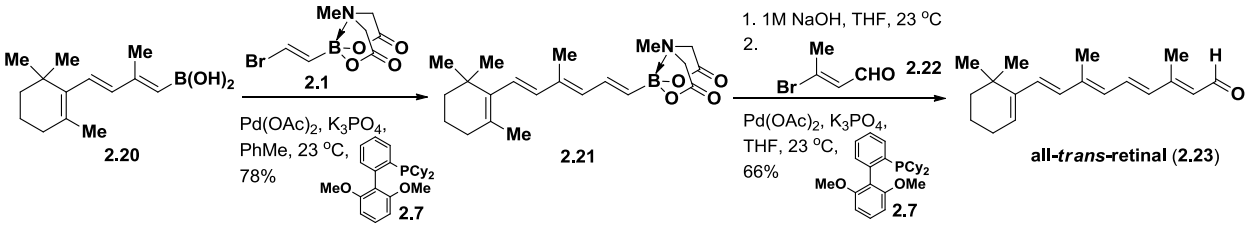
2-3 SYNTHESIS OF ALL-TRANS-RETINAL

With the three targeted building blocks **2.1**-**2.3** in hand and their potential for selective cross-couplings verified, we explored the utility of these new reagents in the context of total syntheses of polyene natural products that perform higher-order functions. For example, the carotenoid all-*trans*-retinal (**2.23**) has the ability to transduce solar energy into mechanical energy and is a critical functional component of the light-driven proton pump found in Halobacteria and the photoreception machinery utilized by most animals.[6] Structure/function studies with this natural product have unique potential to enable the understanding of these phenomena at the molecular level.[6c]

The B-protected haloalkenylboronic acid **2.1** was utilized in a highly modular three-step synthesis of retinal from known starting materials (Scheme 2.3).[24] Specifically, the selective SM coupling between **2.1** and trienylboronic acid **2.20**[24d] yielded the tetraenyl MIDA boronate **2.21**. Notably, although the instability of **2.20** precludes its isolation in concentrated form,[24d] tetraenyl

MIDA boronate **2.21** was isolated via column chromatography as a crystalline solid that can be stored refrigerated for at least 1 month without decomposition.

A key feature of the MIDA protective group is its capacity for removal under mild, aqueous basic conditions.[14a] Given the sensitive nature of polyenylboronic acids,[13] the B-deprotection of intermediate **2.21** presented a rigorous test for this methodology. In the event, this deprotection proceeded smoothly, and subsequent SM coupling of the resulting solution of crude boronic acid with the known α-bromo enal **2.22**[25] succeeded in generating the targeted all-*trans*-retinal.



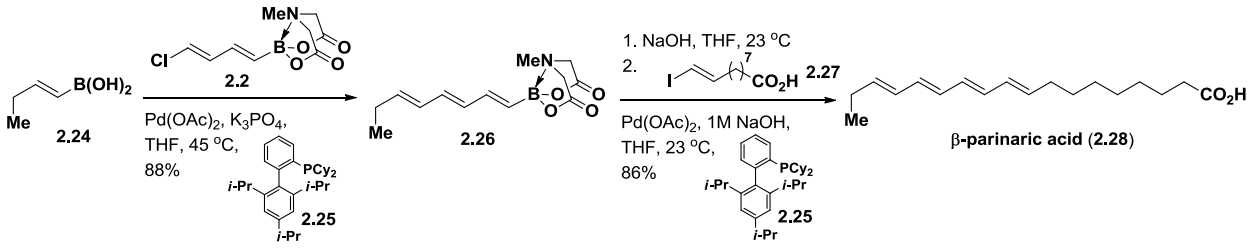
Scheme 2.3. Synthesis of all-*trans*-retinal using bifunctional building block **2.1**.

2-4 SYNTHESIS OF β-PARINARIC ACID

Another interesting polyene, β-parinaric acid **2.28**, has been used for more than three decades as a fluorescent probe for membrane properties.[9,26] In addition, related tetraenoic acids demonstrate remarkable aggregation behaviors,[27] including the formation of antipodal chiral aggregates from a single enantiomer.[27b] The utility of **2.28** and/or its analogues would benefit from more efficient and modular synthetic access to this class of compounds.[28]

In this vein, the B-protected chlorodienylboronic acid **2.2** was employed in a modular synthesis of β-parinaric acid from readily available starting materials (Scheme 2.4). (*E*)-1-Butenylboronic acid **2.24** was synthesized in one step by hydroboration of 1-butyne. A selective coupling between the bifunctional dienylchloride **2.2** and **2.24** yielded the column-stable all-*trans*-trienyl boronate **2.26**. While the coupling of polyenyl chlorides is difficult, Buchwald ligand **2.25** allowed for this reaction to proceed at 23 °C. The B-deprotection of **2.26** was achieved under mild aqueous basic conditions, and subsequent cross-coupling with vinyl iodide **2.27** yielded β-parinaric acid as a fluorescent solid. The capping building block **2.27** was

synthesized in three steps from methyl oleate **2.29** (scheme 2.5). Ozonolysis followed by Takai olefination[29] generated the vinyl iodide in a 10:1 *E*:*Z* ratio. Subsequent saponification of the methyl ester then provided building block **2.27** with all the proper functionality and the correct oxidation state.



Scheme 2.4. Synthesis of β-parinaric acid using bifunctional building block **2.2**.

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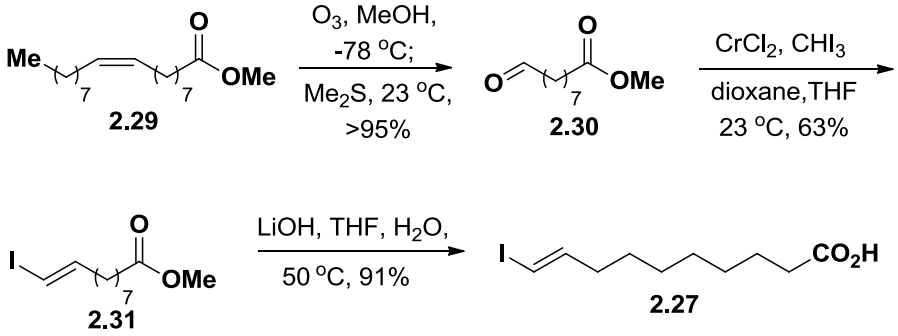


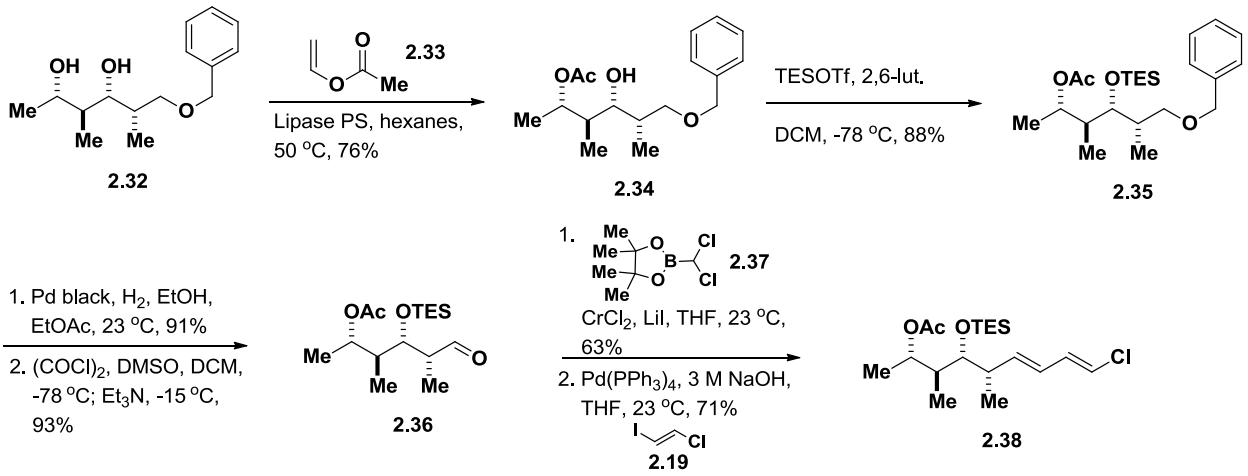
Scheme 2.5. Synthesis of the capping building block (**2.27**) for β-parinaric acid.

2-5 SYNTHESIS OF ONE HALF OF AMPHOTERICIN B

As a final example, the polyene macrolide AmB represents a potential prototype for small molecules that replicate the functions of protein-based ion channels.[30] An efficient and flexible total synthesis of AmB stands to enable the first systematic dissection of the structure/function relationships that underlie this small molecule-based ion channel activity.[4]

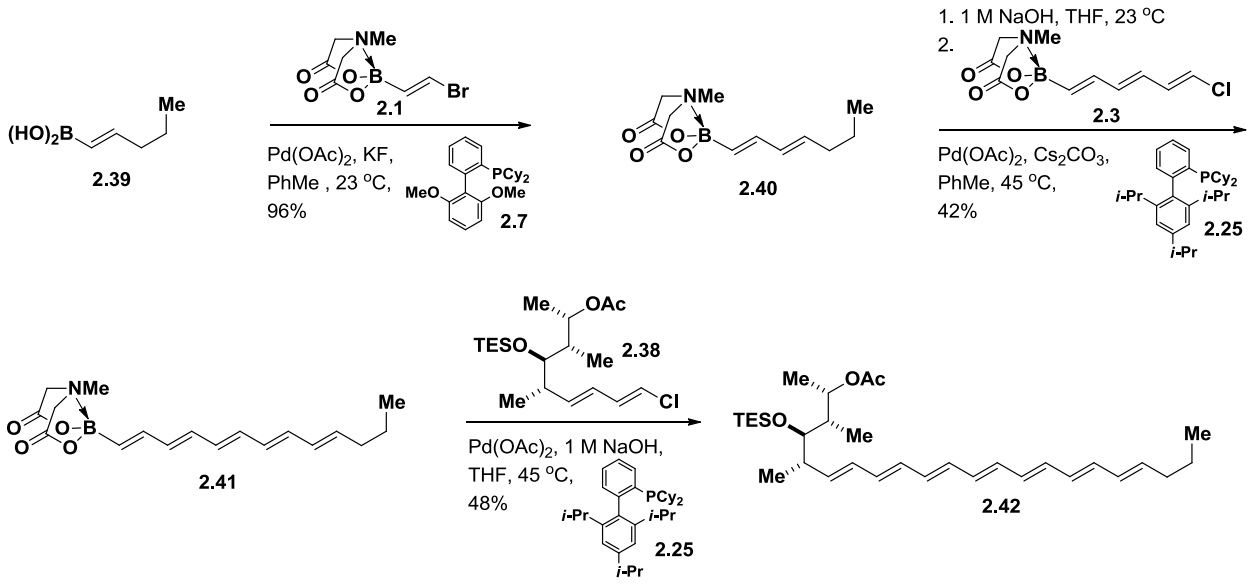
In order to access one half of AmB, the western portion of the molecule needed to be synthesized. The key to a short and effective route to **2.38** (Scheme 2.6) was recognizing that all the desired stereochemistry is contained in previously reported diol **2.32** derived from (*S*)-2-methyl-3-hydroxypropionate via a Paterson aldol reaction.[31] Selective acylation with lipase PS in the presence of vinyl acetate gave a 5:1 mixture of the desired C37 monoacylated hydroxyl

(**2.34**) and the undesired C35 monoacylated hydroxyl, respectively. Secondary alcohol **2.34** was than treated with TESOTf to provide **2.35** in 88% yield. Subsequent benzyl deprotection and Swern oxidation generated aldehyde **2.36** in excellent yields. Finally, exposure to modified Takai olefination conditions[32] followed by SM coupling to **2.19** provided the desired dienyl choride **2.38**.



Scheme 2.6. Synthesis of the western portion of AmB.

In contrast to strategies based on lynchpin-type reagents,[12] the cross-coupling of B-protected haloboronic acids has the theoretical capacity for limitless iteration.[14] Harnessing this potential, the synthesis of one-half of the AmB macrolide skeleton via recursive SM coupling, has been achieved (Scheme 2.7). Specifically, boronic acid **2.39** was joined with **2.1** to generate dienylboronate **2.40**. A subsequent series of B-deprotection and coupling of the resulting dienylboronic acid with trienyl chloride **2.3** yielded column-stable pentaenyl MIDA boronate **2.41**. Finally, taking advantage of the recent discovery in our laboratories that MIDA boronates can be used directly as surrogates for boronic acids under aqueous SM conditions,[33] a one-pot B-deprotection and cross-coupling with dienyl chloride **2.38** yielded one-half of the AmB skeleton **2.42**. At the time of its development this was the longest polyene ever synthesized using the SM reaction. This pathway provides a strong starting point for the development of an efficient and flexible total synthesis of this notoriously challenging natural product.[34]



Scheme 2.7. Synthesis of ½ of AmB via iterative Suzuki-Miyaura cross-coupling of bifunctional building blocks **2.1** and **2.3**.

2-6 SUMMARY

In summary, B-protected haloalkenylboronic acid building blocks such as **2.1**-**2.3** have potential for broad utility in the context of total syntheses of polyene natural products. In particular these buifunctional building blocks were highly enabling for the mild and efficient synthesis of all-*trans*-retinal, β-parinaric acid, and one-half of AmB. In addition to attenuating the reactivity of boronic acid, the MIDA boronate has also been shown to impart outstanding stability to these traditionally difficult to isolate fragments. This simple, efficient, and modular strategy stands to enable the more effective study and widespread utilization of this class of highly functional small molecules.

2-7 EXPERIMENTAL SECTION

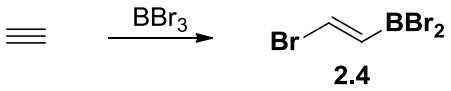
Materials. $Pd(PPh_3)_4$ was a generous gift from Sigma-Aldrich. Commercial reagents were purchased from Sigma-Aldrich, Strem, Fisher Scientific, Alfa Aesar, or Lancaster Synthesis and were used without further purification unless otherwise noted. Solvents were purified *via* passage through packed columns as described by Pangborn and coworkers[35] (THF, Et_2O, CH_3CN, CH_2Cl_2: dry neutral alumina; hexane, benzene, and toluene: dry neutral alumina and Q5 reactant;

DMSO, DMF: activated molecular sieves). Triethylamine and 2,6-lutidine were freshly distilled under an atmosphere of nitrogen from CaH_2. The following compounds were prepared according to literature precedent: (*E*)-(2-bromoethenyl)dibromoborane (**2.4**)[15], (*E*)-1-chloro-2-iodoethylene (**2.19**)[36], (1*E*,3*E*)-2-methyl-4-(2,6,6-trimethylcyclohex-1-enyl)buta-1,3-dienylboronic acid (**2.20**)[37], (*E*)-3-bromobut-2-enal (**2.22**)[38], (E)-(2-(tributylstannyl)vinyl)zinc chloride (**2.17**)[39], (*E*)-methyl 10-iododec-9-enoate (**2.30**)[40], diol **2.32**[31], dichloromethylpinacolboronic ester **2.37**[41].

General Experimental Procedures. All palladium-mediated cross-coupling reactions were performed under an atmosphere of argon in oven- or flame-dried I-Chem or Wheaton vials sealed with PTFE-lined plastic caps. All other reactions were performed in oven- or flame-dried round-bottom or modified Schlenk flasks fitted with rubber septa under a positive pressure of argon or nitrogen unless otherwise indicated. Organic solvents were concentrated *via* rotary evaporation under reduced pressure. Reactions were monitored by analytical thin layer chromatography (TLC) performed using the indicated solvent on E. Merck silica gel 60 F254 plates (0.25 mm). Compounds were visualized by exposure to a UV lamp (λ = 254 and 365 nm), a solution of $KMnO_4$, a solution of ceric ammonium molybdate (CAM), or an acidic solution of *p*-anisaldehyde followed by brief heating using a Varitemp heat gun. Flash column chromatography was performed as described by Still and coworkers[42] using EM Merck silica gel 60 (230-400 mesh) and/or Aldrich Florisil® (an activated magnesium silicate: 100-200 mesh).

Structural Analysis. ^{1}H NMR spectra were recorded at 23 ˚C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CDCl_3$, δ = 7.24; CD_3CN, δ = 1.93; $(CD_3)_2CO$, δ = 2.04; DMSO-d_6, δ = 2.49, center line). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sept = septet, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, b = broad), coupling constant (*J*) in Hertz (Hz), and integration. ^{13}C NMR spectra were recorded at 23 ˚C on one of the following instruments: Varian Unity 500 or Varian Unity Inova 500NB. Chemical shifts (δ) are reported in ppm downfield from tetramethylsilane and referenced to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0; **C**D_3CN, δ = 1.30;

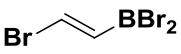
($\mathbf{C}D_3)_2CO$, δ = 29.8; DMSO-d_6, δ = 39.5, center line). Carbons bearing boron substituents were not observed (quadrupolar relaxation).[11]B NMR were recorded using a General Electric GN300WB instrument and referenced to an external standard of (BF_3•Et_2O). High resolution mass spectra (HRMS) were performed by Furong Sun and Dr. Steve Mullen at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory. Infrared spectra were collected from a thin film on NaCl plates on a Mattson Galaxy Series FTIR 5000 spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). X-ray crystallographic analysis of **2.1** and **2.16** were carried out by Dr. Scott Wilson at the University of Illinois George L. Clark X-Ray facility.



2.4

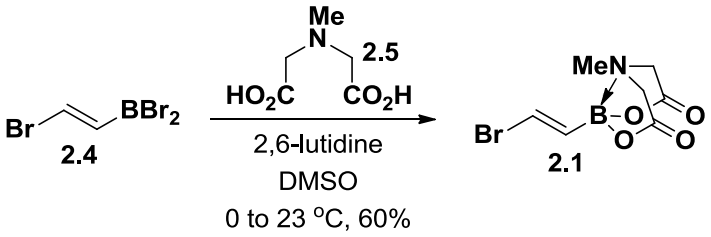
(*E*)-(2-bromoethenyl)dibromoborane (2.4)[15]

In a subdued light environment, an oven-dried 100 mL one-neck round bottom flask, equipped with a magnetic stir bar and a rubber septum, was flushed out with acetylene gas three-times using a five-inch balloon attached to needle. The flask was attached to three balloons filled with acetylene gas and cooled to 0 °C. To a flask at 0 °C was added boron tribromide (75.0 g, 299.4 mmol) dropwise *via* syringe over 15 minutes with stirring. The reaction mixture was allowed to warm to 23 ˚C and then stirred at 23 ˚C for 24 hours. (*Each balloon was refilled with acetylene gas after the acetylene gas in the balloon was consumed*). In a subdued light environment, the resulting dark-blue crude mixture was distilled *three-times* under high vacuum connected with two dry ice/acetone traps to provided **2.4** (45.20 g, 163.4 mmol) as a colorless oil in 55 % yield. (bp = 50-55 °C/13mmHg). (*The fractional vacuum distillation was carried out at 23 ˚C for 30 minutes before heating to remove a small amount of residual boron tribromide and then the crude mixture was slowly heated to around 65 ˚C using an oil-bath until distillation was completed. The oil-bath temperature was carefully maintained below 70 ˚C to inhibit a polymerization reaction*). The freshly distilled title compound **2.4** was used immediately in the next reaction.



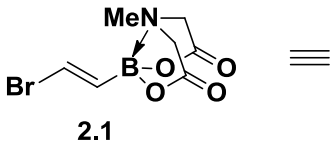
^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.97 (d, *J* = 15.0 Hz, 1H), 7.08 (d, *J* = 15.0 Hz, 1H).



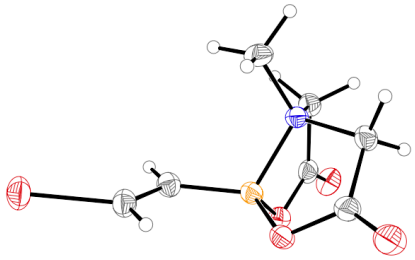
Bromoethenyl MIDA Boronate 2.1

In a subdued light environment, to a stirred mixture of *N*-methyliminodiacetic acid (MIDA, **2.5**) (16.93 g, 113.9 mmol, 1.5 eq) and 2,6-lutidine (17.69 mL, 151.86 mmol, 2 eq) in DMSO (250 mL) at 0 °C under an atmosphere of nitrogen was added freshly distilled **2.4** (21.00 g, 75.93 mmol, 1 eq) dropwise *via* syringe over 15 minutes. The reaction mixture was allowed to warm to 23 ˚C and then stirred at 23 ˚C for 48 hours. The resulting yellow mixture was treated with water (300 mL) and extracted with THF:diethyl ether 1:1 (3 × 500 mL). The combined organic phases were washed with brine (3 × 350 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to provide a light yellow solid. The crude product was purified by column chromatography on silica gel (50% EtOAc/petroleum ether → EtOAc → 10% MeCN/EtOAc) to give the title compound **2.1** as a colorless crystalline solid (11.98 g, 45.75 mmol, 60%). Crystals suitable for X-ray crystallography analysis were grown by slow evaporation from ethyl acetate at 23 ˚C. ***This material was stored under air at 23 ˚C for one year and six months without decomposition.***



2.1

≡



TLC (EtOAc)

R_f = 0.46, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, CD_3CN)

δ 6.69 (d, *J* = 15.0 Hz, 1H), 6.33 (d, *J* = 14.5 Hz, 1H), 3.97 (d, *J* = 17.0 Hz, 2H), 3.82 (d, *J* = 17.0 Hz, 2H), 2.80 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN)

δ 169.0, 118.8, 62.6, 47.9.

HRMS (ESI)

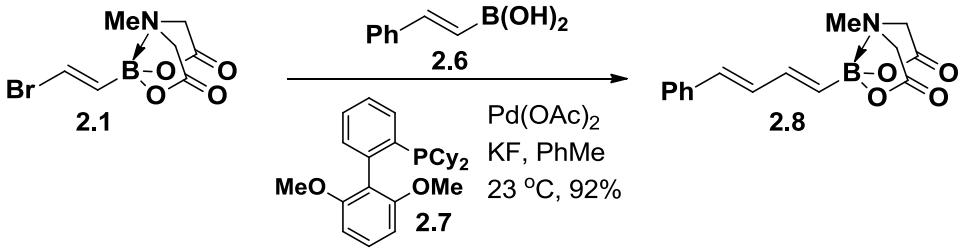
Calculated for $C_7H_9NO_4BrB$ (M+H):	261.9886
Found:	261.9874

^{11}B NMR (100 MHz, CD_3CN)

δ 10.5.

IR (thin film, cm^{-1})

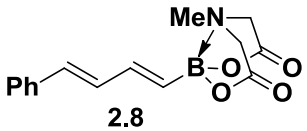
3005.5, 2961.9, 1754.7, 1589.2, 1450.5, 1337.5, 1285.7, 1196.2, 1152.2, 1117.5, 1079.7, 1025.1, 1008.8, 960.9, 893.2, 871.5, 772.7, 677.7.



Phenyl Diene 2.8

A solution of the catalyst was prepared as follows: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 1 eq) and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl **2.7** (20.5 mg, 0.050 mmol, 2 eq) in an argon-filled glovebox. Toluene (3.0 mL) was added and the vial was sealed with a PTFE-lined plastic cap. The resulting mixture was stirred at 23 ˚C for 45 minutes resulting in a yellow Pd/**2.7** catalyst solution (0.00833 M Pd in toluene).

This catalyst solution was then utilized in the following procedure: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1 eq) and *trans*-2-phenylvinylboronic acid (**2.6**) (0.229 g, 1.50 mmol, 1.5 eq) and sealed with a PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into an argon-filled glovebox. KF (0.116 g, 2.00 mmol, 2 eq), toluene (7.0 mL) and the catalyst solution (1.2 mL, 0.01 mmol, 1 mol% Pd) was added and vial was sealed with a PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred for 24 hours at 23 ˚C. The resulting heterogeneous yellow mixture was diluted with acetonitrile (10.0 mL) and filtered through short pad Celite using acetonitrile (100 mL). The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (50% EtOAc/petroleum ether → EtOAc → 33% MeCN/EtOAc) to give the title compound **2.8** as a colorless crystalline solid (0.263 g, 0.922 mmol, 92 %).



TLC (EtOAc)

R_f = 0.85, visualized by UV lamp (λ = 254 nm) or with $KMnO_4$.

^{1}H NMR (500 MHz, DMSO-d_6)

δ 7.48 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 6.93 (dd, J = 15.5, 10.5 Hz, 1H), 6.65 (d, J = 15.5 Hz, 1H), 6.63 (dd, J = 17.0, 10.5 Hz, 1H), 5.78 (d, J = 17.5 Hz, 1H), 4.24 (d, J = 17.5 Hz, 2H), 4.03 (d, J = 17.0 Hz, 2H), 2.78 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6)

δ 169.3, 142.0, 136.9, 132.9, 130.9, 128.7, 127.8, 126.5, 61.4, 46.8.

HRMS (ESI)

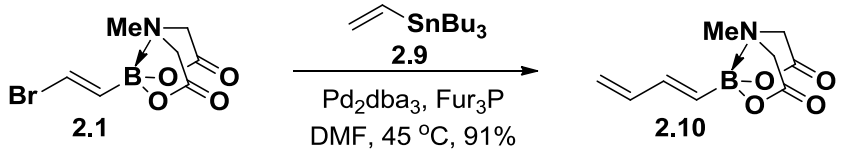
Calculated for $C_{15}H_{16}NO_4B$ (M+H):	286.1251
Found:	286.1249

^{11}B NMR (100 MHz, DMSO-d_6)

δ 11.4.

IR (thin film, cm^{-1})

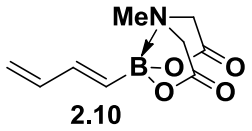
2967.4, 1741.1, 1697.9, 1681.8, 1650.7, 1556.4, 1445.9, 1338.0, 1309.4, 1257.5, 1112.7, 1082.0, 1012.9, 950.0, 884.8, 864.7, 750.4, 693.8, 653.5.



Diene 2.10

An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1 eq) and sealed with a PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into an argon-filled glovebox. Pd_2dba_3 (0.037 g, 0.040 mmol, 4 mol% Pd), Fur_3P (0.021 g, 0.090 mmol, 9 mol%), DMF (8.0 mL) and tributyl(vinyl)tin (**2.9**) (0.346 mL, 1.15 mmol, 1.15 eq) was added and vial was sealed with a PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred for 12 hours at 45 ˚C. The

resulting reddish mixture was diluted with brine (50 mL) and then extracted with ethyl acetate (3 × 100 mL). The combined organic fractions were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (50% EtOAc:petroleum ether → EtOAc → 6% MeCN/EtOAc) to give the title compound **2.10** as a colorless crystalline solid (0.190 g, 0.909 mmol, 91%).



2.10

TLC (EtOAc)

R_f = 0.46, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, CD_3CN)

δ 6.56 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.43 (dtd, *J* = 17.0, 10.0, 0.5 Hz, 1H), 5.66 (dd, *J* = 17.5, 0.5 Hz, 1H), 5.28 (ddt, *J* = 17.0, 2.0, 0.5 Hz, 1H), 5.14 (ddt, *J* = 10.0, 2.0, 0.5 Hz, 1H), 3.96 (d, *J* = 17.0 Hz, 2H), 3.79 (d, *J* = 17.0 Hz, 2H), 2.76 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN)

δ 169.5, 144.3, 140.1, 119.0, 62.3, 47.6.

HRMS (ESI)

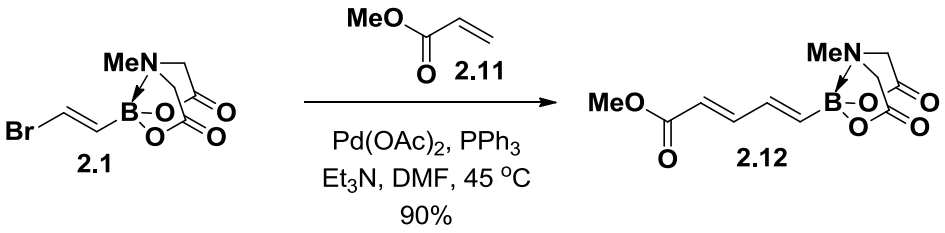
Calculated for $C_9H_{12}BNO_4$ (M+Na):	232.0757
Found:	232.0757

^{11}B NMR (100 MHz, CD_3CN)

δ 10.9.

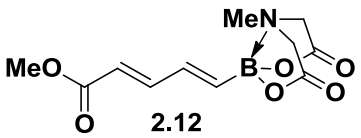
IR (thin film, cm^{-1})

3006.3, 2959.8, 1769.8, 1709.9, 1636.0, 1591.8, 1459.5, 1423.9, 1337.9, 1286.0, 1193.7, 1154.2, 1124.7, 1087.9, 1024.3, 958.4, 892.5, 873.9, 836.6, 719.4, 648.4.



Dienyl Methyl Ester 2.12

An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1 eq), PPh_3 (0.0159 g, 0.060 mmol, 6 mol%) and sealed with a PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into an argon-filled glovebox. $Pd(OAc)_2$ (0.0067 g, 0.030 mmol, 3 mol% Pd), Et_3N (0.279 mL, 2.00 mmol, 2 eq), methyl acrylate (**2.11**) (0.136 mL, 1.50 mmol, 1.5 eq), and DMF (7.0 mL) were added and the vial was sealed with a PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred for 12 hours at 45 ˚C. The resulting mixture was diluted with brine (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (50% EtOAc/petroleum ether 1:1 → EtOAc → 6% MeCN/EtOAc) to give the title compound **2.12** as a light yellow solid (0.240 g, 0.898 mmol, 90%).



TLC (EtOAc)

R_f = 0.33, visualized by UV lamp (λ = 254 nm).

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.20 (dd, *J* = 15.5, 10.5 Hz, 1H), 6.68 (dd, *J* = 17.0, 10.5 Hz, 1H), 6.02 (d, *J* = 17.5 Hz, 1H), 5.89 (d, *J* = 15.5 Hz, 1H), 4.11 (d, *J* = 17.0 Hz, 2H), 3.79 (d, *J* = 17.0 Hz, 2H), 3.67 (s, 3H), 2.82 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 168.8, 167.3, 145.4, 140.9, 122.4, 61.7, 51.6, 47.2.

HRMS (ESI)

Calculated for $C_{11}H_{14}BNO_6$ (M+Na): 290.0812

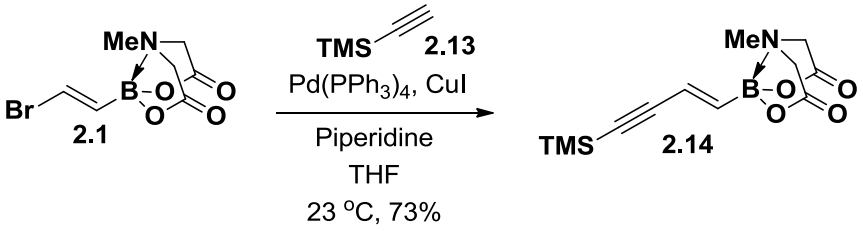
Found: 290.0812

^{11}B NMR (100 MHz, $CDCl_3$)

δ 9.9.

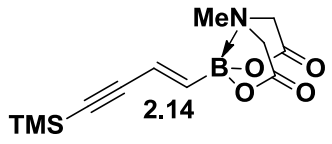
IR (thin film, cm^{-1})

3005.0, 1751.2, 1734.3, 1718.1, 1700.5, 1696.2, 1684.7, 1653.5, 1595.2, 1559.8, 1437.1, 1334.0, 1281.3, 1232.7, 1129.1, 990.8, 862.8, 716.1, 662.4.



Enyne 2.14

An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1 eq) and sealed with a PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into an argon-filled glovebox. $Pd(PPh)_4$ (0.058 g, 0.050 mmol, 5 mol%), CuI (0.019 g, 0.100 mmol, 10 mol%), piperidine (0.227 mL, 2.30 mmol, 2 eq), THF (5.0 mL), and trimethylsilylacetylene (**2.13**) (0.166 mL, 1.15 mmol, 1.5 eq) were added and vial was sealed with a PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred for 3 hours at 23 ˚C. The resulting mixture was diluted with EtOAc (5.0 mL) and filtered through short pad silica gel using EtOAc (100 mL). The filtrate was concentrated *in vacuo*, and the resulting crude product was purified by column chromatography on silica gel (50% EtOAc/petroleum ether → EtOAc) to give the title compound **2.14** as a colorless crystalline solid (0.203 g, 0.728 mmol, 73%).



2.14

TLC (EtOAc)

R_f = 0.60, visualized by UV lamp (λ = 254) or with $KMnO_4$).

^{1}H NMR (500MHz, $CDCl_3$)

δ 6.12 (d, *J* = 18.0 Hz, 1H), 6.04 (d, *J* = 18.5 Hz, 1H), 4.08 (d, *J* = 17.0 Hz, 2H), 3.70 (d, *J* = 17.0 Hz, 2H), 2.82 (s, 3H), 0.15 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 168.7, 123.7, 104.6, 96.4, 61.6, 47.2, -0.2.

HRMS (ESI)

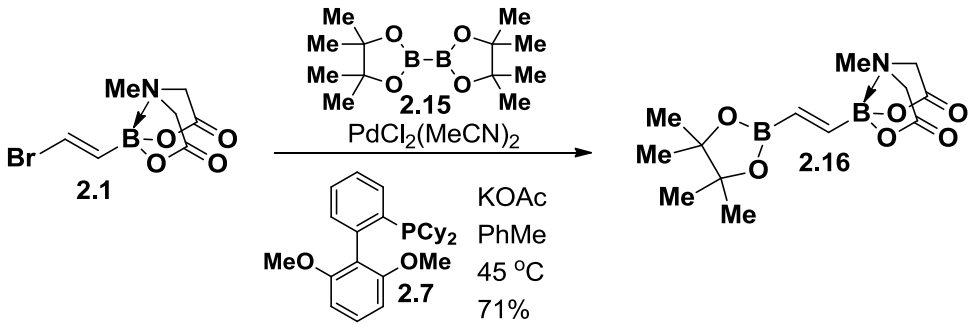
Calculated for $C_{12}H_{18}BNO_4Si$ (M+H):	280.1176
Found:	280.1178

^{11}B NMR (100 MHz, $CDCl_3$)

δ 11.5.

IR (thin film, cm^{-1})

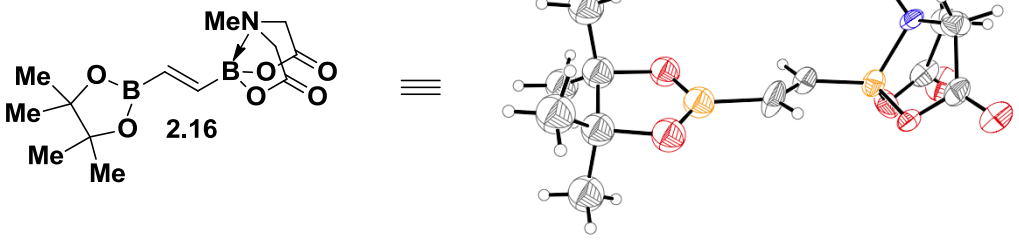
3015.6, 2959.2, 2898.4, 2152.4, 1759.7, 1600.2, 1451.2, 1422.6, 1341.6, 1292.6, 1251.2, 1169.5, 1116.2, 1065.7, 1024.9, 1002.5, 952.9, 841.9, 759.5, 734.4, 678.8.



Pinacolboronic Ester 2.16

A solution of the catalyst was prepared as follows: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with $PdCl_2(CH_3CN)_2$ (7.9 mg, 0.030 mmol, 1 eq) and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl **2.7** (38.0 mg, 0.090 mmol, 3 eq) in an argon-filled glovebox. Toluene (3.0 mL) was added and the vial was sealed with a PTFE-lined plastic cap. The resulting mixture was stirred at 23 ˚C for 30 minutes yielding a clear yellow Pd/**2.7** catalyst solution.

This catalyst solution was then utilized in the following procedure: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1 eq) and sealed with a PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into a glovebox. Bis(pinacolato)diboron (**2.15**) (0.324 g, 1.25 mmol, 1.25 eq), potassium acetate (0.297 g, 3.00 mmol, 3 eq), toluene (5.0 mL) and catalyst solution (3.0 mL, 3 mol% Pd) were then added and the vial was sealed with a PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred for 36 hours at 45 ˚C. The resulting heterogeneous mixture was diluted with ethyl acetate (5.0 mL) and filtered through short pad of Celite. Concentration of the filtrate *in vacuo* provided a light yellow solid. This crude product was purified by column chromatography on silica gel (50% EtOAc/petroleum ether → EtOAc → 6% MeCN/EtOAc) to give the title compound **2.16** as a colorless crystalline solid (0.219 g, 0.710 mmol, 71%). Crystals suitable for X-ray crystallography analysis were grown by slow evaporation from EtOAc at 23 ˚C. ***This material was stored under air at 23 ˚C for one year and six months without decomposition.***



TLC (EtOAc)

R_f = 0.23, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, CD_3CN)

δ 6.67 (d, *J* = 20.5 Hz, 1H), 6.11 (d, *J* = 21.0 Hz, 1H), 3.96 (d, *J* = 17.0 Hz, 2H), 3.80 (d, *J* = 17.0 Hz, 2H), 2.76 (s, 3H), 1.22 (s, 12H).

^{13}C NMR (125 MHz, CD_3CN)

δ 169.4, 84.1, 62.5, 47.7, 25.1.

HRMS (ESI)

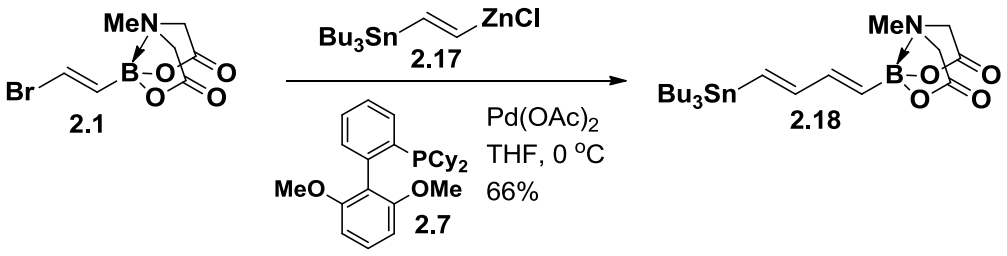
Calculated for $C_{13}H_{21}NO_6B_2$ (M+H):	310.1633
Found:	310.1638

^{11}B NMR (100 MHz, CD_3CN)

δ 29.7 (sp^2), 10.2 (sp^3).

IR (thin film, cm^{-1})

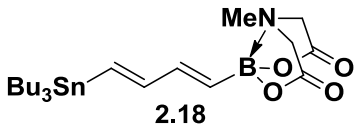
2979.4, 1762.2, 1700.8, 1653.7, 1559.9, 1458.2, 1374.3, 1332.2, 1297.1, 1143.7, 1109.9, 1088.3, 1023.7, 967.2, 877.7, 846.9, 808.5, 673.0.



Dienyl Stannane 2.18

A solution of the catalyst was prepared as follows: To a 4 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (**2.7**) (15.2 mg, 0.037 mmol, 2 eq) was added a solution of $Pd(OAc)_2$ in THF (0.095 M, 0.19 mL, 0.018 mmol, 1 eq). The vial was sealed with a PTFE-lined cap and maintained at 23 ˚C with stirring for 15 minutes yielding a clear yellow Pd/**2.7** catalyst solution.

This catalyst solution was then utilized in the following procedure: (E)-(2-(tributylstannyl)vinyl)zinc chloride (**2.17**) was prepared according to literature precedent:[39] To a solution of trans-1,2-bis(tri-n-butylstannyl)ethylene (231 mg, 0.382 mmol, 2 eq) in THF (0.4 mL) at –78 ˚C was added *n*-butyllithium (1.55 M in hexanes, 0.27 mL, 0.42 mmol, 2.2 eq). After 30 minutes at –78 ˚C, a freshly prepared solution of $ZnCl_2$ (57 mg, 0.42 mmol, 2.2 eq) in THF (0.84 mL) was added causing rapid discoloration. The solution was then warmed to –20 ˚C. During the formation of Negishi reagent **2.17**, to a slurry of **2.1** (50 mg, 0.191 mmol, 1 eq) in THF (0.2 mL) at 23 ˚C was added the catalyst stock solution described above (0.10 mL, 0.0095 mmol Pd, 5 mol% Pd) and the resulting slurry was stirred for 30 minutes before cooling to 0 °C. Negishi reagent **2.17** was then cannulated into the **2.1** solution over 5 minutes. After 2 hours at 0 ˚C the reaction was diluted with EtOAc (10 mL) and was concentrated *in vacuo*. The resulting red oil was dissolved in EtOAc and filtered through a small pad of silica gel with copious amounts of EtOAc, and the filtrate was concentrated *in vacuo*. The resulting crude product was purified by column chromatography on silica gel (50% EtOAc/hexanes → EtOAc) to yield **2.18** as a pale yellow foam (62.2 mg, 0.125 mmol, 66%).



2.18

TLC (EtOAc)

R_f = 0.45, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.65 (dd, *J* = 9.5, 18.5 Hz, 1H), 6.52 (dd, *J* = 10.0, 17.5 Hz, 1H), 6.31 (d, *J* = 18.5 Hz, 1H), 5.63 (d, *J* = 17.0 Hz, 1H), 4.21 (d, *J* = 17.0 Hz, 2H), 4.03 (d, *J* = 17.0 Hz, 2H), 3.00 (s, 3H), 1.54 (m, 6H), 1.32 (m, 6H), 0.95 (t, *J* = 8.0 Hz, 6H), 0.88 (t, *J* = 7.5 Hz, 9H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 169.0, 150.2, 146.2, 135.2, 62.3, 47.3, 29.9, 27.9, 13.9, 9.9.

^{11}B NMR (300 MHz, acetone-d_6)

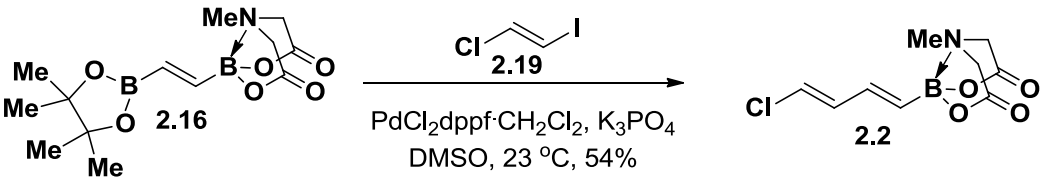
δ 11.3.

HRMS (CI+)

Calculated for $C_{21}H_{38}O_4NBSn$ $(M+H)^+$:	500.1994
Found:	500.1992

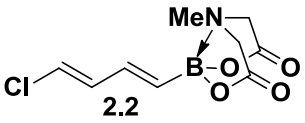
IR (thin film, cm^{-1})

2955, 2925, 2871, 2848, 1762, 1616, 1557, 1463, 1338, 1289, 1167, 1116, 1022, 957, 873, 844.



Dienyl Chloride 2.2

In a glove box, to a 20 mL I-Chem vial equipped with a stir bar was added bis-borylated olefin **2.16** (320 mg, 1.05 mmol, 1 eq), finely ground anhydrous K_3PO_4 (669 mg, 3.15 mmol, 3 eq), $PdCl_2dppf{\bullet}CH_2Cl_2$ (26 mg, 0.32 mmol, 3 mol%), and (*E*)-1-iodo-2-chloroethylene (**2.19**)[36] (396 mg, 2.10 mmol, 2 eq). The vial was sealed with a teflon-lined septum cap and DMSO (8.4 mL) was added via syringe. The resulting mixture was stirred at 23 ˚C for 9 hours. The reaction was quenched with the addition of 0.5 M pH 7 phosphate buffer (8 mL) and the resulting mixture was extracted with THF:Et_2O 1:1 (4 x 15 mL). The combined organic extracts were washed with brine (1 x 25 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was diluted with acetone (15 mL) and concentrated onto Florisil. The resulting powder was dry-loaded on top of a silica gel column and eluted with 50% EtOAc/hexanes → EtOAc → 10% MeCN/EtOAc to yield **2.2** as a colorless crystalline solid (139 mg, 0.571 mmol, 54%).



TLC (EtOAc)

R_f = 0.35, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, CD_3CN)

δ 6.58 (dd, *J* = 10.5, 13 Hz, 1H), 6.53 (dd, *J* = 10.5, 16.5 Hz, 1H), 6.43 (d, *J* = 13.0 Hz, 1H), 5.68 (d, *J* = 17.0 Hz, 1H), 3.94 (d, *J* = 17.0 Hz, 2H), 3.78 (d, *J* = 17.0 Hz, 2H), 2.75 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN)

δ 169.3, 139.3, 136.6, 123.1, 62.4, 47.7.

^{11}B NMR (300 MHz, CD_3CN)

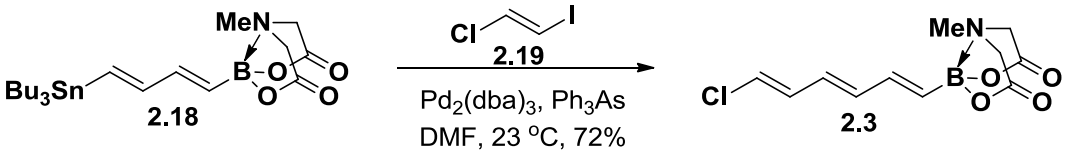
δ 11.1.

HRMS (EI+)

Calculated for $C_9H_{11}O_4NClB$ $(M)^+$:	243.0469
Found:	243.0467

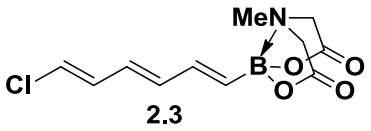
IR (thin film, cm^{-1})

3019, 1767, 1289, 1215, 1026, 1003, 760, 669.



Trienyl Chloride 2.3

In an argon-filled glovebox, an oven-dried Wheaton vial equipped with a magnetic stir bar was charged with $Pd_2(dba)_3$ (0.021 g, 0.023 mmol, 1.5 mol%), Ph_3As (0.014 g, 0.046 mmol, 3 mol%), **2.18** (0.760 g, 1.53 mmol, 1 eq) as a solution in DMF (5.0 mL), and finally (*E*)-1-chloro-2-iodoethylene (0.575 g, 3.05 mmol, 2 eq). The vial was sealed with PTFE-lined plastic cap, removed from the glovebox, and stirred at 23 ˚C for 3.5 hours. To the resulting deep reddish mixture was then added saturated aqueous $Na_2S_2O_3$ (50 mL) and the resulting mixture was extracted with EtOAc (3 × 85 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to provide an orange solid. This crude product was purified by column chromatography on Florisil® (50% EtOAc/petroleum ether → EtOAc → 10% MeCN/EtOAc) to give the title compound **2.3** as a light yellow solid (0.297 g, 1.10 mmol, 72%).



2.3

TLC (EtOAc)

R_f = 0.46, visualized by UV lamp (λ = 254) or with $KMnO_4$.

^{1}H NMR (400 MHz, CD_3CN)

δ 6.61-6.53 (m, 2H), 6.39-6.25 (m, 3H), 5.72 (d, *J* = 17.6 Hz, 1H), 3.95 (d, *J* = 16.8 Hz, 2H), 3.79 (d, *J* = 16.8 Hz, 2H), 2.75 (s, 3H).

^{13}C NMR (100 MHz, CD_3CN)

δ 169.4, 143.1, 136.4, 134.6, 130.2, 122.3, 62.3, 47.6.

^{11}B NMR (100 MHz, CD_3CN)

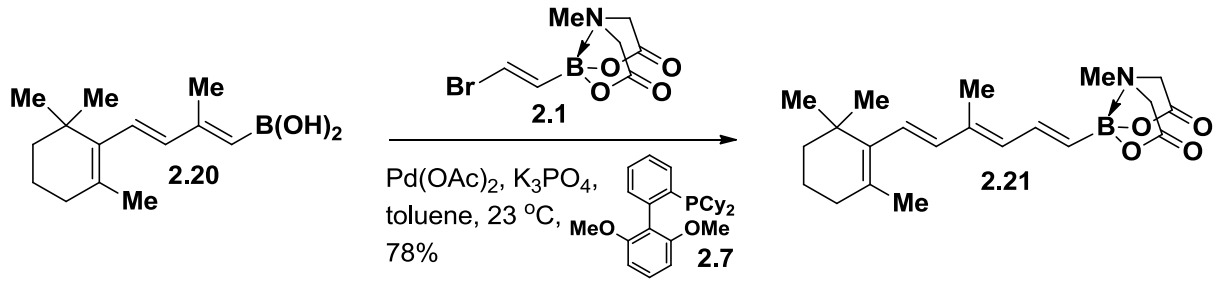
δ 10.7.

HRMS (ESI)

Calculated for $C_{11}H_{13}BNO_4Cl$ (M+H):	270.0704
Found:	270.0717

IR (thin film, cm^{-1})

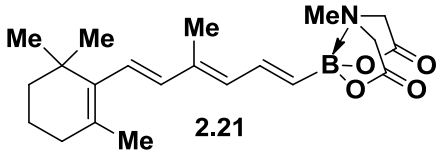
3009.9, 1764.0, 1619.5, 1562.4, 1458.0, 1337.0, 1287.6, 1234.6, 1190.7, 1153.7, 1115.8, 1083.3, 1006.2, 955.4, 890.9, 862.2, 829.4, 721.2.



Tetraenyl MIDA Boronate 2.21

A solution of the catalyst was prepared as follows: To a 4 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl **2.7** (23.1 mg, 0.056 mmol, 2 eq) was added a solution of $Pd(OAc)_2$ in toluene (0.038 M, 0.740 mL, 0.028 mmol, 1 eq). The vial was sealed with a PTFE-lined cap and maintained at 65 ˚C with stirring for 15 minutes.

This catalyst solution was then utilized in the following procedure: To a 40 mL I-Chem vial equipped with a stir bar and containing a solution of **2.20**[37] in toluene (estimated 0.17 M, 11.5 mL, 1.96 mmol, 1.5 eq) was added anhydrous K_3PO_4 as a finely ground powder (0.833 g, 3.92 mmol, 3 eq), **2.1** (0.342 g, 1.30 mmol, 1 eq), and the catalyst solution (0.688 mL, 0.026 mmol Pd, 2 mol% Pd). The resulting mixture was sealed with a PTFE-lined cap and stirred at 23 ˚C for 60 hours. The mixture was then filtered through a pad of silica gel with copious amounts of MeCN. To the resulting solution was added Florisil gel and then the solvent was removed *in vacuo*. The resulting powder was dry-loaded on top of a silica gel column and eluted with 50% EtOAc/hexanes → EtOAc → 10% MeCN/EtOAC to yield the desired product as a yellow powder (0.377 g, 1.02 mmol, 78%).



TLC (EtOAc)

R_f = 0.45, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.98 (dd, J = 11, 17 Hz, 1H), 6.23 (d, J = 16 Hz, 1H), 6.13 (d, J = 11.5 Hz, 1H), 6.10 (d, J = 16 Hz, 1H), 5.71 (d, J = 17 Hz, 1H), 4.21 (d, J = 17 Hz, 2H), 4.03 (d, J = 17 Hz, 2H), 3.00 (s, 3H), 2.01 (app t, J = 6 Hz, 2H), 1.94 (d, J = 1 Hz, 3H), 1.68 (d, J = 1 Hz, 3H), 1.63-1.58 (m, 2H), 1.48-1.45 (m, 2H), 1.01 (s, 6H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 169.1, 140.9, 139.3, 138.7, 136.7, 133.1, 129.6, 127.9, 62.2, 47.4, 40.2, 34.8, 33.5, 29.2, 21.9, 19.9, 12.7.

^{11}B NMR (300 MHz, acetone-d_6)

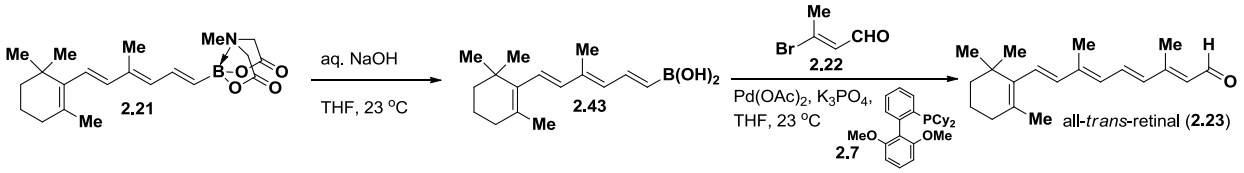
δ 11.7.

HRMS (FAB)

Calculated for $C_{21}H_{30}NBO_4$ $(M+H)^+$:	372.2346
Found:	372.2350

IR (KBr Pellet, cm^{-1})

3021, 2959, 2925, 2865, 1773, 1457, 1338, 1301, 1025, 986, 867.



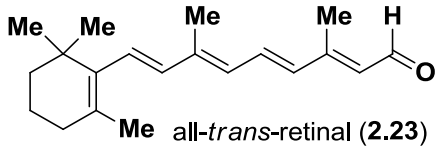
All-*trans*-retinal (2.23)

*MIDA boronate **2.21** was converted to boronic acid **2.43** via the following procedure*: To a stirred solution of **2.21** (35.9 mg, 0.101 mmol, 1 eq) in THF (1.44 mL) at 23 ˚C was added 1 M aq. NaOH (0.30 mL, 0.30 mmol, 3 eq) and the resulting mixture was stirred for 15 minutes. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (1.5 mL) and diluted with Et_2O (1.5 mL). The layers were separated and the aqueous layer was extracted with

THF:Et_2O 1:1 (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo until a small amount of THF (~1 mL) remained, yielding a solution of **2.43**; TLC: (EtOAc) R_f = 0.70, visualized by $KMnO_4$.

A solution of the palladium catalyst was prepared as follows: To a 1.5 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl (3.6 mg, 0.0088 mmol, 2 eq) was added a solution of $Pd(OAc)_2$ in toluene (0.038 M , 0.115 mL, 0.0044 mmol, 1 eq). The vial was sealed with a PTFE-lined cap and maintained at 65 ^oC with stirring for 15 minutes.

This catalyst solution was then utilized in the following procedure: To a 4-mL vial equipped with a stir bar and containing enal **2.22**[38] (10 mg, 0.067 mmol, 1 eq) was added boronic acid **2.43** as a solution in THF (estimated 0.101 M, 1 mL, 0.101 mmol, 1.5 eq), anhydrous K_3PO_4 as a finely ground powder (42.6 mg, 0.201 mmol, 3 eq), and the catalyst stock solution described above (0.035 mL, 0.0013 mmol Pd, 2 mol% Pd). The resulting mixture was sealed with a PTFE-lined cap and stirred at 23 ˚C for 5 hours. The reaction was then quenched with the addition of saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (3% EtOAc/hexanes) to yield all-*trans*-retinal (**2.23**) as a bright yellow solid (12.6 mg, 0.044 mmol, 66%). ^1H NMR[43], ^{13}C NMR[44], HRMS, and IR[45] analysis of synthetic **2.23** were fully consistent with the data reported for the isolated natural product.



all-*trans*-retinal (**2.23**)

TLC (30% EtOAc/hexanes)

R_f = 0.65, visualized with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 10.10 (d, *J* = 8.4 Hz, 1H), 7.14 (dd, *J* = 11.2, 14.8 Hz, 1H), 6.37 (d, *J* = 14.8 Hz, 1H), 6.33 (d, *J* = 16.8 Hz, 1H), 6.18 (d, *J* = 11.2 Hz, 1H), 6.16 (d, *J* = 16.4 Hz, 1H), 5.97 (d, *J* = 8.4 Hz, 1H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.06-2.00 (m, 2H)**,** 2.03 (d, *J* = 0.8 Hz, 3H), 1.72 (d, *J* = 0.8 Hz, 3H), 1.65-1.58 (m, 2H), 1.48-1.45 (m, 2H), 1.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 191.1, 154.8, 141.3, 137.6, 137.0, 134.5, 132.5, 130.5, 129.7, 129.4, 129.0, 39.6, 34.3, 33.1, 29.0, 21.8, 19.2, 13.1, 13.0.

HRMS (FAB)

Calculated for $C_{20}H_{28}O$ $(M+H)^+$:	285.2218
Found:	285.2219

IR (thin film, cm^{-1})

2961, 2929, 1865, 2253, 1655, 1573, 1456, 1386, 1334, 1216, 1164, 1135, 968, 908, 734.

^{1}H NMR data for natural[43] and synthetic all-*trans*-retinal: δ_H/ppm (integration)

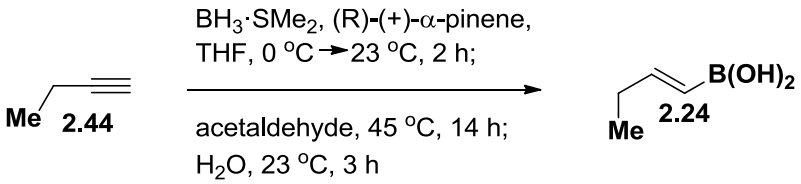
Natural **2.23** (220 MHz, $CDCl_3$)	Synthetic **2.23** (400 MHz, $CDCl_3$)
10.12 (1H)	10.10 (1H)
7.15 (1H)	7.14 (1H)
6.37 (1H)	6.37 (1H)
6.36 (1H)	6.33 (1H)
6.20 (1H)	6.18 (1H)

6.18 (1H)	6.16 (1H)
5.98 (1H)	5.97 (1H)
2.33 (3H)	2.32 (3H)
2.03 (3H)	2.03 (3H)
1.72 (3H)	1.72 (3H)
1.04 (6H)	1.03 (6H)

^{13}C NMR data for natural[44] and synthetic all-*trans*-retinal: δ_C/ppm

Natural **2.23** (22.63 MHz, $CDCl_3$)	Synthetic **2.23** (100 MHz, $CDCl_3$)
190.7	191.1
154.5	154.8
141.1	141.3
137.6	137.6
137.1	137.0
134.5	134.5
132.4	132.5
130.3	130.5
129.6	129.7
129.4	129.4

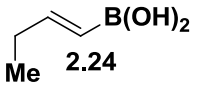
128.9	129.0
39.6	39.6
34.1	34.3
33.2	33.1
29.0	29.0
21.7	21.8
19.3	19.2
13.0	13.1
13.0	13.0



(*E*)-1-Butenylboronic acid (2.24)

In an unoptimized procedure, a 150 mL bomb flask equipped with a stir bar was charged with $BH_3 \bullet SMe_2$ (1.8 mL, 19.4 mmol, 1 eq) and THF (11 mL). The solution was cooled to 0 ˚C and (+)-α-pinene (6.3 mL, 39.7 mmol, 2 eq) was added dropwise. The solution was stirred at 0 ˚C for 10 minutes then allowed to warm to 23 ˚C and stirred at 23 ˚C for 2 hours, during which time a white precipitate formed. The solution was then recooled to 0 ˚C and an excess of 1-butyne (**2.44**) was condensed into the reaction via a balloon resulting in a clear, colorless solution. The flask was then sealed with a Teflon screw cap and was stirred at 0 ˚C for 30 minutes, warmed to 23 ˚C, and stirred at 23 ˚C for 1.5 hours. The solution was recooled to 0 ˚C and acetaldehyde (10.4 mL, 185 mmol, 9.5 eq) was added. The bomb flask was resealed with the Teflon screw cap

and the reaction was stirred at 40 ˚C for 14 hours. The reaction was allowed to cool to 23 ˚C and water (5 mL) was added. After stirring for 3 hours at 23 ˚C, the solution was diluted with EtOAc (50 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was taken up in hexanes (50 mL) and the resulting mixture was extracted with 10% aqueous NaOH (2 x 10 mL). The combined aqueous extractions were washed with hexanes (2 x 20 mL) and then acidified to pH 2-3 with conc. HCl. The acidified aqueous layer was then extracted with EtOAc (3 x 30 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield the title compound **2.24** as a colorless solid (0.928 g, 9.3 mmol, 48%).



2.24

TLC (EtOAc)

R_f = 0.68, visualized with $KMnO_4$.

^{1}H NMR (500 MHz, DMSO-d_6 : D_2O 95:5)

δ 6.49 (td, *J* = 6.5, 17.5 Hz, 1H), 5.32 (d, *J* = 18 Hz, 1H), 2.08 (ddq, *J* = 1.5, 7.0, 7.0 Hz, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, DMSO-d_6 : D_2O 95:5)

δ 151.5, 27.7, 12.5.

^{11}B NMR (300 MHz, DMSO-d_6 : D_2O 95:5)

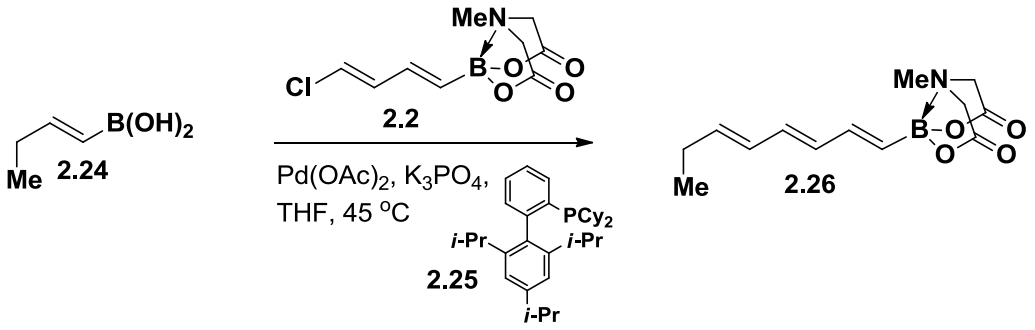
δ 28.8.

HRMS (EI+)

Calculated for $C_4H_9O_2B$ $(M)^+$:	100.0696
Found:	100.0696

IR (thin film, cm^{-1})

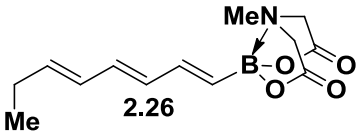
3235, 2970, 1633, 1633, 1356, 1233, 1154, 994.



Trienyl MIDA Boronate 2.26

A solution of the palladium catalyst was prepared as follows: To a 4 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (**2.25**) (17.3 mg, 0.036 mmol, 2 eq) was added a solution of $Pd(OAc)_2$ in THF (0.0109 M, 1.664 mL, 0.018 mmol, 1 eq). The vial was sealed with a PTFE-lined cap and stirred at 23 ˚C for 30 minutes.

This catalyst solution was then utilized in the following procedure: To a 7 mL vial equipped with a stir bar and containing (*E*)-1-butenylboronic acid (**2.24**) (113 mg, 1.13 mmol, 2 eq) was added **2.2** (138 mg, 0.521 mmol, 1 eq), anhydrous K_3PO_4 as a finely ground powder (301 mg, 1.42 mmol, 2.5 eq), and the catalyst stock solution described above (0.780 mL, 0.0085 mmol Pd, 1.5 mol% Pd). The resulting mixture was sealed with a PTFE-lined cap and stirred at 45 ˚C for 23 hours. The mixture was then filtered through a pad of silica gel with copious amounts of acetonitrile. To the resulting solution was added Florisil gel and then the solvent was removed *in vacuo*. The resulting powder was dry-loaded on top of a silica gel column and eluted with Et_2O → 20% $MeCN/Et_2O$ to yield the desired product as a yellow powder (120 mg, 0.456 mmol, 88%).



TLC (EtOAc)

R_f = 0.35, visualized by UV.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.56 (dd, *J* = 10.0, 17.5 Hz, 1H), 6.26 (dd, *J* = 10.5, 15.0 Hz, 1H), 6.19 (dd, *J* = 10.0, 15.0 Hz, 1H), 6.10 (tdd, *J* = 1.5, 10.0, 15.0 Hz, 1H), 5.80 (td, *J* = 6.5, 15.0 Hz, 1H), 5.63 (d, *J* = 17.0 Hz, 1H), 4.19 (d, *J* = 17.0 Hz, 2H), 4.02 (d, *J* = 17.0 Hz, 2H), 2.98 (s, 3H), 2.11 (dq, *J* = 7.5, 7.5 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 168.0, 143.5, 138.3, 134.8, 133.6, 130.4, 62.3, 47.3, 26.4, 13.8.

^{11}B NMR (300 MHz, acetone-d_6)

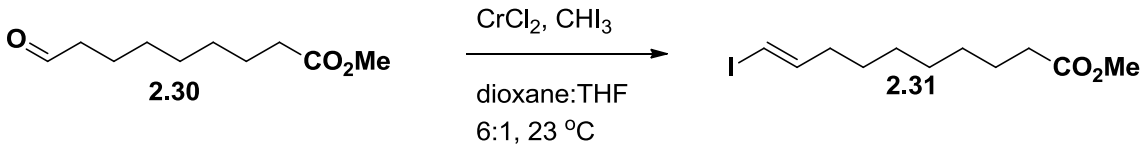
δ 11.6.

HRMS (EI+)

Calculated for $C_{13}H_{18}O_4NB$ $(M)^+$:	263.1329
Found:	263.1331

IR (thin film, cm^{-1})

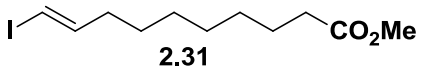
3017, 1768, 1216, 1026, 1010, 756, 668.



Vinyl iodide 2.31

In an unoptimized procedure, to a suspension of $CrCl_2$ (454 mg, 3.75 mmol, 7 eq) in THF (1.5 mL) at 23 ˚C was added dropwise a solution of (*E*)-methyl 10-iododec-9-enoate (**2.30**)[40] (100 mg, 0.537 mmol, 1 eq) and iodoform (422 mg, 1.07 mmol, 2 eq) in dioxane (9.2 mL). After stirring for 12 hours, the reaction mixture was diluted with Et_2O (10 mL) and poured into water (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (hexanes

→ 10% EtOAc/hexanes) provided the title compound as a yellow oil (105 mg, 0.337 mmol, 63%). ^{1}H NMR indicated an *E*:*Z* ratio of 10:1.



2.31

TLC (hexanes:EtOAc 4:1)

R_f = 0.45, visualized with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 6.49 (td, *J* = 7.2, 14.4 Hz, 1H), 5.96 (td, *J* = 1.6, 14 Hz, 1H), 3.66 (s, 3H), 2.29 (t, *J* = 7.6 Hz, 2H), 2.03 (dq, *J* = 1.2, 6.8 Hz, 2H), 1.64-1.56 (m, 2H), 1.42-1.33 (m, 2H), 1.33-1.24 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$)

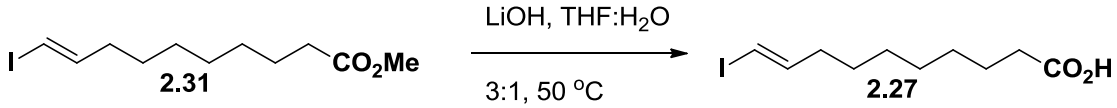
δ 174.2, 146.6, 74.4, 51.5, 36.0, 34.0, 29.0, 28.9, 28.7, 28.2, 24.8.

HRMS (CI+)

Calculated for $C_{11}H_{19}O_2I$ $(M+H)^+$:	311.0508
Found:	311.0508

IR (thin film, cm^{-1})

2927, 2855, 1738, 1435, 1197, 1172, 946.

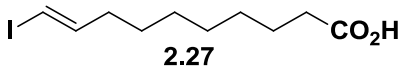


2.31 **2.27**

Carboxylic Acid 2.27

To a solution vinyl iodide **2.31** (51 mg, 0.164 mmol, 1 eq) in THF:H_2O 3:1 (3.3 mL) was added LiOH (69 mg, 1.64 mmol, 10 eq). The reaction was stirred at 50 ˚C for 4 hours before diluting with Et_2O (5 mL) and pouring into 1M aqueous HCl (5 mL). The layers were separated and the

aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the crude product by silica gel chromatography (15% EtOAc/hexanes → EtOAc) provided the title compound as a pale yellow solid (44 mg, 0.149 mmol, 91%). ^{1}H NMR indicated an *E*:*Z* ratio of 10:1



2.27

TLC (hexanes:EtOAc 4:1)

R_f = 0.14, visualized with $KMnO_4$.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 11.32 (br s, 1H), 6.50 (td, *J* = 7.2, 14.4 Hz, 1H), 5.97 (td, *J* = 1.6, 14.4 Hz, 1H), 2.35 (t, *J* = 7.6 Hz, 2H), 2.04 (dq, *J* = 1.2, 7.2 Hz, 2H), 1.66-1.59 (m, 2H), 1.41-1.25 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$)

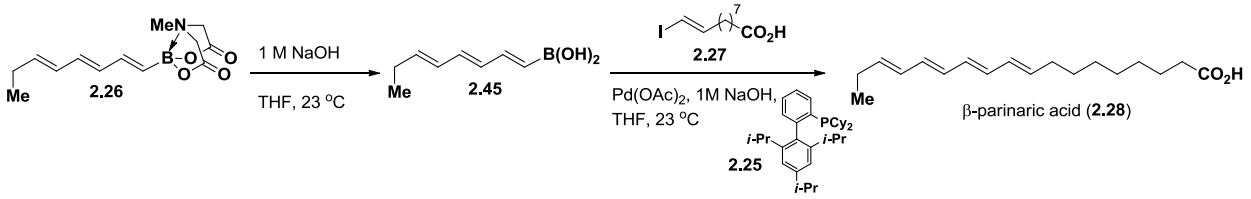
δ 180.0, 146.6, 74.4, 36.0, 34.0, 29.0, 28.9, 28.7, 28.2, 24.6.

HRMS (CI+)

Calculated for $C_{10}H_{17}O_2I$ $(M+H)^+$:	297.0352
Found:	297.0351

IR (thin film, cm^{-1})

3300-2500 (br), 2928, 2851, 1694, 1464, 1407, 1282, 1185, 936.



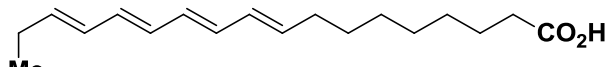
β-parinaric acid (2.28)

*MIDA boronate **2.26** was converted to boronic acid **2.45** via the following procedure*: To a stirred solution of **2.26** (24.7 mg, 0.094 mmol, 1 eq) in THF (1.34 mL) at 23 ˚C was added 1 M aqueous NaOH (0.28 mL, 0.28 mmol, 3 eq) and the resulting mixture was stirred at 23 ˚C for 15 minutes. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (1.5 mL) and diluted with Et_2O (1.5 mL). The layers were separated and the aqueous layer was extracted with THF:Et_2O 1:1 (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* until a small amount of THF (3.7 mL) remained, yielding a solution of **2.45**; TLC (EtOAc): R_f = 0.63, visualized with $KMnO_4$.

A solution of the palladium catalyst was prepared as follows: To a 4 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',4',6'-tri-*iso*-propyl-1,1'-biphenyl ligand (**2.25**) (2.1 mg, 0.0044 mmol, 2 eq) was added a solution of $Pd(OAc)_2$ in THF (0.004 M, 0.545 mL, 0.0022 mmol, 1 eq). The vial was sealed with a PTFE-lined cap and stirred at 23 ˚C for 30 minutes.

This catalyst solution was then utilized in the following procedure: To a 20-mL I-Chem vial equipped with a stir bar and containing **2.27** (18.5 mg, 0.062 mmol, 1 eq; E:Z 7:1 by ^{1}H NMR) was added boronic acid **2.45** (3.7 mL, estimated 0.094 mmol, 1.5 eq) and the catalyst stock solution described above (0.31 mL, 0.0013 mmol Pd, 2 mol% Pd). The resulting mixture was sealed with a teflon-lined septum cap and 1 M NaOH (0.19 mL, 0.190 mmol, 3 eq) was added. The reaction was stirred at 23 ˚C for 40 minutes and was then quenched with the addition of saturated aqueous NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting crude product was purified by silica gel chromatography (20% Et_2O/hexanes → Et_2O) to yield β-parinaric acid as a fluorescent solid (14.8 mg, 0.054 mmol, 86%). ^{1}H NMR indicated a 7:1 mixture of β-parinaric acid:9-(*Z*) parinaric acid (arising from E:Z

7:1 mixture of **2.27**). ^{1}H NMR and ^{13}C NMR analysis of synthetic **2.28** were fully consistent with the data previously reported for β-parinaric acid.[46,47]



β-parinaric acid (**2.28**)

TLC (50% Et_2O/hexanes)

R_f = 0.26, visualized by UV.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 10.96 (br s, 1H), 6.22-6.00 (m, 6H), 5.73 (td, *J* = 7.0 Hz, 15.0 Hz, 1H), 5.68 (td, *J* = 7.0, 15.0 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 2.11-2.06 (m, 4H), 1.64-1.61 (m, 2H), 1.43-1.25 (m, 8H), 1.01 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 179.4, 136.6, 135.0, 132.5, 132.4, 130.9, 130.8, 130.6, 129.6, 33.9, 32.8, 29.2, 29.1, 29.0, 28.9, 25.9, 24.6, 13.5.

HRMS (ESI+)

Calculated for $C_{18}H_{28}O_2$ $(M + Na)^+$:	299.1987
Found:	299.1990

IR (thin film, cm^{-1})

3428, 3020, 2930, 1641, 1215, 761, 669.

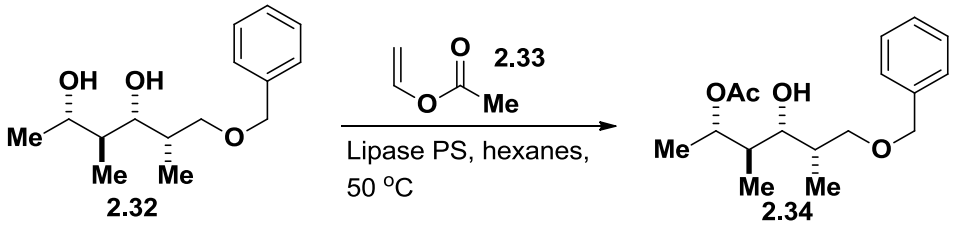
^{1}H NMR data for β-parinaric acid: δ_H/ppm (integration)

Previously reported **2.28**[46] (300 MHz, $CDCl_3$)	Synthetic **2.28** (500 MHz, $CDCl_3$)
6.08 (6H)	6.22-6.00 (6H)
5.75 (2H)	5.73 (1H), 5.68 (1H)
2.32 (2H)	2.34 (2H)
2.11 (2H)	2.11 (2H)
2.10 (2H)	2.13-2.06 (2H)
1.60 (2H)	1.64-1.61 (2H)
1.29 (8H)	1.43-1.25 (8H)
1.08 (3H)	1.01 (3H)

^{13}C NMR data for β-parinaric acid: δ_C/ppm

Previously reported **2.28**[46] (125 MHz, $CDCl_3$)	Synthetic **2.28** (125 MHz, $CDCl_3$)
179.0	179.4
137.0	136.6
135.4	135.0
132.9	132.5
132.8	132.4

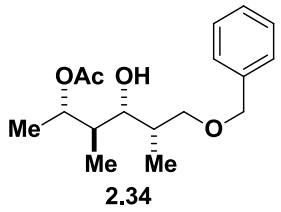
131.3	130.9
131.3	130.8
131.1	130.6
130.0	129.6
34.2	33.9
33.2	32.8
29.6	29.2
29.5	29.1
29.4	29.0
29.4	28.9
26.3	25.9
25.1	24.6
13.9	13.5



Acetate 2.34

A 200 mL recovery flask was charged with diol **2.32**[31] (1.18 g, 4.69 mmol, 1 eq), Lipase PS (295 mg, 0.25 mass eq), and hexanes (115 mL) and the resulting slurry was stirred at 50 °C for 15 minutes. Vinyl acetate (4.33 mL, 47.0 mmol, 10 eq) was then added and the reaction was stirred at 50 °C for 40 hours. The resulting mixture was cooled to 23 °C and filtered, and the residual

enzyme was washed copiously with Et_2O. The filtrate was then concentrated *in vacuo* and the resulting viscous, light yellow oil was purified by flash column chromatography (5% → 50% EtOAc/hexanes) to yield acetate **2.34** as a pale yellow oil (1.05 g, 3.57 mmol, 76%).



2.34

TLC (50% EtOAc/hexanes)

R_f = 0.60, visualized with anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37-7.29 (m, 5H), 5.32 (dq, *J* = 4.0, 6.4 Hz,1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.61-3.53 (m, 3H), 2.66 (d, *J* = 3.2 Hz, 1H), 2.03 (s, 3H), 1.97-1.91 (m, 1H), 1.91-1.84 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$)

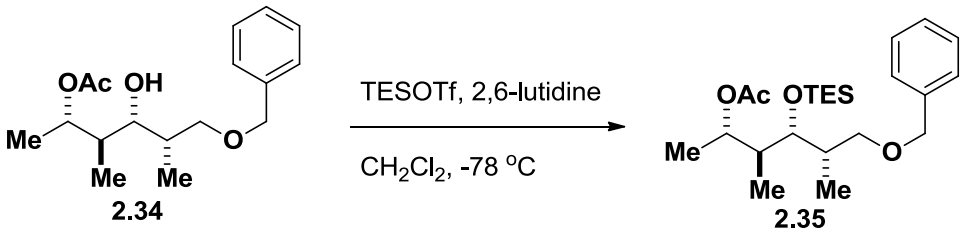
170.4, 138.0, 128.4, 127.7, 127.6, 75.5, 74.9, 73.4, 71.4, 39.6, 34.7, 21.5, 13.8, 10.0, 9.1.

HRMS (CI+)

Calculated for $C_{17}H_{26}O_4$ $(M+H)^+$:	295.1909
Found:	295.1905

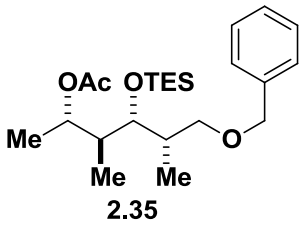
IR (thin film, cm^{-1})

3497, 2970, 2925, 2873, 1731, 1714, 1453, 1371, 1244, 1101, 1053, 1020, 737, 698.



Triethylsilyl Ether 2.35

To acetate **2.34** (5.98 g, 20.31 mmol, 1.0 eq) in CH_2Cl_2 (230 mL) at 0 ˚C was added 2,6-lutidine (7.84 mL, 67.35 mmol, 3.3 eq) and the resulting solution was cooled to –78 °C. TESOTf (7.11 mL, 31.43 mmol, 1.5 eq) was then added dropwise and the resulting solution was stirred at –78 ˚C for 1 hour. The reaction was then quenched with the addition of saturated aqueous $NaHCO_3$ (115 mL) and allowed to warm to 23 ˚C. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Purification by flash column chromatography (12% → 50% EtOAc/hexanes) provided triethylsilyl ether **2.35** as a yellow oil (7.34g, 17.96 mmol, 88%).



TLC (25% EtOAc/hexanes)

R_f = 0.67, visualized with anisaldehyde.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.35-7.26 (m, 5H), 5.00 (dq, *J* = 6.5, 6.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 3.85 (dd, *J* = 2.5, 7.0 Hz, 1H), 3.35 (app t, *J* = 8.5 Hz, 1H), 3.22 (dd, *J* = 6.0, 9.0 Hz, 1H), 1.96-1.86 (m, 2H), 1.91 (s, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 8.5 Hz, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.60 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$)

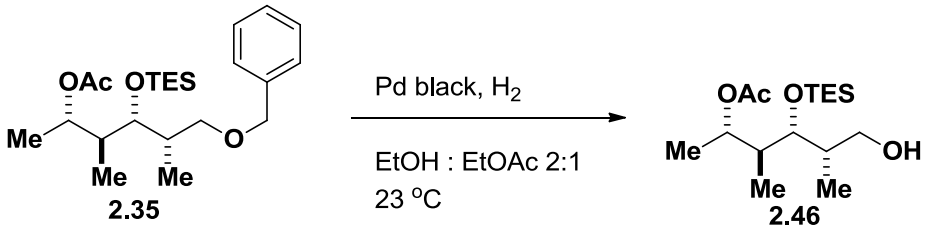
δ 170.4, 138.6, 128.3, 127.7, 127.4, 73.7, 72.9, 72.2, 71.7, 42.6, 35.5, 21.3, 16.1, 11.2, 11.0, 7.0, 5.4.

HRMS (ESI+)

Calculated for $C_{23}H_{40}O_4Si$ $(M)^+$:	408.2696
Found:	408.2690

IR (thin film, cm^{-1})

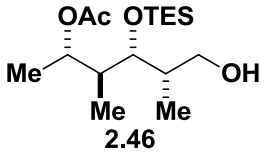
2953, 2875, 1734, 1453, 1369, 1243, 1093, 1046, 1005, 736, 696, 654.



Primary Alcohol 2.46

Caution: palladium black is pyrophoric and should be maintained under inert atmosphere at all times.

To a 25 mL three-neck round-bottomed flask equipped with a stir bar was added palladium black (17.3 mg, 0.163 mmol, 0.6 eq). To this flask was then added via cannula a solution of benzyl ether **2.35** (111.0 mg, 0.271 mmol, 1 eq) in EtOH:EtOAc 2:1 (4.65mL). The reaction flask was purged with H_2 (balloon) and stirred at 23 ˚C for 25 hours under a positive pressure of H_2 (balloon). The resulting mixture was then filtered under N_2 pressure through a short column of Celite, flushing with copious amounts of EtOH. Purification by silica gel chromatography (7% → 20% EtOAc/hexanes) yielded primary alcohol **2.46** as a pale yellow oil (79.1mg, 0.248 mmol, 91%).



2.46

TLC (50% EtOAc/hexanes)

R_f = 0.56, stained by anisaldehyde.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 5.01 (dq, *J* = 6.0, 6.0 Hz, 1H), 3.85 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.47 (m, 2H), 2.01 (s, 3H), 1.93 (m, 1H), 1.79 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.89 (d, *J* = 7.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.62 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$)

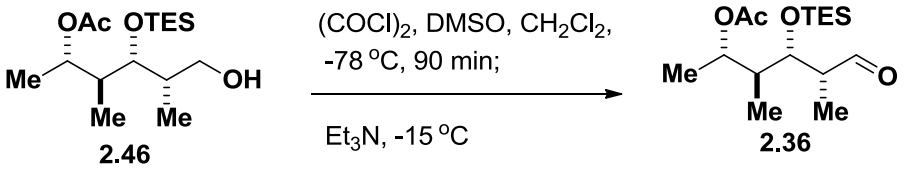
δ 170.7, 72.4, 71.7, 66.2, 42.8, 38.0, 21.4, 16.5, 11.2, 11.2, 7.0, 5.3.

HRMS (ESI+)

Calculated for $C_{16}H_{34}O_4Si$ $(M)^+$:	318.2226
Found:	318.2230

IR (thin film, cm^{-1})

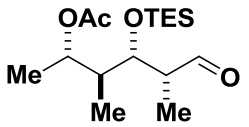
3457, 2954, 2873, 1731, 1714, 1371, 1245, 1044.



Aldehyde 2.36

To a stirred solution of oxalyl chloride (3.44 mL, 40.1 mmol, 5 eq) in CH_2Cl_2 (20 mL) at –78 ˚C was added dropwise DMSO (5.70 mL, 80.23 mmol, 10 eq) and the resulting solution was stirred at –78 ˚C for 30 minutes. To the reaction was then added via cannula a solution of alcohol **2.46** (2.56 g, 8.02 mmol, 1 eq) in CH_2Cl_2 (55.7 mL) and the resulting solution was stirred at –78 ˚C

for 1.5 hours. Triethylamine (28 mL, 201 mmol, 25 eq) was then added and the resulting mixture was allowed to warm to –15 ˚C over 40 minutes. The reaction was then quenched with the addition of saturated aqueous NH_4Cl (50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated *in vacuo* to yield aldehyde **2.36** as a yellow oil (2.36g, 7.46 mmol, 93%).



2.36

TLC (50% EtOAc/hexanes)

R_f = 0.76, stained by anisaldehyde.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 9.67 (d, *J* = 0.8 Hz, 1H), 4.99 (dq, *J* = 6.4, 6.4 Hz, 1H), 4.21 (dd, *J* = 2.8, 6.0 Hz, 1H), 2.44 (ddq, *J* = 0.8, 3.2, 7.2 Hz, 1H), 2.03 (s, 3H), 1.95 (m, 1H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.58 (q, *J* = 7.6 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$)

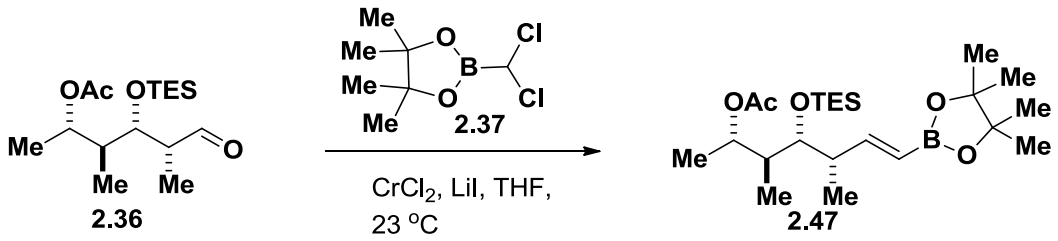
δ 204.7, 170.3, 71.2, 71.2, 49.4, 42.7, 21.3, 16.3, 11.2, 8.3, 6.9, 5.2.

HRMS (ESI+)

Calculated for $C_{16}H_{32}O_4Si$ $(M+Na)^+$:	339.1968
Found:	339.1972

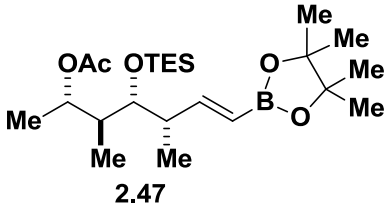
IR (thin film, cm^{-1})

2953, 2877, 1731, 1708, 1458, 1372, 1241, 1049, 1010, 946, 740.



Pinacolboronic Ester 2.47

To a stirred slurry of $CrCl_2$ (0.204 g, 1.66 mmol, 18 eq) in THF (2 mL) at 23 ˚C was added a solution of aldehyde **2.36** (29.2 mg, 0.0923 mmol, 1 eq) and dichlomethylpinacol boronic ester **2.37**[41] (0.117 g, 0.554 mmol, 6 eq) in THF (0.18 mL). A solution of LiI (0.149 g, 1.11 mmol, 12 eq) in THF (0.3 mL) was then added and the resulting slurry was stirred at 23 °C for 7 hours. The reaction was then poured into ice water (2 mL) and extracted with Et_2O (2 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated *in vacuo*. The crude material was purified by Florisil column chromatography (2% → 25% EtOAc/hexanes) providing pinacolboronic ester **2.47** as a pale yellow oil (25.7 mg, 0. 58 mmol, 63%).



TLC (50% EtOAc/hexanes)

R_f = 0.87, visualized with anisaldehyde.

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 6.58 (dd, *J* = 6.8, 18.0 Hz, 1H), 5.43 (dd, *J* = 1.2, 18.0 Hz, 1H), 5.04 (dq, *J* = 6.4, 6.4 Hz, 1H), 3.57 (dd, *J* = 4.8, 6.6 Hz, 1H), 2.45-2.36 (m, 1H), 2.01 (s, 3H), 1.91 (m, 1H), 1.26 (s, 12H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 9H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.60 (q, *J* = 8.0 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$)

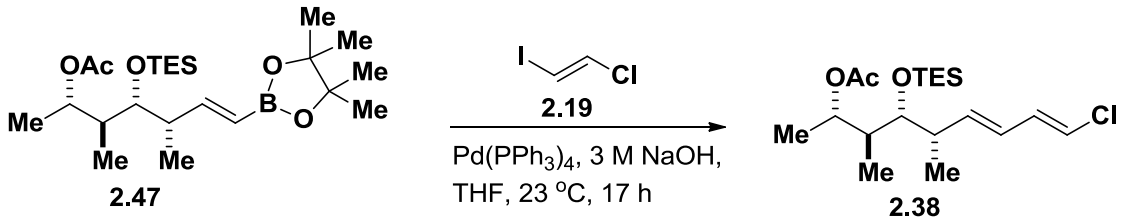
δ 177.2, 158.2, 83.0, 71.5, 42.3, 42.0, 24.8, 24.7, 21.5, 15.7, 13.4, 11.2, 7.1, 5.4.

HRMS (CI+)

Calculated for $C_{23}H_{45}BO_5Si$ $(M+H)^+$:	441.3208
Found:	441.3210

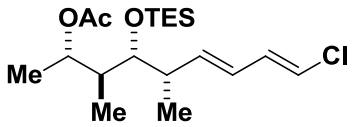
IR (thin film, cm^{-1})

2974, 2873, 1736, 1636, 1458, 1359, 1322, 1241, 1145, 1004, 970, 848, 731.



Dienyl Chloride 2.38

A 15 mL round-bottomed flask fitted with a stir bar was charged with pinacolboronic ester **2.47** (126.9 mg, 0.288 mmol, 1.5 eq). To this flask was then added a solution of (*E*)-1-iodo-2-chloroethylene (**2.19**)[36] (36.2 mg, 0.192 mmol, 1 eq) and $Pd(PPh_3)_4$ (16.6 mg, 0.0144 mmol, 5 mol%) as a solution in THF (4.5 mL) followed by 3M aqueous NaOH (0.192 mL, 0.576 mmol, 2 eq). The resulting mixture was stirred at 23 ˚C for 17 hours and then the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was diluted with diethyl ether (5 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the resulting residue by silica gel chromatography (2% → 15% EtOAc/hexanes/ 1% Et_3N) provided dienyl chloride **2.38** as a yellow oil (51.0 mg, 0.136 mmol, 71%).



2.38

TLC (10% EtOAc/hexanes)

R_f = 0.34, visualized with $KMnO_4$.

^{1}H-NMR (500 MHz, $CDCl_3$)

δ 6.41 (dd, *J* = 11.5, 13.0 Hz, 1H), 6.11 (d, *J* = 13.0 Hz, 1H), 5.96 (dd, *J* = 11, 15.5 Hz, 1H), 5.65 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.05 (dq, *J* = 6.5, 6.5 Hz, 1H), 3.50 (app t, *J* = 5.5 Hz, 1H), 2.37 (m, 1H), 2.01 (s, 3H), 1.88 (m, 1H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.60 (q, *J* = 7.5 Hz, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$)

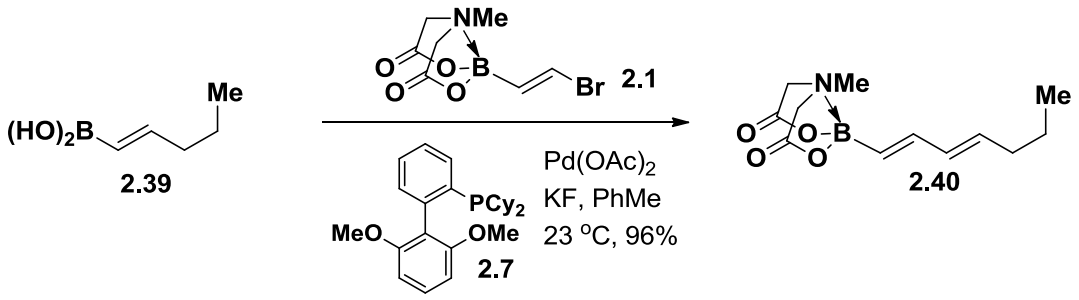
δ 170.2, 139.2, 133.7, 125.6, 119.0, 71.6, 71.4, 42.2, 40.3, 21.4, 16.4, 15.5, 11.2, 7.0, 5.4.

HRMS (CI+)

Calculated for $C_{19}H_{35}ClO_3Si$ $(M+H)^+$:	375.2122
Found:	375.2122

IR (thin film, cm^{-1})

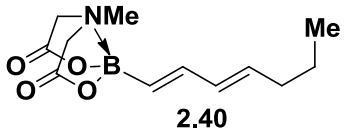
2960, 2873, 1735, 1241, 1015, 800, 655.



Dienyl MIDA Boronate 2.40

A solution of the catalyst was prepared as follows: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 1 eq) and 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl **2.7** (20.5 mg, 0.050 mmol, 2 eq) in a glovebox. Toluene (3.0 mL) was added and the vial was sealed with a PTFE-lined plastic cap. The resulting mixture was stirred at 23 ˚C for 45 minutes resulting in a yellow Pd/**2.7** catalyst solution (0.00833 M Pd in toluene).

This catalyst solution was then utilized in the following procedure: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.1** (0.262 g, 1.00 mmol, 1eq) and (*E*)-1-pentenylboronic acid (**2.39**) (0.171 g, 1.50 mmol, 1.5 eq) and sealed with PTFE-lined plastic cap. The vial was evacuated and refilled with argon three times and then moved into a glovebox. KF (0.116 g, 2.00 mmol, 2 eq), toluene (7.0 mL) and catalyst solution (1.20 mL, 0.01 mmol, 1 mol% Pd) were then added and vial was sealed with PTFE-lined plastic cap. The sealed vial was removed from the glovebox and stirred at 23 ˚C for 36 hours. The resulting heterogeneous light yellow mixture was diluted with acetonitrile (10 mL) and filtered through a short pad of Celite. The filtrate was concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel (50% EtOAc/petroleum ether1 $\rightarrow$ EtOAc $\rightarrow$ 10% MeCN/EtOAc) to give the title compound **2.40** as a colorless crystalline solid (0.241 g, 0.959 mmol, 96 %).



2.40

TLC (EtOAc)

R_f = 0.46, visualized by UV lamp (λ = 254) or with $KMnO_4$.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 6.53 (dd, *J* = 17.5, 10.0 Hz, 1H), 6.06 (dd, *J* = 15.0, 10.5 Hz, 1H), 5.74 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.40 (d, *J* = 17.5 Hz, 1H), 4.06 (d, *J* = 17.0 Hz, 2H), 3.70 (d, *J* = 17.0 Hz, 2H), 2.79 (s, 3H), 2.02 (q, *J* = 7.0 Hz, 2H), 1.37 (sept, *J* = 7.5 Hz, 2H), 0.86 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 168.9, 144.4, 137.3, 132.2, 61.4, 47.0, 34.6, 22.2, 13.7.

HRMS (ESI)

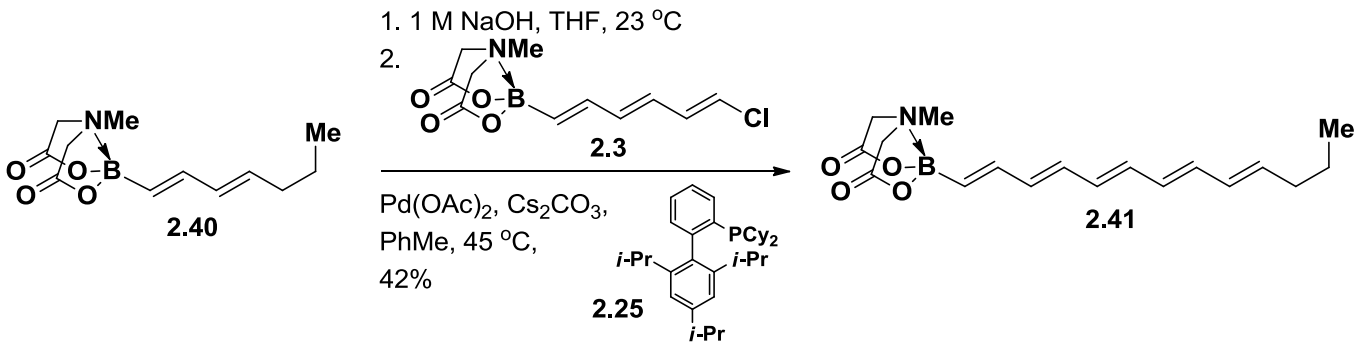
Calculated for $C_{12}H_{18}BNO_4$ (M+H):	252.1407
Found:	252.1404

^{11}B NMR (100 MHz, CD_3CN)

δ 10.8.

IR (thin film, cm^{-1})

2957.9, 1762.2, 1646.6, 1603.6, 1458.0, 1337.3, 1297.0, 1195.9, 1153.1, 1119.8, 1084.0, 1004.7, 954.2, 868.3, 720.0.



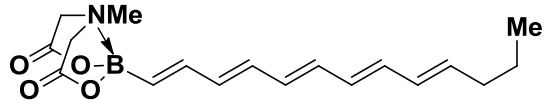
Pentaenyl MIDA Boronate 2.41

*MIDA boronate **2.40** was converted to a boronic acid via the following procedure:* To a stirred mixture of **2.40** (25.6 mg, 0.102 mmol, 1 eq) in THF (1.0 mL) at 23 °C was added 1M aqueous NaOH (0.306 mL, 0.306 mmol, 3 eq) via syringe. The reaction mixture was stirred at 23 °C for 15 minutes. The resulting mixture was treated with 1.0 M pH 7 phosphate buffer solution (0.5 mL) and diluted with Et_2O (1 mL). The organic layer was separated and aqueous layer was extracted with THF:Et_2O 1:1 (3 × 1.5 mL). The combined organic layers were dried over anhydrous magnesium sulfate. After filtration, the resulting colorless solution was concentrated to ~ 0.5 mL volume of THF *in vacuo*. THF (5.0 mL) was added and concentrated again to ~ 0.25 mL volume of THF *in vacuo*. The isolated yield of the boronic acid was assumed to be 90% based on **2.40**, and a 0.184 M solution of boronic acid in THF (0.0918 mmol/0.50 mL of THF) was prepared using a 1.0 mL (*v*/*v*) volumetric vial. This solution was immediately used in the next reaction without further purification. TLC (EtOAc) Rf = 0.88, visualized by UV lamp (λ = 254 nm) *or* with KMnO4.

A solution of the catalyst was prepared as follows: A 20 mL Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5.60 mg, 0.025 mmol, 1 eq) and 2-dicyclohexylphosphino-2'.4',6'-tri*iso*- propyl-1,1'-biphenyl (**2.25**) (24.5 mg, 0.050 mmol, 2 eq). Toluene (3.0 mL) was added and the vial was sealed with a PTFE-lined plastic cap. The resulting mixture was stirred at 23 °C for 1 hour to yield a reddish Pd/**2.25** catalyst solution (0.00833 M Pd in toluene).

This catalyst solution was then utilized in the following procedure: A 10 mL Wheaton vial equipped with a magnetic stir bar was charged with **2.3** (16.5 mg, 0.0612 mmol, 1 eq), Cs_2CO_3

(40.0 mg, 0.1224 mmol, 2 eq), the 0.184 N boronic acid in THF solution (0.0918 mmol, 0.50 mL), and the catalyst solution (0.110 mL, 1.5 mol% Pd). Toluene (1.64 mL) was then added and the vial was sealed with a PTFE-lined plastic cap and stirred for 18 hours at 45 °C. The resulting deep orange mixture was diluted with EtOAc (5 mL) and filtered through a short pad of Florisil®. The filtrate was concentrated *in vacuo* to provide an orange solid. The crude product was purified by flash chromatography on Florisil® (50% EtOAc/petroleum ether → EtOAc → 10% MeCN/EtOAc) to give the title compound **2.41** as a light yellow solid (8.40 mg, 0.0255 mmol, 42%).



2.41

TLC (EtOAc)

R_f = 0.48, visualized by UV lamp (λ = 365 nm) *or* with $KMnO_4$.

^{1}H NMR (400 MHz, CD_3CN)

δ 6.60 (dd, *J* = 17.2, 9.6 Hz, 1H), 6.39-6.17 (m, 6H), 6.12 (ddt, *J* = 15.2, 10.4, 1.6 Hz, 1H), 5.77 (dt, *J* = 15.2, 7.2 Hz, 1H), 5.63 (d, *J* = 17.2 Hz, 1H), 3.93 (d, *J* = 16.8 Hz, 2H), 3.77 (d, *J* = 16.8 Hz, 2H), 2.74 (s, 3H), 2.07 (app q, *J* = 7.2 Hz, 2H), 1.40 (app sext, *J* = 7.2 Hz, 2H), 0.88 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CD_3CN)

δ 169.4, 143.9, 137.0, 135.3, 135.2, 135.0, 133.0, 131.6, 62.3, 47.6, 35.6, 23.1, 13.9.

^{11}B NMR (100 MHz, CD_3CN)

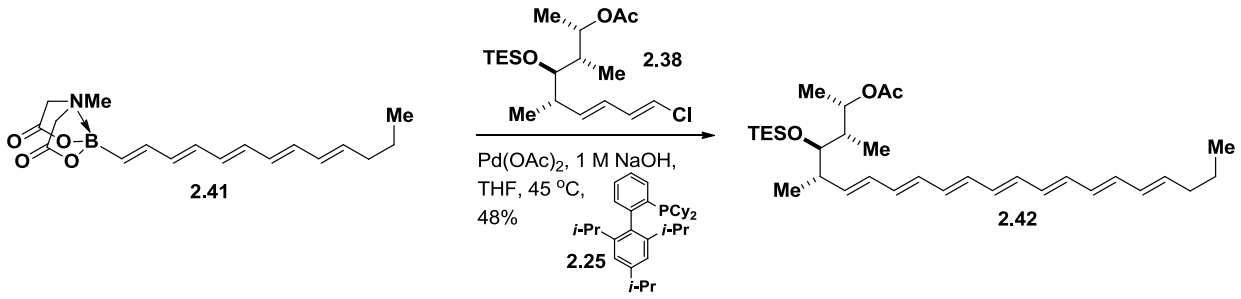
δ 10.4.

HRMS (ESI)

Calculated for $C_{18}H_{24}BNO_4$ $(M+H)^+$:	330.1877
Found:	330.1886

IR (thin film, cm^{-1})

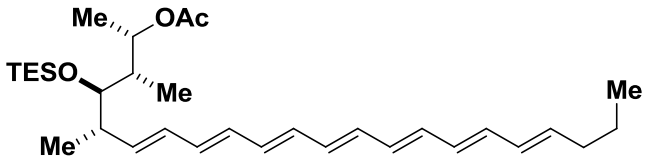
2926, 2359, 1763, 1678, 1463, 1294, 1008, 668.



1/2 of the Amphotericin B Macrolide (2.42)

A solution of the catalyst was prepared as follows: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 1 eq) and 2-dicyclohexylphosphino- 2'.4',6'-tri-*iso*-propyl-1,1'-biphenyl (**2.25**) (24.5 mg, 0.050 mmol, 2 eq). Toluene (3.0 mL) was added and the vial was sealed with a PTFE-lined plastic cap. The resulting mixture was stirred at 23 °C for 1 hour to yield a reddish Pd/**2.25** catalyst solution (0.00833 M Pd in toluene).

This catalyst solution was then utilized in the following procedure: An oven-dried Wheaton vial equipped with a magnetic stir bar was charged with **2.38** (7.0 mg, 0.0187 mmol, 1 eq), **2.41** (14.0 mg, 0.0421 mmol, 2.25 eq), the catalyst solution (0.034 mL, 1.5 mol% Pd), and THF (1.5 mL), and the vial was sealed with a PTFE-lined plastic cap. Degassed 1M aqueous NaOH (0.211 mL, 0.211 mmol, 5 eq based on **2.41**) was added into the vial *via* syringe. The yellow reaction mixture was stirred for 15 minutes at 23 °C and then stirred at 45 °C for 16 hours. The resulting heterogeneous deep reddish mixture was diluted with ethyl acetate (5 mL) and dried over anhydrous magnesium sulfate. The orange solution was filtered through short pad Florisil® and the filtrate was concentrated *in vacuo* to provide an orange solid. The crude product was purified by flash chromatography on Florisil® (1.5% EtOAc/petroleum ether) to give the title compound **2.42** as a yellow solid (4.60 mg, 0.0090 mmol, 48%).



2.42

TLC (27% EtOAc/petroleum ether)

R_f = 0.40, visualized by UV lamp (λ = 365 nm) *or* with CAM.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 6.24-6.18 (m, 10H), 6.11-6.02 (m, 2H), 5.71 (dt, *J* = 14.8, 7.2 Hz, 1H), 5.62 (dd, *J* = 14.8, 8.4 Hz, 1H), 5.03 (qn, *J* = 6.4 Hz, 1H), 3.49 (t, *J* = 5.6 Hz, 1H), 2.38 (app sext, *J* = 6.8 Hz, 1H), 2.06 (app q, *J* = 7.2 Hz, 2H), 1.99 (s, 3H), 1.88 (app sext, *J* = 6.4 Hz, 1H), 1.39 (sext, *J* = 7.2 Hz, 2H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.88 (t, *J* = 7.6 Hz, 3H), 0.87 (d, *J* = 7.6 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$)

δ 170.3, 138.8, 135.8, 133.5, 133.3, 133.2, 133.1, 132.9, 132.7, 132.5, 131.5, 130.9, 130.8, 130.1,71.6, 42.3, 40.5, 35.0, 29.7, 22.5, 21.4, 16.4, 15.7, 13.7, 11.2, 7.0, 5.4.

HRMS (ESI)

Calculated for $C_{32}H_{52}O_3Si$ $(M+H)^+$:	513.3764
Found:	513.3771

IR (thin film, cm^{-1})

3011, 2957, 2928, 2875, 1736, 1456, 1372, 1243, 1069, 1006, 950, 840, 739.

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[17] The same yield was observed whether or not this reaction was set up using a glovebox.

[18] Dienyl boronate **6** was stable to storage for at least 2 weeks on the benchtop under air both as a solid and as a solution in DMSO-*d*6.

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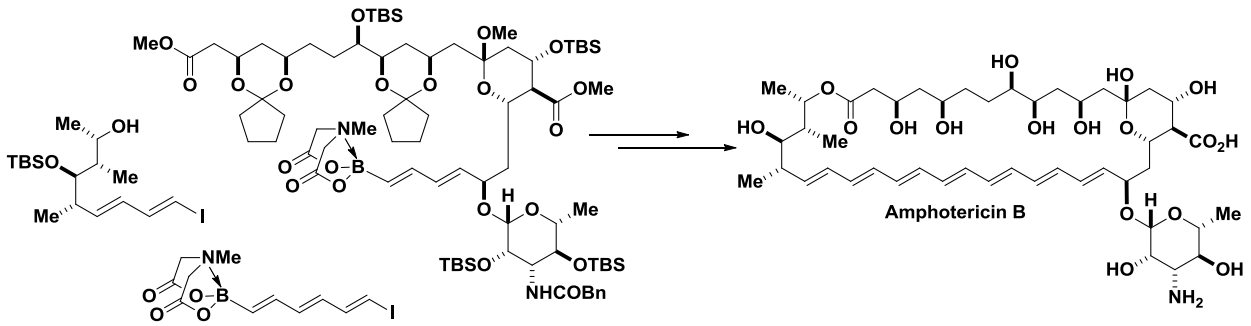
CHAPTER 3

AN ITERATIVE CROSS-COUPLING BASED SEMISYNTHESIS OF AMPHOTERICIN B

Given the power of functional group deletion in understanding the mechanism of action of AmB, our group has targeted the synthesis of all twelve derivatives lacking each one of the protic functional groups. Semisynthesis from AmB has been a powerful tool for accessing modifications to the C21-C40 section of the macrolactone, however, in order to access all of the proposed derivatives, a simple, efficient, and flexible total synthesis of AmB needs to be developed. In our proposed synthesis of AmB we envisioned that the most modular and efficient way to disconnect the molecule was through a series of Suzuki-Miyaura (SM) transforms and a macrolactonization transform giving four key building blocks. With the completion of one half of AmB (see chapter 2) via iterative cross-coupling, the methodology was in place for this total synthesis of AmB to be a feasible route, but the polyol and mycosamine containing building blocks had not yet been completed. However, a near exact model of the product of their putative coupling could be accessed through the utility of semisynthesis from the natural product. This chapter describes the synthesis of this intermediate and its use in testing the endgame strategy for the total synthesis. The iterative Suzuki-Miyaura cross-coupling strategy proved to be mild and efficient in accessing the fully protected AmB core. Subsequent deprotection conditions were found to connect back to the natural product. Brandon Wilcock contributed to this section by finding that phenyl acyl is a compatible protecting group for the amine on AmB. Pulin Wang synthesized model substrate **3.25** used in scheme 3.3.



3-1 BACKGROUND

In order to access all deoxygenated derivatives of AmB, a simple, modular, and flexible total synthesis needed to be designed.[1,2] With the development of the MIDA protecting group by Gillis et al.,[3] the possibility of iterative Suzuki-Miyaura cross-coupling as a synthetic strategy for complex small molecule synthesis was opened. In chapter 2 of this thesis, the expansion of this methodology to the synthesis of polyene natural products was described.[4] The synthesis of one half of AmB was an excellent demonstration of the power of this strategy, however it was still a very simple system in comparison to the complexity of the natural product. In order to validate the proposed endgame strategy for the total synthesis, a better model system needed to be developed. The work of Nicolaou,[5] Rychnovsky,[6] and Murata[7] demonstrated that AmB could be degraded into a form that would be useful for testing the cross-couplings for the total synthesis. In fact, in 2006 Murata and coworkers used the degradation of AmB to access vinyl iodide intermediate **3.1** that was competent to do a Stille coupling with hexanene **3.2**. Subsequent macrolactonization and deprotection provided C28-fluorine labeled derivative **3.3** (Figure 3.1).[7a] We recognized that a similar degradative strategy may provide access to an advanced intermediate to enable the endgame strategy of our synthesis to be tested.

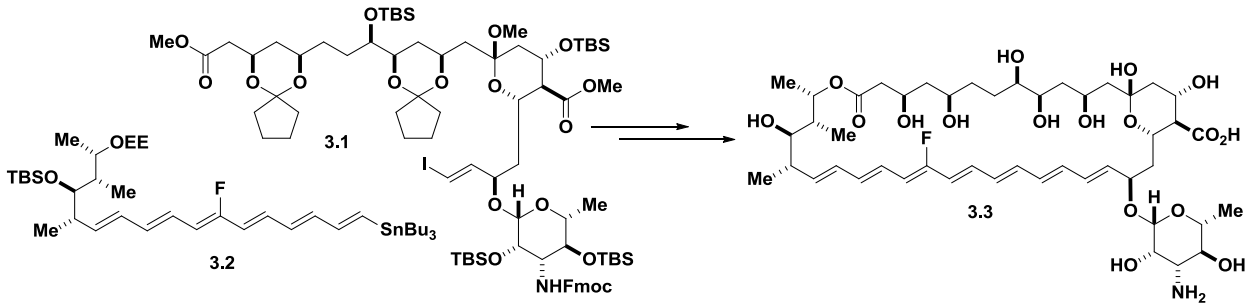


Figure 3.1. Murata's semisynthesis of C28-fluorine labeled AmB **3.3**.

3-2 DEGRADATION OF AMPHOTERICIN B

In the context of our proposed total synthesis of AmB, we targeted the advanced intermediate **3.9** via a SM cross-coupling of building blocks **3.5** and **3.6** (Figure 3.2). These polyol and mycosamine containing sections of the molecule are the most complex and synthetically challenging pieces in our synthesis and so we wanted to target a model system of the endgame strategy that would make us confident that coupled product **3.9** would give access to AmB given the high value of this intermediate. It was recognized that almost this exact

intermediate could be accessed via a degradation of the natural product,[6,7] where all of the complexity is preinstalled in the starting material. From this intermediate we would have an excellent model to test the iterative cross-coupling endgame strategy. Moreover, this accessible intermediate provides a very efficient platform for synthesizing C21-C40 derivatives of the macrolactone via semisynthesis.

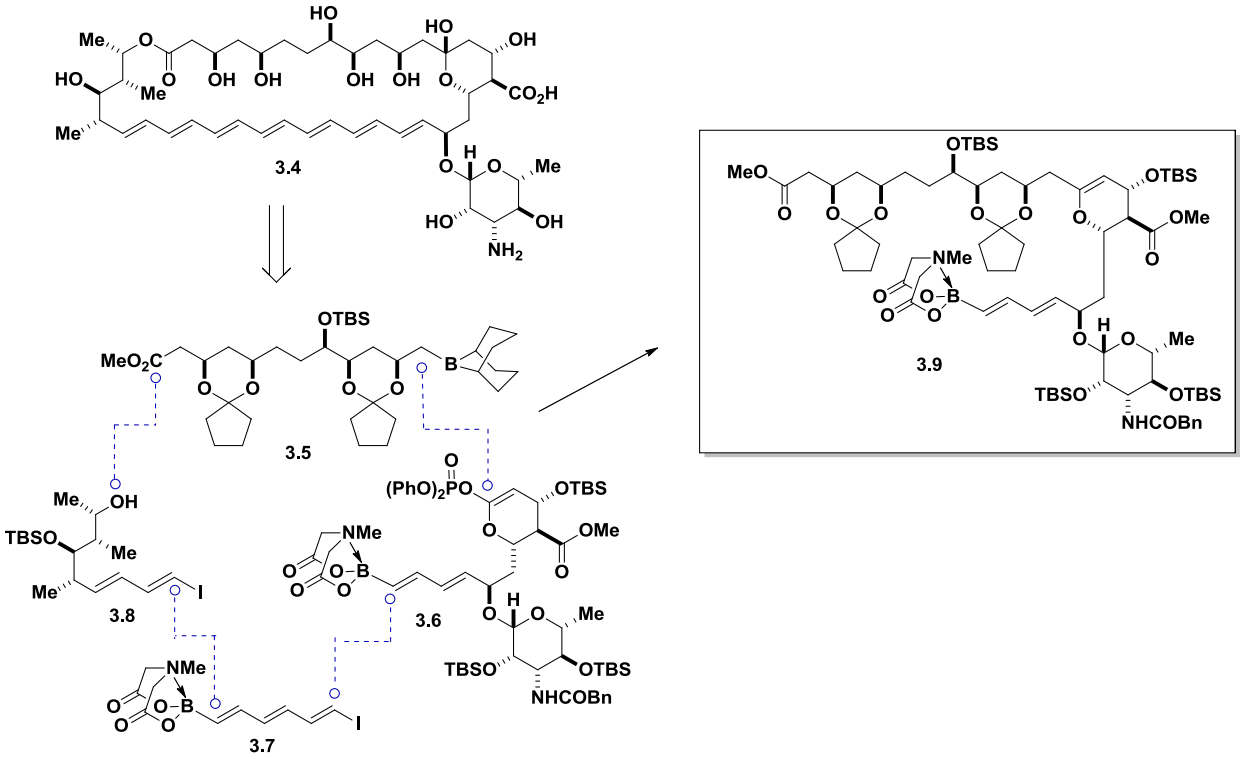
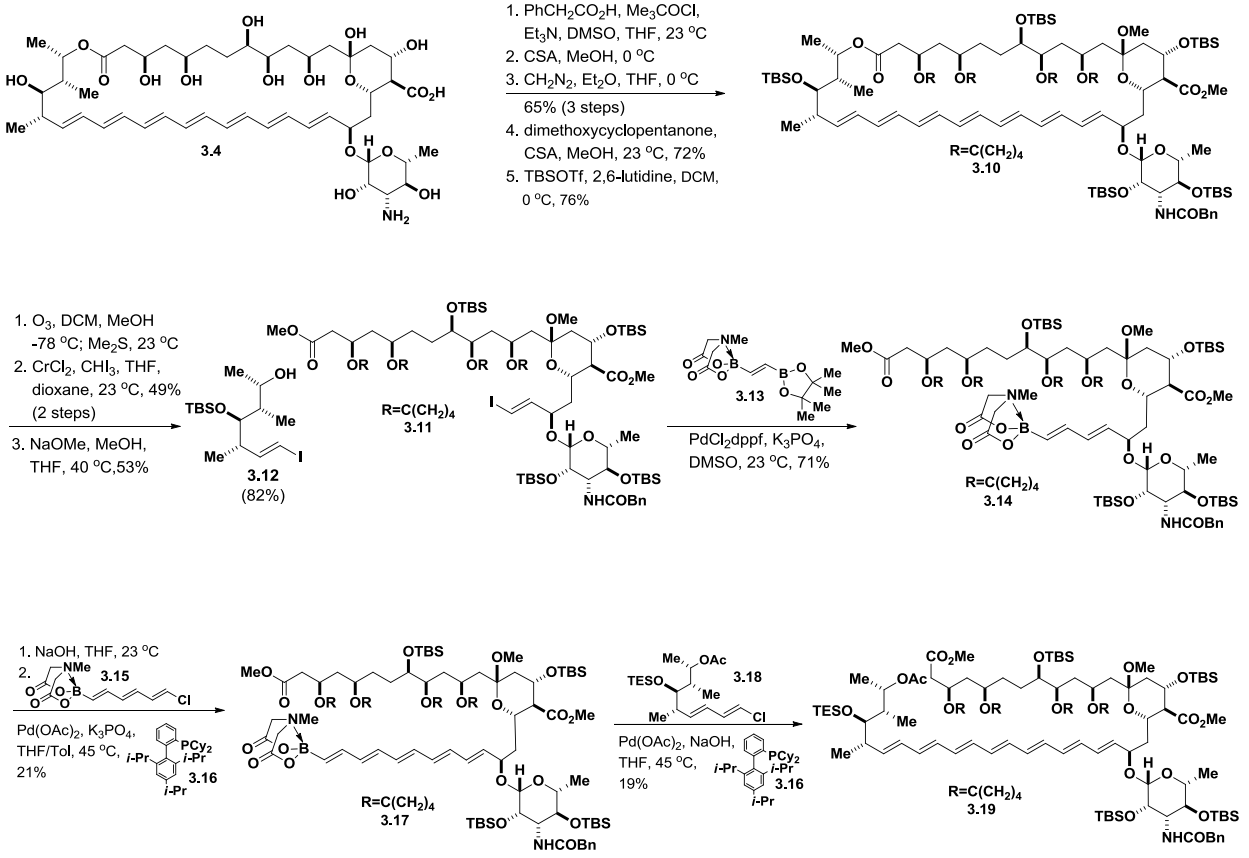


Figure 3.2. Our proposed retrosynthesis of AmB into four key building blocks. The cross-coupling of **3.5** and **3.6** would yield dienyl MIDA boronate **3.9**, a near exact model of which could be accessed from a top-down degradation of AmB.

AmB is notoriously difficult to work with. It is light, oxygen, and acid sensitive, as well as insoluble in most organic solvents.[8,9] Protection of the amine as a benzyl amide,[10] followed by formation of a methyl ketal and a methyl ester made the compound much easier to work with by increasing its solubility. Subsequent ketalization with 1,1'-dimethoxycyclopentanone[11] and *tert*-butyldimethylsilyl (TBS) protection provided globally protected AmB **3.10** in 36% yield over 5 steps (Scheme 3.1). Exhaustive ozonolysis effectively cleaved the polyene and double Takai olefination gave the bis-vinyl iodide.[6,7,12] Transesterification using sodium methoxide then cleaved the western half of AmB providing polyol fragment **3.11** as well as alcohol **3.12**. In order to be an accurate model for the total synthesis, the vinyl iodide of **3.11** needed to be converted to a dienyl MIDA boronate. Anhydrous SM coupling of vinyl iodide **3.11** and

pinacolboronic ester **3.13**[4] proceeded smoothly in 71% yield providing **3.14**, the model for the total synthesis. Subsequent MIDA deprotection with sodium hydroxide, isolation as a solution in THF, and coupling to trienyl chloride **3.15**[4] then provided pentaenyl MIDA boronate **3.17**. Surprisingly this highly complex boronate was found to be stable to silica gel chromatography and storage for at least 6 months in the freezer.[13] One pot deprotection and SM coupling to **3.18**[4] using aqueous sodium hydroxide at 45 °C for 17h then gave the heptaenyl framework for AmB (**3.19**) in 19% yield.[4,14]



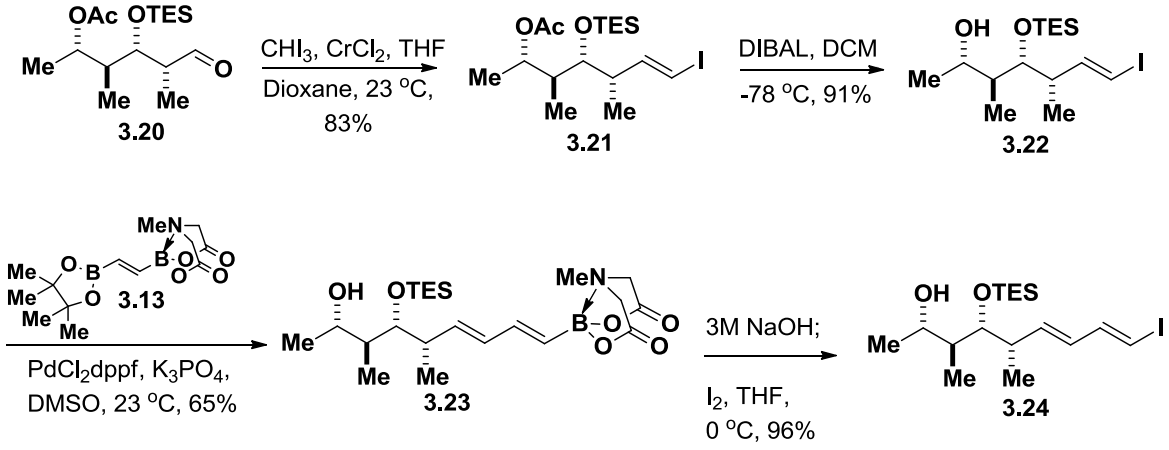
Scheme 3.1. Semisynthesis of the all carbon framework of AmB. Degradation followed by cross-coupling to bisborylated compound **3.11** provided **3.14**. With the exception of the methyl ketal, **3.14** is the same intermediate that will be accessed in the proposed total synthesis. **3.14** was competent to do Suzuki-Miyaura cross-couplings to generate the all carbon framework of AmB. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

3-3 SYNTHESIS OF THE WESTERN HALF OF AMPHOTERICIN B

While we were satisfied that the heptaene core of amphotericin B could be made using this methodology, a 19% yield was not practical as a late stage step in the total synthesis. We hypothesized that the low yield stemmed from the long reaction time, providing opportunities for

the pentaenylboronic acid as well as the heptaene product to decompose. We predicted that the reaction time could be shortened by switching the coupling partner from a dienyl chloride to a more reactive dienyl iodide.[15]

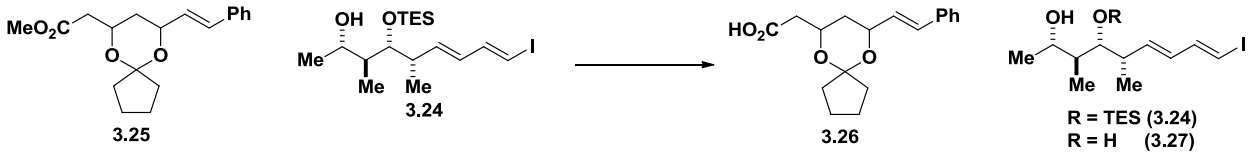
Starting from the known aldehyde **3.20**,[4] Takai olefination provided vinyl iodide **3.21** with >20:1 *E*:*Z* selectivity (Scheme 3.2).[12] First attempts at deacylation using K_2CO_3 in MeOH removed the acyl group but also cleaved the TES protecting group. Use of a diisobutylaluminum hydride (DIBAL) reduction was able to avoid the desilyation and provide the free alcohol in 91% yield. SM cross-coupling to bisborylated **3.13**[4] then gave dienyl MIDA boronate **3.23**. We were satisfied to see that this MIDA boronate was compatible with the free alcohol under the basic conditions of the cross-coupling.[16] This dienyl MIDA boronate then needed to be converted to a dienyl iodide. Brown and coworkers had previously shown that vinylboronic acids could be converted to vinyl iodides by first treating with sodium hydroxide then iodine.[17] Given that sodium hydroxide is the exact condition to deprotect MIDA boronates, we hypothesized that the dienyl MIDA boronate **3.23** could be directly converted to the dienyl iodide using these same conditions. Indeed, treatment of **3.23** with sodium hydroxide followed by iodine generated dienyl iodide **3.24** with retention of stereochemistry in 96% yield.[18]



Scheme 3.2. Synthesis of the TES protected western half of AmB. Dienyl MIDA boronate **3.23** was able to be converted to dienyl iodide **3.24** in one pot with retention of stereochemistry.

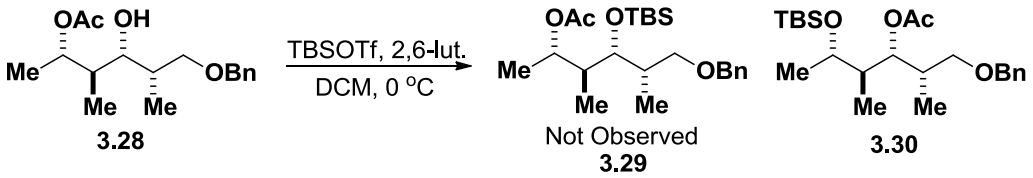
At this time we had been using a TES protecting group on the C35 hydroxyl group due to its greater lability relative to TBS ethers. We predicted that we could have a higher yielding desilylation during the deprotection sequence using this group. However, during the synthesis of building block **3.24** it was noted that the TES group was labile to the basic conditions attempted to remove the acyl group. In their degradative studies of AmB, chemists at SmithKline Beecham

had noted that the C35 hydroxyl group was capable of forming the 36-membered macrolide.[8] Given this observation, we were concerned that if the TES group was removed prior to macrolactonization that we would get competitive cyclization onto the C35 alcohol over the C37 alcohol. Given that the methyl ester at C1 needed to be hydrolyzed prior to macrolactonization, a model system was set up to see if the TES group on building block **3.24** would survive a saponification (Scheme 3.3). Even the use of mild reagents such as potassium cyanide and barium hydroxide caused extensive desilylation in the time it took to convert methyl ester **3.25** to the free acid. Given this problem, we decided to switch to a TBS on the C35 alcohol for both the model system as well as the building block for the total synthesis.

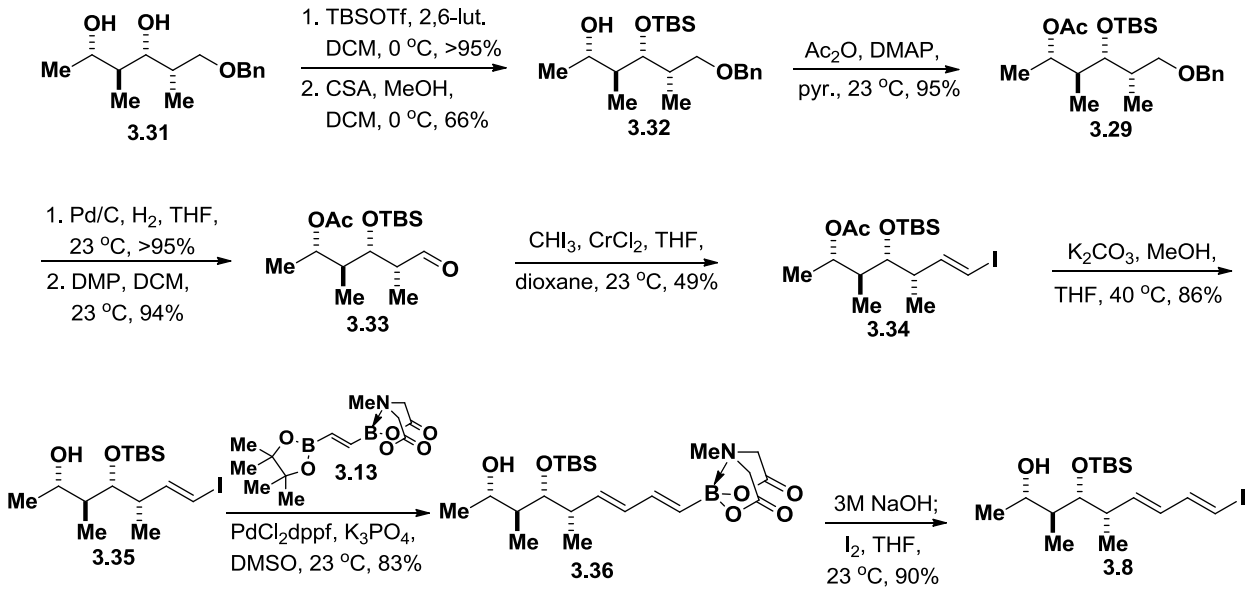


Scheme 3.3. Model methyl ester deprotection to explore the viability of a TES ether surviving at the C35 position. All conditions tried gave a significant amount of deprotection to form **3.27**.

The initial route to TBS protected **3.8** started with the monoacylated intermediate **3.28**.[4] However, treatment of **3.28** with *tert*-butyldimethylsilyl trifluoromethane sulfonate (TBSOTf) did not give the predicted product **3.29**. Instead, acyl migration followed by silylation of the C37 alcohol was the only observed product (Scheme 3.4). To avoid this problem we used a protection/deprotection strategy reported by Patterson and coworkers.[19] Double TBS protection followed by selective acid deprotection of the C37 TBS group resulted in formation of **3.32** (Scheme 3.5). Subsequent acylation of the free alcohol gave fully protected **3.29** in 95% yield. Debenzylation, Dess-Martin oxidation[20] of the free alcohol, and Takai olefination[12] then provided vinyl iodide **3.34**. Unlike with the TES protected intermediate **3.21**, treatment with K_2CO_3 in MeOH smoothly made **3.35** in 86% yield without removing the TBS group. Subsequent SM cross-coupling to bisborylated **3.13**[4] followed by MIDA boronate to iodine exchange gave desired **3.8** in 7 steps from known intermediates.



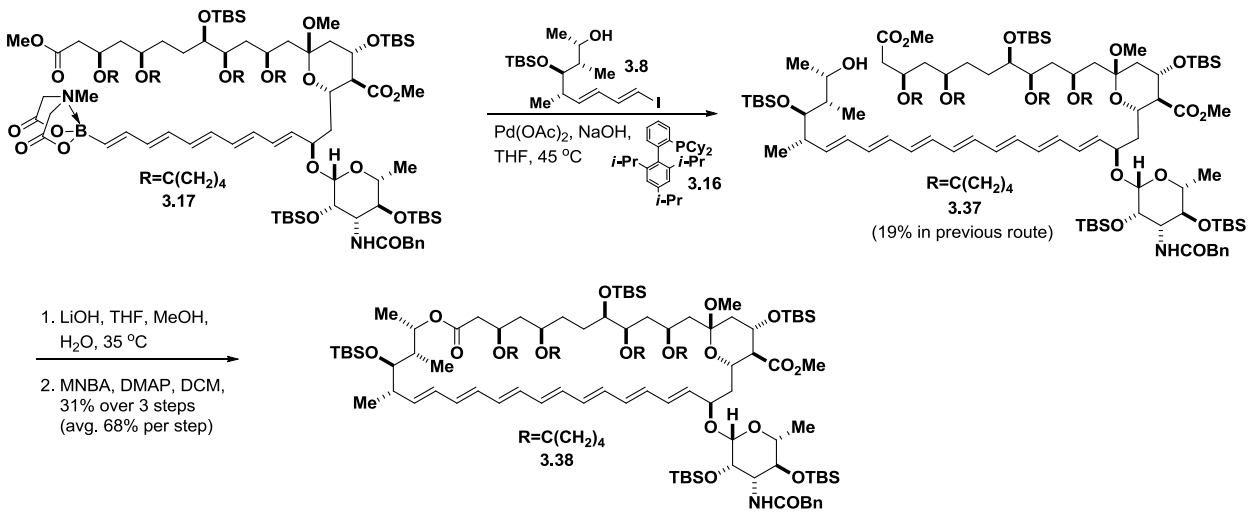
Scheme 3.4. TBS protection of **3.28**. Treatment of **3.28** with TBSOTf did not form the desired product (**3.29**). Instead, acyl migration followed by TBS ether formation at the wrong alcohol was observed, forming **3.30** as the only observed product.



Scheme 3.5. Synthesis of the TBS protected western half of AmB.

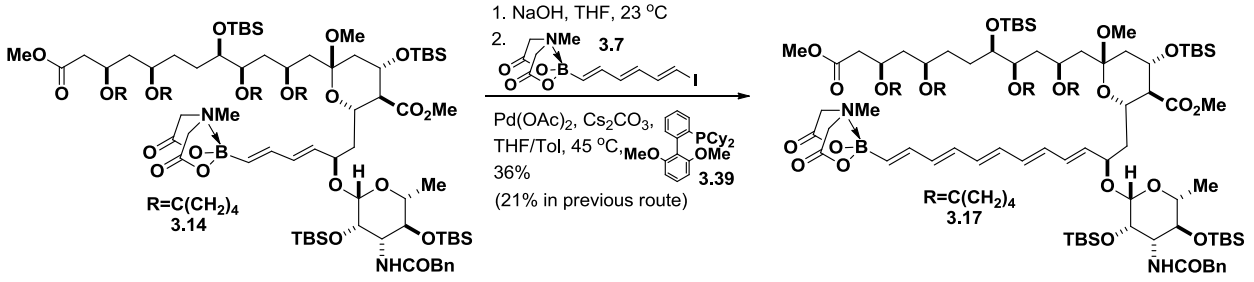
3-4 SYNTHESIS OF THE AMPHOTERICIN B MACROLACTONE

With dienyl iodide **3.8** in hand, we were able to test its effectiveness in the final SM cross-coupling of the AmB synthesis. One pot deprotection and SM coupling of dienyl iodide **3.8** and pentaenyl MIDA boronate **3.17** gave complete and clean conversion to heptaene **3.37** in less than four hours (Scheme 3.6). The product was carried forward without purification to address our concerns that the lower yield was also due, in part, to heptaene decomposition. Subsequent selective deprotection of the C1 methyl ester using lithium hydroxide followed by macrolactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA)[21] as an activator provided the macrolactone of AmB (**3.38**) in 31% over 3 steps (an average of 68% per step).[7] This was a dramatic improvement in yield from the 19% obtained for assembling **3.17** through coupling to dienyl chloride **3.18** (Scheme 3.1).



Scheme 3.6. Modified cross-coupling reaction and macrolactonization sequence using dienyl iodide **3.8**. Switching from a dienyl chloride to the dienyl iodide dramatically improved the cross-coupling yield from 19% to 68% (based on average of 31% over 3 steps). A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

Given the success of switching from the chloride to the iodide with respect to the final coupling, we predicted that changing trienyl chloride **3.15** to a trienyl iodide would improve the yield of the previous coupling. Trienyl iodide **3.7** was accessed using a synthesis reported by Lee et al.[22] Deprotection of dienyl MIDA boronate **3.14** followed by SM cross-coupling to iodide **3.7** provided pentaenyl MIDA boronate **3.17** in 36% yield nearly doubling the throughput compared to the chloride coupling (Scheme 3.7). However, 36% was still low for a late stage reaction in the context of the total synthesis.

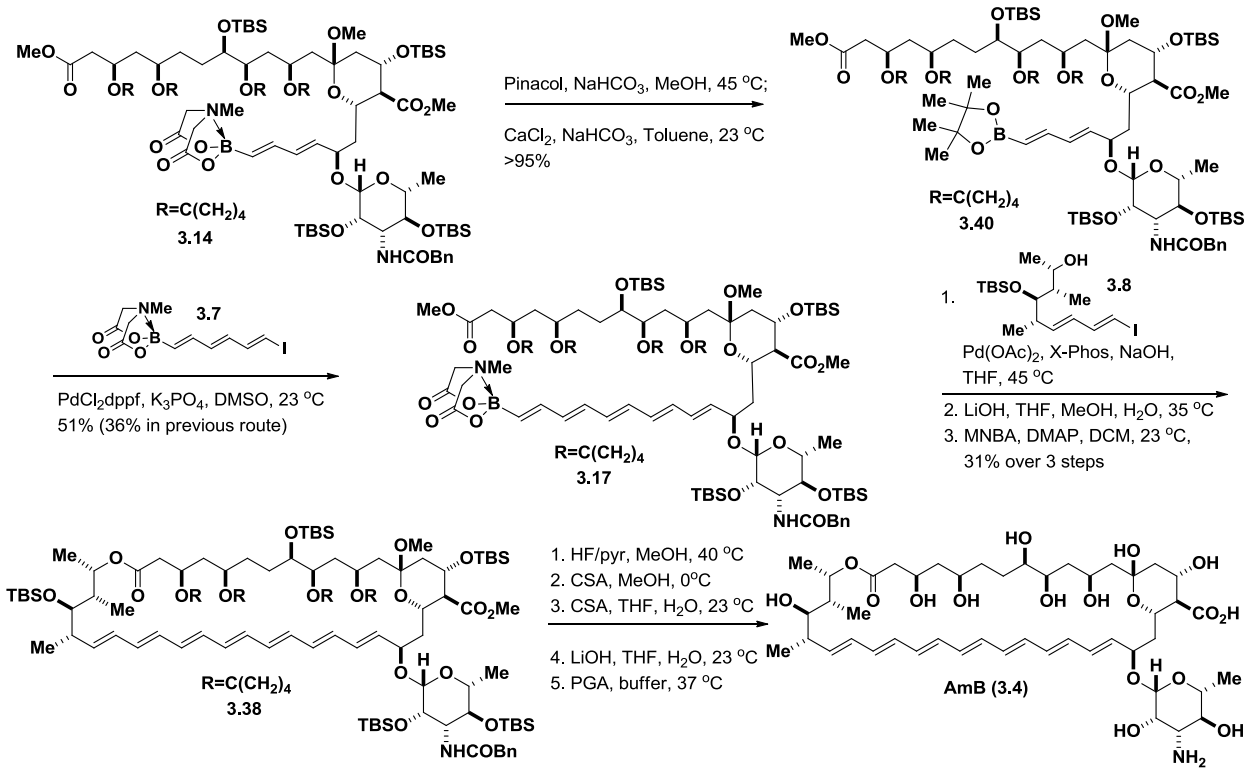


Scheme 3.7. Cross-coupling of trienyl iodide **3.7** to the dienyl boronic acid of AmB. By switching from the trienyl chloride to the trienyl iodide the yield was improved from 21% to 36%. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

At the same time this reaction was being optimized, Woerly et al. had shown, in the context of the total synthesis of peridinin, that MIDA boronates could directly be converted to pinacolboronic esters.[23] We predicted that the use of this chemistry on dienyl MIDA boronate **3.14** to provide the dienyl pinacolboronic ester would make a more stable cross-coupling partner

than the corresponding boronic acid and thus increase the yield of the triene coupling by preventing decomposition of the diene precursor *in situ*.[24] Conversion of **3.14** to the dienyl pinacolboronic ester proceeded smoothly in near quantitative yield (Scheme 3.8). This intermediate was stable to storage for at least 3 days without decomposition, whereas the boronic acid counterpart had to be isolated in solution and carried forward immediately to the cross-coupling. Subsequent SM cross-coupling to trienyl iodide **3.7** gave the pentaene in 51% yield thus a total improvement of 30% yield as compared to the original conditions. Interestingly, the optimal cross-coupling conditions used in this reaction seem to be somewhat general for the cross-coupling of vinyl pinacolboronic esters to vinyl iodides as they are the same conditions used to make **3.23** and **3.36**.

With the cross-couplings optimized, all that remained to reach the natural product was a series of deprotections (Scheme 3.8). These steps were tested on small scale using known HPLC standards to monitor the success of the reactions. Removal of the silyl protecting groups required the use of HF/pyridine in MeOH at elevated temperature to give good conversion. It was noted that the TBS groups on the mycosamine came off rapidly, while the harsher conditions were necessary to remove the C35 TBS group. This is presumably due to the fact that the rigid nature of the molecule[25] locks the C35 alcohol in a sterically encumbered environment. Subsequent acid hydrolysis of the ketals and saponification of the methyl ester left only the benzyl amide to be cleaved. The reason this protecting group was chosen in the first place was its great stability to a wide variety of chemical conditions, but its lability to mild enzyme hydrolysis.[10] Indeed, unoptimized treatment with penicillin G amidase (PGA) in water provided AmB, completing a semisynthesis of the natural product.



Scheme 3.8. Semisynthesis of AmB. By converting to dienyl pinacolboronic ester **3.40** instead of the boronic acid, the yield of the cross-coupling with **3.7** was improved to 51% from the 36% yield in the previous route. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

3-5 MODELING OF THE DEPROTECTION SEQUENCE FOR THE TOTAL SYNTHESIS

The above model system demonstrated that the iterative cross-coupling strategy is a viable endgame strategy for the total synthesis. Since the development of this model system many of the protecting groups for the total synthesis have been modified. In the context of synthesizing C35-deoxy AmB (see chapter 4) it was discovered that by simply removing a single alcohol, AmB becomes more sensitive to deprotection conditions, in particular to hydroxide nucleophiles.[26] For this reason, the methyl ester was exchanged for a 2-(trimethylsilyl)ethyl (TMSE) ester protecting group that can be removed by simple treatment with fluoride. Additionally, the benzyl amide was exchanged for an azide protecting group as it was required to access building block **3.6**. Finally, in the context of the total synthesis the coupling of building blocks **3.5** and **3.6** will generate a dihydropyran instead of a methyl ketal. Given these modifications, we targeted the synthesis of **3.41** from the natural product to screen deprotection conditions (Figure 3.3).

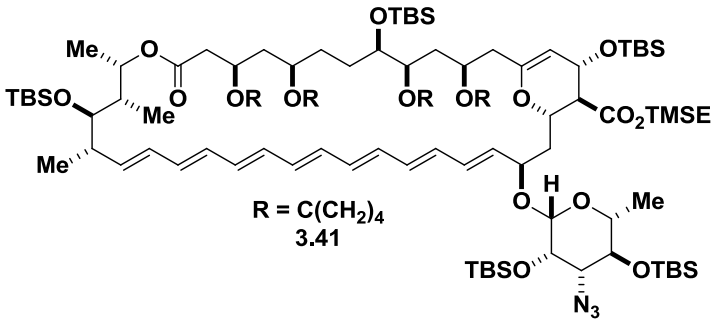
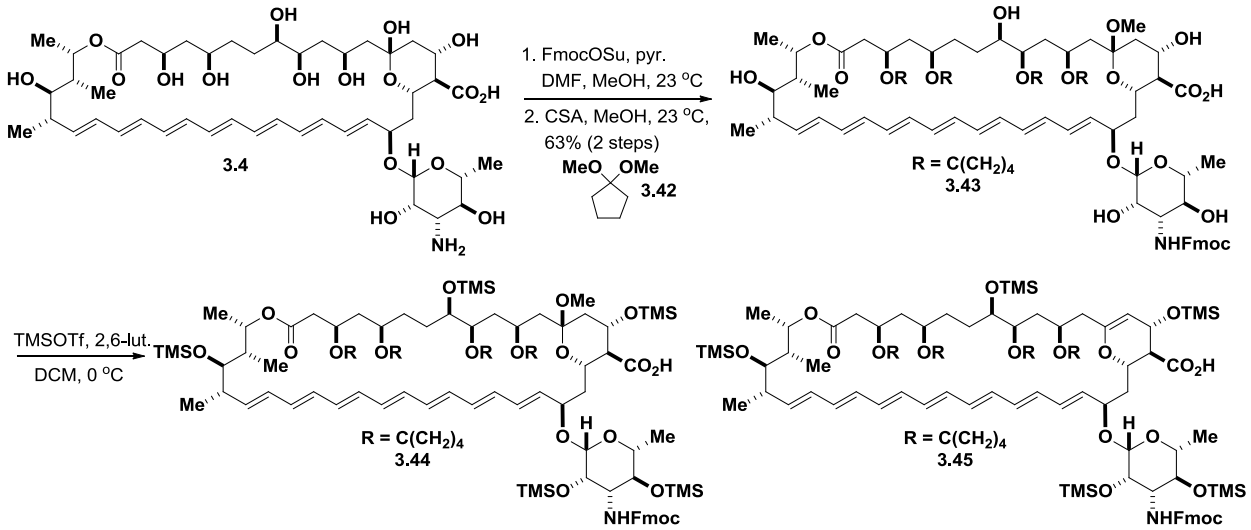


Figure 3.3. New protecting group strategy for the total synthesis of AmB.

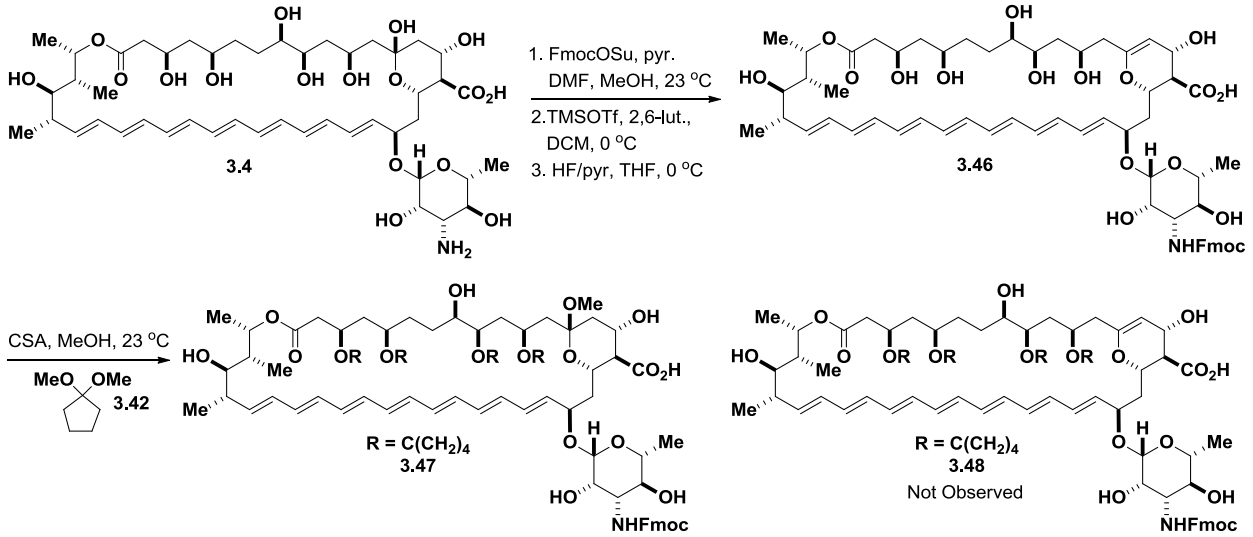
Given the low solubility of AmB, the amine was initially protected as a Fmoc carbamate that would later be converted to the azide (Scheme 3.9).[8] From here the challenge was trying to find conditions to put on both the cyclopentylidene ketals as well as form the dihydropyran. Given that the ketalization conditions involve the use of acid and MeOH, conditions that would presumably convert a dihydropyran to a methyl ketal, the ketalization was done first. It is known in the literature that on substrates lacking the cyclopentylidene ketals the treatment of AmB with TMSOTf in DCM gives complete elimination to the dihydropyran.[8] However, it was found that with the ketals present, only small amounts of elimination were observed and the dihydropyran (**3.45**) was inseparable from the methyl ketal product (**3.44**).



Scheme 3.9. Initial attempts to make dihydropyran **3.45**. Treatment of **3.43** with TMSOTf only formed small amounts of dihydropyran that were inseparable from methyl ketal **3.44**. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

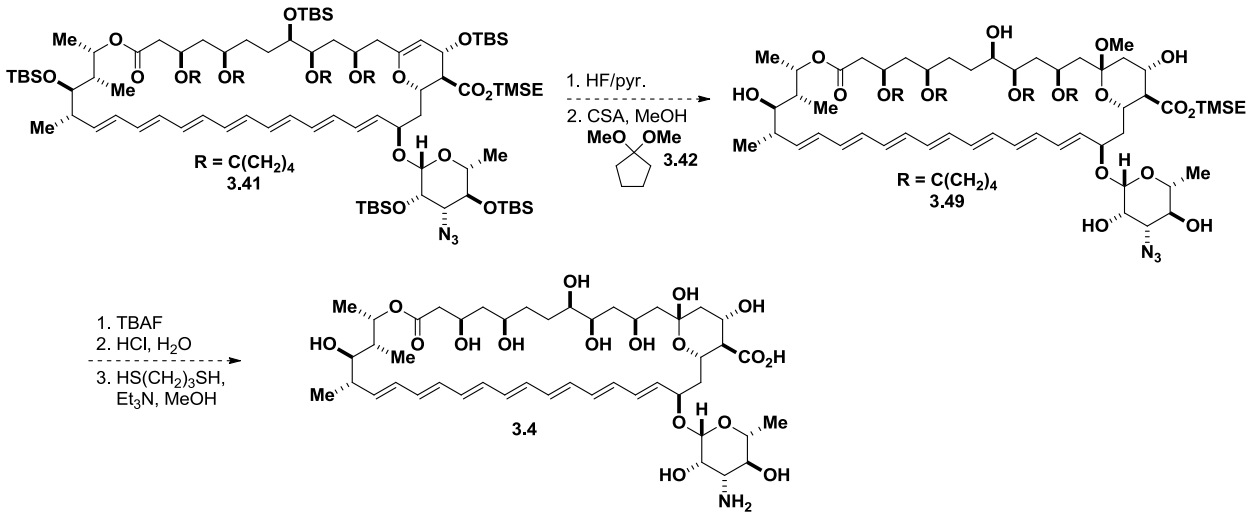
We next attempted to form the dihydropyran prior to ketalization (Scheme 3.10).[8] After Fmoc protection, treatment with TMSOTf in DCM followed by desilylation provided the desired

product as the dihydropyran. However, all attempts to ketalize intermediate **3.46** caused complete conversion of the dihydropyran to the methyl ketal. While this result made it difficult for us to access the model system we were targeting, it suggested that in the presence of cyclopentylidene ketals the molecule prefers to exist as the methyl ketal over the dihydropyran, which could be used to our advantage in the actual deprotection sequence. Specifically, based on this result, we now envision that treatment of the dihydropyran intermediate with CSA in the presence of MeOH and 1,1'-dimethoxycyclopentanone will give us the desired methyl ketal in the actual deprotection sequence.



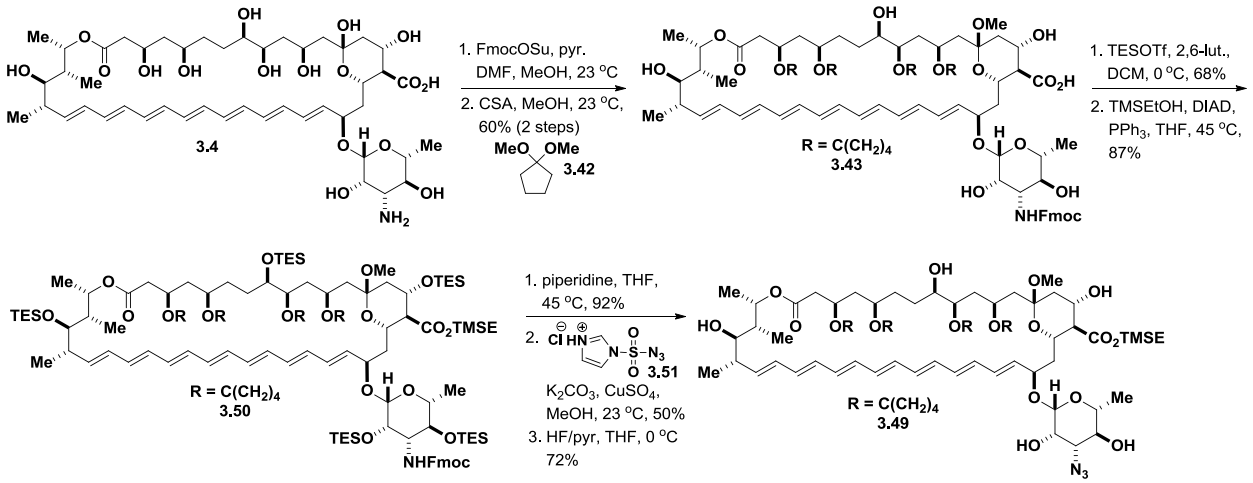
Scheme 3.10. Attempted synthesis of dihydropyran **3.48**. Formation of the cyclopentylidene ketals cause concomitant formation of the methyl ketal from the dihydropyran. This suggests that for the total synthesis, the dihydropyran can be converted to the methyl ketal if the cyclopentylidene ketals are present.

In looking at the proposed deprotection sequence, we identified an alternative intermediate that we expected could be access more readily. In the forward direction the proposed deprotection sequence is as follows: 1. Desilylation with HF/pyridine, 2. Formation of the methyl ketal using acid in the presence of 1,1'-dimethoxycyclopentanone and MeOH, 3. Removal of the TMSE protecting group, 4. Hydrolysis of the ketals, and 5. Reduction of the azide (Scheme 3.11). The intermediate made from formation of the methyl ketal could still be accessed from AmB to test the final three deprotection steps.



Scheme 3.11. Proposed deprotection sequence for the total synthesis.

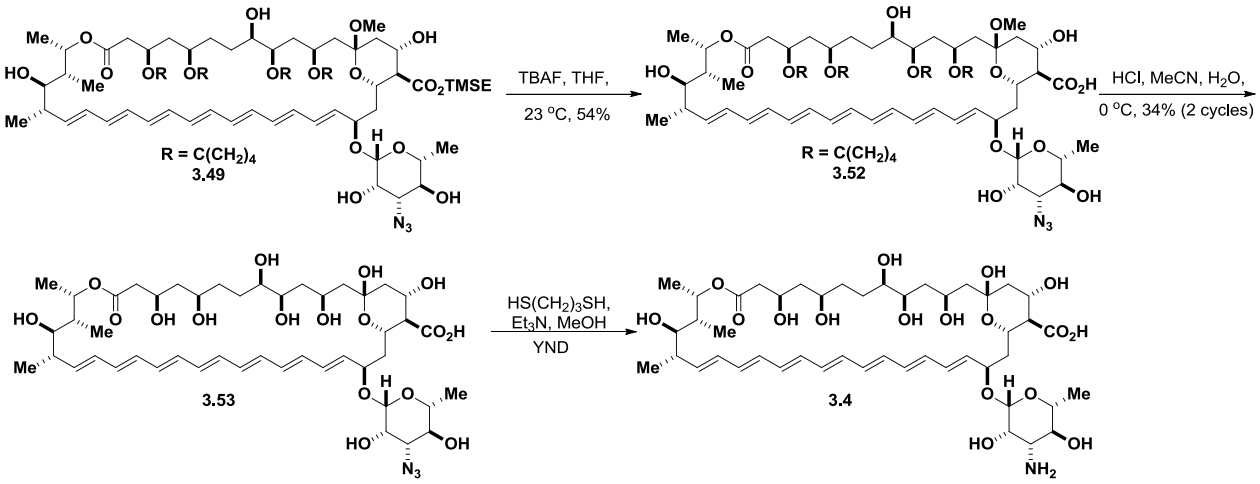
As before, the amine was protected as the Fmoc carbamate followed by ketalization with 1,1'-dimethoxycyclopentanone in MeOH (Scheme 3.12). TES protection of the remaining alcohols followed by formation of the TMSE ester gave fully protected intermediate **3.50** in 35% yield over 4 steps. Subsequent Fmoc removal and treatment with imidazole-1-sulfonylazide[27] then generated the azide at C3'. Treatment with HF/pyridine then cleaved the TES protecting groups providing **3.49**, the intermediate that should be accessed in the context of the total synthesis.



Scheme 3.12. Synthesis of **3.49**. This is the exact intermediate that will be accessed in the proposed deprotection sequence for the total synthesis. A 2.5:1 mixture of ketal constitutional isomers was carried through the route. Only the 1,3 ketal is shown for simplicity.

With this intermediate in hand, deprotections could then be tested. Treatment of **3.49** with TBAF to remove the TMSE provided access to **3.52** in 54% yield (Scheme 3.13). Subsequent

treatment with HCl in MeCN and water then provided **3.53**. During this reaction a series of partially deprotected intermediates are isolated. This material is then resubjected to the reaction conditions to drive the conversion forward. **3.53** was isolated in 34% after two reaction cycles. Finally, treatment of penultimate compound **3.53** with 1,3-propanedithiol and triethylamine in MeOH provided AmB.[2d] Once these steps are fully optimized, valuable time and material will be saved when the total synthesis reaches this late stage.



Scheme 3.13. Deprotection of **3.49** to access AmB. YND = yield not determined.

3-6 SUMMARY

The complexity of AmB makes it both an interesting as well as challenging target for total synthesis. We have proposed a highly modular and efficient way to access this molecule as well as its derivatives through the iterative cross-coupling of four key building blocks. It was recognized that the late stage steps of this synthesis could actually be tested on a model system accessed through semisynthesis from AmB itself. Through degradation, dienyl MIDA boronate **3.14** was synthesized and tested in the proposed polyene synthesis. This model allowed for optimization of the cross-coupling partners and conditions as well as confirmed that this is a viable endgame strategy for the total synthesis. Additionally, one of the exact intermediates that will be encountered during actual deprotection strategy was synthesized and has been used to find conditions for the last three steps of the total synthesis. Semisynthesis has thus proven to be a valuable tool when exploring the total synthesis of a molecule as complicated and challenging as AmB. As will be shown in the next chapter, the semisynthesis also represents a powerful platform for accessing C21-C40 derivatives of AmB.

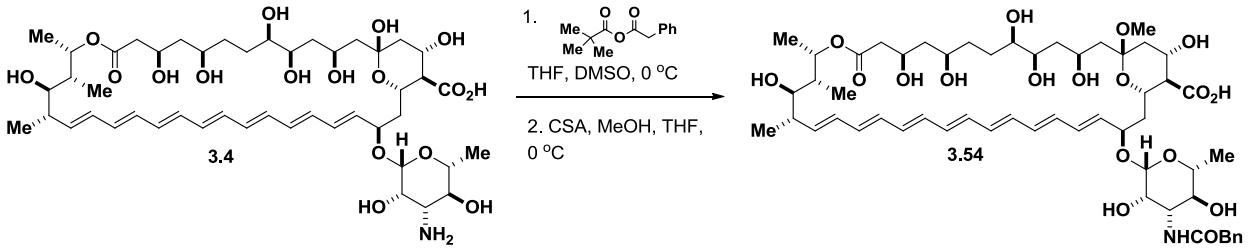
3-7 EXPERIMENTAL SECTION

Materials. Commercial reagents were purchased from Sigma-Aldrich, Alfa Aesar, or Strem, and were used without further purification unless stated otherwise. Amphotericin B was a generous gift from Bristol-Myers Squibb Company. Iodoform (methanol) and camphorsulfonic acid (ethyl acetate) were recrystallized from the indicated solvents prior to use. All solvents were dispensed from a solvent purification system that passes solvents through packed columns according to the method of Pangborn and coworkers[28] (THF, Et_2O, CH_2Cl_2, toluene, dioxane, hexanes: dry neutral alumina; DMSO, DMF, CH_3OH : activated molecular sieves). 2,6-Lutidine and pyridine were freshly distilled under nitrogen from CaH_2. EtOAc and EtOH were freshly distilled under nitrogen from activated molecular sieves. Water was doubly distilled or obtained from a Millipore MilliQ water purification system. The following compounds were prepared according to literature precedent: 1,1-dimethoxycyclopentanone[29], bisborylated compound **3.13**[4,30], aldehyde **3.20**[4]**,** monosilylated alcohol **3.32**[19]**,** trienyl iodide **3.7**[22], imidazole-1-sulfuryl azide **3.51**.[27]

Reactions. Due to the light and air sensitivity of polyenes, all manipulations of polyenes were carried out under low light conditions and compounds were stored under an argon atmosphere. All reactions were performed in oven- or flame-dried glassware under an atmosphere of argon unless otherwise indicated. Reactions were monitored by analytical thin layer chromatography performed using the indicated solvent on E. Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized using a UV (λ_{254}) lamp or stained by an acidic solution of *p*-anisaldehyde or $KMnO_4$. Alternatively, reactions were monitored by RP-HPLC using an Agilent 1100 series HPLC system equipped with a Symmetry® C_{18} 5 micron 4.6 x 150 mm column (Waters Corp. Milford, MA) with UV detection at 406 nm and the indicated eluent and flow rate.

Purification and Analysis. Flash chromatography was performed as described by Still and coworkers[31] using the indicated solvent on E. Merck silica gel 60 230-400 mesh. ^{1}H NMR spectra were recorded at 23 °C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced internally to the residual protium in the NMR solvent ($CDCl_3$, δ = 7.24; $(CD_3)_2CO$, δ = 2.04; DMSO-d_6, δ = 2.49, center line) or to

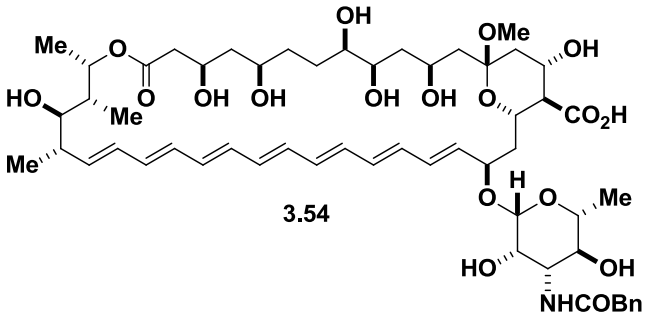
added tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, app. = apparent), coupling constant (*J*) in Hertz (Hz) and integration. ^{13}C spectra were recorded at 23 °C with a Varian Unity 500. Chemical shifts (δ) are reported downfield of tetramethylsilane and are referenced to the carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0, center line, $(CD_3)_2C(O)$, δ = 29.8, center line) or to added tetramethylsilane. Carbons bearing boron substituents were not reported (quadrapolar relaxation). ^{11}B NMR were recorded using a General Electric GN300WB instrument and referenced to an external standard of $BF_3 \cdot Et_2O$. High resolution mass spectra (HRMS) were obtained at the University of Illinois mass spectrometry facility. All synthesized compounds gave HRMS within 5 ppm of calculated values. Infrared spectra were collected from a thin film on NaCl plates or as a KBr pellet on a Mattson Galaxy Series FTIR 5000 spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).



Methyl Ketal 3.54

To phenyl acetic acid (0.662 g, 4.86 mmol, 3 eq) in THF (30 mL) was added trimethyl acetyl chloride (0.4 mL, 3.24 mmol, 2 eq). Et_3N (0.9 mL, 6.48 mmol, 4 eq) was added dropwise to the solution resulting in the formation of a white precipitate. The mixture was stirred at 23 °C for 4 hours then DMSO (30 mL) was added and the solution was cooled to 0 °C. Amphotericin B (**3.4**, 1.5 g, 1.62 mmol, 1 eq) was added and the reaction was stirred at 0 °C for 1.5 hours. The reaction mixture was then poured into Et_2O (1.8 L) stirring at 0 °C. After stirring for 30 minutes the resulting yellow precipitate was isolated via Büchner filtration using Whatman 50 filter paper and washed with copious amounts of diethyl ether to afford a yellow solid which was analyzed by HPLC (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in 1% formic acid over 30 minutes, flow rate = 1.2 mL/min, t_R = 17.9 min). The resulting yellow solid was placed in a 250-mL round bottom flask and left under vacuum for one hour. To the

solid was added THF (30 mL) and MeOH (30 mL) and the slurry was cooled to 0 ^{o}C. CSA (0.075 g, 0.324 mmol) was added and the reaction was stirred at 0 ^{o}C for 1 hour over which time the mixture went clear. The reaction was then quenched at 0 ^{o}C with Et_3N (0.05 mL, 0.359 mmol) and concentrated *in vacuo* until a yellow solid began to precipitate. The resulting solution was poured into hexanes: diethyl ether 1:1 (1200 mL) at 0 ^{o}C and the yellow precipitate was collected via Büchner filtration using Whatman 50 filter paper and washed with 50% EtOAc/Et_2O (250 mL) to yield **3.54** (1.9 g crude, >100% over two steps) as a yellow solid. This material was carried forward without further purification.



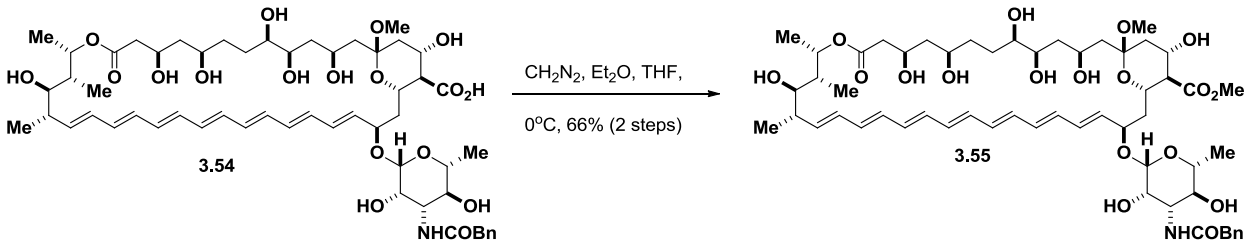
3.54

HPLC

tR = 17.1 min; flow rate = 1.2 mL/min, Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in 0.1% formic acid over 30 min.

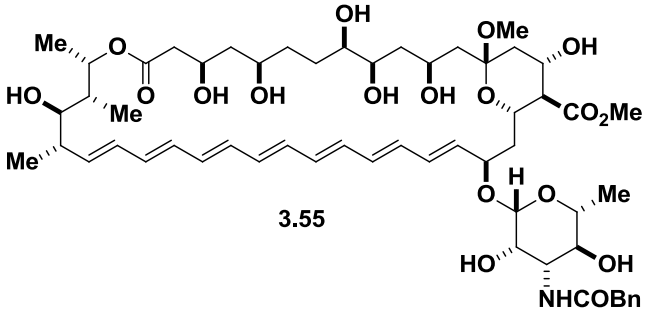
HRMS (ESI)

Calculated for $C_{56}H_{81}NO_{18}$ $(M + Na)^+$:	1078.5351
Found:	1078.5310



Methyl Ester 3.55

To methyl ketal **3.54** (1.9 g, estimated 1.62 mmol) in THF (60 mL) at 0 °C was added dropwise CH_2N_2[32] (9.72 mmol in ~30 mL diethyl ether) over 15 minutes. The reaction was stirred at 0 °C an additional 45 minutes then was quenched with AcOH (1.05 mL) and allowed to warm to 23 °C over 10 minutes. Et_3N (4 mL) was added and the reaction was concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 7% → 10% MeOH/CH_2Cl_2) furnishing **3.55** (1.15 g, 1.07 mmol, 66% over 3 steps) as a yellow powder.



TLC (10% MeOH/CH_2Cl_2)

R_f = 0.25, stained by anisaldehyde.

HPLC

t_R = 13.9 min; flow rate = 1.2 mL/min, Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 30 → 95% MeCN in water over 30 min.

^{1}H NMR (500 MHz, pyridine-d_5:CD_3OD 10:1)

δ 8.95 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 7.0 Hz, 2H), 7.28-7.20 (m, 3H), 6.57-6.30 (m, 12H), 6.21 (dd, *J* = 7.0, 14.5 Hz, 1H), 5.72-5.63 (m, 2H), 4.93 (broad t, *J* = 7.5 Hz, 1H), 4.87 (s, 1H), 4.81 (dt, *J* = 4.5, 10.5 Hz, 1H), 4.69-4.60 (m, 2H), 4.46-3.39 (m, 2H), 3.35 (d, *J* = 3.5 Hz, 1H), 4.14 (app. t, *J* = 9.0 Hz, 1H), 4.00-3.96 (m, 2H), 3.86 (d, *J* = 14.0 Hz, 1H), 3.82 (d, *J* = 14.0 Hz, 1H), 3.76-3.65 (m, 2H), 3.73 (s, 3H), 3.54 (app. d, *J* = 11.0 Hz,

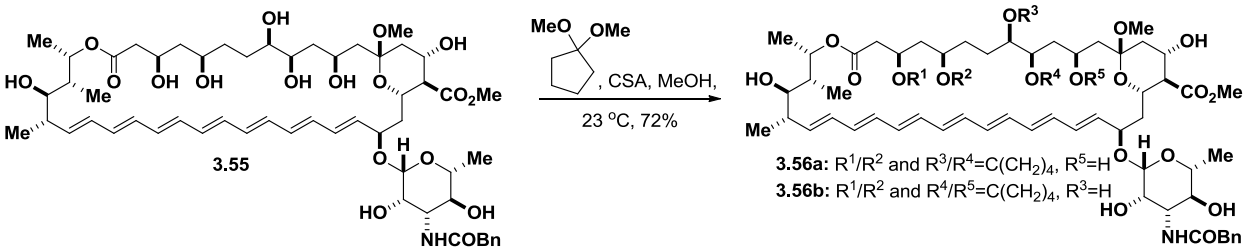
1H), 3.24 (s, 3H), 2.89 (dd, *J* = 4.5, 13.0 Hz, 1H), 2.81 (t, *J* = 10.5 Hz, 1H), 2.70-2.65 (m, 2H), 2.51 (dd, *J* = 8.5, 16.5 Hz, 1H), 2.26 (dd, *J* = 7.5, 14.0 Hz, 1H), 2.21-2.15 (m, 3H), 2.07-2.02 (m, 3H), 2.00-1.79 (m, 6H), 1.55 (d, *J* = 6.0 Hz, 3H), 1.42 (d, *J* = 6.0 Hz, 3H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, pyridine-d_5:CD_3OD 10:1)

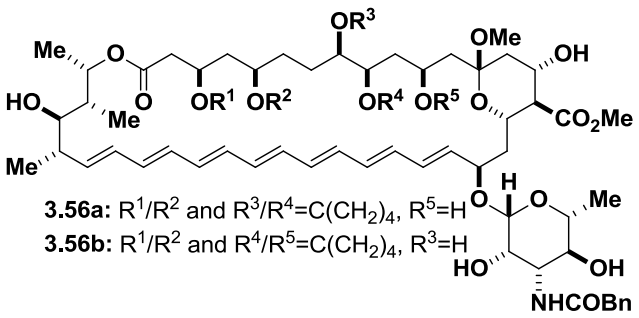
δ 173.9, 172.1, 171.6, 137.6, 137.2, 136.9, 134.5, 134.4, 134.0, 133.9, 133.5, 133.4, 133.3, 133.2, 132.8, 132.6, 132.2, 130.2, 129.8, 128.9, 127.0, 102.0, 99.1, 77.9, 75.5, 75.4, 75.1, 74.7, 71.8, 71.1, 70.6, 68.2, 67.5, 67.4, 66.8, 57.4, 56.7, 56.5, 51.9, 46.9, 44.9, 43.9, 43.8, 43.6, 43.5, 43.3, 41.7, 37.7, 36.3, 30.7, 18.9, 18.6, 17.7, 12.5.

HRMS (ESI)

Calculated for $C_{57}H_{83}NO_{18}$ $(M + Na)^+$:	1092.5508
Found:	1092.5496



Bisketal 3.56. To methyl ester **3.55** (3.34 g, 3.12 mmol, 1 eq) in MeOH (52 mL) and 1,1-dimethoxy cyclopentanone[29] (16.4 mL) was added CSA (0.15 g, 0.62 mmol, 0.2 eq). The reaction was stirred at 23 °C for 1 hour and was then quenched with saturated aqueous $NaHCO_3$ (50 mL). The resulting mixture was then diluted with EtOAc (200 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 3% → 7% MeOH/CH_2Cl_2) furnishing **3.56** (2.79 g, 2.32 mmol, 72%) as an orange solid. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



3.56a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, $R^5=H$

3.56b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, $R^3=H$

TLC (10% $MeOH/CH_2Cl_2$)

R_f = 0.39, stained by anisaldehyde.

HPLC

t_R = 25.0 and 26.1 min; flow rate = 1.2 mL/min, Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 30 → 95% MeCN in water over 30 min.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.0 Hz, 4H), 7.21 (dd, 7.5, 14.5 Hz, 4H), 6.41-6.15 (m, 24H), 5.93-5.87 (m, 2H), 5.58 (t, *J* = 15.0 Hz, 1H), 5.56 (t, *J* = 15.0 Hz, 1H), 5.24 (m, 1H), 5.18 (m, 1H), 4.64 (broad t, *J* = 5.5 Hz, 2H), 4.58 (s, 2H), 4.20 (d, *J* = 3.0 Hz, 1H), 4.18-4.05 (m, 5H), 4.02 (dd, *J* = 3.0, 6.0 Hz, 1H), 3.97-3.94 (m, 3H), 3.91-3.85 (m, 4H), 3.76-3.73 (m, 3H), 3.68-3.58 (m, 4H), 3.66 (s, 3H), 3.65 (s, 3H), 3.51-3.46 (m, 2H), 3.38-3.24 (m, 5H), 3.09 (s, 3H), 3.03 (s, 3H), 2.43-2.35 (m, 4H), 2.31-2.11 (m, 8H), 1.99-1.73 (m, 21H), 1.71-1.49 (m, 29H), 1.44-1.29 (m, 8H), 1.21 (d, *J* = 5.5 Hz, 3H), 1.20 (d, *J* = 5.5 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 6H).

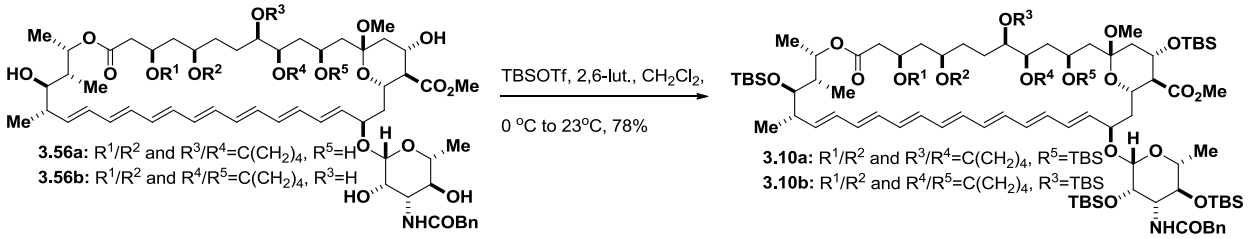
^{13}C NMR (125 MHz, acetone-d_6)

δ 173.7, 173.6, 172.7, 169.9, 169.8, 137.5, 136.9, 136.2, 134.6, 134.4, 134.3, 134.2, 134.0, 133.9, 133.7, 133.5, 133.2, 132.9, 132.8, 132.6, 132.2, 132.1, 130.0, 129.6, 129.2, 129.0, 127.2, 118.6, 110.8, 110.7, 110.6, 101.7, 100.9, 98.1, 98.0, 94.9, 94.6, 81.7, 79.9, 77.9, 77.8, 75.6, 74.7, 74.5, 74.4, 74.0, 73.5, 73.0, 72.6, 71.4, 71.3, 70.8, 70.6, 70.5, 70.0, 69.8, 69.2, 68.8, 67.6, 67.3, 67.0, 66.9, 66.3, 57.4, 57.3, 56.2, 54.8, 52.0, 48.5, 48.4, 43.3, 42.7, 42.4, 42.2, 41.9, 41.6, 41.5, 40.9, 40.8, 40.7, 38.1, 38.0, 37.8, 37.7, 37.2, 33.9, 33.8,

33.4, 31.8, 31.7, 28.6, 28.3, 24.9, 24.8, 24.0, 23.9, 22.9, 22.8, 18.9, 18.8, 18.2, 17.7, 17.6, 11.9, 11.8.

HRMS (ESI)

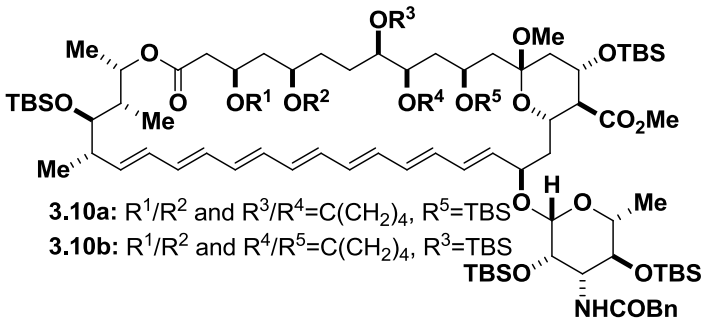
Calculated for $C_{67}H_{95}NO_{18}$ $(M + Na)^+$:	1224.6447
Found:	1224.6409



TBS Ether 3.10

Prior to the reaction ketal **3.56** was azeotropically dried via coevaporation with acetonitrile (3 x 25 mL) and was left under vacuum for a minimum of four hours. To the resulting yellow powder (2.84 g, 2.36 mmol, 1 eq) was added CH_2Cl_2 (70 mL) and 2,6-lutidine (3.0 mL, 25.98 mmol, 11 eq) and the resulting solution was cooled to 0 ^oC. TBSOTf (4.5 mL, 19.36 mmol, 8.2 eq) was added dropwise over 10 minutes and the resulting dark red solution was stirred for 1 hour at 0 ^oC. Additional 2,6-lutidine (3.0 mL, 25.98 mmol, 11 eq) was added followed by additional TBSOTf (4.5 mL, 19.36 mmol, 8.2 eq) dropwise over 10 minutes. The reaction was stirred at 0 ^oC for 15 minutes then the ice bath was removed and the reaction was allowed to stir an additional 45 minutes. The solution was recooled to 0 ^oC and was quenched with saturated aqueous $NaHCO_3$ (70 mL). Et_2O (500 mL) was added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 250 mL) and water (1 x 250 mL), and the combined aqueous layers were back-extracted with Et_2O (100 mL). The combined organic layers were then washed with saturated copper(II) sulfate (1 x 750 mL) and the aqueous layer was back-extracted with Et_2O (200 mL). The combined organic layers were washed with water (3 x 200 mL) and brine (1 x 200 mL). The third set of aqueous washes were combined and back-extracted with Et_2O (200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 5% →

15% EtOAc/hexanes) to yield **3.10** (3.25 g, 1.83 mmol, 78%) as a yellow solid. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



TLC (20% EtOAc/hexanes)

R_f = 0.63, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.33-7.28 (m, 8H), 7.24-7.21 (m, 2H), 6.38-6.15 (m, 24H), 6.03 (dd, *J* = 10.0, 15.5 Hz, 2H), 5.89 (dd, *J* = 7.0, 15.5 Hz, 1H), 5.82 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.67-5.62 (m, 2H), 4.82 (broad s, 2H), 4.63-4.58 (m, 2H), 4.55 (s, 2H), 4.31-4.23 (m, 2H), 4.17-4.07 (m, 3H), 4.03 (t, *J* = 9.5 Hz, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.97-3.86 (m, 5H), 3.80-3.85 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.62-3.52 (m, 8H), 3.43-3.37 (m, 4H), 3.15 (s, 3H), 3.04 (s, 3H), 2.44-2.36 (m, 2H), 2.34-2.25 (m, 4H), 2.20-2.12 (m, 2H), 1.99-1.73 (m, 24H), 1.70-1.46 (m, 32H), 1.40-1.25 (m, 6H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 6H), 1.01 (d, *J* = 7.5 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.5 Hz, 3H), 0.93-0.84 (m, 90H), 0.16- -0.01 (m, 60H).

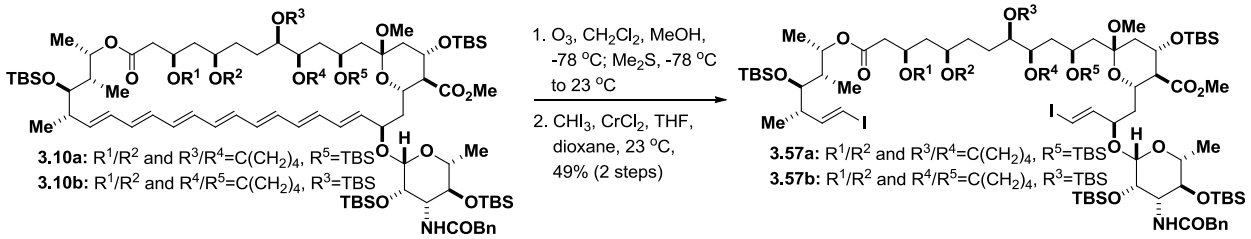
^{13}C NMR (125 MHz, acetone-d_6)

δ 173.6, 173.5, 173.4, 170.3, 170.2, 170.1, 137.0, 136.4, 134.5, 134.4, 134.3, 134.1, 133.7, 133.6, 133.5, 133.4, 133.0, 132.9, 131.3, 131.0, 130.2, 129.0, 127.4, 118.6, 118.5, 110.7, 110.6, 110.5, 103.7, 101.8, 101.3, 101.2, 100.9, 100.0, 99.2, 98.7, 81.6, 81.2, 77.8, 76.7, 76.1, 75.9, 75.5, 75.3, 74.8, 73.5, 73.1, 72.6, 72.5, 72.0, 70.2, 69.5, 68.9, 68.8, 68.2, 67.5, 67.2, 66.9, 66.7, 57.3, 56.3, 56.2, 52.2, 48.8, 48.5, 44.1, 43.8, 43.5, 41.6, 41.3, 41.2, 40.8, 40.7, 38.4, 38.2, 36.7, 33.9, 33.7, 32.6, 32.2, 31.7, 31.6, 38.4, 38.2, 37.6, 36.7, 33.9, 33.7, 32.6, 32.2, 31.7, 31.6, 38.5, 27.9, 26.6, 26.4, 26.3, 26.2, 26.0, 25.5, 25.0, 24.9, 24.2,

24.1, 24.0, 23.4, 22.9, 19.6, 18.9, 18.8, 18.7, 18.6, 18.5, 18.4, 18.3, 18.2, 18.1, -3.1, -3.2, -3.3, -3.4, -3.5, -3.7, -3.9, -4.1, -4.2, -4.3, -4.7, -4.8, -4.9.

HRMS (ESI)

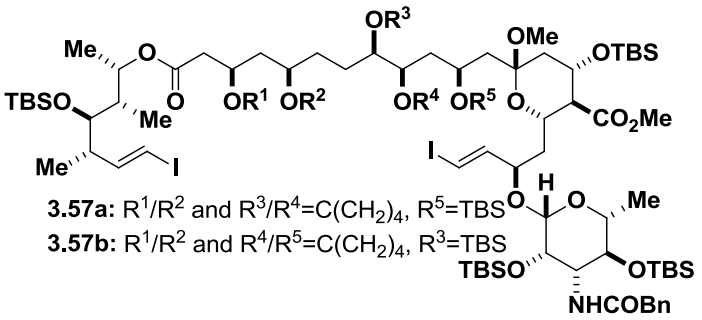
Calculated for $C_{97}H_{165}NO_{18}Si_5$ $(M + Na)^+$:	1795.0771
Found:	1795.0759



Bisvinyl Iodide 3.57

TBS ether **3.10** (1.12 g, 0.631 mmol, 1 eq) was dissolved in CH_2Cl_2 (49 mL) and MeOH (2.2 mL) and was cooled to -78 °C. Ozone was bubbled through the solution until a blue color persisted (~10 minutes) and the excess ozone was bubbled out with a stream of nitrogen. Dimethyl sulfide (0.7 mL, 9.47 mmol, 15 eq) was added at -78 °C with stirring and the cold bath was removed. The reaction was stirred at 23 °C overnight (~14 h). The mixture was concentrated and the residue was dissolved in diethyl ether (100 mL) and washed with saturated aqueous $NaHCO_3$ (75 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting white foam was azeotropically dried via coevaporation with benzene (3 x 10 mL) and left under vacuum for at least 1 hour. In a separate 100 mL round bottom flask equipped with a stir bar and charged with $CrCl_2$ (2.40 g, 19.56 mmol, 31 eq) was added THF (14 mL) and dioxane (3.6 mL). To the $CrCl_2$ slurry was added dropwise a solution of the bisaldehyde intermediate and iodoform (2.03 g, 5.17 mmol, 8.2 eq) in THF (10.5 mL) and dioxane (7 mL). The resulting dark red slurry was stirred at 23 °C for 2 hours before quenching with saturated aqueous $NaHCO_3$ (30 mL). The resulting green slurry was diluted with Et_2O (100 mL) and filtered through celite. The filtrate layers were separated and the organic layer was washed with saturated aqueous $Na_2S_2O_3$ (30 mL). The combined aqueous layers were extracted with diethyl ether (2 x 75 mL), then the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by

flash chromatography (SiO_2; 0% → 10% EtOAc/hexanes) to furnish bisvinyl iodide **3.57** (0.582 g, 0.307 mmol, 49% over two steps) as a white solid. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



TLC (20% EtOAc/hexanes)

R_f = 0.48, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.33-7.28 (m, 8H), 7.25-7.22 (m, 2H), 6.59-6.47 (m, 6H), 6.37 (d, *J* = 8.5 Hz, 1H), 6.36 (d, *J* = 9.0 Hz, 1H), 6.21 (d, *J* = 14.5 Hz, 2H), 5.15-5.11 (m, 2H), 4.61 (s, 1H), 4.58 (s, 1H), 4.37-4.33 (m, 2H), 4.31-4.15 (m, 6H), 4.00 (t, *J* = 9.0 Hz, 1H), 3.99 (t, *J* = 9.0 Hz, 1H), 3.94-3.89 (m, 3H), 3.88-3.82 (m, 2H), 3.74-3.66 (m, 5H), 3.69 (s, 3H), 3.68 (s, 3H), 3.62-3.54 (m, 8H), 3.38-3.33 (m, 2H), 3.18 (s, 3H), 3.13 (s, 3H), 2.53-2.49 (m, 2H), 2.41 (d, *J* = 6.5 Hz, 4H), 2.30-2.04 (m, 6H), 2.00-1.87 (m, 10H), 1.85-1.71 (m, 14H), 1.70-1.31 (m, 34H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 6H), 0.94-0.84 (m, 96H), 0.14- -0.01 (m, 60H).

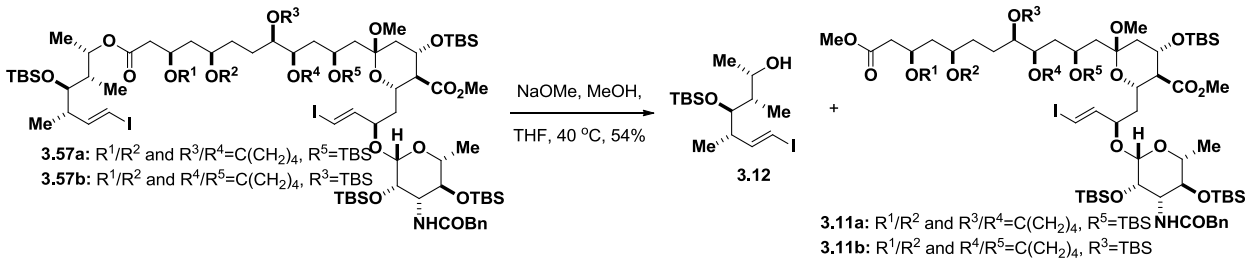
^{13}C NMR (125 MHz, acetone-d_6)

δ 173.3, 173.2, 170.2, 151.2, 151.1, 147.5, 136.3, 130.2, 129.1, 127.4, 118.6, 110.9, 110.8, 101.4, 101.2, 100.2, 100.0, 81.7, 81.4, 80.1, 79.9, 79.5, 79.3, 78.2, 76.7, 76.2, 75.3, 74.8, 74.6, 73.3, 72.4, 72.2, 71.6, 71.0, 70.5, 68.5, 68.4, 67.5, 67.4, 67.2, 58.1, 58.0, 56.2, 56.1, 51.9, 48.5, 44.2, 44.0, 43.9, 43.7, 43.6, 43.2, 43.0, 42.3, 42.2, 41.2, 41.0, 39.5, 39.3, 38.2, 38.1, 37.4, 33.4, 33.2, 32.2, 31.9, 31.8, 28.5, 28.3, 26.5, 26.4, 26.3, 26.2, 26.0, 25.9, 25.4, 25.1, 25.0, 24.1, 23.9, 23.4, 23.1, 19.7, 18.9, 18.8, 18.6, 18.5, 18.3, 18.2, 16.4, 14.1, 11.2, -3.3, -3.6, -3.7, -3.8, -3.9, -4.1, -4.2, -4.3, -4.8, -4.9, -5.1.

HRMS (ESI)

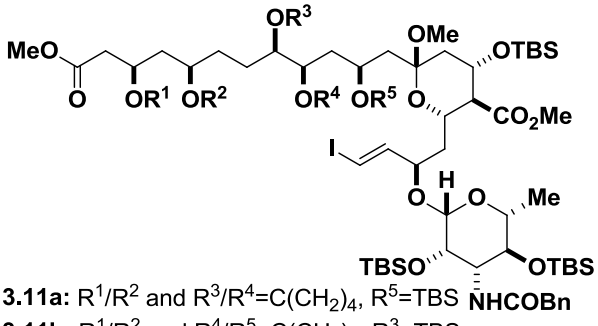
Calculated for $C_{87}H_{155}I_2NO_{18}Si_5$ $(M + Na)^+$: 1918.8078

Found: 1918.8020



Methyl Ester 3.11 and Alcohol 3.12

Prior to the reaction, bisvinyl iodide **3.57** was azeotropically dried via coevaporation with benzene (3 x 10 mL) and was left under vacuum for at least eight hours. To bisvinyl iodide **3.57** (0.580 g, 0.305 mmol, 1 eq) in THF (4.1 mL) and MeOH (4.1 mL) was added NaOMe (0.165 g, 3.05 mmol, 10 eq) in MeOH (4.1 mL) via cannula. The reaction was stirred at 40 °C for 12 hours and was then quenched with 0.5 M pH 7 phosphate buffer (10 mL). The mixture was diluted with Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2; 0% → 15% EtOAc/hexanes) yielded alcohol **3.12** (0.100 g, 0.251 mmol, 82%) and methyl ester **3.11** (0.254 g, 0.166 mmol, 54%). **3.11** was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



TLC (20% EtOAc/hexanes)

R_f = 0.40, stained by anisaldehyde

^{1}H NMR (500 MHz, acetone-d_6)

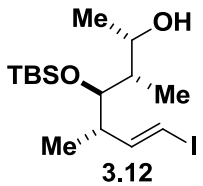
δ 7.35-7.30 (m, 8H), 7.28-7.24 (m, 2H), 6.60-6.49 (m, 4H), 6.39 (d, *J* = 9.0 Hz, 1H), 6.38 (d, *J* = 8.5 Hz, 1H), 4.63 (s, 1H), 4.60 (s, 1H), 4.39-4.35 (m, 2H), 4.33-4.25 (m, 2H), 4.25-4.17 (m, 4H), 4.02 (t, *J* = 9.0 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.96-3.29 (m, 3H), 3.89-3.83 (m, 1H), 3.79-3.68 (m, 4H), 3.71 (s, 3H), 3.70 (s, 3H), 3.66-3.56 (m, 8H), 3.64 (s, 3H), 3.60 (s, 3H), 3.39-3.52 (m, 2H), 3.20 (s, 3H), 3.15 (s, 3H), 2.44 (d, *J* = 4.5 Hz, 4H), 2.31-2.16 (m, 6H), 1.96-1.89 (m, 8H), 1.84-1.72 (m, 10H), 1.71-1.47 (m, 30H), 1.38-1.29 (m, 4H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.22-1.18 (m, 4H), 0.94-0.86 (m, 72H), 0.17-0.01 (m, 48H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 173.3, 173.2, 171.5, 171.4, 170.2, 147.5, 136.3, 130.2, 129.1, 129.0, 127.4, 118.6, 110.9, 110.8, 101.4, 101.2, 100.2, 100.0, 81.6, 80.0, 79.9, 79.5, 79.4, 78.2, 75.3, 74.8, 74.6, 74.5, 73.3, 72.3, 72.2, 71.0, 70.5, 68.5, 68.4, 68.3, 67.5, 67.4, 67.2, 58.1, 58.0, 56.2, 56.1, 51.9, 51.6, 48.5, 44.0, 43.9, 43.7, 43.6, 43.2, 42.2, 41.5, 41.2, 40.8, 39.5, 39.3, 38.1, 38.0, 37.3, 33.4, 33.2, 32.2, 31.8, 31.7, 28.5, 28.3, 26.5, 26.4, 26.2, 26.0, 25.9, 25.4, 25.0, 24.9, 24.0, 23.9, 23.3, 23.0, 22.9, 19.7, 18.9, 18.8, 18.6, 18.5, 18.3, 18.2, -3.3, -3.5, -3.6, -3.8, -3.9, -4.1, -4.2, -4.3, -4.4, -4.8, -4.9.

HRMS (ESI)

Calculated for $C_{73}H_{128}INO_{18}Si_4$ $(M + Na)^+$:	1552.7202
Found:	1552.7260



3.12

TLC (20% EtOAc/hexanes)

R_f = 0.49, stained by anisaldehyde

^{1}H NMR (500 MHz, acetone-d_6)

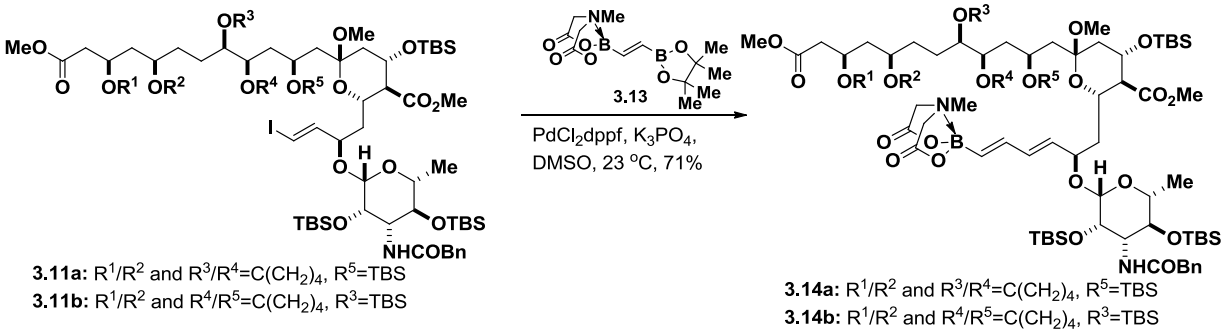
δ 6.59 (dd, *J* = 8.0, 14.5 Hz, 1H), 6.16 (dd, *J* = 1.0 Hz, 14.5 Hz, 1H), 3.89 (t, *J* = 5.5 Hz, 1H), 3.80-3.74 (m, 1H), 3.52 (d, *J* = 4.5 Hz, 1H), 2.56-2.49 (m, 1H), 1.76-1.69 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.85 (d, *J* = 7.5 Hz, 3H), 0.08 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 152.0, 76.7, 75.4, 68.4, 68.3, 47.0, 46.9, 44.3, 26.4, 21.2, 21.1, 18.8, 15.1, 11.4, -3.9.

HRMS (ESI)

Calculated for $C_{15}H_{31}O_2SiI$ $(M + H)^+$:	399.1216
Found:	399.1235



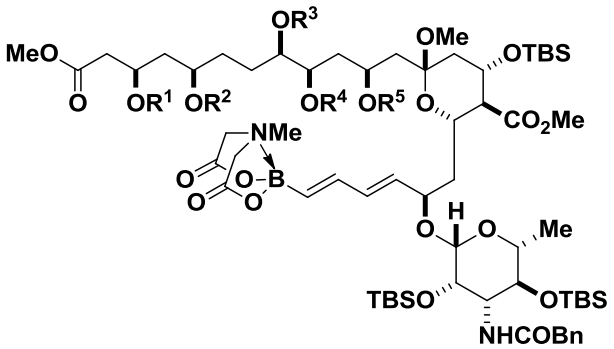
3.11a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS
3.11b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

3.14a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS
3.14b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

Dienyl MIDA Boronate 3.14

A 20 mL I-Chem vial equipped with a stir bar was charged with methyl ester **3.11** (0.173 g, 0.113 mmol) and bisborylated compound **3.13**[4,30] (0.072 g, 0.237 mmol), sealed under argon, and was taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.0048 g, 0.0059 mmol) and K_3PO_4 as a finely ground powder (0.0719 g, 0.339 mmol) were added followed by DMSO (3.8 mL). The reaction was sealed with a PTFE-lined cap and stirred at 23 °C for 24 h. The solution was diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (100 mL). The filtrate was washed with brine (3 x 20 mL) and the combined aqueous layers were back-extracted with EtOAc (75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 50% → 100 %

EtOAc/hexanes) to furnish dienyl MIDA boronate **3.14** as a white solid (0.128 g, 0.081 mmol, 71%). The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



3.14a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=TBS
3.14b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=TBS

TLC (EtOAc)

R_f = 0.50, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.32-7.28 (m, 8H), 7.25-7.22 (m, 2H), 6.61 (dd, *J* = 10.0, 17.0 Hz, 1H), 6.60 (dd, *J* = 10.5, 17.5 Hz, 1H), 6.40 (d, *J* = 8.5 Hz, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 10.5, 15.0 Hz, 1H), 6.32 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.69 (d, *J* = 17.5 Hz, 1H), 5.68 (d, *J* = 17.5 Hz, 1H), 5.63 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.62 (dd, *J* = 8.0, 15.5 Hz, 1H), 4.62 (s, 1H), 4.61 (s, 1H), 4.39-4.35 (m, 2H), 4.29-4.14 (m, 10H), 4.06-3.98 (m, 6H), 3.94-3.89 (m, 3H), 3.88-3.81 (m, 1H), 3.79-3.71 (m, 4H), 3.69 (s, 3H), 3.68 (s, 3H), 3.65-3.53 (m, 8H), 3.61 (s, 3H), 3.56 (s, 3H), 3.40-3.34 (m, 2H), 3.14 (s, 3H), 3.10 (s, 3H), 2.99 (s, 6H), 2.42 (d, *J* = 6.0 Hz, 4H), 2.29-2.10 (m, 6H), 1.92-1.89 (m, 8H), 1.85-1.71 (m, 10H), 1.68-1.46 (m, 32H), 1.37-1.22 (m, 6H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.92-0.84 (m, 72H), 0.15- -0.02 (m, 48H).

^{13}C NMR (125 MHz, acetone-d_6)

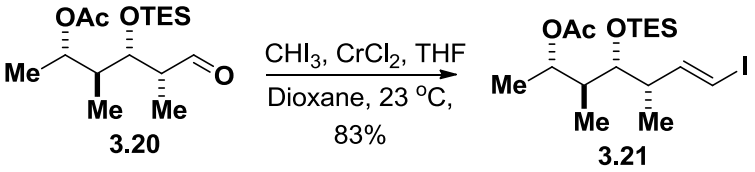
δ 173.4, 173.3, 171.5, 170.3, 170.2, 169.0, 168.9, 142.7, 142.6, 136.3, 136.1, 135.9, 135.0, 134.8, 130.2, 129.1, 127.4, 118.5, 110.9, 110.8, 110.5, 101.3, 101.1, 99.8, 99.7, 81.7, 78.2, 77.7, 77.6, 75.4, 74.8, 74.7, 74.5, 73.4, 71.9, 71.0, 70.5, 68.6, 68.4, 68.3, 67.8, 67.4, 67.2, 62.4, 62.3, 58.4, 58.3, 56.0, 51.9, 51.6, 48.5, 47.4, 44.1, 43.9, 43.7, 43.6, 43.2, 42.0, 41.6, 41.2, 40.9, 40.8, 40.3, 38.1, 38.0, 37.3, 33.4, 33.2, 32.2, 31.7, 28.5, 28.4, 26.5,

26.4, 26.3, 26.2, 26.0, 25.9, 25.4, 25.2, 25.0, 24.9, 24.0, 23.9, 23.3, 23.0, 22.9, 19.9, 18.9, 18.8, 18.6, 18.5, 18.3, 18.2, -3.4, -3.5, -3.6, -3.7, -3.8, -3.9, -4.0, -4.2, -4.3, -4.4, -4.8, -4.9.

HRMS (ESI)

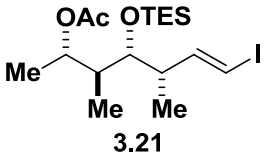
Calculated for $C_{80}H_{137}BN_2O_{21}Si_4$ $(M + Na)^+$: 1607.8782

Found: 1607.8798



Vinyl iodide 3.21

To a slurry of $CrCl_2$ (10.4 g, 86.25 mmol, 15 eq) in THF (48 mL) was added dropwise via cannulation aldehyde **3.20**[4] (1.82 g, 5.75 mmol, 1 eq) and iodoform (11.3 g, 28.75 mmol, 5 eq) in dioxane:THF 2:1 (100 mL). After stirring at 23 °C for 5 minutes, the reaction was poured into saturated aqueous $NaHCO_3$ (500 mL) and diluted with Et_2O (500 mL). The green mixture was filtered through celite, washing with Et_2O (250 mL) and the filtrate layers were separated. The aqueous layer was extracted with Et_2O (2 x 250 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; 0 → 10% EtOAc/hexanes) provided the title compound **3.21** (2.10 g, 4.77 mmol, 83%) as a pale yellow oil.



TLC (10% EtOAc/hexanes)

R_f = 0.38, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.56 (dd, *J* = 10.5, 18.0 Hz, 1H), 6.22 (dd, *J* = 1.0, 18.0 Hz, 1H), 5.07 (p, *J* = 7.0 Hz, 1H), 3.65 (dd, *J* = 5.5, 8.0 Hz, 1H), 2.54-2.44 (m, 1H), 1.97 (s, 3H), 1.95-1.86 (m, 1H),

1.12 (d, J = 8.0 Hz, 3H), 0.99 (t, J = 9.0 Hz, 9H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 9.0 Hz, 3H), 0.65 (q, J = 10.5 Hz, 6H).

^{13}C NMR (100 MHz, acetone-d_6)

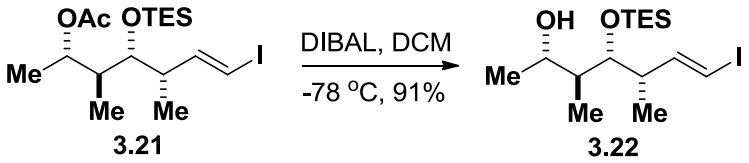
δ 170.1, 151.2, 77.3, 76.3, 71.3, 44.2, 42.7, 21.2, 16.1, 13.7, 11.1, 7.3, 6.0.

HRMS (ESI+)

Calculated for $C_{17}H_{33}O_3SiI$ $(M + H)^+$:	441.1332
Found:	441.1317

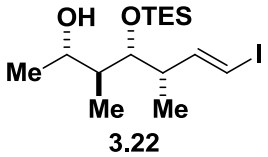
IR (thin film, cm^{-1})

2960, 2912, 2877, 2254, 1724, 1460, 1375, 1250, 1082. 1018, 953, 910, 732, 649.



Secondary Alcohol 3.22

To vinyl iodide **3.21** (2.10 g, 4.77 mmol, 1 eq) in DCM (80 mL) at -78 °C was added dropwise DIBAL (1M in hexanes, 21 mL, 21 mmol, 4.4 eq). The reaction was stirred at -78 °C for 30 minutes then MeOH (50 mL) was added and the ice bath was removed. The reaction was allowed to warm for 10 minutes then was poured into saturated aqueous potassium sodium tartrate (500 mL). The mixture was stirred at 23 °C for 1h and was then extracted with Et_2O (3 x 500 mL), dried over Na_2SO_4, and concentrated. The crude material was purified via flash chromatography (SiO_2; 25% EtOAc/hexanes) to yield **3.22** (1.73 g, 4.34 mmol, 91%) as a pale yellow oil.



TLC (25% EtOAc/hexanes)

R_f = 0.55, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 6.59 (dd, *J* = 8.0, 14.4 Hz, 1H), 6.19 (dd, *J* = 1.2, 14.8 Hz, 1H), 3.84-3.79 (m, 2H), 3.51 (d, *J* = 4.0 Hz, 1H), 2.54-2.46 (m, 1H), 1.77-1.68 (m, 1H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.63 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (100 MHz, acetone-d_6)

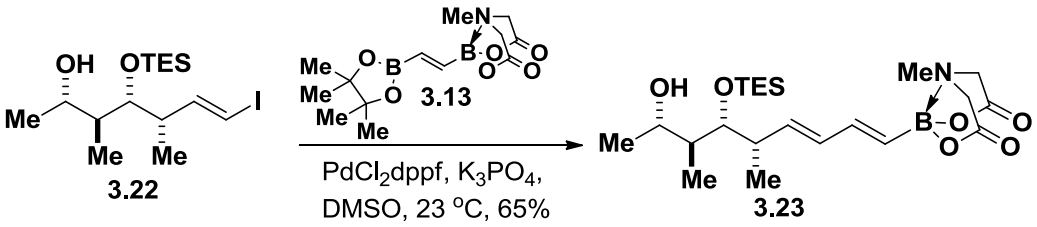
δ 151.9, 77.4, 75.7, 68.1, 46.5, 44.3, 20.6, 14.5, 11.2, 7.3, 5.9.

HRMS (ESI+)

Calculated for $C_{15}H_{31}O_2SiI$ $(M + H)^+$:	399.1216
Found:	399.1223

IR (thin film, cm^{-1})

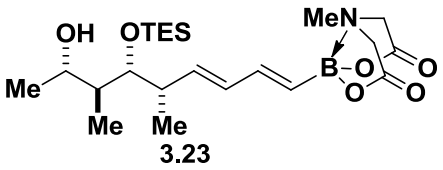
3498, 2962, 2912, 2879, 2254, 1459, 1383, 1242, 1093, 1004, 908, 733.



Dienyl MIDA Boronate 3.23

A 40 mL I-Chem vial equipped with a stir bar was charged with vinyl iodide **3.22** (0.250 g, 0.635 mmol, 1 eq) and bisborylated compound **3.13**[4,30] (0.174 g, 0.572 mmol, 0.9 eq), sealed under argon, and was taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.026 g, 0.0318 mmol, 5 mol%) and K_3PO_4 as a finely ground powder (0.405 g, 1.91 mmol, 3 eq) were added, followed by DMSO (21 mL). The reaction was sealed with a PTFE-lined cap, removed from the glovebox, and stirred at 23 °C for 24 hours. The solution was then diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (70 mL). The filtrate was washed with water (3 x 50 mL) and brine (1 x 50 mL) and the combined aqueous layers were extracted with EtOAc (3

x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone (10 mL), celite was added to the solution, and the mixture was concentrated *in vacuo*. The resulting powder was dry-loaded on top of a flash column and purified (SiO_2; 50% EtOAc/hexanes → EtOAc → 10% MeCN/EtOAc) to yield the desired product **3.23** (0.168 g, 0.370 mmol, 65%) as a pale yellow solid.



3.23

TLC (EtOAc)

R_f = 0.38, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

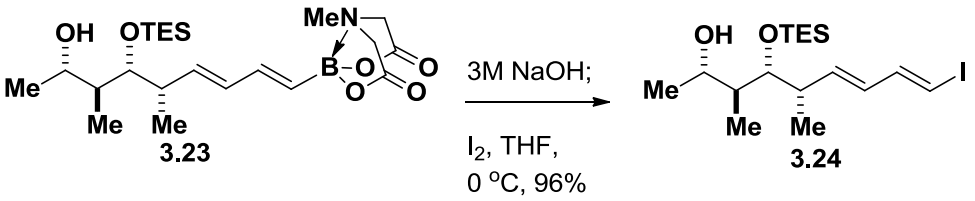
δ 6.54 (dd, *J* = 10.0, 17.5 Hz, 1H), 6.12 (dd, *J* = 10.0, 15.5 Hz, 1H), 5.81 (dd, *J* = 8.0, 15.0 Hz, 1H), 5.56 (d, *J* = 15.5 Hz, 1H), 4.19 (dd, *J* = 1.5, 17.0 Hz, 2H), 4.00 (dd, *J* = 1.0, 17.0 Hz, 2H), 3.84-3.80 (m, 2H), 3.47 (d, *J* = 4.0 Hz, 1H), 2.98 (s, 3H), 2.49-2.43 (m, 1H), 1.76-1.69 (m, 1H), 1.05 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.62 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 169.1, 169.0, 143.7, 140.6, 132.6, 78.4, 68.3, 62.2, 47.3, 46.7, 40.9, 20.8, 16.0, 11.5, 7.3, 5.9.

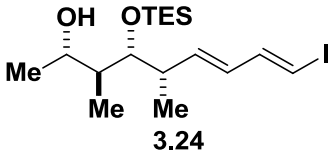
HRMS (ESI+)

Calculated for $C_{22}H_{40}O_6NBSi$ $(M + H)^+$:	454.2796
Found:	454.2801



Dienyl iodide 3.24

To dienyl MIDA boronate **3.23** (25 mg, 0.0551 mmol, 1 eq) in THF (0.280 mL) was added 3 M NaOH (0.092 mL, 0.275 mmol, 5 eq). The reaction was stirred at 23 °C for 10 minutes then cooled to 0 °C over 5 minutes. A solution of I_2 (0.2M in THF, 0.290 mL, 0.058 mmol, 1.05 eq) was added dropwise over 5 minutes. The reaction was stirred at 0 °C for 15 minutes and was then quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was pushed through a plug of silica gel with Et_2O to give dienyl iodide **3.24** (22.5 mg, 0.0530 mmol, 96%) as a pale yellow oil.



TLC (20% EtOAc/hexanes)

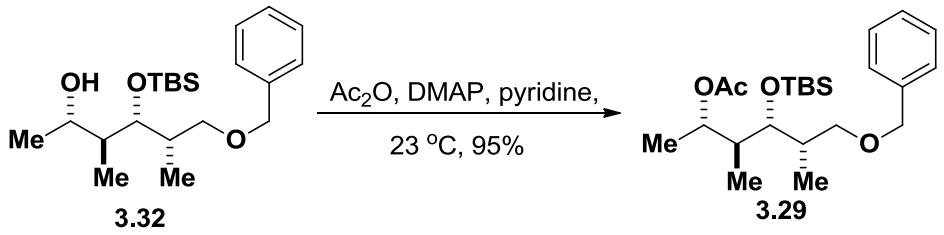
R_f = 0.48, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 7.05 (dd, *J* = 10.4, 14.4 Hz, 1H), 6.38 (d, *J* = 14.4 Hz, 1H), 6.08 (dd, *J* = 10.8, 15.6 Hz, 1H), 5.86 (dd, *J* = 8.0, 15.2 Hz, 1H), 3.85-3.76 (m, 2H), 3.46 (d, *J* = 5.5 Hz, 1H), 2.49-2.40 (m, 1H), 1.76-1.68 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.84 (d, *J* = 7.2 Hz, 3H), 0.62 (q, *J* = 7.6 Hz, 6H).

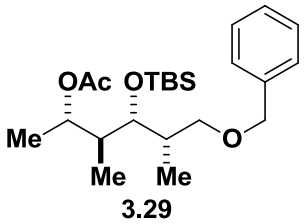
HRMS (ESI+)

Calculated for $C_{17}H_{33}O_2SiI$ $(M + H)^+$:	425.1373
Found:	425.1376



Acylated alcohol 3.32

To monosilylated alcohol **3.32**[19] (0.875 g, 2.39 mmol, 1 eq) in pyridine (24 mL) at 0 °C was added DMAP (0.029g, 0.239 mmol, 0.1 eq) and acetic anhydride (0.45 mL, 4.77 mmol, 2 eq). The reaction was stirred at 23 °C for 6 hours and then concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 10% EtOAc/hexanes) to yield the title compound **3.29** as a colorless oil (0.924 g, 2.26 mmol, 95%).



TLC (25% EtOAc/hexanes)

R_f = 0.56, stained by anisaldehyde.

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.35-7.27 (m, 5H), 4.96 (p, *J* = 6.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 12 Hz, 1H), 3.91 (dd, *J* = 2.0, 6.0 Hz, 1H), 3.33 (app t, *J* = 8.5 Hz, 1H), 3.20 (dd, *J* = 6.0, 8.5 Hz, 1H), 1.96-1.86 (m, 2H), 1.88 (s, 3H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 170.5, 138.6, 128.3, 127.7, 127.4, 73.7, 72.8, 71.9, 71.2, 43.1, 35.2, 26.0, 21.2, 18.3, 16.8, 11.3, 11.1, -4.0, -4.5.

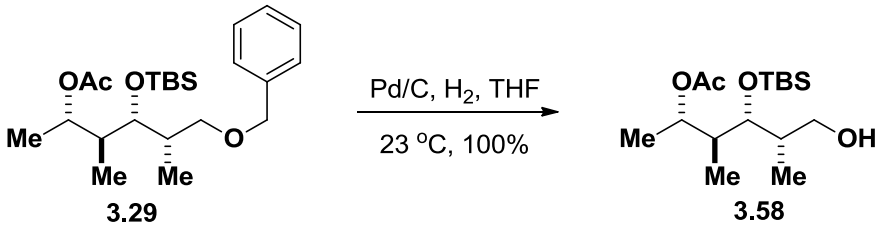
HRMS (ESI+)

calculated for $C_{23}H_{40}O_4Si$ $(M+H)^+$: 409.2774

found: 409.2780

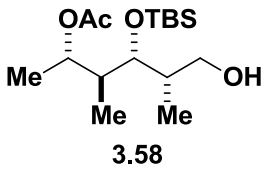
IR (thin film, cm^{-1})

2254, 1724, 1471, 1379, 1254, 1095, 1045, 908, 735, 650.



Primary alcohol 3.58

To acylated alcohol **3.29** (0.920 g, 2.25 mmol, 1 eq) in THF (23 mL) was added palladium on activated carbon (5 wt. % dry basis, wet, Degussa type E101 NO/W) (480 mg, 0.113 mmol Pd, 0.05 eq). The flask was purged with H_2 and the reaction was stirred at 23 °C under H_2 balloon pressure for 1h. The reaction was filtered through a pad of silica gel with EtOAc and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 50% EtOAc/hexanes) to provide primary alcohol **3.58** as a colorless oil (0.715 g, 2.24 mmol, 100%).



TLC (25% EtOAc/hexanes)

R_f = 0.27, stained by anisaldehyde.

^1H NMR (500 MHz, $CDCl_3$)

δ 5.00 (p, *J* = 7.0 Hz, 1H), 3.88 (dd, *J* = 2.0, 5.5 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 2H), 2.03 (s, 3H), 1.93 (app sext, *J* = 6.0 Hz, 1H), 1.81 (d sext, *J* = 2.0, 7.0 Hz, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$)

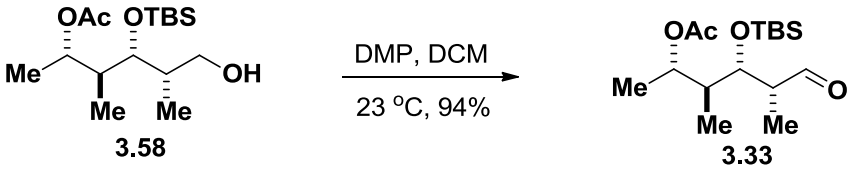
δ 170.8, 71.8, 71.4, 66.2, 43.3, 37.8, 26.0, 21.4, 18.3, 17.0, 11.4, 11.2, -4.1, -4.5.

HRMS (ESI+)

calculated for $C_{16}H_{34}O_4Si$ $(M+Na)^+$:	341.2124
found:	341.2125

IR (thin film, cm^{-1})

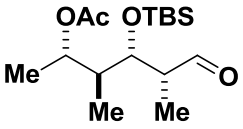
3475, 2956, 2931, 2887, 2858, 1736, 1716, 1471, 1375, 1252, 1092, 1045, 837, 773.



3.58 3.33

Aldehyde 3.58

To primary alcohol **3.58** (0.715 g, 2.24 mmol, 1 eq) in CH_2Cl_2 (32 mL) was added Dess-Martin periodinane (1.43 g, 3.37 mmol, 1.5 eq) and water (0.012 mL, 0.67 mmol, 0.3 eq). The reaction was stirred at 23 °C for 30 minutes. Saturated aqueous $NaHCO_3$ (80 mL) and saturated aqueous $Na_2S_2O_3$ (40 mL) were added, and the reaction was stirred an additional 30 minutes. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield aldehyde **3.33** (0.665 g, 2.10 mmol, 94%), which was used without further purification.



3.33

TLC (25% EtOAc/hexanes)

R_f = 0.42, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 9.68 (s, 1H), 5.03 (p, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 2.8, 6.8 Hz, 1H), 2.55 (dq, *J* = 2.8, 7.2 Hz, 1H), 2.03-1.94 (m, 1H), 1.98 (s, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100 MHz, acetone-d_6)

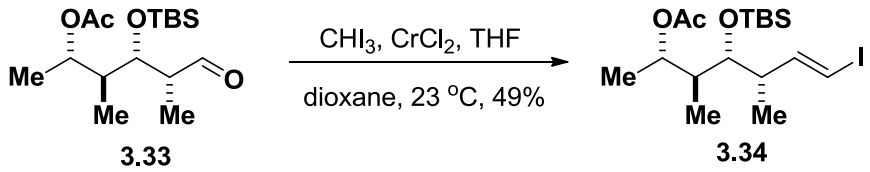
δ 204.9, 170.3, 71.6, 71.4, 49.9, 43.5, 26.3, 21.1, 18.8, 16.2, 11.1, 8.0, -4.0, -4.2.

HRMS (ESI+)

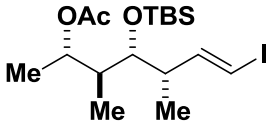
calculated for $C_{16}H_{32}O_4Si$ $(M+Na)^+$:	339.1968
found:	339.1966

IR (thin film, cm^{-1})

2956, 2931, 2887, 2858, 2710, 1732, 1464, 1373, 1244, 1090, 1030, 949, 839, 775, 673.



Vinyl iodide 3.34. To a slurry of $CrCl_2$ (3.81 g, 31.5 mmol, 15 eq) in THF (19 mL) was added dropwise via cannulation aldehyde **3.33** (0.665 g, 2.10 mmol, 1 eq) and iodoform (4.14 g, 10.5 mmol, 5 eq) in dioxane:THF 2:1 (36 mL). After stirring at 23 °C for 5 minutes, the reaction was poured into saturated aqueous $NaHCO_3$ (250 mL) and diluted with Et_2O (250 mL). The green mixture was filtered through celite, washing with Et_2O (100 mL) and the filtrate layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; 0 → 10% EtOAc/hexanes) provided the title compound **3.34** as a pale yellow oil (0.450 g, 1.02 mmol, 49%).



3.34

TLC (25% EtOAc/hexanes)

R_f = 0.60, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 6.56 (dd, *J* = 7.6, 14.4 Hz, 1H), 6.20 (d, *J* = 14.4 Hz, 1H), 5.07 (p, *J* = 6.4 Hz, 1H), 3.67 (dd, *J* = 4.4, 6.0 Hz, 1H), 2.54-2.45 (m, 1H), 1.97 (s, 3H), 1.96-1.87 (m, 1H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C NMR (100 MHz, acetone-d_6)

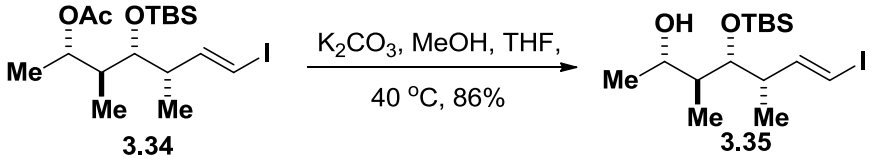
δ 170.2, 151.3, 76.7, 76.0, 71.5, 44.2, 43.2, 26.5, 21.2, 18.9, 16.5, 14.2, 11.2, -3.7, -3.9.

HRMS (ESI+)

calculated for $C_{17}H_{33}O_3SiI$ $(M+Na)^+$:	463.1141
found:	463.1142

IR (thin film, cm^{-1})

2956, 2931, 2885, 2858, 1732, 1705, 1462, 1373, 1246, 1063, 951, 837, 775, 669.

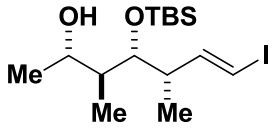


3.34 **3.35**

Secondary alcohol 3.35

To vinyl iodide **3.34** (0.450 g, 1.02 mmol, 1 eq) in MeOH:THF 2:1 (27 mL) was added K_2CO_3 (1.41 g, 10.2 mmol, 10 eq). The reaction was stirred at 40 °C for 2.5 hours and then the reaction was poured into water (200 mL) and diluted with Et_2O (200 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 200 mL). The combined organic extracts were

dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 10% EtOAc/hexanes) to provide secondary alcohol **3.35** (0.350 g, 0.879 mmol, 86%).



3.35

TLC (25% EtOAc/hexanes)

R_f = 0.50, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.59 (dd, *J* = 8.5, 14.0 Hz, 1H), 6.16 (dd, *J* = 1.0, 14.0 Hz, 1H), 3.89 (app t, *J* = 5.0 Hz, 1H), 3.80-3.73 (m, 1H), 3.52 (d, *J* = 4.5 Hz, 1H), 2.56-2.49 (m, 1H), 1.76-1.69 (m, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, acetone-d_6)

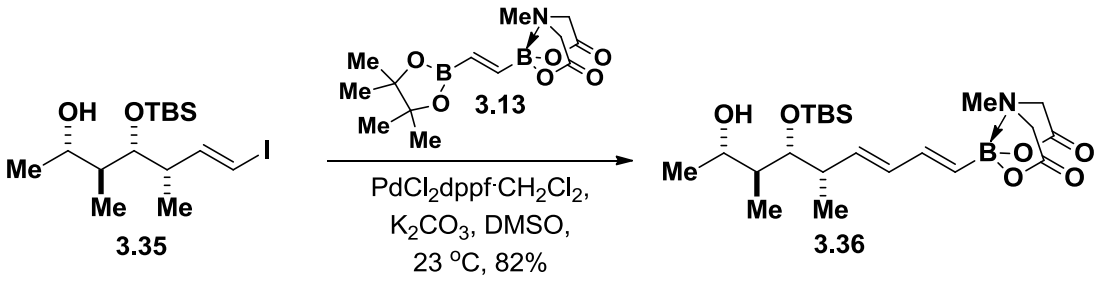
δ 151.8, 76.6, 75.3, 68.3, 46.8, 44.2, 26.4, 21.2, 18.7, 15.1, 11.5, -3.9.

HRMS (ESI+)

calculated for $C_{15}H_{31}O_2SiI$ $(M+H)^+$:	399.1216
found:	399.1235

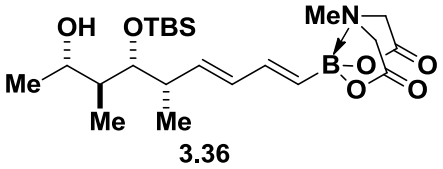
IR (thin film, cm^{-1})

3431, 1958, 2929, 2885, 2858, 1605, 1462, 1383, 1255, 1188, 1082, 1022, 955, 837, 775, 669.



Dienyl MIDA boronate 3.36

A 40 mL I-Chem vial equipped with a stir bar was charged with vinyl iodide **3.35** (0.350 g, 0.879 mmol, 1 eq) and bisborylated compound **3.13**[4,30] (0.241 g, 0.791 mmol, 0.9 eq), sealed under argon, and was taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.037 g, 0.046 mmol, 5 mol%) and K_3PO_4 as a finely ground powder (0.560 g, 2.64 mmol, 3 eq) were added, followed by DMSO (29 mL). The reaction was sealed with a PTFE-lined cap, removed from the glovebox, and stirred at 23 °C for 24 hours. The solution was then diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (70 mL). The filtrate was washed with water (3 x 50 mL) and brine (1 x 50 mL) and the combined aqueous layers were extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in acetone (10 mL), celite was added to the solution, and the mixture was concentrated *in vacuo*. The resulting powder was dry-loaded on top of a flash column and purified (SiO_2; 50% EtOAc/hexanes → EtOAc → 10% MeCN:EtOAc) to yield the desired product **3.36** (0.293 g, 0.646 mmol, 82%) as a pale yellow solid.



TLC (EtOAc)

R_f = 0.30, stained by $KMnO_4$.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.53 (dd, *J* = 10.0, 17.0 Hz, 1H), 6.11 (dd, *J* = 10.5, 15.5 Hz, 1H), 5.81 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.55 (d, *J* = 17.0 Hz, 1H), 4.20 (dd, *J* = 2.0, 17.0 Hz, 2H), 4.00 (d, *J* = 16.5 Hz, 2H), 3.88 (t, *J* = 5.5 Hz, 1H), 3.81-3.75 (m, 1H), 3.47 (d, *J* = 4.0 Hz, 1H), 2.98 (s,

3H), 2.52-2.45 (m, 1H), 1.76-1.69 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (100 MHz, acetone-d_6)

δ 169.1, 143.8, 140.7, 132.4, 77.7, 68.4, 62.2, 47.3, 47.1, 40.9, 26.4, 21.3, 18.8, 16.6, 11.7, -3.8, -3.9.

^{11}B NMR (128 MHz, acetone-d_6)

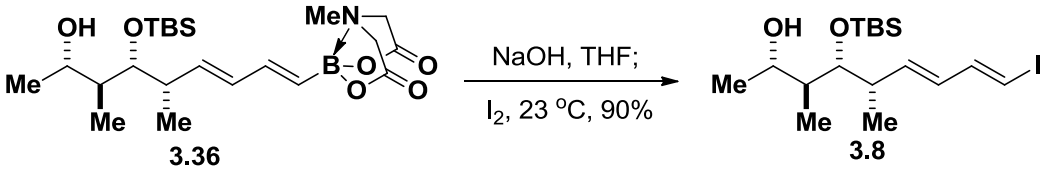
δ 11.3.

HRMS (EI+)

calculated for $C_{22}H_{40}O_6NSiB$ $(M)^+$:	453.27180
found:	453.27235

IR (thin film, cm^{-1})

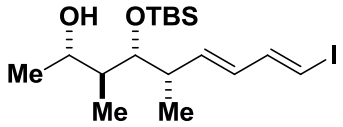
3502, 2960, 2931, 2894, 2858, 1764, 1701, 1645, 1604, 1462, 1338, 1292, 1251, 1120, 1084, 1006, 837, 775.



Dienyl iodide 3.8

To dienyl MIDA boronate **3.36** (10 mg, 0.0221 mmol, 1 eq) in THF (0.060 mL) was added 3 M aqueous NaOH (0.037 mL, 0.110 mmol, 5 eq). The reaction was stirred at 23 °C for 10 minutes, then I_2 (11.2 mg, 0.044 mmol, 2 eq) in THF (0.220 mL) was added dropwise over 5 minutes. The reaction was stirred at 23 °C for 2 hours and then was quenched with 0.5 M pH 7 phosphate buffer (1 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with saturated $Na_2S_2O_3$ (10 mL). The aqueous layer was back-extracted with Et_2O (10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was pushed through a plug

of silica gel with 20% EtOAc/hexanes to give dienyl iodide **3.8** (8.4 mg, 0.0198 mmol, 90 %) as a pale yellow oil.



3.8

TLC (25% EtOAc/hexanes)

R_f = 0.72, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.04 (dd, *J* = 10.5, 14.5 Hz, 1H), 6.37 (d, *J* = 14.5 Hz, 1H), 6.07 (dd, *J* = 10.5, 15.5 Hz, 1H), 5.86 (dd, *J* = 8.0, 15.5 Hz, 1H), 3.88 (t, *J* = 5.0 Hz, 1H), 3.78-3.74 (m, 1H), 3.44 (d, *J* = 4.5 Hz, 1H), 2.46 (app. sextet, *J* = 7.0 Hz, 1H), 1.74-1.69 (m, 1H), 1.07 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.85 (d, *J* = 7.0, 3H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

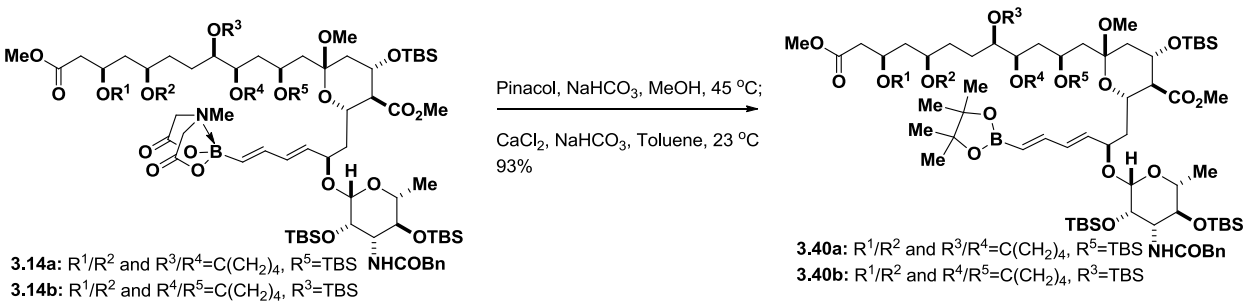
δ 146.7, 141.4, 130.1, 77.4, 77.3, 68.5, 47.2, 40.8, 26.4, 26.3, 21.4, 18.8, 16.4, 11.7, -3.8, -3.9.

HRMS (ESI+)

calculated for $C_{17}H_{33}O_2SiI$ $(M+Na)^+$:	447.1192
found:	447.1172

IR (thin film, cm^{-1})

3452, 2956, 2929, 2856, 1639, 1462, 1381, 1362, 1254, 1064, 1004, 983, 837, 775.

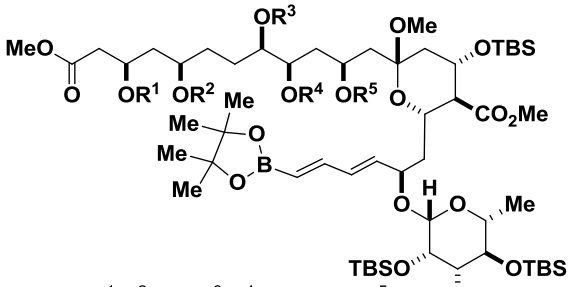


3.14a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS **NHCOBn**
3.14b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

3.40a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS **NHCOBn**
3.40b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

Dienyl pinacolboronic ester 3.40

A 20-mL I-Chem vial was charged with dienyl MIDA boronate **3.14** (0.050 g, 0.0315 mmol, 1 eq), pinacol (4.5 mg, 0.0378 mmol, 1.2 eq), solid $NaHCO_3$ (13.2 mg, 0.158 mmol, 5 eq) and MeOH (0.630 mL) was then added. The reaction was stirred at 45 °C for 3 hours and then was concentrated *in vacuo* and finely ground anhydrous $CaCl_2$ (7.0 mg, 0.063 mmol, 2 eq), solid $NaHCO_3$ (5.3 mg, 0.063 mmol, 2 eq), and toluene (0.925 mL) were added to the resulting residue. The mixture was stirred at 23 °C for 45 minutes, filtered through a pad of celite with toluene (25 mL) and concentrated to yield **3.40** (0.046 g, 0.0295 mmol, 93%) as a white solid. The product was used directly in the next reaction without further purification. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



3.40a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS **NHCOBn**
3.40b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

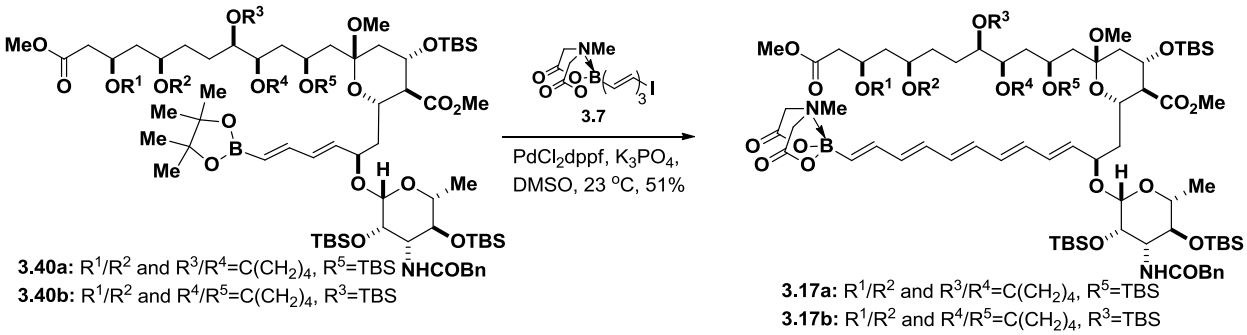
TLC (EtOAc)

R_f = 0.80, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.35-7.11 (m, 10H), 6.96 (dd, *J* = 9.5, 17.5 Hz, 1H), 6.95 (dd, *J* = 10.0, 17.5 Hz, 1H), 6.39-6.33 (m, 2H), 5.82 (dd, *J* = 7.5, 15.5 Hz, 2H), 5.49 (dd, *J* = 3.5, 17.5 Hz, 2H), 4.64 (s, 1H), 4.62 (s, 1H), 4.42-4.38 (m, 2H), 4.28-4.14 (m, 4H), 4.02-3.98 (m, 2H), 3.96-3.89 (m, 2H), 3.80-3.72 (m, 4H), 3.69 (s, 3H), 3.68 (s, 3H), 3.67-3.56 (m, 10H), 3.61 (s, 3H), 3.57 (s, 3H), 3.37 (q, *J* = 7.0 Hz, 2H), 3.15 (s, 3H), 3.11 (s, 3H), 2.42-2.38 (m, 4H), 2.26-

2.14 (m, 6H), 1.98-1.89 (m, 8H), 1.84-1.49 (m, 44H), 1.36-1.33 (m, 8H), 1.24 (s, 12H), 1.19 (d, *J* = 6.5 Hz, 6H), 1.16 (s, 12H), 0.93-0.84 (m, 72H), 0.15-0.00 (m, 48H).

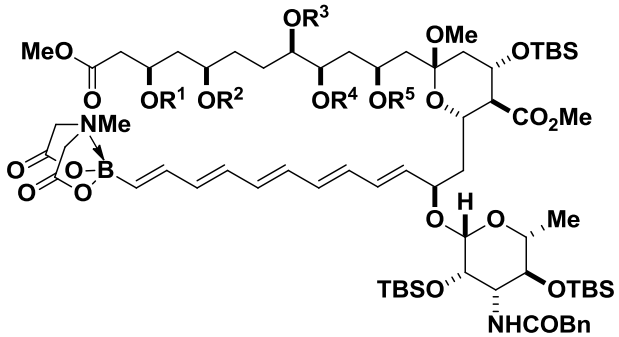


3.40a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS
3.40b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

3.17a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS
3.17b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

Pentaenyl MIDA Boronate 3.17

A 7 mL Wheaton vial equipped with a stir bar was charged with pinacolboronic ester **3.40** (0.014 g, 0.00899 mmol, 1 eq) and trienyl iodide **3.7**[22] (4.9 mg, 0.0135 mmol, 1.5 eq), sealed under argon, and taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (1.5 mg, 0.00179 mmol, 20 mol%) and K_3PO_4 as a finely ground powder (11.4 mg, 0.0539 mmol, 6 eq) were added, followed by DMSO (0.450 mL). The reaction was sealed with a PTFE-lined cap, removed from the glove box and stirred at 45 °C for 12.5 hours. The solution was diluted with EtOAc (5 mL) and filtered through a pad of silica gel, washing with EtOAc (25 mL). The filtrate was washed with water (3 x 25 mL) and brine (25 mL). The combined aqueous layers were back-extracted with EtOAc (1 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 50% → 100% EtOAc/hexanes) to furnish pentenyl MIDA boronate **3.17** (7.6 mg, 0.00457 mmol, 51%) as a white solid. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



3.17a: R^1/R^2 and R^3/R^4=$C(CH_2)_4$, R^5=TBS
3.17b: R^1/R^2 and R^4/R^5=$C(CH_2)_4$, R^3=TBS

TLC (EtOAc)

R_f = 0.31, stained by anisaldehyde.

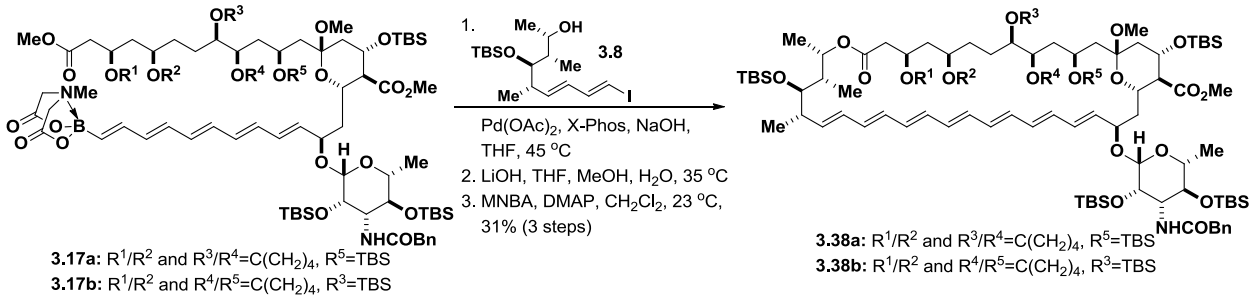
^{1}H NMR (500 MHz, acetone-d_6)

δ 7.32-7.28 (m, 8H), 7.25-7.22 (m, 2H), 6.62 (dd, *J* = 10.0, 17.5 Hz, 2H), 6.40-6.34 (m, 16H), 5.72 (d, *J* = 17.0 Hz, 2H), 5.69-5.61 (m, 2H), 4.62 (s, 1H), 4.60 (s, 1H), 4.40-4.36 (m, 2H), 4.27-4.14 (m, 10H), 4.07-3.98 (m, 6H), 3.94-3.91 (m, 3H), 3.88-3.81 (m, 1H), 3.80-3.71 (m, 4H), 3.69 (s, 3H), 3.73 (s, 3H), 3.64-3.54 (m, 8H), 3.61 (s, 3H), 3.56 (s, 3H), 3.38-3.34 (m, 2H), 3.15 (s, 3H), 3.10 (s, 3H), 2.99 (s, 6H), 2.42 (d, *J* = 7.0 Hz, 4H), 2.28-2.12 (m, 6H), 1.98-1.89 (m, 8H), 1.85-1.71 (m, 10H), 1.69-1.48 (m, 32H), 1.40-1.25 (m, 6H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 0.92-0.84 (m, 72H), 0.15- -0.02 (m, 48H).

HRMS (ESI)

Calculated for $C_{86}H_{143}BN_2O_{21}Si_4$ $(M + Na)^+$: 1685.9251

Found: 1685.9270

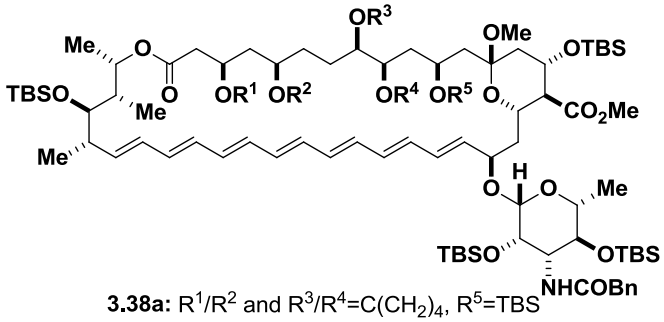


Amphotericin B Macrolactone 3.38

A solution of the palladium catalyst was prepared as follows: To a 1.5 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl ligand (1.3 mg, 0.0027 mmol) was added a solution of $Pd(OAc)_2$ in toluene (0.0073 M , 0.188 mL, 0.0014 mmol). The vial was sealed with a PTFE-lined cap and maintained at 23 ^{o}C with stirring for 15 minutes.

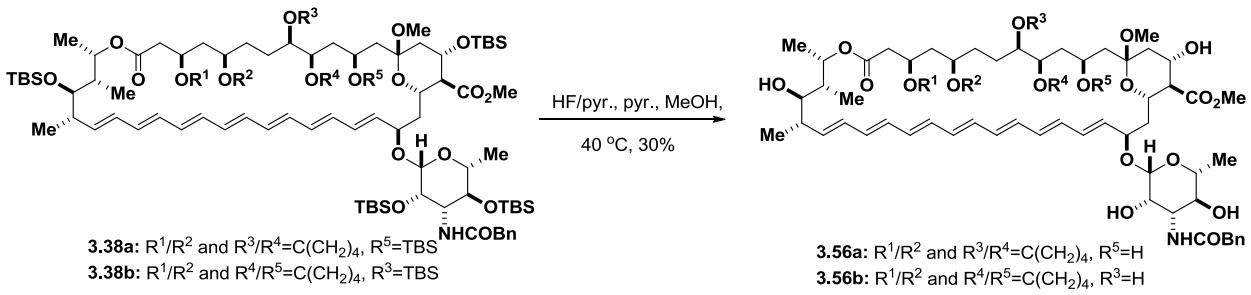
This catalyst solution was then utilized in the following procedure: To pentaenyl MIDA boronate **3.17** (6.0 mg, 0.0036 mmol, 1.5 eq) and dienyl iodide **3.8** (1.0 mg, 0.0024 mmol, 1.5 eq) was added the catalyst stock solution described above (0.033 mL, 0.00024 mmol Pd, 10 mol%). The resulting mixture was sealed with a teflon-lined septum cap and 1M aqueous NaOH (0.024 mL,

0.024 mmol, 10 eq) was added. The reaction was stirred at 23 °C for 30 minutes then at 45 °C for 4 hours. The reaction was diluted with EtOAc (10 mL), filtered through a short plug of silica gel with EtOAc, and concentrated. The residue was taken up in THF:MeOH:H_2O 3:1:1 (0.370 mL), LiOH (7.8 mg, 0.186 mmol, 78 eq) was added and the vial was sealed under argon. The reaction was stirred at 35 °C for 1 hour and was then diluted with EtOAc (10 mL) and was poured into water (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (0.6 mL) and was added dropwise over 4 hours to a solution of MNBA (1.1 mg, 0.0032 mmol, 1.3 eq) and DMAP (0.8 mg, 0.0064 mmol, 2.6 eq) in CH_2Cl_2 (0.97 mL). The reaction was stirred an additional 1.5 hours, cooled to 0 °C, and quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 5% → 15% EtOAc/hexanes) to yield macrolactone **3.38** (1.3 mg, 0.00073 mmol, 31% over 3 steps) as a yellow solid. The product was isolated as a 1:1 mixture of 1,2- and 1,3-ketal constitutional isomers.



3.38a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=TBS
3.38b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=TBS

^{1}H NMR and HRMS analysis of **3.38** were fully consistent with the data reported above from the global protection of amphotericin B (**3.10**).

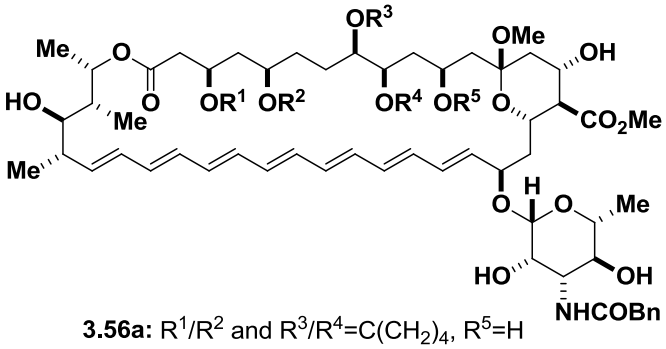


3.38a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=TBS
3.38b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=TBS

3.56a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=H
3.56b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=H

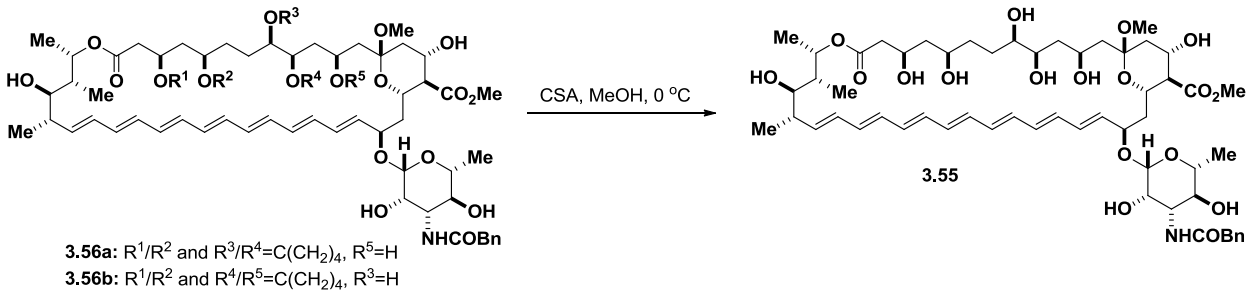
Bisketal 3.56

To macrolactone **3.38** (20 mg, 0.0112 mmol, 1 eq) in MeOH (0.165 mL) at 0 °C was added 0.122 mL of HF·4 pyridine complex (prepared by adding 0.342 mL 70% HF·pyridine complex to 2 mL pyridine at 0 °C). The resulting reaction mixture was heated to 40 °C and stirred for 33 hours. The reaction was poured into saturated aqueous $NaHCO_3$ (5 mL), extracted with EtOAc (3 x 10 mL), and dried over Na_2SO_4. The solution was concentrated and purified by flash chromatography (SiO_2; 2% → 10% MeOH/DCM) to furnish **3.56** (4.0 mg, 0.00336 mmol, 30%) as a yellow solid. HPLC analysis (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in water over 30 minutes) of the reaction mixture matched the known product standard.



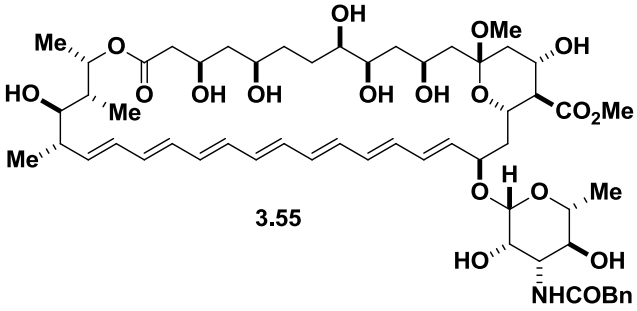
3.56a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=H
3.56b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=H

^{1}H NMR, HPLC, and MS analysis of **3.56** were fully consistent with the data reported above from the ketalization of amphotericin B.

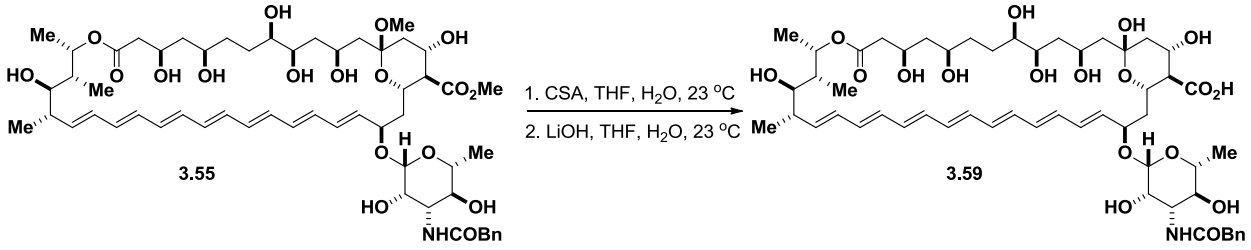


Methyl Ketal 3.55

To bisketal **3.56** (2.0 mg, 0.00166 mmol, 1 eq) in MeOH (0.170 mL) at 0 °C was added CSA (0.8 mg, 0.00344 mmol, 2 eq). The reaction was stirred at 0 °C for 3 hours and quenched with Et_3N (0.050 mL) and analyzed by analytical HPLC (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 30 → 95% MeCN in water over 30 minutes).



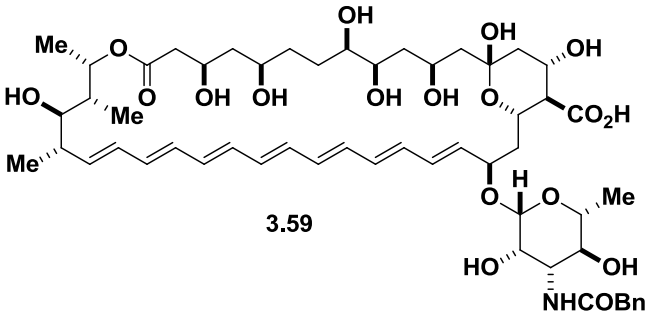
HPLC analysis of the reaction mixture matched known product standard **3.55** from above.



N-phenylacyl AmB 3.59

To methyl ketal **3.55** (10.0 mg, 0.00934 mmol, 1 eq) in THF:H_2O 2:1 (0.9 mL) was added CSA (0.5 mg, 0.00233 mmol, 0.25 eq). The reaction was stirred at 23 °C for 16 hours and quenched with the addition of solid $NaHCO_3$ (10 mg). The mixture was filtered through celite, concentrated *in vacuo*, and analyzed by analytical HPLC (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in water over 30 minutes, t_R = 22.1 min). The material was taken into the next reaction without purification. To the crude material (~0.00934

mmol, 1 eq) in THF:H_2O 2:1 (0.315 mL) at 0 °C was added 1M aqueous LiOH (0.094 mL, 0.094 mmol, 10 eq) and the reaction was allowed to warm to 23 °C. The reaction was stirred at 23 °C for 2 hours, concentrated, filtered through celite with MeOH, and analyzed by analytical HPLC (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in 1% formic acid over 30 minutes).



3.59

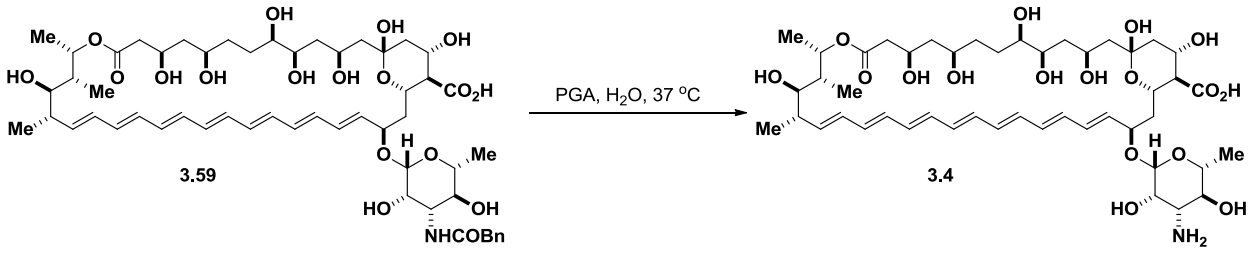
HPLC analysis of the reaction mixture matched the known product standard (see procedure for formation of **3.54** above).

Purification of Penicillin G Amidase

Penicillin G amidase (PGA) was purchased from Clea Technologies (Delft, The Netherlands) as a crude solution and was purified within one month of use using the following procedure. 2.5 mL of the crude PGA solution and 1.6 mL of saturated aqueous ammonium sulfate were each added to twelve individual 15 mL centrifuge tubes. The tubes were inverted several times to mix and were then left to stand for 5 minutes. Subsequently, the PGA/$(NH_4)_2SO_4$ solutions were centrifuged at 4500xg for 20 minutes at 23 °C and after centrifugation the supernatants were transferred to fresh 15 mL centrifuge tubes and the brown pellets were discarded. To each supernatant was added 6 mL of saturated $(NH_4)_2SO_4$ and the tubes were inverted several times to mix and then let stand for 5 minutes. Next, the samples were again centrifuged at 4500xg for 20 minutes at 23 °C. The supernatants were discarded and the pellets were dissolved in 1.1M $(NH_4)_2SO_4$ 50 mM TRIS (pH 7.5). The samples were then purified using a 15 x 5 cm phenyl sepharose 6 (Sigma-Aldrich, St. Louis, MO) gel column. The sepharose column was pre-equilibrated with 2 column volumes of 1.1M $(NH_4)_2SO_4$ 50 mM TRIS (pH 7.5) and the samples were then loaded. The protein was then eluted with one column volume each of 50 mM TRIS (pH 7.5) buffer of decreasing ionic strength in the order: 1.1M $(NH_4)_2SO_4$, 0.9M $(NH_4)_2SO_4$, 0.7M $(NH_4)_2SO_4$, 0.45M $(NH_4)_2SO_4$, 0.25M $(NH_4)_2SO_4$ and then two column volumes of MilliQ

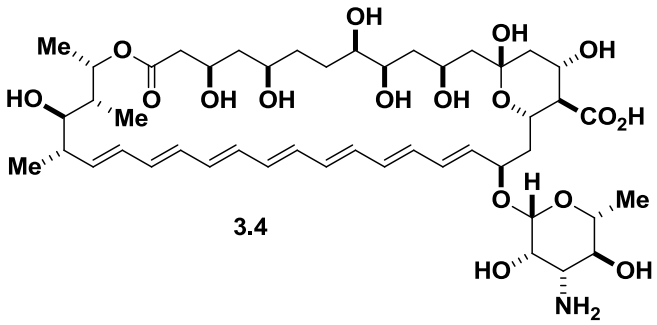
H_2O. Fractions were collected beginning with the 0.25M $(NH_4)_2SO_4$ eluent and were analyzed for the presence of PGA using SDS-PAGE.

The loading buffer was prepared by dissolving 20 mg of dithiothreitol in 500 μL Laemmli sample buffer (Bio-Rad, Hercules, CA). Then, 15 μL of each fraction and 15 μL of the loading buffer were added to individual 0.6 mL microcentrifuge tubes, mixed and then incubated at 95 °C for 5 minutes. The samples were cooled by incubating at 23 °C for 15 minutes and then 12.5 μL of each sample was loaded onto precast Mini-PROTEAN TGX (Bio-Rad) gels. The gels were run at 190V for 35 minutes using TRIS/glycine running buffer (125mM TRIS, 1.92M glycine, 0.5% SDS, pH 8.3). The gels were then stained with Brillant Blue staining solution (Sigma-Aldrich) for 30 minutes with gentle shaking. The stain was decanted and the gels were destained by three successive 30 minute destaining cycles using H_2O:MeOH:AcOH (45:45:10, v/v/v). Fractions containing PGA were then concentrated using Amicon Ultra centrifugal filter units (Sigma-Aldrich). PGA containing fractions were added to the filter units and centrifuged at 4500xg for 20 minutes at 4 °C. Once all the samples had been concentrated, the collected PGA was suspended in 12 mL MilliQ H_2O and stored at 4 °C.



AmB (3.4)

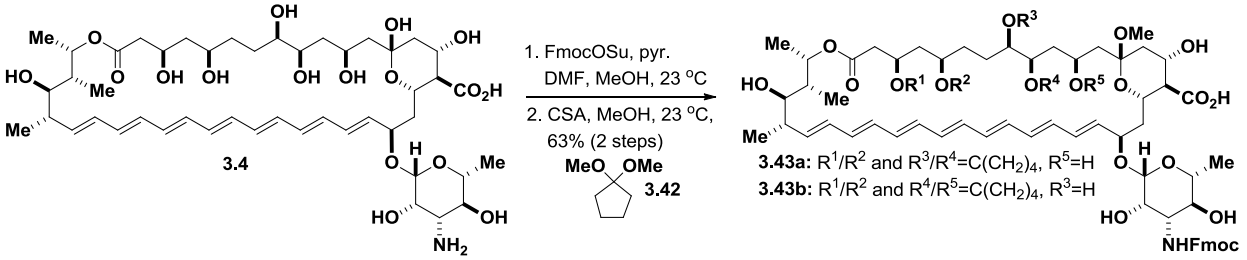
To N-phenylacyl AmB **3.59** (1.0 mg, 0.000959 mmol) was added freshly purified PGA solution (1 mL). The reaction was stirred at 37 °C for 72 hours then analyzed directly by analytical HPLC (Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 95% MeCN in 25 mM ammonium acetate over 30 minutes). The reaction had reached 80% conversion at 72 hours and the chromatogram matched the known AmB standard.



3.4

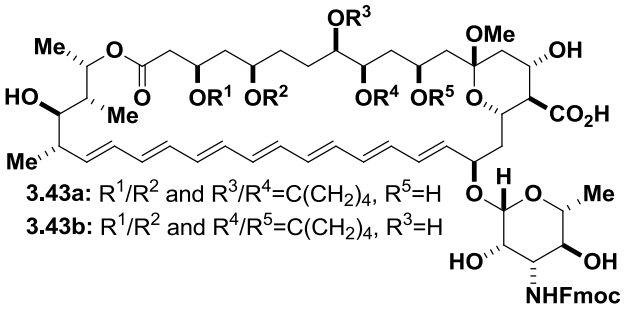
HPLC

t_R = 20.4 min; flow rate = 1.2 mL/min, Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column gradient of 5 → 65% MeCN in 25 mM ammonium acetate over 30 min. Coinjection of the reaction and AmB showed a single product peak.



Bisketal 3.43

A round bottom flask was charged with amphotericin B (1.5 g, ~55% pure, *ca.* 0.891 mmol, 1 eq) and Fmoc-succinimide (0.840 g, 2.48 mmol, 2.8 eq) which were dissolved in a mixture of DMF:MeOH 2:1 (105 mL) at 23 °C. Pyridine (0.84 mL, 10.22 mmol, 11.5 eq) was subsequently added and the reaction stirred for 12 hours. The reaction mixture was then poured into Et_2O (1.8 L) stirring at 23 °C. After stirring for 15 minutes the resulting yellow precipitate was isolated via Büchner filtration using Whatman 50 filter paper to afford a yellow solid. Two 1.5 g batches were combined and the yellow powder was suspended in MeOH (50 mL) and 1,1' dimethoxycyclopentanone[29] (15 mL). CSA (0.140 g, 0.605 mmol, 0.2 eq) was added and the reaction was stirred at 23 °C for 1 hour. Et_3N (0.200 mL, 1.43 mmol, 0.47 eq) was added and the reaction concentrated. The crude material was purified via flash chromatography (SiO_2; 1% → 10% MeOH/DCM/0.1% AcOH) to yield **3.43** (2.27g, 1.76 mmol, 60%) as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (10% MeOH/DCM/0.1% AcOH)

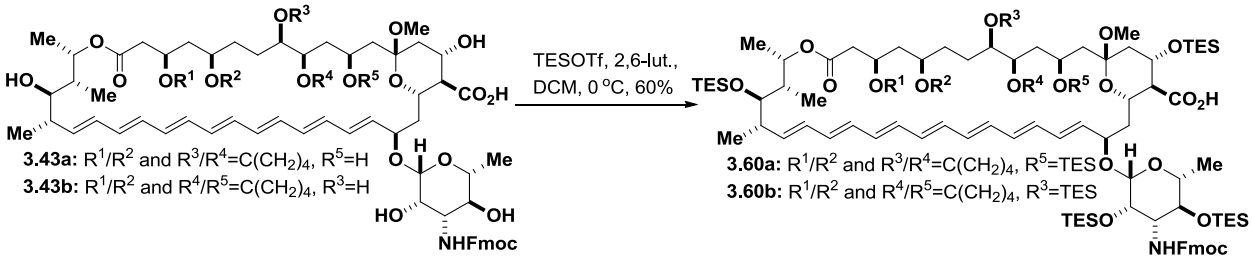
R_f = 0.39, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 6.39-6.20 (m, 12H), 5.98-5.89 (m, 1H), 5.61-5.52 (m, 1H), 5.28-5.20 (m, 1H), 4.72-4.66 (m, 1H), 4.64 (s, 1H), 4.33-4.29 (m, 2H), 4.25-4.09 (m, 4H), 3.97-3.83 (m, 4H), 3.66-3.58 (m, 3H), 3.37-3.25 (m, 5H), 3.05 (s, 3H), 2.42-2.35 (m, 2H), 2.24-2.09 (m, 4H), 1.98-1.75 (m, 9H), 1.71-1.53 (m, 14H), 1.43-1.32 (m, 4H), 1.24 (d, *J* = 5.6 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 7.2 Hz, 3H).

HRMS (ESI)

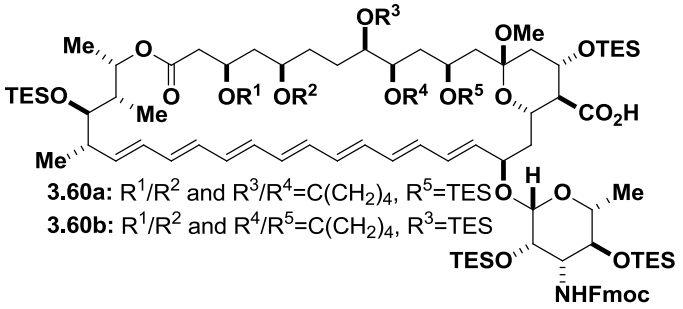
Calculated for $C_{73}H_{97}NO_{19}$ $(M + Na)^+$:	1314.6553
Found:	1314.6534



TES ether 3.60

To **3.43** (1.33 g, 1.03 mmol, 1 eq) in DCM (52 mL) and 2,6-lutidine (3.1 mL, 26.77 mmol, 26 eq) at 0 °C was added dropwise TESOTf (4.7 mL, 20.59 mmol, 20 eq). The reaction was stirred at 0 °C for 1 hour and was quenched with saturated aqueous $NaHCO_3$ (50 mL) for 10 minutes at 0 °C. The mixture was extracted with Et_2O (1 x 250 mL) and the organic layer was washed with

saturated aqueous $NaHCO_3$ (1 x 100 mL) and water (1 x 100 mL). The combined aqueous layers were extracted with Et_2O (1 x 100 mL). The combined organic layers were washed with saturated aqueous $Cu(II)SO_4$ (1 x 250 mL). The aqueous layer was extracted with Et_2O (1 x 100 mL). The combined organic layers were washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The yellow residue was purified via flash chromatography (SiO_2; 0% → 20% EtOAc/hexanes) to yield **3.60** (1.31 g, 0.703 mmol, 68%) as a yellow solid. The product was isolated as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (20% EtOAc/hexanes)

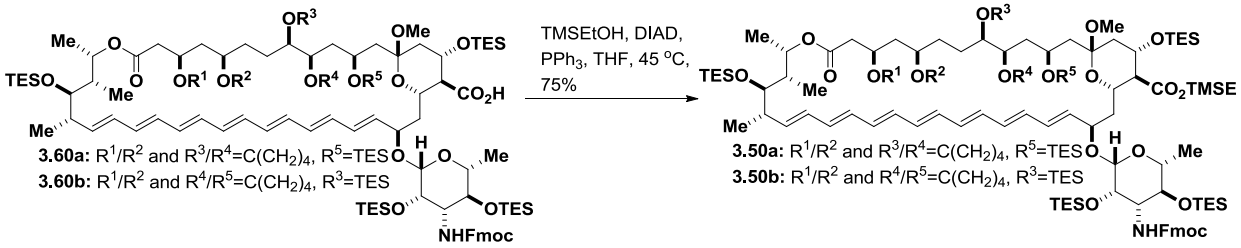
R_f = 0.30, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.0 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 6.38-6.15 (m, 12H), 5.85 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.63 (dd, *J* = 9.5, 14.5 Hz, 1H), 5.38 (d, *J* = 10.0 Hz, 1H), 4.90 (broad s, 1H), 4.69 (s, 1H), 4.56-4.47 (m, 3H), 4.35-4.28 (m, 2H), 4.24 (t, *J* = 6.0 Hz, 1H), 4.12-4.05 (m, 2H), 3.94-3.86 (m, 2H), 3.78-3.73 (m, 2H), 3.60-3.52 (m, 4H), 3.44 (t, *J* = 9.0 Hz, 1H), 3.32-3.26 (m, 1H), 3.05 (s, 3H), 2.41-2.10 (m, 6H), 1.98-1.80 (m, 8H), 1.71-1.41 (m, 16H), 1.37-1.28 (m, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.05-0.84 (m, 51H), 0.70-0.52 (m, 30H).

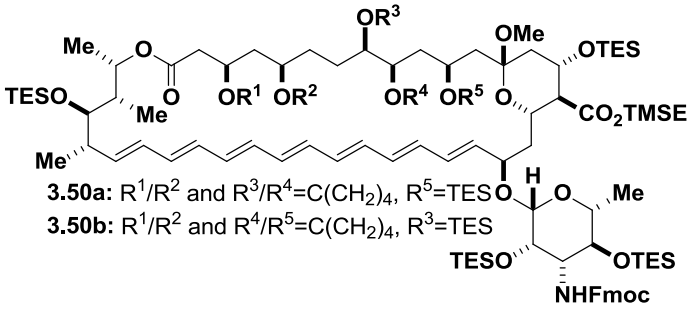
HRMS (ESI)

Calculated for $C_{102}H_{167}NO_{19}Si_5$ $(M + Na)^+$:	1885.0876
Found:	1885.0833



TMSE ester 3.50

To **3.60** (1.31 g, 0.703 mmol, 1 eq) in THF (35 mL) at 0 °C was added PPh_3 (0.461 g, 1.76 mmol, 2.5 eq), 2-(trimethylsilyl)ethanol (0.30 mL, 2.11 mmol, 3 eq), and DIAD (0.30 mL, 1.54 mmol, 2.2 eq). The reaction was stirred at 45 °C for 2 hours and was concentrated *in vacuo*. The residue was stirred with hexanes (25 mL) for 15 minutes and was filtered. The filtrate was concentrated and purified by flash chromatography (SiO_2; 0% → 15% EtOAc/hexanes) to provide **3.50** (1.19 g, 0.606 mmol, 87%) as a yellow solid. The product was isolated as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (20% EtOAc/hexanes)

R_f = 0.55, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

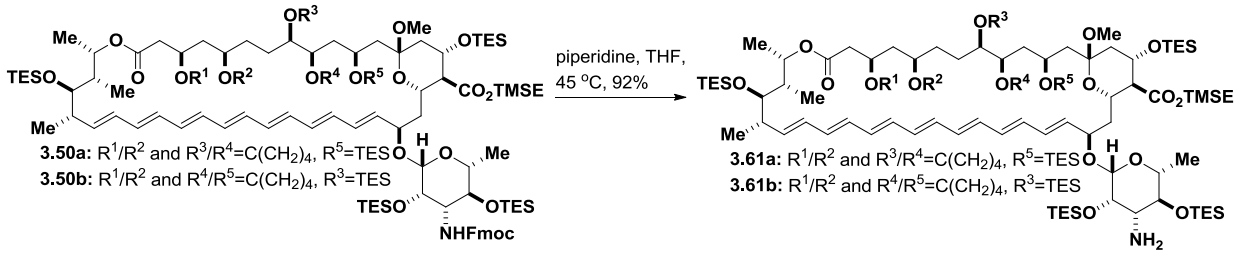
δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 6.41-6.06 (m, 12H), 5.86 (dd, *J* = 5.5, 15.0 Hz, 1H), 5.64 (dd, *J* = 9.0, 14.5 Hz, 1H), 5.36 (d, *J* = 9.5 Hz, 1H), 4.90 (broad s, 1H), 4.64 (t, *J* = 6.0 Hz, 1H), 4.52 (s, 1H), 4.47 (dd, *J* = 6.0, 10.0 Hz, 1H), 4.35-4.17 (m, 6H), 4.11-4.08 (m, 1H), 3.93-3.86 (m, 3H), 3.76-3.73 (m, 1H), 3.66-3.59 (m, 3H), 3.48-3.41 (m, 2H), 3.32-3.27 (m, 2H), 3.06 (s, 3H), 2.40-2.13 (m, 6H), 1.99-1.79 (m, 8H), 1.72-1.41 (m, 16H), 1.37-1.26 (m, 5H),

1.23 (d, *J* = 5.5 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.05-0.84 (m, 51H), 0.71-0.54 (m, 30H), 0.08 (s, 9H).

HRMS (ESI)

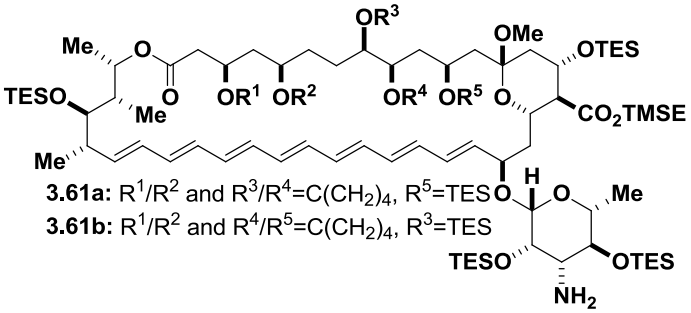
Calculated for $C_{108}H_{179}NO_{19}Si_6$ $(M + Na)^+$: 1985.1585

Found: 1985.1624



Amine 3.61

To **3.50** (1.19 g, 0.606 mmol, 1 eq) in THF (30 mL) was added piperidine (6.00 mL, 6.06 mmol, 100 eq). The reaction was stirred at 45 °C for 3 hours. The mixture was poured into water (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 0% → 15% EtOAc/hexanes) to yield **3.61** (0.958 g, 0.551 mmol, 92%) as a yellow solid. The product was isolated as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (20% EtOAc/hexanes)

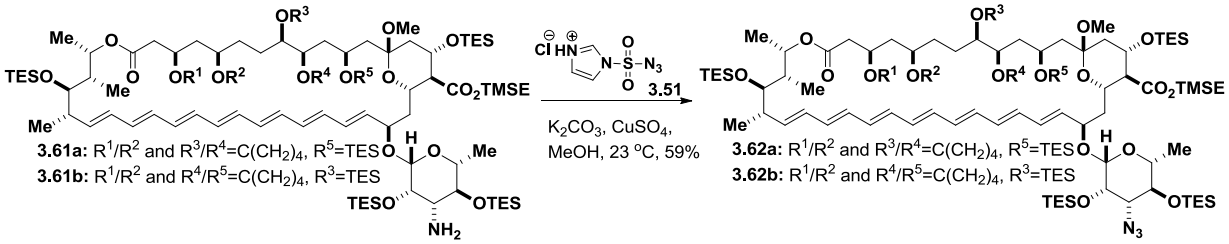
R_f = 0.07, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.41-6.15 (m, 11H), 6.08 (dd, *J* = 10.0, 15.0 Hz, 1H), 5.86 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.64 (dd, *J* = 9.0, 14.5 Hz, 1H), 4.89 (broad s, 1H), 4.66-4.60 (m, 1H), 4.40 (s, 1H), 4.32-4.22 (m, 2H), 4.16-4.08 (m, 2H), 3.93-3.86 (m, 2H), 3.79-3.74 (m, 3H), 3.62-3.51 (m, 3H), 3.28 (t, *J* = 9.0 Hz, 1H), 3.06 (s, 3H), 2.43-2.13 (m, 6H), 2.01-1.77 (m, 9H), 1.74-1.41 (m, 16H), 1.34-1.25 (m, 6H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.05-0.91 (m, 51H), 0.73-0.54 (m, 30H), 0.08 (s, 9H).

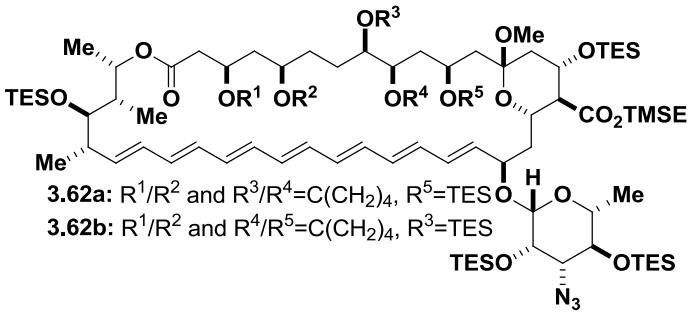
HRMS (ESI)

Calculated for $C_{93}H_{169}NO_{17}Si_6$ $(M + H)^+$:	1741.1085
Found:	1741.1091



Azide 3.62

To **3.61** (0.239 g, 0.137 mmol, 1 eq) in THF (0.685 mL) and MeOH (0.685 mL) was added K_2CO_3 (0.076 g, 0.549 mmol, 4 eq), Cu(II)SO_4·5 H_2O (1.4 mg, 0.00549 mmol, 0.04 eq), and imidazole-1-sulfuryl azide **3.51**[27] (0.069 g, 0.329 mmol, 2.4 eq). The reaction was stirred at 23 °C for 3 hours then was poured into brine (50 mL) and extracted with Et_2O (3 x 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 0% → 5% EtOAc/hexanes) to give **3.62** (0.121 g, 0.068 mmol, 50%) as a yellow solid. The product was isolated as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (20% EtOAc/hexanes)

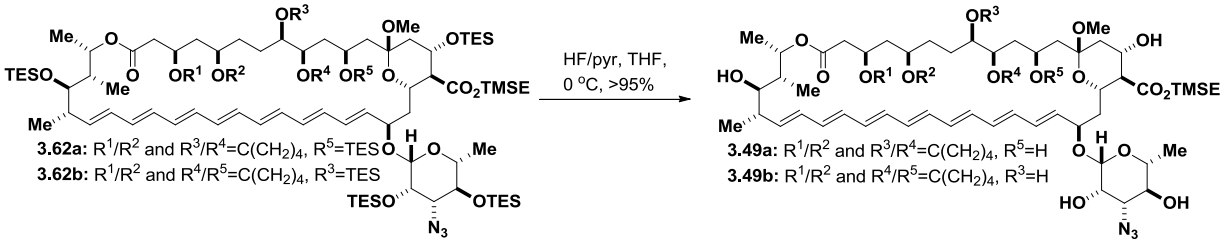
R_f = 0.23, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.42-6.15 (m, 11H), 6.08 (dd, *J* = 10.0, 14.5 Hz, 1H), 5.84 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.64 (dd, *J* = 9.0, 14.5 Hz, 1H), 4.90 (broad s, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 4.48 (s, 1H), 4.35-4.14 (m, 5H), 4.11-4.07 (m, 1H), 3.93-3.86 (m, 2H), 3.78-4.73 (m, 2H), 3.62-3.51 (m, 3H), 3.34-3.25 (m, 2H), 3.05 (s, 3H), 2.40-2.12 (m, 6H), 2.01-1.79 (m, 9H), 1.73-1.44 (m, 17H), 1.40-1.26 (m, 4H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.03-0.92 (m, 51H), 0.74-0.54 (m, 30H), 0.08 (s, 9H).

HRMS (ESI)

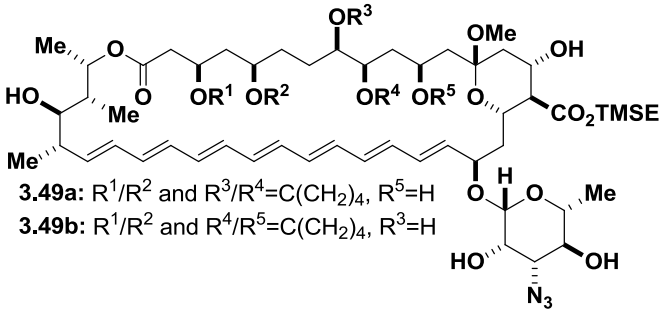
Calculated for $C_{93}H_{167}N_3O_{17}Si_6$ $(M + Na)^+$:	1789.0809
Found:	1789.0801



Bisketal 3.49

To **3.62** (0.055 g, 0.0311 mmol, 1 eq) in THF (3.75 mL) and pyridine (2.5 mL) at 0 °C was added dropwise 70% HF/pyridine (0.280 mL, 10.88 mmol, 350 eq). The reaction was allowed to warm to 23 °C and stirred for 6 hours. TMSOMe (2 mL) was added and the reaction stirred at 23 °C an additional 30 minutes. The reaction was concentrated *in vacuo* and purified by flash

chromatography (SiO_2; 5% MeOH/DCM) to yield **3.49** (0.029 g, 0.0223 mmol, 72%) as a yellow solid. The product was isolated as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



TLC (10% MeOH/DCM)

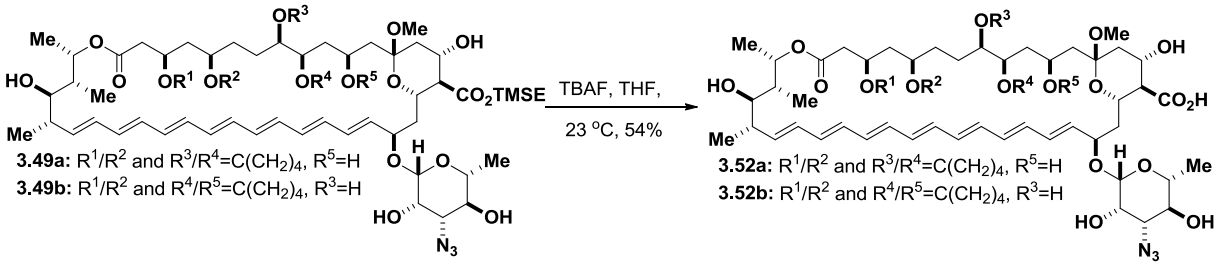
R_f = 0.46, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.39-6.14 (m, 12H), 5.90 (dd, *J* = 5.0, 15.0 Hz, 1H), 5.55 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.25-5.21 (m, 1H), 4.67-4.63 (m, 2H), 4.56 (s, 1H), 4.26-4.07 (m, 4H), 4.03-3.85 (m, 4H), 3.67-3.59 (m, 3H), 3.33-3.26 (m, 3H), 3.05 (s, 3H), 2.47-2.13 (m, 5H), 2.00-1.73 (m, 10H), 1.68-1.49 (m, 16H), 1.44-1.31 (m, 5H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.5 Hz, 3H), 0.07 (s, 9H).

HRMS (ESI)

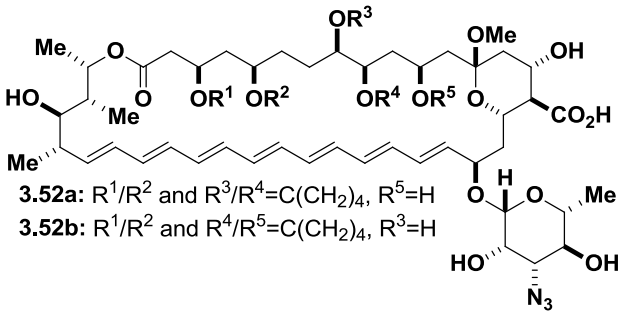
Calculated for $C_{63}H_{97}N_3O_{17}Si$ $(M + Na)^+$:	1218.6485
Found:	1218.6462



Carboxylic Acid 3.52

To **3.49** (0.022 g, 0.0184 mmol, 1 eq) in THF (2.1 mL) was added TBAF (1M in THF, 0.063 mL, 0.063 mmol, 3 eq). The reaction was stirred at 23 °C for 2 hours then MeOH (10 mL),

$CaCO_3$ (0.200 g), and DOWEX 50WX8-400 (triturated with MeOH 3 x 2 mL, 0.600 g). The reaction was stirred at 23 °C for an additional 30 minutes and filtered through celite. The solution was concentrated and purified by preparative RP-HPLC (Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm; 25 mL/min flow rate; gradient of 5 → 95% MeCN in 25 mM aqueous ammonium acetate over 23 min) to furnish **3.52** (0.011 g, 0.010 mmol, 54%) as a yellow solid. The product formed as a 2.5:1 mixture of ketal constitutional isomers. Only the major isomer characterization is reported.



HPLC

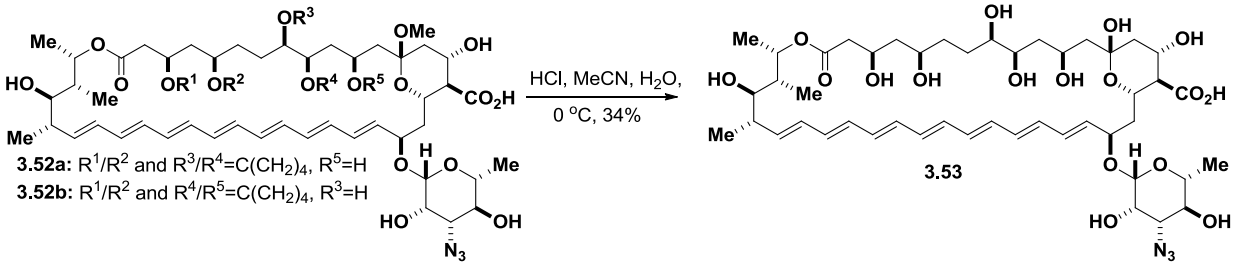
tR = 18.3 and 19.1 min; flow rate = 25 mL/min, Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm column gradient of 5 → 95% MeCN in 25 mM ammonium acetate over 23 min.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.41-6.15 (m, 12H), 5.92 (dd, *J* = 5.0, 15.0 Hz, 1H), 5.54 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.26-5.22 (m, 1H), 4.67 (s, 1H), 4.68-4.64 (m, 1H), 4.10-4.06 (m, 2H), 3.97 (d, *J* = 2.5 Hz, 1H), 3.93-3.86 (m, 2H), 3.65-3.57 (m, 4H), 3.43-3.32 (m, 3H), 3.26-3.09 (m, 4H), 3.05 (s, 3H), 2.42-2.37 (m, 3H), 2.25-2.12 (m, 4H), 1.93-1.88 (m, 3H), 1.85-1.76 (m, 6H), 1.70-1.64 (m, 5H), 1.61-1.52 (m, 7H), 1.42-1.30 (m, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H).

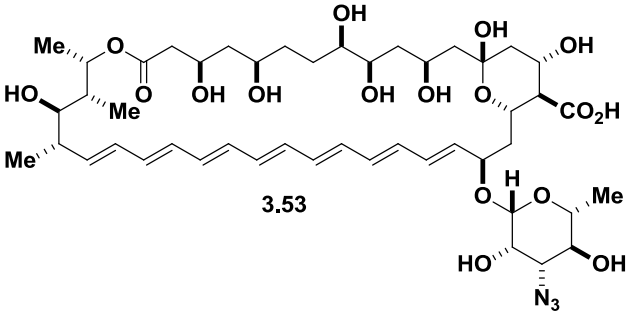
HRMS (ESI)

Calculated for $C_{58}H_{85}N_3O_{17}$ $(M + Na)^+$:	1118.5777
Found:	1118.5758



Azide 3.53

Prior to the reaction, acetyl chloride was freshly distilled from quinoline (20% v/v) and used immediately. The distillation apparatus was set up immediately before the distillation and was used only once per reaction. A 20 mL I-Chem vial was charged with acetonitrile (10 mL), water (400 μL) and acetyl chloride (100 μL). The vial was enclosed with a PTFE-lined cap and was stirred for 30 minutes at 23 °C and then was cooled to 0 °C and stirred for an additional 15 minutes. Subsequently, the cooled acetonitrile:water solution (7 mL) was added to a 40 mL I-Chem vial containing **3.52** (6.7 mg, 0.00611 mmol, 1eq). The vial was enclosed with a PTFE-lined cap and stirred at 0 °C for 30 min. The reaction was quenched with triethylamine (300 μL) and the resulting hazy solution was solubilized with the minimal amount of methanol. The crude was immediately purified by preparative RP-HPLC (Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm 25 mL/min flow rate MeCN:25 mM aqueous ammonium acetate 5% → 95% over 23 minutes) to yield the title compound **3.53** (2.0 mg, 0.00211 mmol, 34% over 2 cycles) as a yellow solid.



HPLC

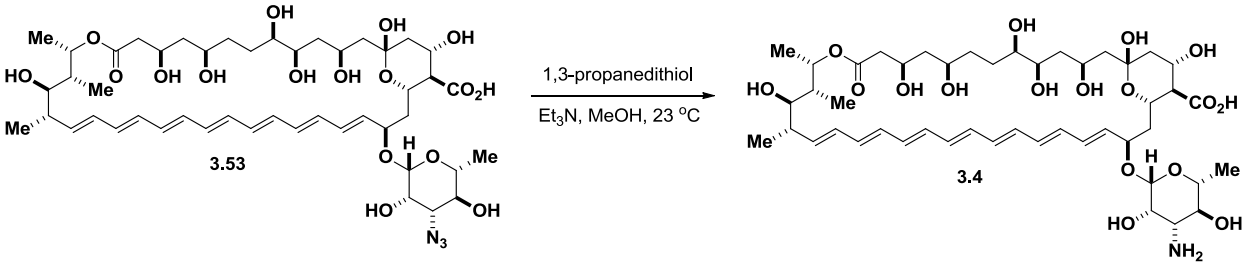
t_R = 14.5 min; flow rate = 25 mL/min, Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm column gradient of 5 → 95% MeCN in 25 mM ammonium acetate over 23 min.

^{1}H NMR (500 MHz, CD_3OD)

δ 6.48-6.10 (m, 12H), 6.02 (dd, *J* = 8.5, 15.5 Hz, 1H), 5.38-5.31 (m, 2H), 4.54 (s, 1H), 4.46-4.43 (m, 1H), 4.39-4.33 (m, 1H), 4.27-4.21 (m, 1H), 4.17 (tt, *J* = 3.5, 9.5 Hz, 1H), 3.97 (s, 1H), 3.71 (t, *J* = 5.5 Hz, 1H), 3.62 (d, *J* = 6.0 Hz, 1H), 3.49-3.44 (m, 1H), 3.20-3.15 (m, 3H), 2.40-2.35 (m, 1H), 2.31-2.13 (m, 3H), 2.08-1.95 (m, 3H), 1.92 (s, 1H), 1.81-1.68 (m, 5H), 1.59-1.53 (m, 2H), 1.51-1.31 (m, 6H), 1.26 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H).

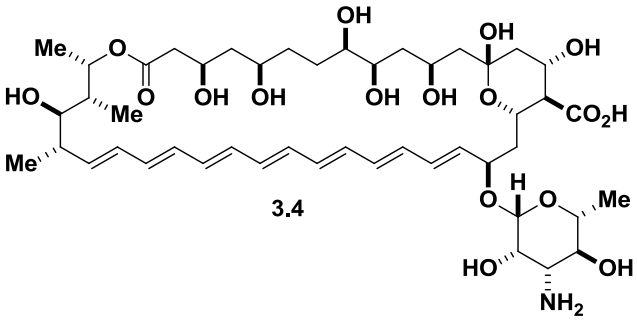
HRMS (ESI)

Calculated for $C_{47}H_{71}N_3O_{17}$ $(M + Na)^+$:	972.4681
Found:	972.4682



AmB (3.4)

To 1,3-propanedithiol (0.050 mL) in MeOH (2.65 mL) was added Et_3N (0.075 mL). 0.055 mL of this stock solution was added to azide **3.53** (0.5 mg, 0.000326 mmol, 1 eq). The reaction was stirred at 23 °C for 42 hours then analyzed directly by analytical HPLC (Agilent Zorbax C_{18} XDB 3.5 micron 4.6 x 75 mm column gradient of 5 → 95% MeCN in 25 mM ammonium acetate over 8 minutes).The reaction had reached 35% conversion at 42 hours and the chromatogram matched the known AmB standard.



HPLC

t_R = 4.7 min; flow rate = 1.2 mL/min, Agilent Zorbax C_{18} XDB 3.5 micron 4.6 x 75 mm column gradient of 5 → 95% MeCN in 25 mM ammonium acetate over 8 min. Coinjection of the reaction and AmB showed a single product peak.

HRMS (ESI)

Calculated for $C_{47}H_{73}NO_{17}$ $(M + H)^+$:	924.4957
Found:	924.5069

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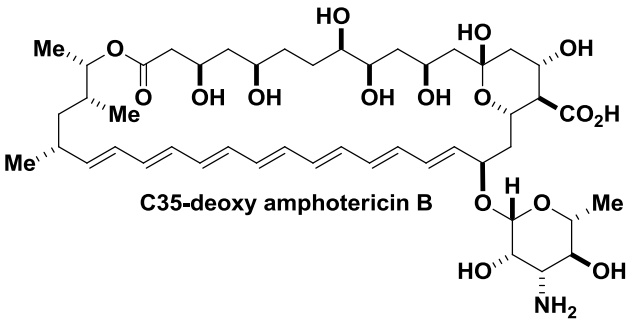
CHAPTER 4

SEMISYNTHESIS OF C35-DEOXY AMPHOTERICIN B

The ultimate goal of the total synthesis of AmB is not only to access the natural product, but to enable modular and flexible synthetic access to any of its targeted derivatives, including those lacking specific functional groups. In the previous chapter, a degradation of the natural product was described that allowed for a modeling of the endgame strategy of the total synthesis. We recognized that in this route, the western half of the molecule that contains the C35 hydroxyl group is removed allowing for the possibility of a semisynthesis of C35-deoxy amphotericin B (C35deOAmB). This chapter details the development of a synthesis of C35deOAmB in milligram quantities from the natural product AmB. While many different strategies were tried, in the end, the iterative SM cross-coupling strategy was the most effective route to this derivative. Ultimately, the main challenge of this synthesis was the development of a protecting group strategy that is compatible with the highly sensitive nature of the deoxygenated core of C35deOAmB. The discoveries made in the context of this synthesis have helped to inform the protecting group strategy for the total synthesis and will hopefully enable the synthesis of all ten deoxygenated derivatives of this interesting natural product. Dan Palacios contributed to the work in this chapter by synthesizing large quantities of **4.45** as well as optimizing the final two deprotection steps in scheme 4.11. Brice Uno synthesized building block **4.41**. Ian Dailey also made building block **4.41** and helped make large amounts of advanced intermediate **4.46**. Finally, Matt Endo and Brandon Wilcock processed material to intermediate **4.45**.



C35-deoxy amphotericin B

4-1 BACKGROUND

The leading model for the AmB ion channel, supported primarily by extensive computer modeling studies,[1] involves self-assembly into C_8-symmetric pores which allow for efflux of ions. The proposed interactions include a ring of stabilization formed by polar interactions between the C41 carboxylate and C3' amine and a hydrogen bond between the C8 and C9 hydroxyls (Figure 4.1). Additionally, AmB is approximately half the length of the lipid bilayer. In some models the C35 hydroxyl group is predicted to be crucial for a tail-to-tail dimerization between two pore complexes in order to span the bilayer.[2] In other models, AmB is proposed to form a single barrel channel, dimpling the membrane in order to span across it.[2] Following the deletion strategy used previously by Palacios et al. to test the salt bridge hypothesis,[3] removal of the C35 hydroxyl group would allow for a probe of its role in the mechanism of action of AmB.

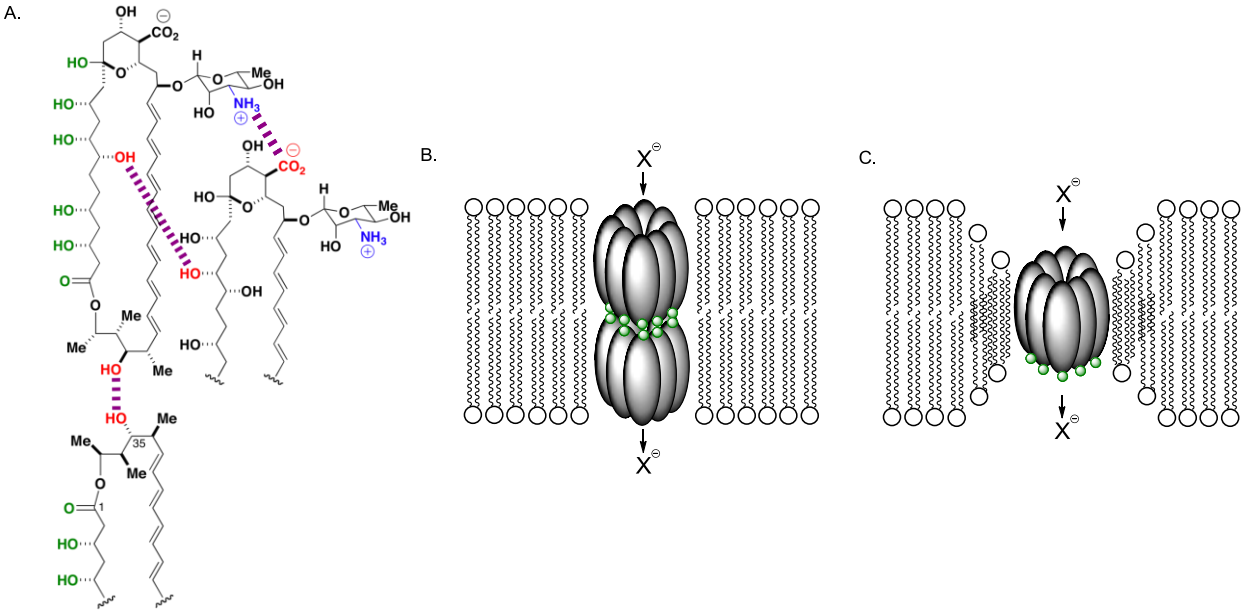


Figure 4.1. (A) The proposed critical interactions involved in AmB channel formation. (B) The double-barrel model of AmB channel formation. (C) The single-barrel model of channel formation.

A doubly modified derivative of AmB, C35-deoxy amphotericin B methyl ester, was synthesized by Carreira and coworkers in 2008.[4] It was found that this derivative was substantially less active than AmB methyl ester against yeast. This derivative also demonstrated a diminished ability to induce permeability in a liposome assay. We pursued the preparation of a singly modified derivative, C35deOAmB, to enable head-to-head studies against other singly modified derivatives of AmB in biological and biophysical assays as part of a systematic effort to probe its mechanism of action in atomistic detail.

4-2 SYNTHESIS VIA TRADITIONAL METHODS

To help simplify some of the challenges of synthesizing such a complex derivative as C35-deoxy amphotericin B, a hybrid bottom-up/top-down synthesis was employed (Figure 4.2). Rychnovsky[5] and Murata[6] have shown that a hybrid synthesis could be utilized to modify the C22-C37 fragment of amphotericin B. In particular, Murata and coworkers were able to use semisynthesis to access complex intermediate **4.2**, then using cross-coupling chemistry and Horner-Wadsworth-Emmons olefination they were able to rebuild the polyene with a fluorine label.[6a] Modifying this route to include a C35-deoxygenated building block (**4.5**) as one of the cross-coupling partners could theoretically yield C35deOAmB. The power of this hybrid approach is that the densely packed stereochemistry of the polyol and mycosamine is obtained from the natural product, leaving only the polyene and C34-C37 fragments to be set by total synthesis.

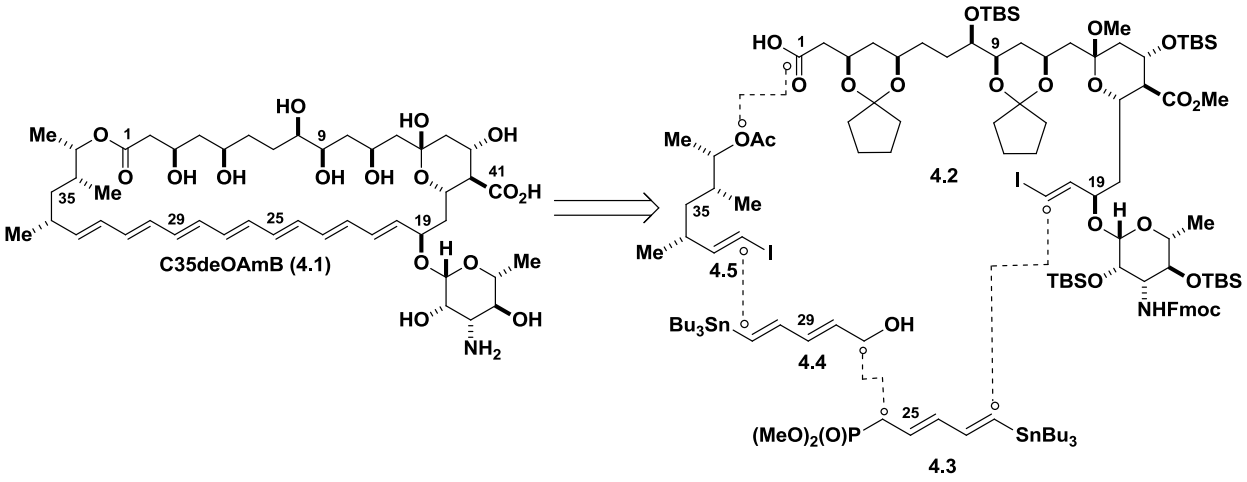
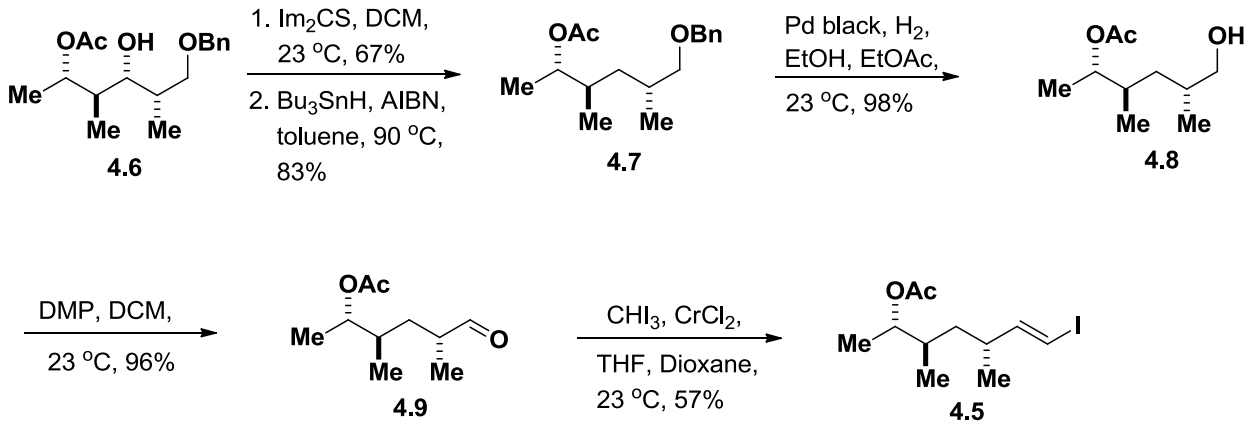


Figure 4.2. Retrosynthesis of C35deOAmB using traditional chemistry.

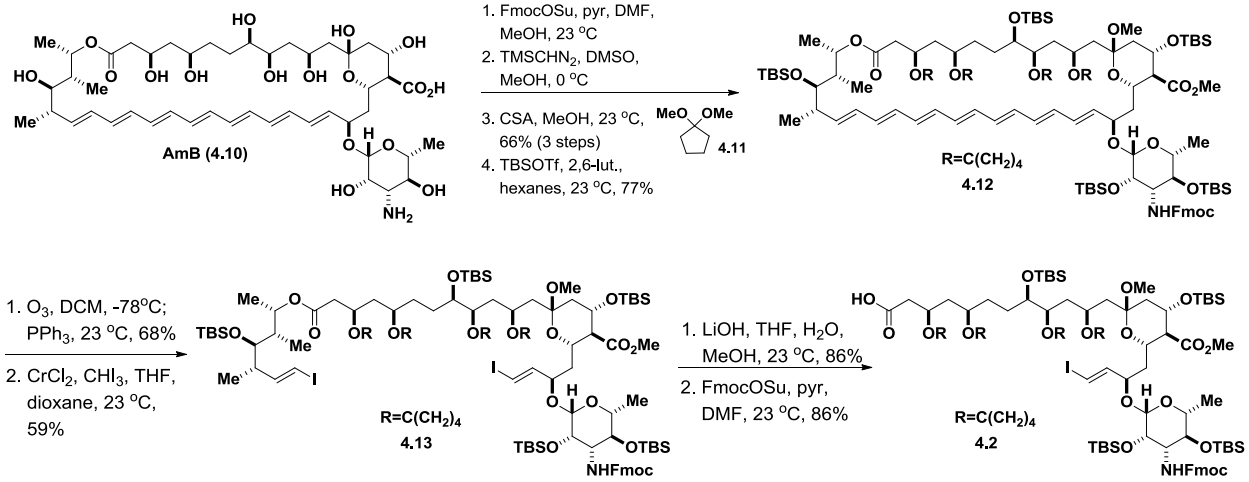
Initial efforts focused on the synthesis of C35-deoxygenated building block **4.5**. The key to a short and effective route to **4.5** (Scheme 4.1) was recognizing that all the desired stereochemistry as well as the correct protecting group strategy was contained in previously reported intermediate **4.6** derived from (*S*)-2-methyl-3-hydroxypropionate in five steps.[7] **4.6** was treated with thiocarbonyl diimidazole to install a thiocarbamate at C35, which was then subjected to Barton-McCombie deoxygenation conditions[8] providing C35-deoxygenated **4.7** in 56% yield over two steps. Subsequent debenzylation and Dess-Martin oxidation[9] generated aldehyde **4.9** in excellent yields. Finally, exposure to Takai olefination conditions[10] provided the desired vinyl

iodide **4.5**. The synthesis proceeded in a net 30% yield over five steps from known intermediate **4.6**.



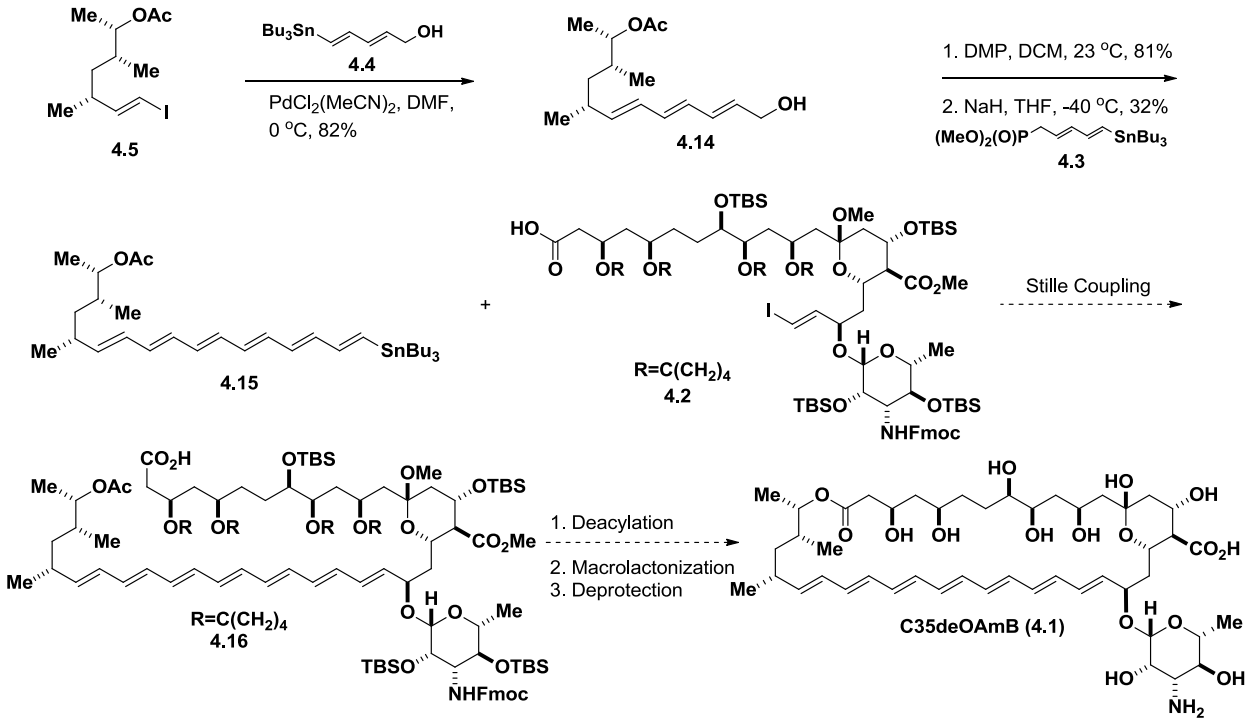
Scheme 4.1. Synthesis of C35-deoxygenated building block **4.5**.

The polyol and mycosamine-containing building block of amphotericin B was prepared via Murata's top-down degradation of the natural product (Scheme 4.2).[6a] The route began with protection of the amine and carboxylic acid as an Fmoc carbamate and a methyl ester, respectively.[11] Subsequent treatment of the polyol with 1,1'-dimethoxycyclopentanone and CSA in MeOH yielded the bis-ketal with concomitant conversion of the hemiketal at C13 to a methyl ketal. This reaction yielded a 1:1 mixture of the C8/C9 and C9/C11 protected diols that were inseparable by flash chromatography and this mixture was carried through the synthesis. The five remaining hydroxyl groups were then protected as TBS ethers yielding fully protected amphotericin B (**4.12**). The heptaene was then excised by exhaustive ozonolysis to provide the corresponding bis-aldehyde.[12] A double Takai olefination then provided bis-vinyl iodide **4.13**.[5] Lithium hydroxide-promoted cleavage of the C32-C37 fragment in the presence of the C41 methyl ester proceeded with concomitant cleavage of Fmoc. The Fmoc protecting group was then reinstalled to yield polyol building block **4.2**[6a] as a mixture of ketal constitutional isomers.



Scheme 4.2. Route to polyol building block **4.2**. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

With **4.2** and **4.5** in hand, reconstruction of the amphotericin B core commenced with a Stille coupling between diene **4.4**[13] and vinyl iodide **4.5** affording triene **4.14** in excellent yield (Scheme 4.3). Subsequent Dess-Martin oxidation cleanly provided the conjugated aldehyde in 81% yield. However, serious challenges were encountered following the oxidation. Phosphonate **4.3**[13] was made following literature procedures; however, it could only be isolated in a 30% yield over two steps. (The yield reported in the literature is 43%.) Horner-Wadsworth-Emmons reaction of the conjugated aldehyde with phosphonate **4.3** gave hexaene **4.15** as a mixture of isomers in low yield. Completion of the synthesis of C35deOAmB via this route required coupling of hexaene **4.15** with polyol building block **4.2**. Screening of standard Stille coupling conditions including $Pd_2dba_3{\cdot}CHCl_3$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $PdCl_2(MeCN)_2$ as palladium sources with additives such as Ph_3As, $i Pr_2NEt$, and CuI failed to yield any desired product and these reactions exhausted the supply of coupling partner **4.15**.[6a,14] Given the drawbacks of these conventional polyene synthesis methods (e.g. mixtures of stereoisomers, the use of toxic organotin reagents, and the apparent inefficiencies of the key Stille coupling) as well as the lack of material, we switched our efforts to developing a route based on the iterative SM cross-coupling strategy described in chapters 2 and 3.[15,16]

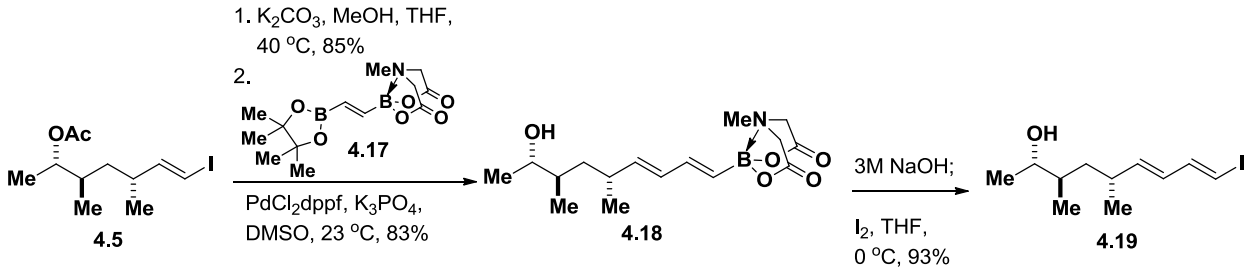


Scheme 4.3. Proposed route to C35deOAmB (**4.1**). Low yields, poor stereoselectivities and an inefficient Stille coupling between **4.15** and **4.2** led to the abandonment of this approach.

4-3 EARLY DEVELOPMENT OF THE ITERATIVE CROSS-COUPLING ROUTE

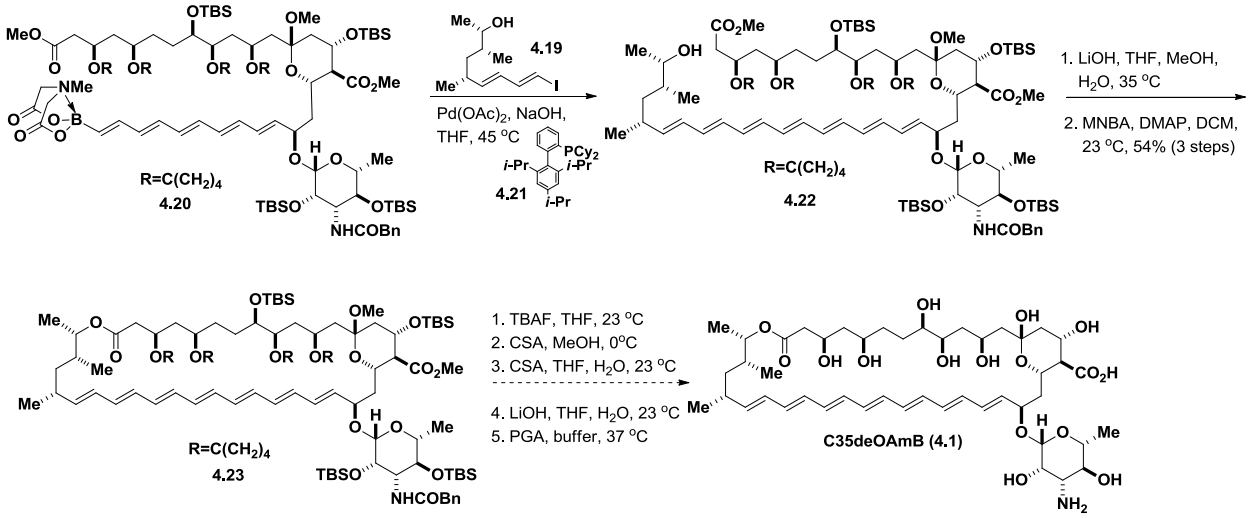
Given the success of the SM cross-coupling route for testing the endgame strategy of the total synthesis described in the previous chapter, we decided to try the same system for accessing the targeted deoxygentated derivative. In fact, since the C35 alcohol is installed late stage in the synthesis, the exact same route could be used to access pentaenyl MIDA boronate **4.20** (Scheme 4.5, see chapter 3 for its synthesis) leaving only the synthesis of deoxygenated building block **4.19** to be developed.

Beginning with vinyl iodide **4.5** from the original route, deacylation using potassium carbonate in methanol followed by SM coupling with pinacolboronic ester **4.17**[16] provided **4.18** in 83% yield (Scheme 4.4). One pot deprotection and iodine exchange then gave dienyl iodide **4.19** which was ready to be used in the coupling reaction with pentaenyl MIDA boronate **4.20**.[17,18]



Scheme 4.4. Synthesis of C35-deoxygenated building block **4.19**.

SM coupling of **4.19** to pentaenyl MIDA boronate **4.20**, selective deprotection of the methyl ester at C1, and macrolactonization[6] provided the core structure of C35deOAmB (**4.23**) in 54% over 3 steps which is an average of 81% yield per step (Scheme 4.5). Up to this point the synthesis had gone smoothly; however, the deprotections proved to be extremely challenging. Treatment with TBAF was able to provide low yields of desilylated product however, it was difficult to purify and was not reproducible. Subsequent attempts to cleave the cyclopentylidene ketals resulted in low conversion and large amounts of decomposition. The C35-deoxygenated core of AmB proved to be much more sensitive than its oxygenated counterpart to a wide variety of conditions. This observation made it clear that this protecting group strategy would not allow access to C35deOAmB in large enough quantities to test.



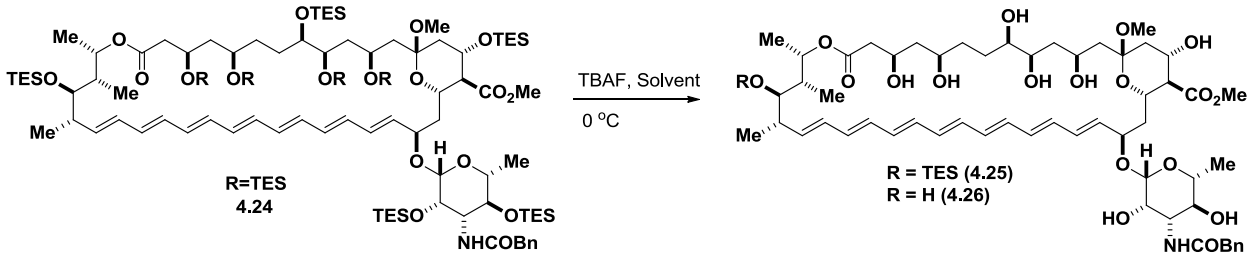
Scheme 4.5. Synthesis of the macrolactone of C35deOAmB (**4.23**). Attempts at deprotecting this intermediate were unsuccessful, giving large amounts of decomposition. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

4-4 TOP DOWN SYNTHESIS STRATEGY

Before altering the protecting group strategy for the iterative cross-coupling strategy, we decided to explore if there were other, more efficient, routes to this particular derivative. In the

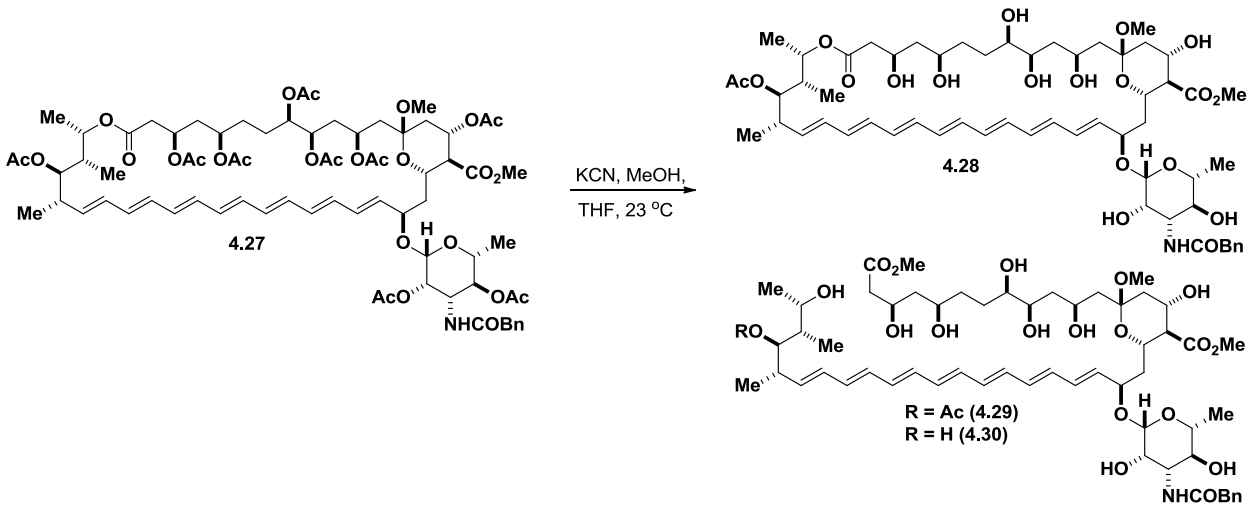
context of studying the TBS deprotection of AmB in the previous chapter, it was noted that the C35 alcohol is the last and most difficult alcohol to deprotect. Given its selective reactivity we decided to explore the possibility of performing a selective protecting group manipulation to isolate the C35 hydroxyl from the top down and a subsequent deoxygenation on AmB to remove it.

Given the difficulty of removing TBS groups from AmB, we first explored whether TES protecting groups would have the same type of deprotection selectivity. Treatment of fully protected intermediate **4.24** with TBAF in THF provided C35 monosilylated intermediate **4.25** in 20% yield with a large amount of fully desilylated material (**4.26**) recovered (Scheme 4.6). By switching to a mixed solvent system of 3:1 MeCN:THF, the yield of **4.25** was increased to 79%.



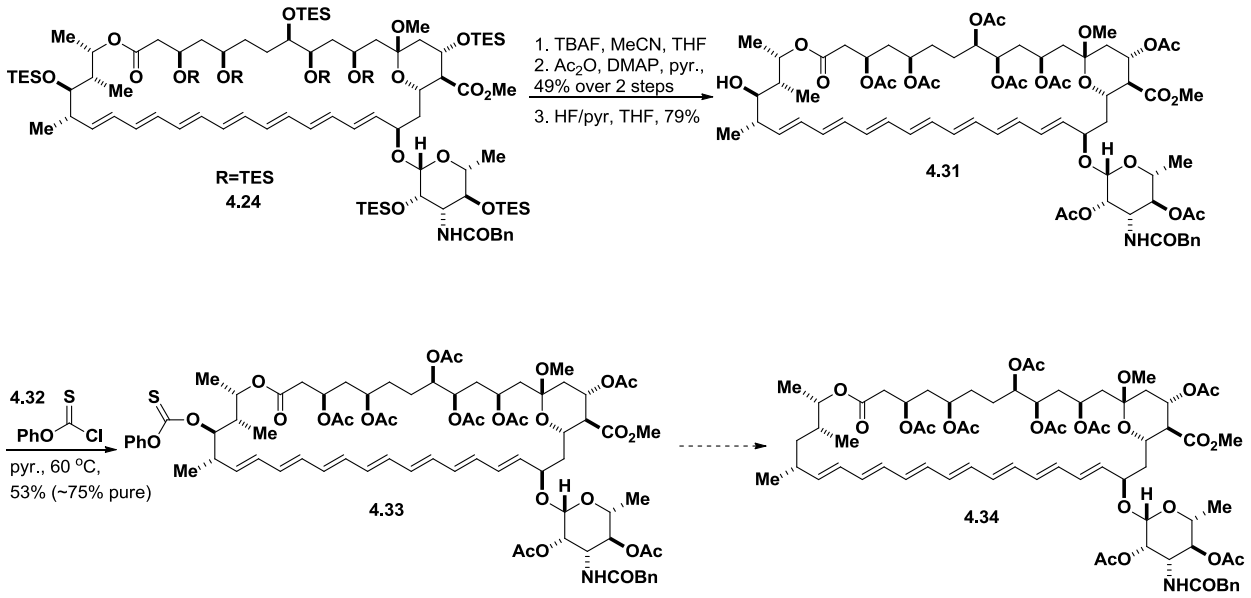
Scheme 4.6. Selective desilylation of **4.24**. Use of TBAF in THF gave fully desilylated **4.26** as the major product. By switching to 3:1 MeCN:THF, **4.25** was isolated in 79% yield.

With a selective silylation sequence targeting the C35 alcohol in place, an orthogonal protecting group for the remaining alcohols needed to be found. A simple acyl group was ideal given its compatibility with silyl groups and the wide variety of deprotection conditions available. To test whether or not it was compatible with AmB, we synthesized peracylated derivative **4.27** and explored its ability to be deacylated (Scheme 4.7). Treatment with potassium cyanide in MeOH produced three products. The major product was monoacylated **4.28** and minor amounts of open chain **4.29** and **4.30** were observed. Given the steric hinderance at the C35 alcohol, the macrolactone appears to open before this encumbered center can be deprotected. Despite these interesting results, the acyl protecting group could be used given that the C35 hydroxyl would be missing in this particular derivative of AmB.



Scheme 4.7. Model deprotection of fully acylated AmB (**4.27**).

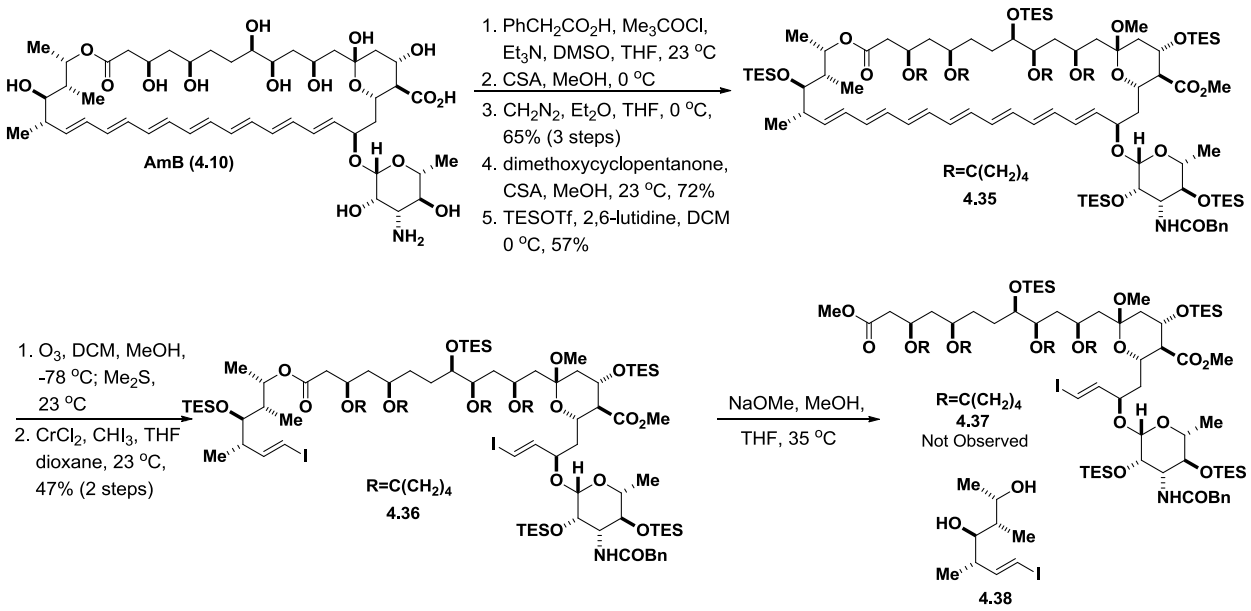
Starting from fully protected **4.24**, treatment with TBAF followed by acylation of the remaining alcohols provided the fully protected intermediate in 49% yield over 2 steps (Scheme 4.8). Subsequent removal of the C35 TES protecting group with HF/pyridine gave **4.31**. With this alcohol effectively isolated we then needed to find conditions to remove this group. Attempts to convert the alcohol to an iodide,[19] as well as activate it as a mesylate or tosylate, resulted in only recovery of starting material. However, treatment with phenyl chlorothionoformate (**4.32**) provided **4.33** in 53% yield but only about 75% purity. All attempts to deoxygenate this material either led to no conversion or massive amounts of decomposition.[8] For this reason, we decided to return to the iterative cross-coupling strategy for accessing this derivative. In the future, intermediate **4.31** could be useful for accessing other types of AmB derivatives.



Scheme 4.8. Proposed route to **4.34** through deoxygenation on AmB. All attempts to deoxygenate the C35-alcohol either gave no conversion or large amounts of decomposition.

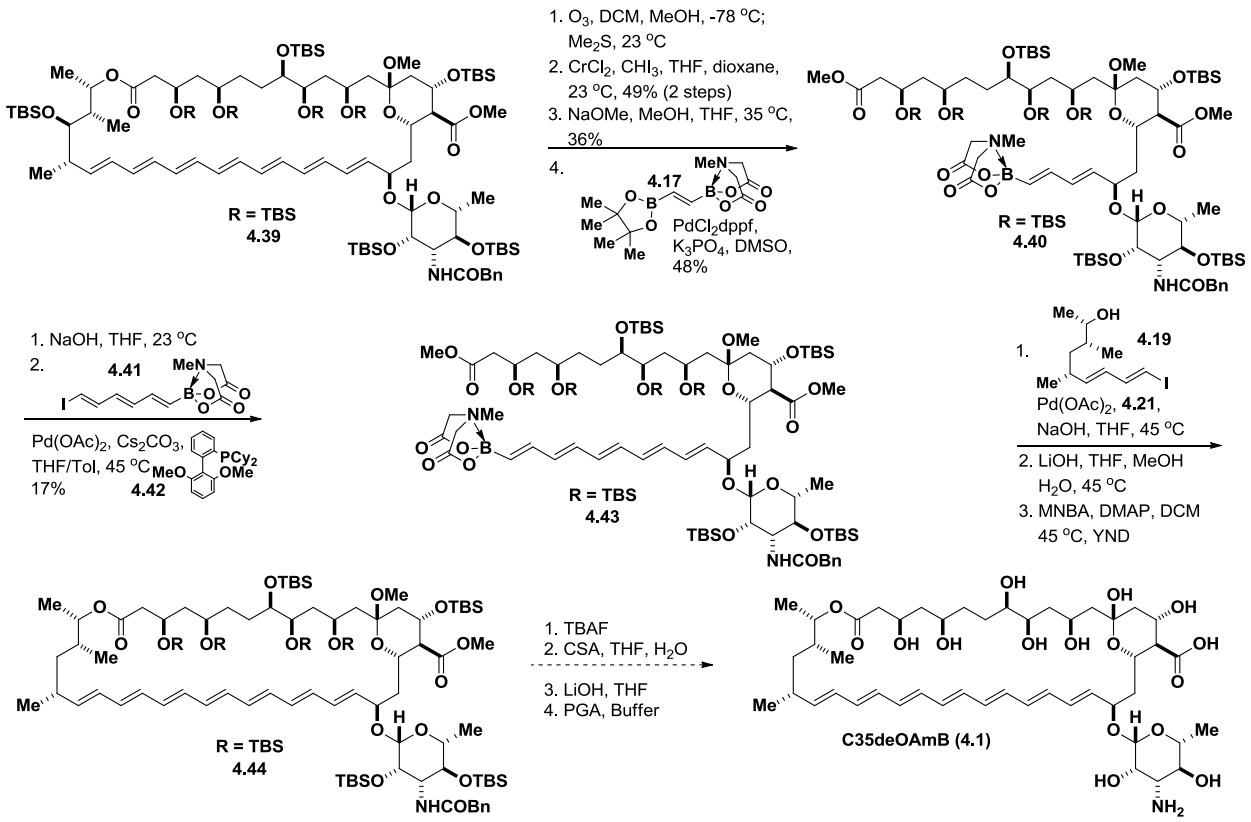
4-5 DEVELOPMENT OF A PROTECTING GROUP STRATEGY

While the SM coupling strategy allowed access to the C35deOAmB macrolactone, the protecting groups described above proved to be challenging to remove. Given the harsh conditions required to remove TBS groups from the AmB core, the use of TES groups as a replacement was explored (Scheme 4.9). Global protection of AmB gave **4.35** in five steps from the natural product. Ozonolysis[12] followed by Takai olefination[10] then provided **4.36** in good yield. However, transesterification conditions to cleave the western half of the molecule resulted in only the isolation of **4.38**. The TES groups were too labile to survive this step and resulted in decomposition of the desired product.



Scheme 4.9. Use of TES ethers in the degradation of AmB. Attemps to cleave the western half of the molecule led to undesired desilylation. A 1:1 mixture of the 1,2 and 1,3 ketal protected diol at C8-C11 was carried through the route. Only the 1,3 ketal is shown for simplicity.

An alternate protecting group strategy was then proposed involving global TBS protection, negating the need for the difficult to remove cyclopentylidene ketals (Scheme 4.10). Ozonolysis[12] followed by Takai olefination[10] of globally protected intermediate proceeded smoothly. Transesterification to cleave the western half took much longer than with the ketals present and gave only a 36% yield. This was hypothesized to be due to the larger steric hindrance and lack of ability to direct the nucleophile to the ester.[20] SM cross-coupling with bisborylated **4.17**[16] then gave **4.40** in 48% yield. MIDA boronate deprotection followed by coupling to trienyl iodide **4.41**[21] provided pentaenyl MIDA boronate **4.43**. Cross-coupling with **4.19** went smoothly; however, saponification of the C1 methyl ester required extended reaction times to get full conversion. Final macrolactonization then needed increased reaction temperature to proceed. These results suggested that the ketals provided some rigidity to the polyol portion of the molecule, helping to promote macrolactonization. While we were able to make a small amount of macrolactone **4.44**, the yields in this sequence were not satisfactory to scale this route up.



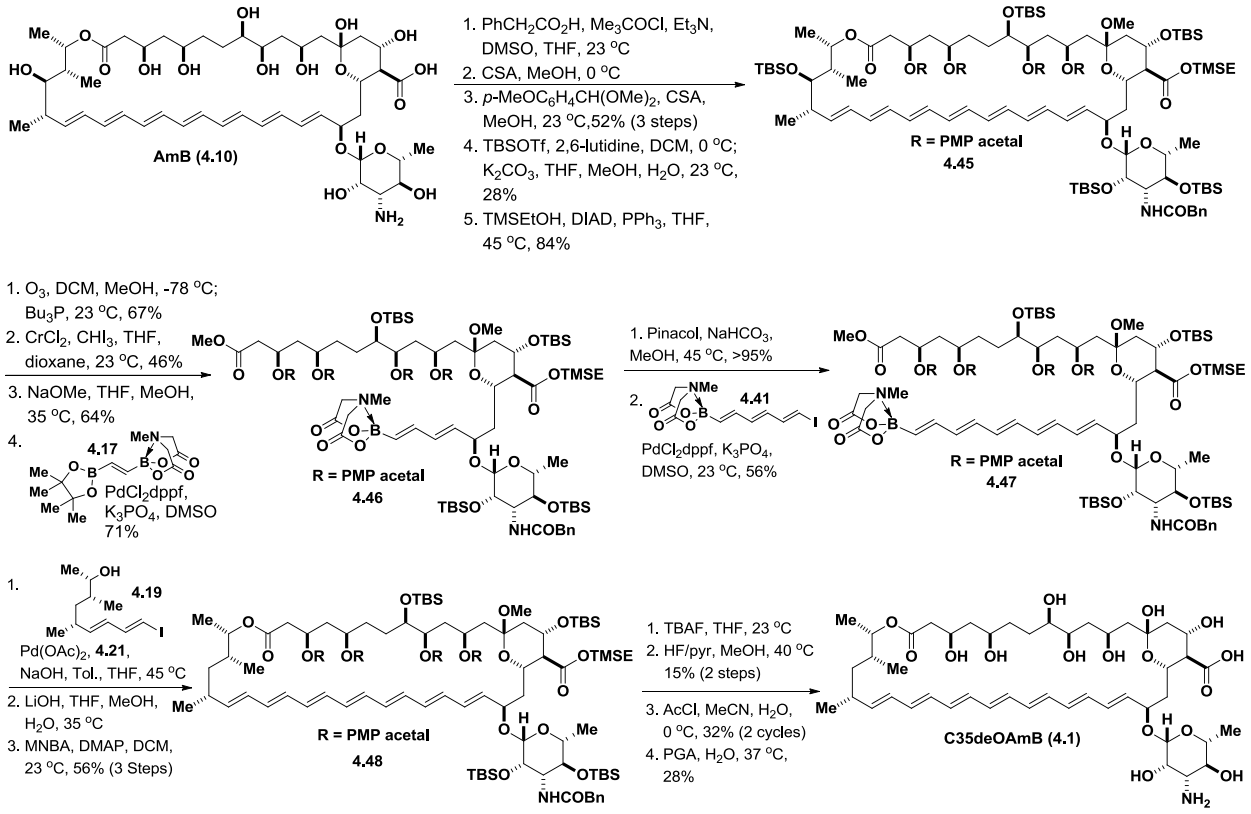
Scheme 4.10. Route to **4.44** using globally TBS protected AmB. **4.44** was observed, but it was isolated in low yield and purity. Additionally, many of the other steps proceeded slowly and in low yields so the decision was made to move away from this protecting group strategy. YND = yield not determined.

While these two protecting group strategies did not end up providing C35deOAmB, they did give insight as to what the ultimate strategy should be. Since TES groups were too labile to the transesterification conditions, the alcohols needed to be protected with TBS groups. Additionally, ketals were found to be important for allowing nucleophilic cleavage at the C1 position as well as promoting macrolactonization. Due to the difficulties in cleaving the cyclopentylidene ketals at a late stage, they were replaced with more labile *p*-methoxyphenyl (PMP) acetals. We had also noted a dramatically increased sensitivity of the C35deOAmB core to a wide variety of reagents and were therefore concerned about the nucleophilic cleavage of the methyl ester. Consistent with these concerns, in the context of synthesizing C35deOAmB methyl ester, Carreira and coworkers found that this derivative is not stable to the hydroxide conditions necessary to cleave the methyl ester.[4] To address this issue, the methyl ester was exchanged for a 2-(trimethylsilyl)ethyl (TMSE) ester[22] which can be cleaved with nucleophilic fluoride.

4-6 COMPLETION OF THE SEMISYNTHESIS OF C35-DEOXY AMPHOTERICIN B

As before, the C3' amine of AmB was protected as a benzyl amide and the hemiketal exchanged for a methyl ketal (Scheme 4.11). Subsequent ketalization with *para*-methoxyphenyl (PMP) acetals formed a single constitutional isomer with protection of only the 1,3 diols.[6b] Protection of the remaining alcohols as TBS ethers and the acid as a TMSE ester generated **4.45**. Ozonolysis exhaustively cleaved the polyene,[12] although the initial conditions proceeded in low yield. We hypothesized that the reduced yield stemmed from the choice of quench. In order to quench the ozonide, the reaction was stirred overnight with dimethyl sulfide. Over this time, the solution became acidic enough to cleave the more labile PMP acetals. In order to account for this, the dimethyl sulfide quench was exchanged for tributylphosphine, which can destroy the ozonide in 30 minutes versus overnight.[23] With this change, the acetals remained stable and the bisaldehyde was isolated in 67% yield. Takai olefination,[10] transesterification, and SM cross-coupling then gave dienyl MIDA boronate **4.46**. The MIDA boronate was exchanged for a pinacolboronic ester[24] and was then coupled to trienyl iodide **4.41**[21] giving **4.47** in 56% yield. The three step macrolactonization sequence subsequently provided the fully protected macrolactone of C35deOAmB (**4.48**).

Desilylation and ester deprotection of **4.48** was attempted with extended treatment with TBAF. Initially, it appeared that this reaction generated a mixture of a monosilylated product and the desired product; however, there were inconsistencies with this reaction. During the course of the reaction *p*-anisaldehyde was observed, consistent with the loss of a PMP acetal, and the NMR of the product showed a single TBS group remained. Upon closer examination of the spectrum it was determined that what was thought to be desired product was actually **4.49**, the product of the elimination of the PMP acetal at C3/C5 (Figure 4.49). Since this product only started to appear with longer reaction times, the reaction time in the presence of TBAF was reduced and the remaining silyl groups were cleaved with HF/pyridine. Subsequent acid hydrolysis with HCl and enzyme mediated deacylation[25] of the amine completed the synthesis of C35deOAmB.



Scheme 4.11. Synthesis of C35deOAmB.

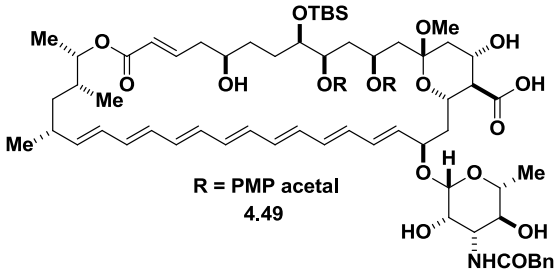


Figure 4.3. Elimination by product observed on treatment with TBAF.

4-7 THESIS SUMMARY

This dissertation describes the development of strategies and methods targeting the synthesis of polyene natural products, in particular AmB and its derivatives. Toward this end, the application of iterative SM cross-coupling via bifunctional MIDA boronates needed to be extended to use in polyene synthesis. A series of small polyene building blocks, including bifunctional building blocks with one, two, or three olefins were generated. These three bifunctional molecules were then used in the efficient syntheses of all-*trans*-retinal, *β*-parinaric acid, and one half of AmB.

With the ultimate goal of using this iterative cross-coupling strategy to complete the total synthesis of AmB and its derivatives, a better model of this endgame strategy was sought. It was realized that almost the exact model for the polyol and mycosamine containing intermediate targeted in our synthesis could be accessed via degradation of the natural product. With the dienyl MIDA boronate in hand, the iterative cross-coupling endgame strategy was tested. This model allowed for the discovery that replacing the vinyl chloride cross-coupling partners with vinyl iodides greatly enhances the yields of the SM reactions. Additionally, transesterifying the dienyl MIDA boronate to a dienyl pinacolboronic acid instead of deprotecting to the boronic acid improved the stability of this intermediate as well as its yield in the coupling reaction. These optimizations allowed for the development of an effective endgame strategy for reaching the natural product from the dienyl MIDA boronate intermediate.

Finally, the semisynthesis strategy used to access the model system for the total synthesis was recognized to provide a useful intermediate to make one of the deoxygenated derivatives, C35deOAmB. It was found, however, that simply deleting this one functional group makes the polyene macrolide core extremely sensitive to certain deprotection sequences. With this in mind, a series of protecting group strategies and manipulations was explored to access this interesting derivative. While many of these routes were not successful, they were extremely informative and eventually led to a strategy that provided the complete synthesis of C35deOAmB. It is anticipated that the strategies and methods developed herein will contribute strongly to the synthesis-enabled understanding of this fascinating natural product.

4-8 EXPERIMENTAL SECTION

Materials.

Commercially available materials were purchased from Sigma-Aldrich, Alfa Aesar, Strem, or Fisher Scientific, and were used without further purification unless stated otherwise. Amphotericin B was a generous gift from Bristol-Myers Squibb Company. Iodoform (methanol), camphorsulfonic acid (ethyl acetate), and triphenylphosphine (hexanes) were recrystallized from the indicated solvents prior to use. All solvents were dispensed from a solvent purification system that passes solvents through packed columns according to the method of Pangborn and coworkers[26] (THF, Et_2O, CH_2Cl_2, toluene, dioxane, hexanes : dry neutral alumina; DMSO, DMF, CH_3OH : activated molecular sieves). 2,6-Lutidine and pyridine were

freshly distilled under nitrogen from CaH_2. EtOAc and EtOH were freshly distilled under nitrogen from activated molecular sieves. Water was doubly distilled or obtained from a Millipore MilliQ water purification system. Ozone was generated using an ozone solutions ozone generator. The following compounds were prepared according to literature precedent: alcohol **4.6**[16], Diene **4.4**[13], phosphonate **4.3**[13], bisborylated compound **4.17**[16,27], triene **4.41**[21]

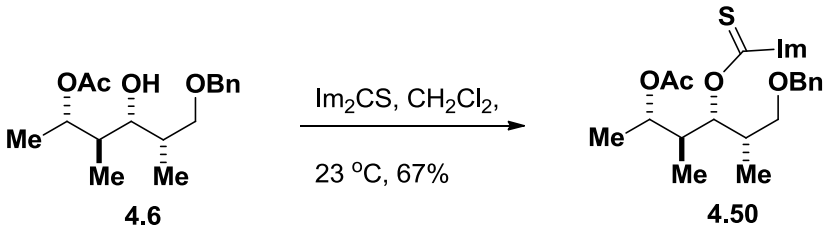
Reactions.

Due to the light and air sensitivity of polyenes, all manipulations of polyenes were carried out under low light conditions and compounds were stored under an argon atmosphere. All reactions were performed in oven- or flame-dried glassware under an atmosphere of argon unless otherwise indicated. Reactions were monitored by analytical thin layer chromatography performed using the indicated solvent on E. Merck silica gel 60 F_{254} plates (0.25mm). Compounds were visualized using a UV (λ_{254}) lamp or stained by an acidic solution of *p*-anisaldehyde or $KMnO_4$. Alternatively, reactions were monitored by RP-HPLC using an Agilent 1100 series HPLC system equipped with a Symmetry® C_{18} 5 micron 4.6 x 150 mm column (Waters Corp. Milford, MA) with UV detection at 406 nm and the indicated eluent and flow rate.

Purification and Analysis.

Flash chromatography was performed as described by Still and coworkers[28] using the indicated solvent on E. Merck silica gel 60 230-400 mesh. ^{1}H NMR spectra were recorded at 23 °C on one of the following instruments: Varian Unity 400, Varian Unity 500, Varian Unity Inova 500NB. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane and referenced internally to the residual protium in the NMR solvent ($CHCl_3$, δ = 7.26, $CD_3C(O)CHD_2$, δ = 2.04, center line) or to added tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, sept = septet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, m = multiplet, b = broad, app. = apparent), coupling constant (*J*) in hertz (Hz) and integration. ^{13}C spectra were recorded at 23 °C with a Varian Unity 500. Chemical shifts (δ) are reported downfield of tetramethylsilane and are referenced to the carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0, center line, $CD_3C(O)CD_3$, δ = 29.8, center line) or to added tetramethylsilane. Carbons bearing boron substituents were not reported (quadrapolar

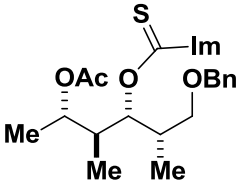
relaxation). ^{11}B NMR were recorded using a General Electric GN300WB instrument and referenced to an external standard of $BF_3 \cdot Et_2O$. High resolution mass spectra (HRMS) were obtained at the University of Illinois mass spectrometry facility. All synthesized compounds gave HRMS within 5 ppm of calculated values. Infrared spectra were collected from a thin film on NaCl plates or as a KBr pellet on a Mattson Galaxy Series FTIR 5000 spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}).



4.6 **4.50**

Thiocarbamate 4.50

To a stirred solution of alcohol **4.6**[16] (3.32 g, 11.3 mmol, 1 eq) in CH_2Cl_2 (16.6 mL) in a 25 mL round-bottomed flask was added thiocarbonyl diimidizole (3.02 g, 16.95 mmol, 1.5 eq). The resulting yellow solution was stirred for 60 hours at 23 °C. The reaction mixture was poured into a mixture of water (60 mL) and CH_2Cl_2 (60 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with 1N HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2; 25% $\rightarrow$ 50% EtOAc/hexanes) furnished the desired product **4.50** (3.06 g, 7.57 mmol, 67%) as a yellow oil.



4.50

TLC (1:1 hexanes : EtOAc)

R_f = 0.40, stained by anisaldehyde

^1H NMR (500 MHz, $CDCl_3$)

δ 8.35 (s, 1H), 7.63 (t, *J* = 1Hz, 1H), 7.34-7.26 (m, 5H), 7.03 (t, *J* = 1Hz, 1H), 5.91 (dd, *J*

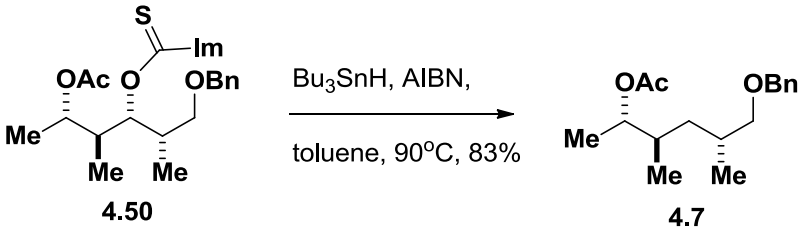
= 2.5, 9Hz, 1H), 4.92 (dq, *J* = 4.5, 6.4Hz, 1H), 4.46 (d, *J* = 11.5Hz, 1H), 4.37 (d, *J* = 11.5Hz, 1H), 3.40-3.30 (m, 2H), 2.44-2.34 (m, 1H), 2.32-2.22 (m, 1H), 1.97 (s, 3H), 1.22 (d, *J* = 6.5Hz, 3H), 1.04 (d, *J* = 7Hz, 3H), 0.99 (d, *J* = 7Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 184.4, 170.3, 138.0, 137.1, 130.9, 128.3, 127.7, 127.6, 117.8, 84.8, 73.3, 72.4, 70.3, 38.9, 35.7, 21.2, 15.4, 11.0, 10.8.

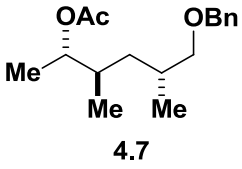
HRMS (CI+)

Calculated for $C_{21}H_{29}N_2O_4S$ $(M+H)^+$:	405.1848
Found:	405.1850



C35-Deoxy Intermediate 4.7

A 250 mL 2-neck round-bottomed flask equipped with a condenser was charged with thiocarbambate **4.50** (2.60 g, 6.43 mmol, 1 eq), Bu_3SnH (3.44 mL, 12.79 mmol, 2 eq), AIBN (0.53 g, 3.23 mmol, 0.5 eq), and toluene (122 mL). The reaction mixture was stirred at 90 °C for 2 hours and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (SiO_2; 5% → 10% EtOAc/hexanes) to yield **4.7** (1.39 g, 4.99 mmol, 83%) as a clear colorless oil.



TLC (3:1 hexanes : EtOAc)

R_f = 0.71, stained by anisaldehyde

^{1}H NMR (500 MHz, $CDCl_3$)

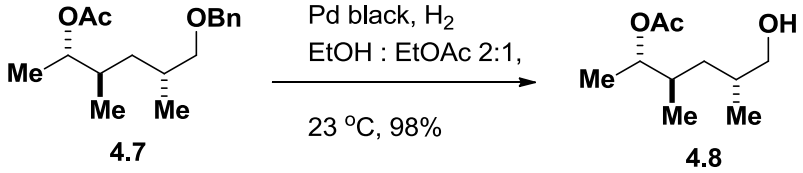
δ 7.36-7.26 (m, 5H), 4.78 (app. p, *J* = 6.5Hz, 1H), 4.52 (d, *J* = 12.5Hz, 1H), 4.49 (d, *J* = 12.5Hz, 1H), 3.30 (dd, *J* = 6, 9Hz, 1H), 3.26 (dd, *J* = 6, 9Hz, 1H), 2.03 (s, 3H), 1.84 (dpd, *J* = 4, 6.5, 10.5Hz, 1H), 1.80-1.72 (m, 1H), 1.28-1.20 (m, 1H), 1.4 (d, *J* = 6.5Hz, 3H), 1.14-1.10 (m, 1H), 0.90 (d, *J* = 6.5Hz, 3H), 0.87 (d, *J* = 7Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 170.7, 138.7, 128.3, 127.5, 127.4, 76.5, 74.7, 72.9, 36.1, 34.4, 30.8, 21.4, 16.5, 16.0, 14.4.

HRMS (EI+)

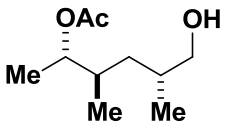
Calculated for $C_{17}H_{26}O_3$ $(M)^+$:	278.1882
Found:	278.1883



4.7 **4.8**

Primary Alcohol 4.8

A 250 mL 3-neck round-bottomed flask was charged with Pd black (0.429 g, 1.03 mmol, 0.22 eq). A solution of **4.7** (1.29 g, 4.63 mmol, 1 eq) in 2:1 EtOH : EtOAc (75 mL) was cannulated into this flask and the argon atmosphere was blown off with hydrogen gas. The reaction was stirred under a balloon of hydrogen gas at 23 °C for 4 hours. The reaction was filtered through celite making sure to keep the Pd black under solvent at all times. The filtrate was concentrated yielding primary alcohol **4.8** (0.860 g, 4.57 mmol, 98%) as a colorless oil (0.860 g, 4.57 mmol, 98%).



4.8

TLC (3:1 hexanes : EtOAc)

R_f = 0.31, stained by anisaldehyde

^{1}H NMR (500 MHz, $CDCl_3$)

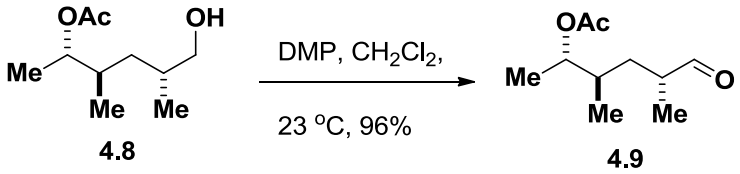
δ 4.79 (app. p, *J* = 6.5 Hz, 1H), 3.50-3.43 (m, 2H), 2.04 (s, 3H), 1.81-1.74 (m, 1H), 1.74-1.66 (m, 1H), 1.22-1.08 (m, 1H), 1.24-1.18 (m, 1H), 1.16-1.10 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 170.8, 74.6, 68.8, 35.8, 34.4, 33.0, 21.3, 15.9, 15.8, 14.4.

HRMS (CI+)

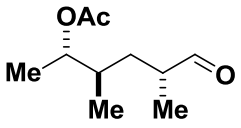
Calculated for $C_{10}H_{21}O_3$ $(M + H)^+$:	189.1491
Found:	189.1486



4.8 4.9

Aldehyde 4.9

To a 25 mL round-bottomed flask with a solution of **4.8** (81 mg, 0.43 mmol, 1 eq) in CH_2Cl_2 (6.1 mL) was added Dess-Martin periodinane (273 mg, 0.64 mmol, 1.5 eq). The reaction was stirred at 23 °C for 2 hours. To the solution was added saturated aqueous $NaHCO_3$ (4 mL) and saturated aqueous $Na_2S_2O_3$ (2 mL) and the reaction was stirred an additional 30 min. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield aldehyde **4.9** (76 mg, 0.41 mmol, 96%) which was used without further purification.



4.9

TLC (1:1 hexanes : EtOAc)

R_f = 0.61, stained by anisaldehyde

^{1}H NMR (500 MHz, acetone-d_6)

δ 9.64 (d, *J* = 1.5 Hz, 1H), 4.77 (app. p, *J* = 6.5 Hz, 1H), 2.49-2.42 (m, 1H), 2.00 (s, 3H), 1.83-1.77 (m, 1H), 1.59 (ddd, *J* = 5.0, 10.0, 13.5 Hz, 1H), 1.36 (ddd, *J* = 4.5, 9.5, 14.0 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

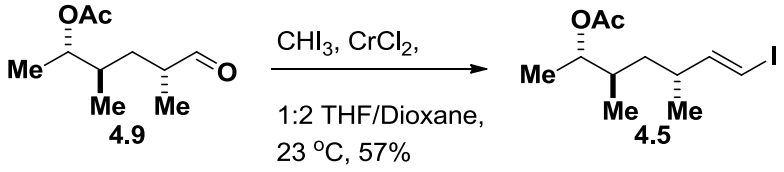
δ 204.9, 170.4, 74.5, 44.5, 35.5, 33.3, 21.1, 16.5, 14.8, 13.2.

HRMS (ESI)

Calculated for $C_{10}H_{18}O_3Na$ $(M+Na)^+$:	209.1154
Found:	209.1158

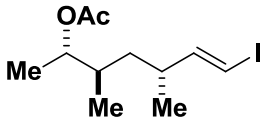
IR (thin film, cm^{-1})

2977, 2938, 2879, 2814, 2712, 1736, 1459, 1373, 1247, 1104, 1047, 1020, 949.



Vinyl Iodide 4.5

To a suspension of $CrCl_2$ (740 mg, 6.1 mmol, 15 eq) in THF (2.2 mL) in a 25 mL round-bottomed flask was added dropwise a solution of aldehyde **4.9** (76 mg, 0.41 mmol, 1 eq) and iodoform (803 mg, 2.04 mmol, 5 eq) in dioxane : THF 2:1 (7.0 mL). After stirring for 15 minutes, the reaction was poured into saturated aqueous $NaHCO_3$ (40 mL) and diluted with Et_2O (50 mL). The green mixture was filtered through celite with Et_2O (100mL) and the filtrate layers were separated. The aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the crude product by column chromatography (SiO_2; 0% → 10% EtOAc/hexanes) provided title compound **4.5** (72 mg, 0.23 mmol, 57%) as a pale yellow oil.



4.5

TLC (1:1 hexanes : EtOAc)

R_f = 0.75, stained by anisaldehyde

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.47 (dd, *J* = 8.5, 14.5 Hz, 1H), 6.18 (dd, *J* = 0.5, 14.5 Hz, 1H), 4.76 (app. p, *J* = 6.5, 1H), 2.38-2.29 (m, 1H), 1.96 (s, 3H), 1.78-1.70 (m, 1H), 1.35 (ddd, *J* = 5.5, 8.0, 14.0 Hz, 1H), 1.17 (ddd, *J* = 7.0, 8.5, 14.0 Hz, 1H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

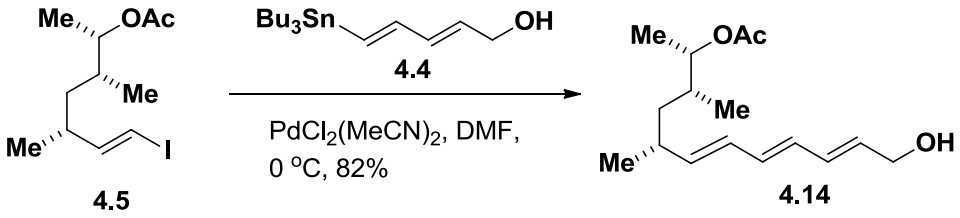
δ 170.4, 153.2, 74.5, 74.1, 39.6, 38.9, 35.4, 30.3, 21.1, 19.3, 15.8, 15.1.

HRMS (ESI+)

Calculated for $C_{11}H_{19}O_2I$ $(M+Na)^+$:	333.0328
Found:	333.0335

IR (thin film, cm^{-1})

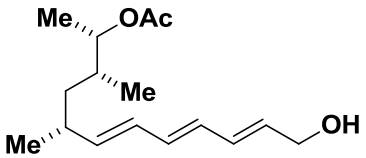
2965, 2966, 2874, 1732, 1456, 1372, 1247, 1187, 1106, 1044, 1018, 949.



Triene 4.14

Diene **4.4** was prepared by the literature procedure.[13] A 10 mL round-bottomed flask was charged with vinyl iodide **4.5** (36 mg, 0.12 mmol, 1 eq), diene **4.4** (48 mg, 0.13 mmol, 1.05 eq) and DMF (3.4 mL). The solution was cooled to 0 °C and $PdCl_2(MeCN)_2$ (1.5 mg, 0.0058 mmol,

5 mol%) in DMF (0.4 mL) was added in five portions over 2 hours. The reaction was warmed to 23 ^{o}C and stirred for 1 hour. The reaction was poured into water (5 mL) and Et_2O (5 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (SiO_2; 15% EtOAc/hexanes) to yield **4.14** (25 mg, 0.095 mmol, 82%) as a yellow oil.



4.14

TLC (3:1 hexanes : EtOAc)

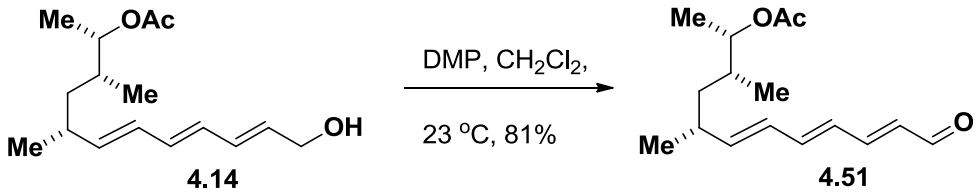
R_f = 0.14, visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$)

δ 6.26 (dd, *J* = 10.0, 15.0 Hz, 1H), 6.22-6.12 (m, 2H), 6.06 (dd, *J* = 9.5, 14.5 Hz, 1H), 5.81 (td, *J* = 6.0, 15.0 Hz, 1H), 5.63 (dd, *J* = 7.5, 15.0 Hz, 1H), 4.81 (app. p, *J* = 6.0 Hz, 1H), 4.19 (t, *J* = 5.5 Hz, 2H), 2.30-2.23 (m, 1H), 2.03 (s, 3H), 1.76-1.68 (m, 1H), 1.34-1.22 (m, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H).

HRMS (ESI+)

Calculated for $C_{16}H_{26}O_3$ $(M+Na)^+$:	289.1780
Found:	289.1765

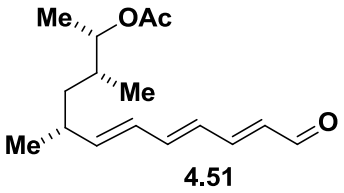


4.14 **4.51**

Aldehyde 4.51

To a 7 mL vial with a solution of **4.14** (8 mg, 0.029 mmol, 1 eq) in CH_2Cl_2 (0.5 mL) was added Dess-Martin periodinane (19 mg, 0.044 mmol, 1.5 eq). The reaction was stirred at room temperature for 10 minutes. To the solution was added saturated aqueous $NaHCO_3$ (0.4 mL) and

saturated aqueous $Na_2S_2O_3$ (0.2 mL) and the reaction was stirred an additional 30 minutes. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to yield clean aldehyde **4.51** (6 mg, 0.023 mmol, 81%).



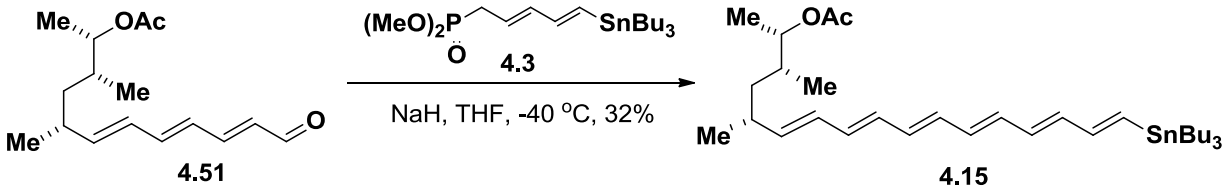
4.51

TLC (1:1 hexanes : EtOAc)

R_f = 0.58, visualized by UV.

^{1}H NMR (500 MHz, acetone-d_6)

δ 9.55 (d, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 11.0, 14.5 Hz, 1H), 6.78 (dd, *J* = 10.5, 14.5 Hz, 1H), 6.49 (dd, *J* = 11.0, 14.5 Hz, 1H), 6.29 (dd, *J* = 10.5, 15.0 Hz, 1H), 6.11 (dd, *J* = 8.0, 15.5 Hz, 1H), 6.00 (dd, *J* = 8.0, 15.5 Hz, 1H), 4.81-4.76 (m, 1H), 2.42-2.35 (m, 1H), 1.80-1.73 (m, 1H), 1.42-1.36 (m, 1H), 1.24-1.16 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H).

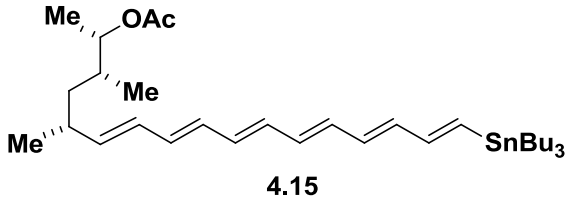


4.51 **4.15**

Hexaene 4.15

To a 7 mL vial charged with NaH washed with pentane (1.5 mg, 0.059 mmol, 3 eq) in THF (0.5 mL) and cooled to –78 °C was added dropwise a solution of phosphonate **4.3**[13] (27 mg, 0.059 mmol, 3 eq) in THF (0.25 mL). The solution was warmed to 0 °C for 30 minutes then cooled to -40 °C. A solution of aldehyde **4.51** (5.2 mg, 0.02 mmol, 1 eq) in THF (0.25 mL) was added dropwise and the solution was stirred at -40 °C for 36 hours. The reaction was quenched with saturates aqueous $NaHCO_3$ (0.5 mL) and extracted with Et_2O (3 x 2 mL). The combined organic layers were concentrated *in vacuo* and the crude material purified by flash chromatography

(SiO_2; 0% → 8% EtOAc/hexanes) to yield **4.15** (4 mg, 0.0063 mmol, 32%) as an inseparable mixture of *E* and *Z* isomers.



4.15

TLC (1:1 hexanes : EtOAc)

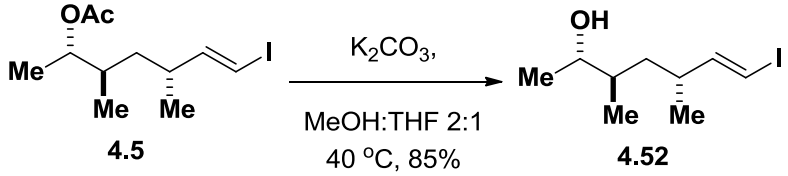
R_f = 0.77, visualized by UV.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.46-6.20 (m, 8H), 6.14 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.67 (dd, 7.5, 15.0 Hz, 1H), 5.21 (d, *J* = 16.5 Hz, 1H), 5.06 (d, *J* = 10 Hz, 1H), 4.77 (app. p, *J* = 6.0 Hz, 1H), 2.34-2.26 (m, 1H), 1.96 (s, 3H), 1.78-1.70 (m, 1H), 1.40-1.20 (m, 7H), 1.20-1.10 (m, 7H), 1.00-0.92 (m, 6H), 0.91-0.82 (m, 9H).

LRMS (ESI)

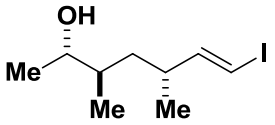
Calculated for $C_{33}H_{56}O_2SnNa$ $(M + Na)^+$:	627.3
Found:	627.3



4.5 **4.52**

Secondary alcohol 4.52

K_2CO_3 (390 mg, 2.81 mmol, 10 eq) was added to vinyl iodide **4.5** (87.3 mg, 0.281 mmol, 1 eq) in MeOH:THF 2:1 (11.2 mL). The reaction was stirred at 40 °C for 2 hours and then the reaction was poured into water (15 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 10% → 50% EtOAc/hexanes) to provide alcohol **4.52** (54.2 mg, 0.202 mmol, 85%).



4.52

TLC (50% EtOAc/hexanes)

R_f = 0.52, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.48 (dd, *J* = 8.0, 14.5 Hz, 1H), 6.14 (d, *J* = 14.5 Hz, 1H), 3.57 (app. sext, *J* = 6.0 Hz, 1H), 3.42 (d, *J* = 4.5 Hz, 1H), 2.33 (app. sept, *J* = 7.0 Hz, 1H), 1.58-1.51 (m, 1H), 1.44 (ddd, *J* = 5.0, 8.5, 13.5 Hz, 1H), 1.12 (ddd, *J* = 6.0, 8.5, 13.5 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

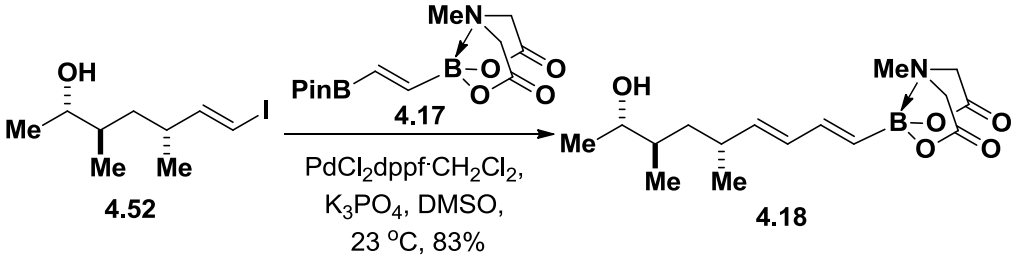
δ 153.9, 73.8, 71.1, 40.0, 39.1, 38.1, 19.6, 19.3, 15.2.

HRMS (EI)

calculated for $C_9H_{17}OI$ $(M)^+$:	268.0325
found:	268.0328

IR (thin film, cm^{-1})

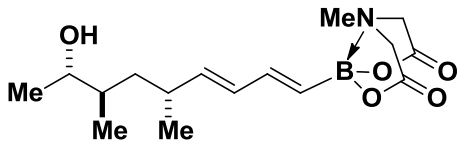
3370, 2968, 2926, 2881, 1713, 1603, 1455, 1379, 1281, 1185, 1096, 1053, 951, 926, 672.



Dienyl MIDA boronate 4.18

A 20 mL I-Chem vial equipped with a stir bar was charged with vinyl iodide **4.52** (52.1 mg, 0.194 mmol, 1 eq) and bisborylated compound **4.17**[16,27] (46.6 mg, 0.153 mmol, 0.8 eq.), sealed under argon, and was taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (8.3 mg, 0.010 mmol, 5 mol%)

and K_3PO_4 as a finely ground powder (124 mg, 0.583 mmol, 3 eq) were added, followed by DMSO (6.5 mL). The reaction was sealed with a PTFE-lined cap, removed from the glovebox, and stirred at 23 °C for 24 hours. The solution was then diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (70 mL). Celite was added to the filtrate and the mixture was concentrated *in vacuo*. The resulting powder was dry-loaded on top of a flash column and purified (SiO_2; 50% EtOAc/hexanes → EtOAc → 10% MeCN:EtOAc) to yield the desired product **4.18** (40.8 mg, 0.126 mmol, 83%) as a pale yellow solid.



4.18

TLC (EtOAc)

R_f = 0.19, stained by $KMnO_4$.

^{1}H NMR (500 MHz, acetone-d_6)

δ 6.52 (dd, *J* = 10.0, 17.5 Hz, 1H), 6.10 (dd, *J* = 10.5, 15.5 Hz, 1H), 5.69 (dd, *J* = 8.0, 15.0 Hz, 1H), 5.54 (d, *J* = 18.0 Hz, 1H), 4.19 (d, *J* = 17.0 Hz, 2H), 3.41 (d, *J* = 17.0 Hz, 2H), 3.59 (app. p, *J* = 5.5 Hz, 1H), 2.98 (s, 3H), 2.30-2.25 (m, 1H), 1.61-1.53 (m, 1H), 1.43 (ddd, *J* = 4.5, 8.0, 13.5 Hz, 1H), 1.12 (ddd, *J* = 6.0, 8.5, 13.5 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 169.0, 143.9, 143.1, 131.2, 71.1, 62.2, 47.3, 40.8, 38.2, 35.0, 20.1, 19.5, 15.1.

^{11}B NMR (128 MHz, acetone-d_6)

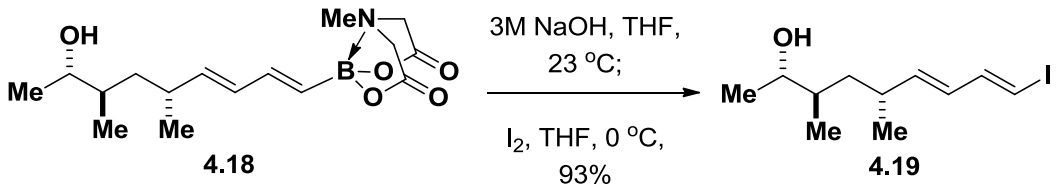
δ 11.5.

HRMS (EI)

Calculated for $C_{16}H_{26}O_5NB$ $(M)^+$:	323.1904
Found:	323.1903

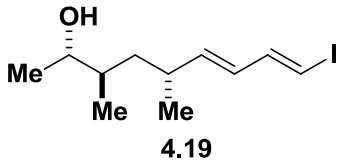
IR (thin film, cm^{-1})

3420, 2963, 2899, 1742, 1642, 1604, 1453, 1337, 1287, 1249, 1154, 1084, 1004, 957, 890.



Dienyl iodide 4.19

3 M NaOH (0.258 mL, 0.773 mmol, 5 eq) was added to dienyl MIDA boronate **4.18** (50 mg, 0.16 mmol, 1 eq) in THF (0.775 mL). The reaction was stirred at 23 °C for 10 minutes then cooled to 0 °C over 5 minutes. I_2 (41.2 mg, 0.162 mmol, 1.2 eq) in THF (0.810 mL) was added dropwise over 5 minutes. The reaction was stirred at 0 °C for 15 minutes and was then quenched with saturated aqueous $Na_2S_2O_3$ (5 mL) and diluted with Et_2O (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was pushed through a plug of silica gel with Et_2O to give dienyl iodide **4.19** (42.4 mg, 0.144 mmol, 93 %) as a pale yellow oil.



TLC (1:1 EtOAc/hexanes)

R_f = 0.54, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.03 (dd, *J* = 10.5, 14.0 Hz, 1H), 6.34 (d, *J* = 14.5 Hz, 1H), 6.05 (dd, *J* = 10.5, 15.5 Hz, 1H), 5.73 (dd, *J* = 8.0, 15.5 Hz, 1H), 3.58-3.54 (m, 1H), 3.38 (d, *J* = 4.5 Hz, 1H), 2.28-2.20 (m, 1H), 1.58-1.51 (m, 1H), 1.42 (ddd, *J* = 5.5, 9.0, 13.5 Hz, 1H), 1.09 (ddd, *J* = 6.5, 9.0, 14.0 Hz, 1H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

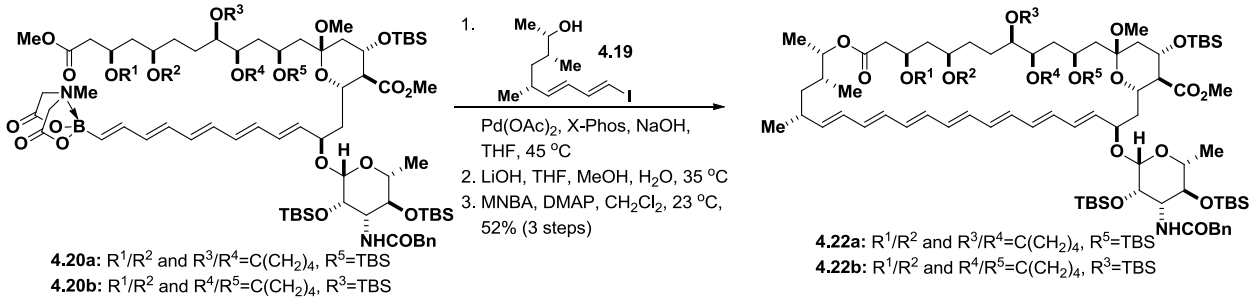
δ 146.8, 143.6, 129.0, 76.9, 71.1, 40.6, 38.3, 35.0, 19.9, 19.6, 15.2.

HRMS (CI+)

Calculated for $C_{11}H_{19}OI$ $(M+H)^+$:	295.0559
Found:	295.0562

IR (thin film, cm^{-1})

3360, 2961, 2921, 2851, 1729, 1452, 1378, 1322, 1261, 1097, 980, 796.

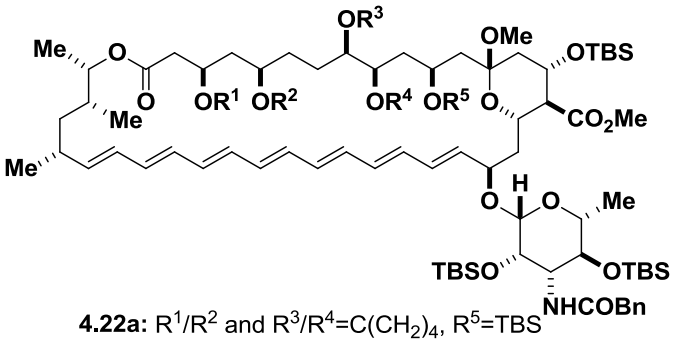


Macrolactone 4.22

A solution of the palladium catalyst was prepared as follows: A 20 mL Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol) and 2-cyclohexylphosphino-2',4',6'-isopropyl-1,1'-biphenyl (X-Phos, 9.3 mg, 0.0196 mmol). Toluene (1.35 mL) was added and the vial was sealed with a PTFE lined cap. The resulting mixture was stirred at 23 °C for 15 minutes resulting in a yellow catalyst stock solution (0.00725 M in Pd).

This catalyst solution was then utilized in the following procedure: To pentaenyl MIDA boronate **4.20**[29] (92.0 mg, 0.0553 mmol, 1 eq) and dienyl iodide **4.19** (15.4 mg, 0.0525 mmol, 0.95 eq) in THF (2.8 mL) was added the catalyst stock solution described above (0.381 mL, 0.00276 mmol Pd, 5 mol% Pd). The resulting mixture was sealed with a teflon-lined septum cap and 1 M NaOH (0.276 mL, 0.276 mmol, 5 eq) was added. The reaction was stirred at 23 °C for 30 minutes then at 45 °C for 4 hours. The reaction was diluted Et_2O (50 mL) and was quenched with 0.5 M pH 7 phosphate buffer (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were filtered through a short plug of silica gel with Et_2O and concentrated. The residue was taken up in THF:MeOH:H_2O 3:1:1 (5.4 mL), LiOH

(113 mg, 2.686 mmol, 50 eq) was added and the vial was sealed under argon. The reaction was stirred at 35 °C for 1 h and was then diluted with EtOAc (50 mL) and was poured into water (50 mL). The aqueous layer was extracted with EtOAc (5 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (13.1 mL) and was added dropwise over 15 hours to a solution of MNBA (22 mg, 0.0628 mmol, 1.2 eq) and DMAP (15 mg, 0.126 mmol, 2.4 eq) in CH_2Cl_2 (21 mL). The reaction was stirred an additional 45 min, cooled to 0 °C, and quenched with saturated $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 5% → 10% EtOAc/hexanes) to yield macrolactone **4.22** (44.9 mg, 0.0273 mmol, 52% over 3 steps) as a 1:1 mixture of ketal constitutional isomers.



4.22a: R^1/R^2 and $R^3/R^4=C(CH_2)_4$, R^5=TBS
4.22b: R^1/R^2 and $R^4/R^5=C(CH_2)_4$, R^3=TBS

TLC (20% EtOAc/hexanes)

R_f = 0.52, stained by anisaldehyde.

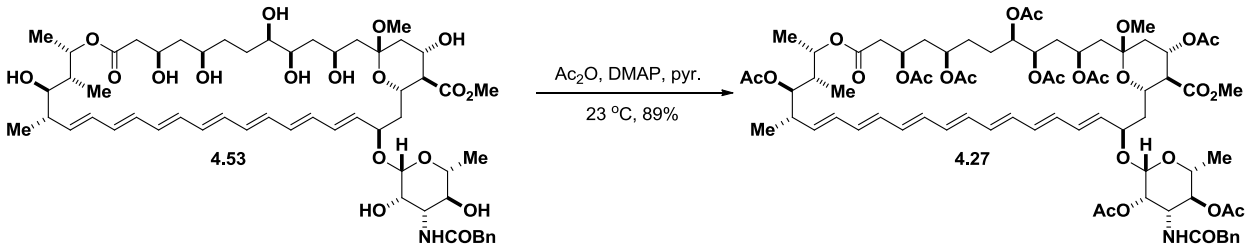
^{1}H NMR

δ 7.33-7.21 (m, 8H), 7.24-7.21 (m, 2H), 6.41 (m, 26H), 5.99 (dd, *J* = 7.5, 14.0 Hz, 1H), 5.86 (dd, *J* = 6.5, 14.0 Hz, 1H), 5.43-5.34 (m, 2H), 5.15 (dd, *J* = 4.5, 6.5 Hz, 1H), 5.10 (dd, *J* = 4.5, 6.5 Hz, 1H), 4.61-4.57 (m, 2H), 4.53 (s, 2H), 4.31-4.23 (m, 2H), 4.21-4.10 (m, 3H), 4.05-3.96 (m, 2H), 3.93-3.86 (m, 5H), 3.72-3.66 (m, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.64-3.50 (m, 10H), 3.40-3.35 (m, 2H), 3.22 (s, 3H), 3.08 (s, 3H), 2.48-2.42 (m, 2H), 2.33-2.20 (m, 6H), 1.98-1.48 (m, 66H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 6H), 0.92-0.84 (m, 78H), 0.16- -0.01 (m, 48H).

HRMS (ESI)

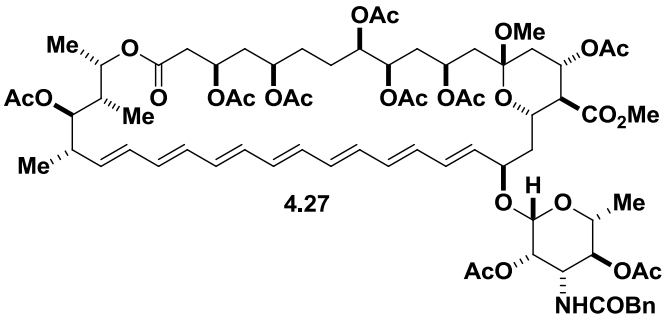
Calculated for $C_{91}H_{152}NO_{17}Si_4$ $(M + H)^+$: 1643.0137

Found: 1643.0071



Per-Acylated 4.27

To methyl ester **4.53**[29] (50 mg, 0.0467 mmol, 1 eq) in pyridine (4.7 mL) was added DMAP (5.7 mg, 0.0467 mmol, 1 eq) and acetic anhydride (0.22 mL, 2.33 mmol, 50 eq). The reaction was stirred at 23 °C for 15 hours then was poured into saturated aqueous $NaHCO_3$ (10 mL) and Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (50% → 100% EtOAc/hexanes) to yield **4.27** (60.5 mg, 0.0418 mmol, 89%) as a yellow solid.



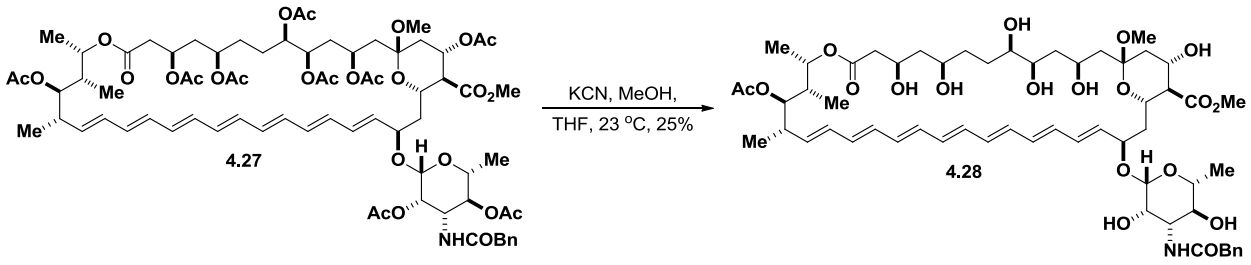
TLC (EtOAc)

R_f = 0.73, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

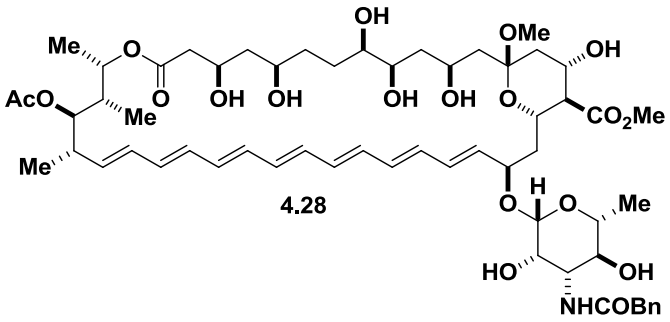
δ 7.29-7.19 (m, 4H), 7.07 (d, *J* = 9.5 Hz, 1H), 6.64-6.09 (m, 13H), 5.53 (dd, *J* = 9.0, 15.0 Hz, 1H), 5.34-5.25 (m, 3H), 5.22-5.09 (m, 2H), 5.07-4.92 (m, 5H), 4.81-4.75 (m, 2H), 4.68 (t, *J* = 9.5 Hz, 1H), 4.50 (t, *J* = 6.0 Hz, 1H), 4.36-4.31 (m, 1H), 4.10-3.99 (m, 3H), 3.67 (s, 3H), 3.56 (dd, *J* = 6.0, 9.5 Hz, 1H), 3.42 (q, *J* = 15.0 Hz, 2H), 3.17 (s, 3H), 2.59-

2.45 (m, 4H), 2.29 (t, *J* = 10.5 Hz, 1H), 2.19-2.16 (m, 1H), 2.09-1.92 (m, 24H), 1.86-1.81 (m, 2H), 1.79 (s, 3H), 1.65-1.55 (m, 3H), 1.49-1.28 (m, 5H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H).



Monoacylated 4.28

To per-acylated **4.27** (10 mg, 0.0069 mmol, 1 eq), in MeOH:THF 2:1 (0.69 mL) at 0 °C was added KCN (2 mg, 0.0138 mmol, 2 eq). The reaction was allowed to warm to 23 °C and was stirred for 21 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and was extracted with 20% MeOH/DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 5% → 8% MeOH/DCM) to yield **4.28** (1.9 mg, 0.00177 mmol, 25%).



TLC (10% MeOH/DCM)

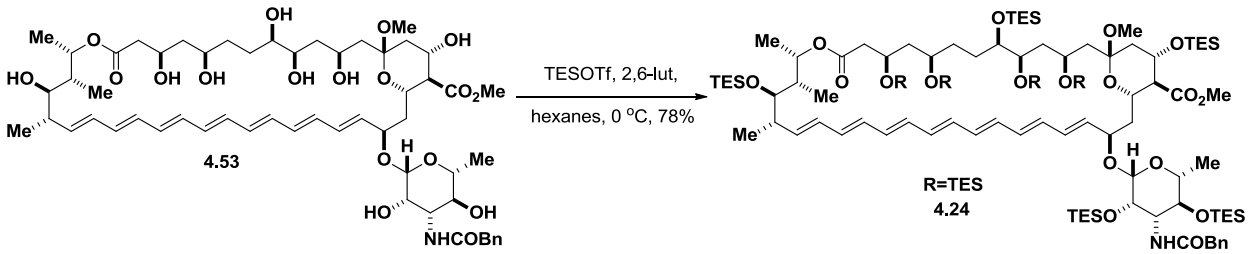
R_f = 0.37, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.36-7.20 (m, 5H), 6.47-6.16 (m, 12H), 5.87 (dd, *J* = 6.5, 14.5 Hz, 1H), 5.57 (dd, *J* = 9.5, 15.5 Hz, 1H), 5.26-5.24 (m, 1H), 4.83-4.76 (m, 2H), 4.63-4.58 (m, 2H), 4.21-4.14 (m, 3H), 4.04-3.92 (m, 5H), 3.87-3.80 (m, 2H), 3.78-3.68 (m, 2H), 3.67 (s, 3H), 3.63-3.52 (m, 2H), 3.17 (s, 3H), 2.51 (s, 3H), 2.34-2.24 (m, 3H), 1.99-1.93 (m, 2H), 1.87-1.81 (m, 2H), 1.62-1.40 (m, 10H), 1.20 (d, *J* = 5.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H).

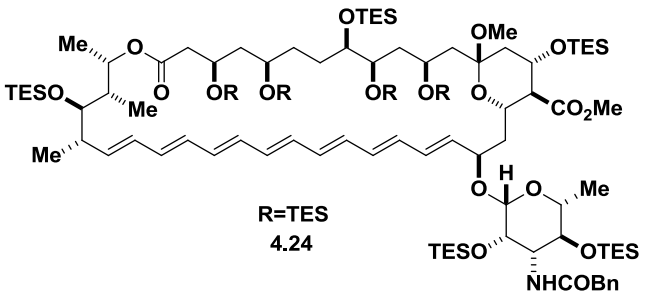
HRMS (ESI)

Calculated for $C_{59}H_{85}NO_{19}S$ $(M + Na)^+$:	1134.5614
Found:	1134.5607



TES Protected 4.24

To methyl ester **4.53**[29] (0.450 g, 0.420 mmol, 1 eq) in hexanes (21 mL) and 2,6-lutidine (1.27 mL, 10.93 mmol, 26 eq) at 0 °C was added dropwise TESOTf (1.9 mL, 8.41 mmol, 20 eq). The reaction was stirred at 0 °C for 2h then more 2,6-lutidine (0.32 mL, 2.73 mmol, 6.5 eq) and TESOTf (0.48 mL, 2.10 mmol, 5 eq) was added. The reaction was stirred at 0 °C for an additional 15 minutes then more 2,6-lutidine (0.32 mL, 2.73 mmol, 6.5 eq) and TESOTf (0.48 mL, 2.10 mmol, 5 eq) was added. The reaction was stirred an additional 1 hour then quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was transferred to a separatory funnel and was diluted with diethyl ether (300 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 x 100 mL) and water (1 x 100 mL). The combined aqueous washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with saturated aqueous copper sulfate (1 x 100 mL). The combined copper sulfate washings were back-extracted with diethyl ether (1 x 100 mL) and the combined organic extracts were washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 5% → 10% EtOAc/hexanes) to give **4.24** (0.686 g, 0.327 mmol, 78%) as a yellow solid.

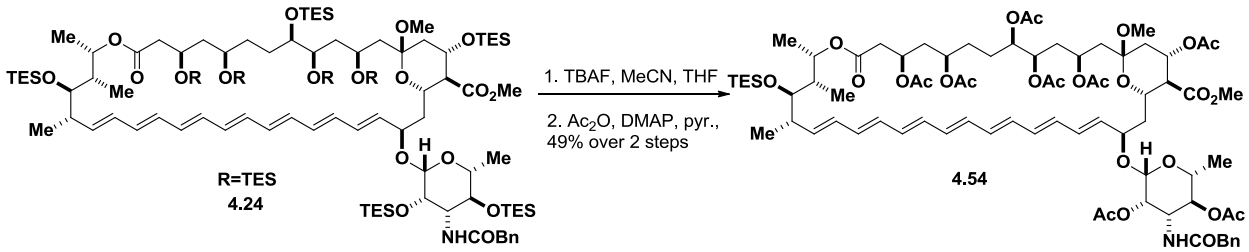


TLC (20% EtOAc/hexanes)

R_f = 0.47, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

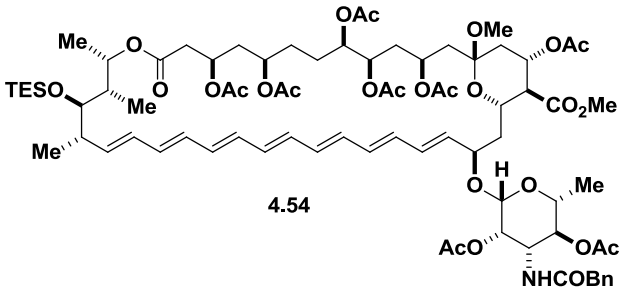
δ 7.37-7.25 (m, 5H), 6.58-6.10 (m, 12H), 5.92 (dd, *J* = 5.5, 15.5 Hz, 1H), 5.48 (dd, *J* = 9.5, 15.0 Hz, 1H), 4.67-4.60 (m, 2H), 4.48 (s, 1H), 4.42 (dt, *J* = 4.5, 10.0, 1H), 4.25-4.19 (m, 1H), 4.12 (t, *J* = 8.0 Hz, 1H), 4.03-3.93 (m, 3H), 3.86-3.83 (m, 2H), 3.71 (s, 3H), 3.70-3.67 (m, 2H), 3.64-3.56 (m, 3H), 3.50 (t, *J* = 4.5 Hz, 1H), 3.33 (dd, *J* = 6.5, 8.5 Hz, 1H), 3.11 (s, 3H), 2.56 (d, *J* = 7.0 Hz, 1H), 2.48-2.40 (m, 2H), 2.33 (t, *J* = 10.0 Hz, 1H), 2.01-1.49 (m, 15H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.05-0.89 (m, 87H), 0.77-0.51 (m, 54H).



Acyl alcohol 4.54

To **4.24** (0.635 g, 0.303 mmol, 1 eq) in MeCN:THF 3:1 (16 mL) at 0 °C was added dropwise TBAF (1M in THF, 2.42 mL, 2.42 mmol, 8 eq). The reaction was stirred at 0 °C for 1.5 hours then was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with 20% MeOH/DCM (3 x 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was pushed through a plug of silica gel with 10% MeOH/DCM and taken into the next step without further purification. To the semi-crude material in pyridine (42 mL) was added DMAP (0.051 g, 0.418 mmol, 1.4 eq) and acetic anhydride (2.0 mL, 2.08 mmol, 69 eq). The reaction was stirred at 23 °C for 12 hours then partitioned between saturated aqueous

$NaHCO_3$:H_2O 1:1 (250 mL) and Et_2O (500 mL). The organic layer was washed with water (1 x 200 mL). The combined aqueous layers were extracted with Et_2O (2 x 150 mL). The combined organic layers were washed with brine (1 x 250 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 50% → 75% EtOAc/hexanes) to yield **4.54** (0.228 g, 0.150 mmol, 49% over 2 steps) as a yellow solid.



4.54

TLC (50% EtOAc/hexanes)

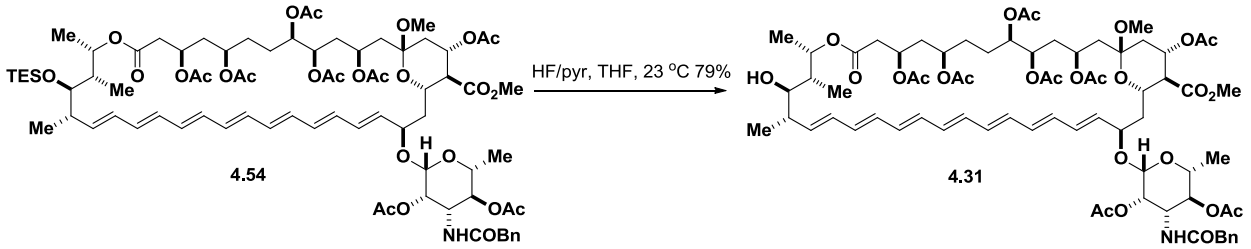
R_f = 0.20, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.29-7.19 (m, 5H), 1.07 (d, *J* = 9.5 Hz, 1H), 6.64-6.04 (m, 13H), 5.62 (dd, *J* = 9.0, 14.5 Hz, 1H), 5.53 (dd, *J* = 9.5, 15.0 Hz, 1H), 5.35-5.28 (m, 4H), 5.19-5.12 (m, 2H), 5.06-4.92 (m, 8H), 4.82 (s, 1H), 4.81-4.76 (m, 1H), 4.69 (t, *J* = 9.5 Hz, 1H), 4.53 (t, *J* = 6.5 Hz, 1H), 4.37-4.32 (m, 1H), 4.06 (t, *J* = 10.5 Hz, 1H), 3.67 (s, 3H), 3.61-3.53 (m, 2H), 3.47-3.39 (m, 4H), 3.16 (d, *J* = 2.5 Hz, 1H), 3.14 (s, 3H), 2.56-2.50 (m, 2H), 2.48-2.38 (m, 3H), 2.29 (t, *J* = 6.0 Hz, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H), 1.98-1.93 (m, 1H), 1.96 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H), 1.79 (s, 3H), 1.50-1.45 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.65 (q, *J* = 8.0 Hz, 6H).

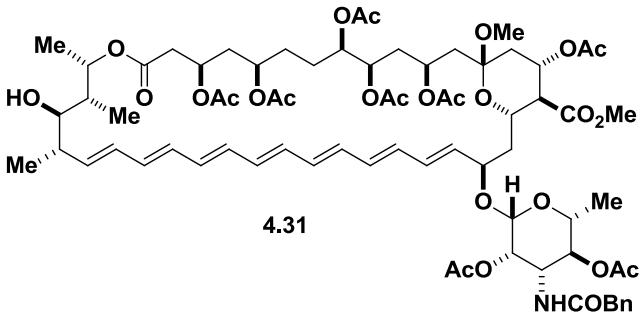
HRMS (ESI)

Calculated for $C_{79}H_{113}NO_{26}Si$ $(M + Na)^+$:	1542.7218
Found:	1542.7177



C35 Alcohol 4.31

To pyridine (31 mL) at 0 °C was added cautiously HF/pyridine (3.58 mL) and was stirred for 10 minutes. This solution was added to **4.54** (0.599 g, 0.394 mmol, 1 eq) in THF (47 mL) at 0 °C. The reaction was allowed to warm to 23 °C and was stirred for 14 hours. The reaction was recooled to 0 °C and was quenched slowly with $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (3 x 150 mL) and the combined organic layers were washed with water (1 x 100 mL) and brine (1 x 100 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 50% → 75% EtOAc/hexanes) to give **4.31** (0.437 g, 0.311 mmol, 79%) as a yellow solid.

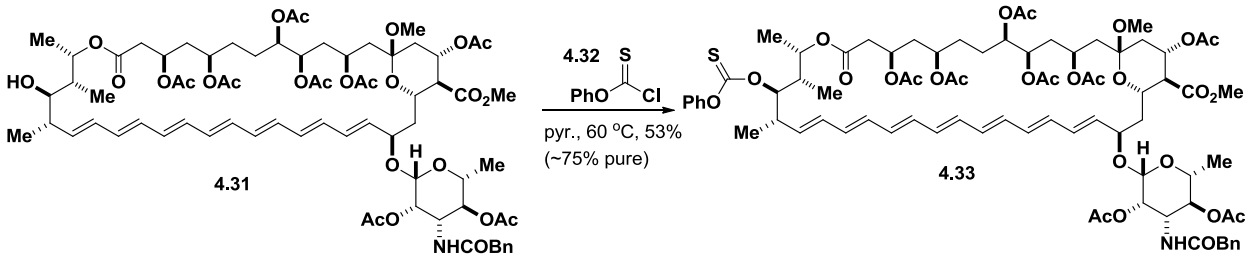


TLC (75% EtOAc/hexanes)

R_f = 0.29, stained by anisaldehyde.

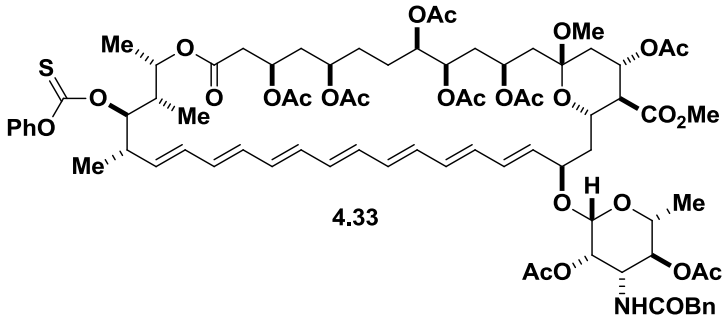
^{1}H NMR (500 MHz, acetone-d_6)

δ 7.29-7.19 (m, 4H), 7.06 (d, *J* = 9.0 Hz, 1H), 6.64-6.10 (m, 13H), 5.50 (dd, *J* = 9.5, 14.0 Hz, 1H), 5.33-5.28 (m, 3H), 5.21-5.15 (m, 1H), 5.09-4.93 (m, 4H), 4.80 (s, 1H), 4.68 (t, *J* = 10.0 Hz, 1H), 4.50 (t, *J* = 6.0 Hz, 1H), 4.36-4.32 (m, 1H), 4.10-4.00 (m, 2H), 3.95 (d, *J* = 5.5 Hz, 1H), 3.67 (s, 3H), 3.57 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.42 (q, *J* = 9.5 Hz, 2H), 3.27-3.25 (m, 2H), 3.17 (s, 3H), 2.53-2.38 (m, 4H), 2.29 (t, *J* = 11.0 Hz, 1H), 2.07-1.79 (m, 28H), 1.65-1.55 (m, 3H), 1.49-1.40 (m, 2H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H).



Thiocarbonate 4.33

To **4.31** (20 mg, 0.0142 mmol, 1 eq) in pyridine (1.42 mL) was added phenyl chlorothionoformate (0.019 mL, 0.142 mmol, 10 eq). The reaction was stirred at 40 °C for 3 hours then quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 50% → 70% EtOAc/hexanes) to yield **4.33** (12.2 mg, 0.00790 mmol, 56%) in only ~70% purity.



TLC (75% EtOAc/hexanes)

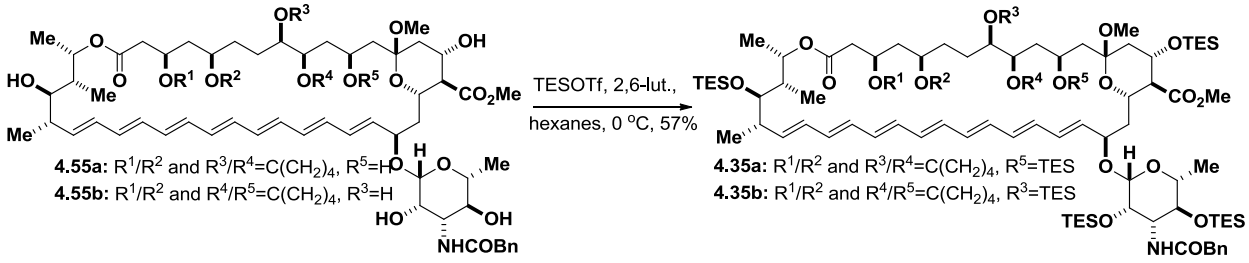
R_f = 0.47, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.48-7.42 (m, 2H), 7.32-7.06 (m, 8H), 6.64-6.08 (m, 14H), 5.50 (dd, *J* = 9.5, 14.5 Hz, 1H), 5.32-5.28 (m, 3H), 5.22-5.18 (m, 2H), 5.08-4.93 (m, 4H), 4.80 (s, 1H), 4.68 (t, *J* = 11.0 Hz, 2H), 4.50 (d, *J* = 7.0 Hz, 1H), 4.34 (t, *J* = 6.0 Hz, 1H), 4.08 (t, *J* = 5.5 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 1H), 3.67 (s, 3H), 3.60-3.55 (m, 1H), 3.42 (q, *J* = 11.0 Hz, 2H), 3.17 (s, 3H), 2.59-2.27 (m, 6H), 2.13-1.78 (m, 24H), 1.65-1.40 (m, 8H), 1.34-1.25 (m, 4H), 1.19-0.97 (m, 12H).

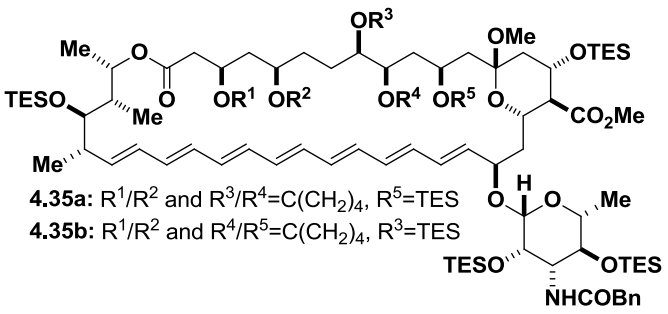
LRMS (ESI)

Calculated for $C_{80}H_{103}NO_{27}S$ $(M + Na)^+$:	1564.6
Found:	1564.5



TES Protected 4.35

To bisketal **4.55**[29] (0.100 g, 0.0.0832 mmol, 1 eq) in hexanes (4.2 mL) and 2,6-lutidine (0.140 mL, 1.198 mmol, 14.4 eq) at 0 °C was added dropwise TESOTf (0.209 mL, 0.924 mmol, 11.1 eq). The reaction was stirred at 0 °C for 2h then more 2,6-lutidine (0.035 mL, 0.299 mmol, 3.6 eq) and TESOTf (0.050 mL, 0.224 mmol, 2.7 eq) was added. The reaction was stirred at 0 °C for an additional 15 minutes then more 2,6-lutidine (0.035 mL, 0.299 mmol, 3.6 eq) and TESOTf (0.050 mL, 0.224 mmol, 2.7 eq) was added. The reaction was stirred an additional 1 hour then quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was transferred to a separatory funnel and was diluted with diethyl ether (100 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 x 50 mL) and water (1 x 50 mL). The combined aqueous washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with saturated aqueous copper sulfate (1 x 50 mL). The combined copper sulfate washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 0% → 15% EtOAc/hexanes) to give **4.35** (0.084 g, 0.474 mmol, 57%) as a yellow solid. The product was isolated as a 1:1 mixture of ketal constitutional isomers.

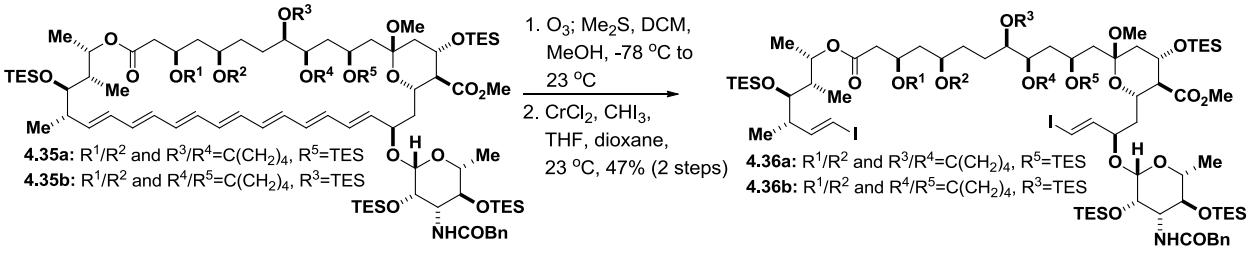


TLC (20% EtOAc/hexanes)

R_f = 0.30, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

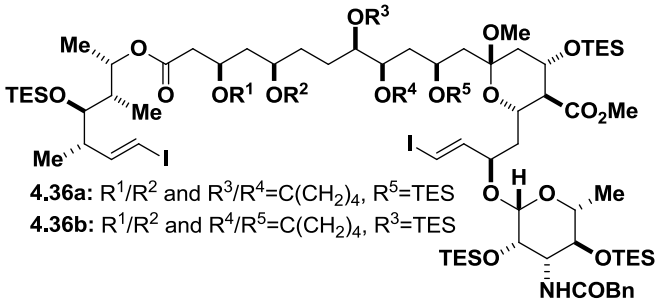
δ 7.36-7.25 (m, 10H), 6.38 (m, 20H), 6.07 (dd, *J* = 10.0, 14.5 Hz, 2H), 5.89 (dd, *J* = 5.5, 14.5 Hz, 1H), 5.83 (dd, *J* = 5.5, 15.0 Hz, 1H), 5.65-5.60 (m, 2H), 4.94-4.87 (m, 2H), 4.63-4.58 (m, 2H), 4.50 (s, 2H), 4.34-4.26 (m, 2H), 4.19-4.13 (m, 2H), 4.11-4.06 (m, 2H), 4.01-3.97 (m, 2H), 3.95-3.85 (m, 4H), 3.84-3.82 (m, 2H), 3.77-3.73 (m, 2H), 3.71 (s, 3H), 3.68 (s, 3H), 3.58-3.44 (m, 12H), 3.36-3.30 (m, 2H), 3.14 (s, 3H), 3.04 (s, 3H), 2.41-2.13 (m, 10H), 2.00-1.91 (m, 8H), 1.90-1.76 (m, 10H), 1.72-1.56 (m, 22H), 1.55-1.43 (m, 14H), 1.36-1.25 (m, 6H), 1.21 (d, *J* = 6.5 Hz, 6H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.04-0.90 (m, 102H), 0.70-0.53 (m, 60H).



Bisvinyl Iodide 4.36

TES ether **4.35** (0.300 g, 0.169 mmol, 1 eq) was dissolved in CH_2Cl_2 (13 mL) and MeOH (0.590 mL) and was cooled to -78 ^{o}C. Ozone was bubbled through the solution until a blue color persisted (~10 minutes) and the excess ozone was bubbled out with a stream of nitrogen. Dimethyl sulfide (0.124 mL, 1.691 mmol, 10 eq) was added at -78 ^{o}C with stirring and the cold bath was removed. The reaction was stirred at 23 ^{o}C overnight (~14 h). The mixture was concentrated and the residue was dissolved in diethyl ether (100 mL) and washed with saturated $NaHCO_3$ (75 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined

organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting white foam was azeotropically dried via coevaporation with benzene (3 x 10 mL) and left under vacuum for at least 1 hour. In a separate round bottom flask equipped with a stir bar and charged with $CrCl_2$ (0.650 g, 5.29 mmol, 31 eq) was added THF (3.8 mL) and dioxane (0.96 mL). To the $CrCl_2$ slurry was added dropwise a solution of the bisaldehyde intermediate and iodoform (0.551 g, 1.399 mmol, 8.2) in THF (2.9 mL) and dioxane (1.9 mL). The resulting dark red slurry was stirred at 23 ^oC for 1.5 hours before quenching with saturated $NaHCO_3$ (30 mL). The resulting green slurry was diluted with Et_2O (100 mL) and filtered through celite. The filtrate layers were separated and the organic layer was washed with saturated $Na_2S_2O_3$ (30 mL). The combined aqueous layers were extracted with diethyl ether (2 x 50 mL), then combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 0% → 15% EtOAc/hexanes) to furnish bisvinyl iodide **4.36** (0.151 g, 0.0796 mmol, 47% over two steps) as a white solid. The product was isolated as a 1:1 mixture of ketal constitutional isomers.

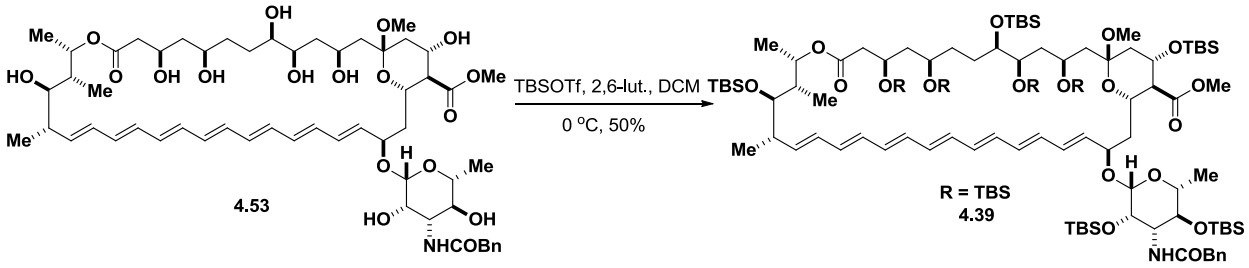


TLC (20% EtOAc/hexanes)

R_f = 0.33, stained by anisaldehyde.

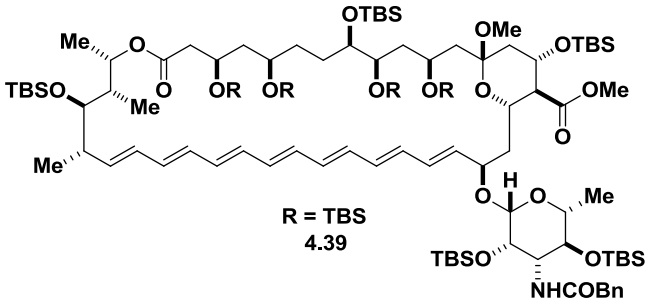
^1H NMR (500 MHz, acetone-d_6)

δ 7.36-7.25 (m, 10H), 6.59-6.49 (m, 4H), 6.28 (d, *J* = 9.0 Hz, 2H), 6.23 (d, *J* = 14.5 Hz, 2H), 5.13 (p, *J* = 6.5 Hz, 2H), 4.57 (s, 1H), 4.55 (s, 1H), 4.38-4.27 (m, 4H), 4.24-4.16 (m, 4H), 3.97-3.90 (m, 4H), 3.83 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.66-3.56 (m, 12H), 3.47 (t, *J* = 4.5 Hz, 2H), 3.32-3.27 (m, 2H), 3.17 (s, 3H), 3.13 (s, 3H), 2.54-2.47 (m, 2H), 2.43-2.38 (m, 4H), 2.31-2.14 (m, 6H), 2.00-1.84 (m, 12H), 1.75-1.41 (m, 42H), 1.36-1.28 (m, 6H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 6H), 1.01-0.88 (m, 102H), 0.69-0.53 (m, 60H).



TBS ether 4.39

To methyl ester **4.53**[29] (0.250 g, 0.234 mmol, 1 eq) in DCM (11.7 mL) and 2,6-lutidine (0.707 mL, 6.07 mmol, 26 eq) at 0 °C was added dropwise TBSOTf (1.07 mL, 4.67 mmol, 20 eq). The reaction was stirred at 0 °C for 1 hour then quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was transferred to a separatory funnel and was diluted with diethyl ether (100 mL). The layers were separated and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 x 50 mL) and water (1 x 50 mL). The combined aqueous washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with saturated aqueous copper sulfate (1 x 50 mL). The combined copper sulfate washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with water (1 x 50 mL) and brine (1 x 50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 0% → 5% EtOAc/hexanes) to give **4.39** (0.248 g, 0.118 mmol, 50%) as a yellow solid.



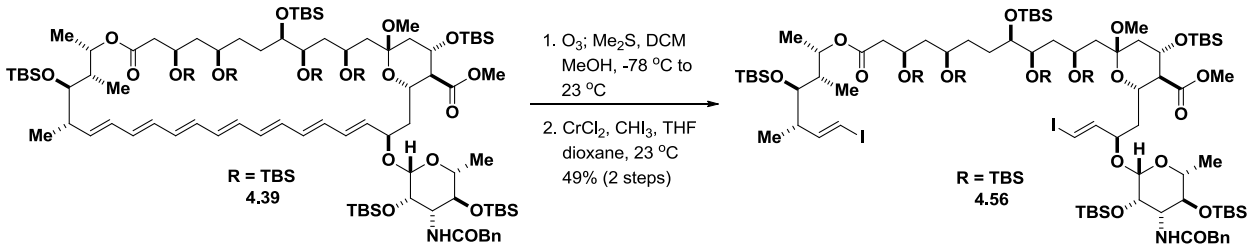
TLC (15% EtOAc/hexanes)

R_f = 0.50, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

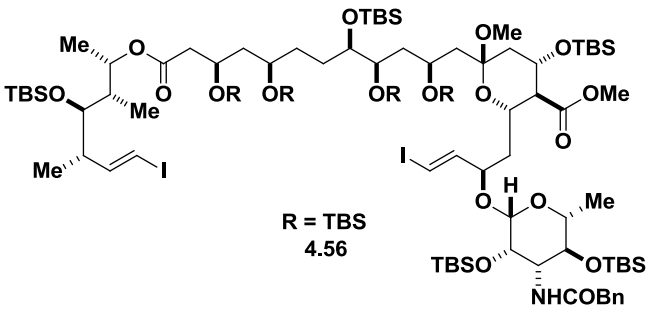
δ 7.34-7.20 (m, 5H), 6.69-6.57 (m, 3H), 6.42-6.10 (m, 9H), 5.95 (dd, *J* = 4.5, 15.5 Hz, 1H), 5.45 (dd, *J* = 10.0, 15.0 Hz, 1H), 4.63 (broad s, 1H), 4.49 (s, 1H), 4.49-4.46 (m, 1H), 4.41 (dt, *J* = 4.5, 9.5 Hz, 1H), 4.13-4.10 (m, 2H), 4.07-4.01 (m, 3H), 3.92-3.88 (m, 2H),

3.71-3.68 (m, 1H), 3.70 (s, 3H), 3.59-3.55 (m, 4H), 3.40-3.37 (m, 1H), 3.09 (s, 3H), 2.65-2.55 (m, 2H), 2.48-2.40 (m, 1H), 2.34 (t, *J* = 10.0 Hz, 1H), 2.21 (t, *J* = 9.0 Hz, 1H), 1.97-1.87 (m, 5H), 1.84-1.61 (m, 7H), 1.58-1.47 (m, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 5.5 Hz, 3H), 0.99-0.84 (m, 87H), 0.26-0.00 (m, 54H).



Bisvinyl Iodide 4.56

TBS ether **4.39** (1.12 g, 0.534 mmol, 1 eq) was dissolved in CH_2Cl_2 (49 mL) and MeOH (2.2 mL) and was cooled to -78 °C. Ozone was bubbled through the solution until a blue color persisted (~10 minutes) and the excess ozone was bubbled out with a stream of nitrogen. Dimethyl sulfide (0.124 mL, 1.691 mmol, 10 eq) was added at -78 °C with stirring and the cold bath was removed. The reaction was stirred at 23 °C overnight (~14 h). The mixture was concentrated and the residue was dissolved in diethyl ether (300 mL) and washed with saturated $NaHCO_3$ (150 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting white foam was azeotropically dried via coevaporation with benzene (3 x 10 mL) and left under vacuum for at least 1 hour. In a separate round bottom flask equipped with a stir bar and charged with $CrCl_2$ (2.03 g, 16.55 mmol, 31 eq) was added THF (11.8 mL) and dioxane (3.0 mL). To the $CrCl_2$ slurry was added dropwise a solution of the bisaldehyde intermediate and iodoform (1.72 g, 4.38 mmol, 8.2) in THF (8.9 mL) and dioxane (5.9 mL). The resulting dark red slurry was stirred at 23 °C for 1.5 hours before quenching with saturated $NaHCO_3$ (100 mL). The resulting green slurry was diluted with Et_2O (300 mL) and filtered through celite. The filtrate layers were separated and the organic layer was washed with saturated $Na_2S_2O_3$ (50 mL). The combined aqueous layers were extracted with diethyl ether (2 x 100 mL), then combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 0% → 10% EtOAc/hexanes) to furnish bisvinyl iodide **4.56** (0.578 g, 0.260 mmol, 49% over two steps) as a white solid.

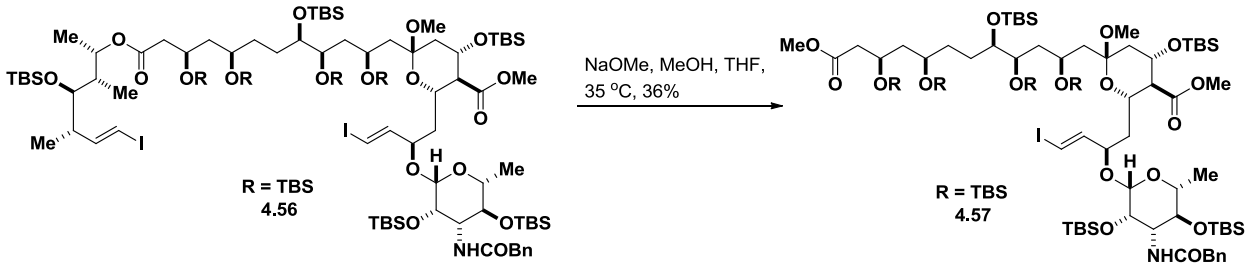


TLC (15% EtOAc/hexanes)

R_f = 0.52, stained by anisaldehyde.

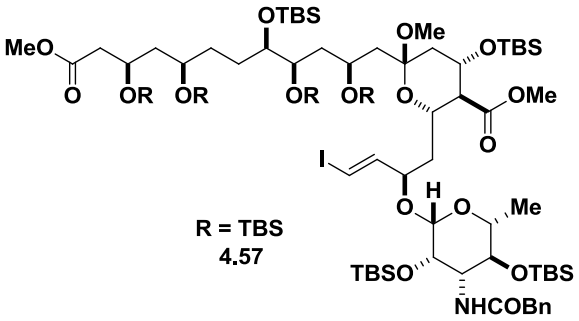
^{1}H NMR (500 MHz, acetone-d_6)

δ 7.31-7.22 (m, 5H), 5.59 (dd, *J* = 7.5, 14.5 Hz, 1H), 6.47 (dd, *J* = 7.5, 14.5 Hz, 1H), 6.35 (d, *J* = 8.5 Hz, 1H), 6.20 (d, *J* = 14.5 Hz, 1H), 5.17-5.14 (m, 1H), 4.57 (s, 1H), 4.33-4.26 (m, 2H), 4.06-3.98 (m, 2H), 3.90-3.84 (m, 2H), 3.70 (s, 3H), 3.67-3.54 (m, 4H), 3.37-3.34 (m, 1H), 3.19 (s, 3H), 2.56-2.49 (m, 2H), 2.41 (dd, *J* = 8.0, 15.0 Hz, 1H), 2.24 (t, *J* = 10.5 Hz, 1H), 1.99-1.93 (m, 4H), 1.85-1.46 (m, 16H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.96-0.85 (m, 84H), 0.18-0.00 (m, 54H).



Methyl Ester 4.57

To bisvinyl iodide **4.56** (0.575 g, 0.259 mmol, 1 eq) in MeOH:THF 1:1 (7 mL) was added NaOMe (0.140 g, 2.59 mmol, 10 eq) in MeOH (3.5 mL) via cannula. The reaction was stirred at 50 °C for 3 hours then more NaOMe (0.140 g, 2.59 mmol, 10 eq) was added as a solid. After 22 hours at 50 °C the reaction was cooled to 0 °C then quenched with 0.5 M pH 7 phosphate buffer (10 mL). The mixture was diluted with Et_2O (100 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (2 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2; 0% → 10% EtOAc/hexanes) yielded **4.57** (0.172 g, 0.093 mmol, 36%) as a colorless solid.

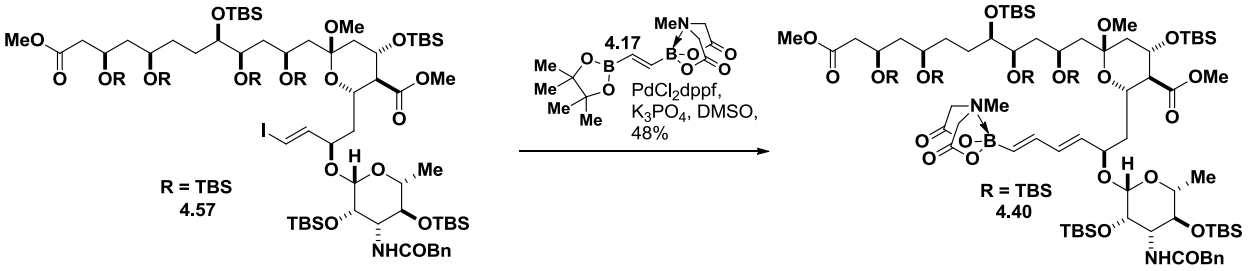


TLC (15% EtOAc/hexanes)

R_f = 0.44, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

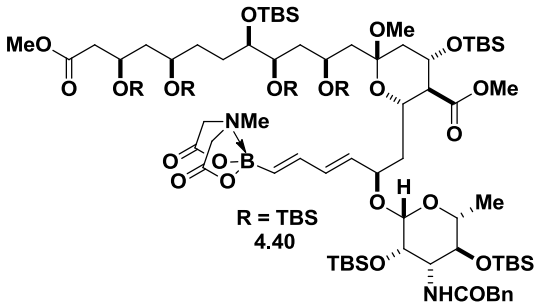
δ 7.33-7.22 (m, 5H), 6.56 (d, *J* = 14.5 Hz, 1H), 6.47 (dd, *J* = 7.5, 14.5 Hz, 1H), 6.36 (d, *J* = 9.0 Hz, 1H), 4.57 (s, 1H), 4.32 (m, 3H), 4.05-3.97 (m, 2H), 3.89 (d, *J* = 2.5 Hz, 1H), 3.88-3.83 (m, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.57-3.52 (m, 7H), 3.37-3.33 (m, 1H), 3.19 (s, 3H), 2.59 (dd, *J* = 6.0, 15.0 Hz, 1H), 2.37 (dd, *J* = 8.0, 15.0 Hz, 1H), 2.24 (t, *J* = 10.5 Hz, 1H), 2.15-2.11 (m, 1H), 1.98-1.91 (m, 1H), 1.82-1.51 (m, 14H), 1.44-1.39 (m, 2H), 1.30-1.26 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.95-0.84 (m, 72H), 0.18-0.00 (m, 48H).



Dienyl MIDA Boronate 4.40

A 20 mL I-Chem vial equipped with a stir bar was charged with methyl ester **4.57** (0.170 g, 0.0916 mmol, 1 eq) and bisborylated compound **4.17**[16,27] (0.056 g, 0.183 mmol, 2 eq), sealed under argon, and was taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.015 g, 0.0183 mmol, 20 mol%) and K_3PO_4 as a finely ground powder (0.117 g, 0.549 mmol, 6 eq) were added followed by DMSO (4.6 mL). The reaction was sealed with a PTFE-lined cap and stirred at 23 ^oC for 24 h. The solution was diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (100 mL). The filtrate was washed with brine (3 x 20 mL) and the combined aqueous layers were back-extracted with EtOAc (75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash

chromatography (SiO_2; 50% → 70% EtOAc/hexanes) to furnish dienyl MIDA boronate **4.40** (0.083 g, 0.043 mmol, 48%) as a white solid.

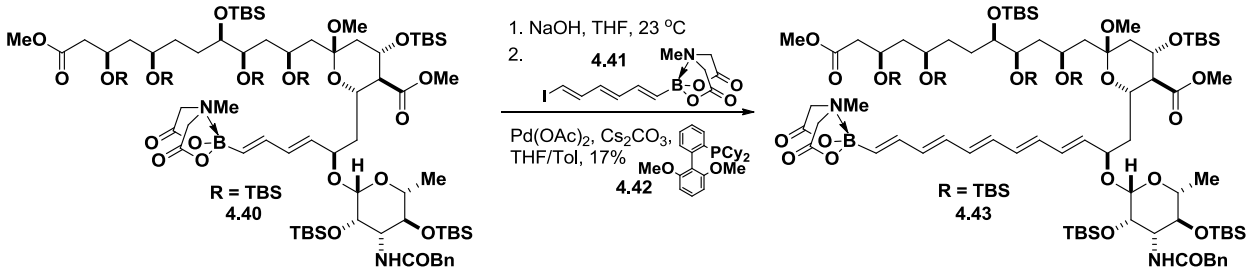


TLC (EtOAc)

R_f = 0.73, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.30-7.22 (m, 5H), 6.61 (dd, *J* = 10.5, 17.5 Hz, 1H), 6.40 (d, *J* = 9.0 Hz, 1H), 6.32 (dd, 10.5, 15.5 Hz, 1H), 5.68 (d, *J* = 17.5 Hz, 1H), 5.59 (dd, *J* = 8.5, 15.0 Hz, 1H), 4.59 (s, 1H), 4.38-4.32 (m, 1H), 4.29-4.20 (m, 2H), 4.08-3.99 (m, 2H), 3.90 (d, *J* = 2.5 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.58-3.54 (m, 1H), 3.38-3.35 (m, 1H), 3.14 (s, 3H), 3.00 (s, 3H), 2.62-2.57 (m, 1H), 2.40-2.34 (m, 1H), 2.23 (t, *J* = 10.0 Hz, 1H), 2.13 (s, 1H), 1.81-1.65 (m, 9H), 1.57-1.48 (m, 4H), 1.43-1.32 (m, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.95-0.84 (m, 72H), 0.18--0.02 (m, 48H).



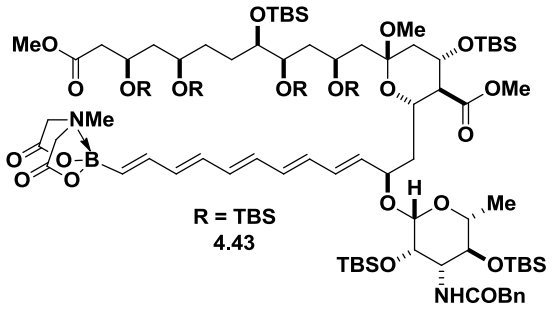
Pentaenyl MIDA Boronate 4.43

*MIDA boronate **4.43** was converted to a boronic acid via the following procedure*: To a stirred solution of dienyl MIDA boronate **4.43** (80 mg, 0.0419 mmol, 1 eq) in THF (4.2 mL) at 23 ˚C was added 1 M aq. NaOH (1.3 mL, 1.3 mmol, 30 eq) and the resulting mixture was stirred for 10 min. The reaction was then quenched with the addition of 0.5 M pH 7 phosphate buffer (10 mL) and diluted with Et_2O (10 mL). The layers were separated and the aq. layer was extracted with

Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo until a small amount of THF (~0.6 mL) remained, yielding a solution of boronic acid.

A solution of the palladium catalyst was prepared as follows: To a 1.5 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl ligand (S-Phos, 6.8 mg, 0.0167 mmol) was added a solution of $Pd(OAc)_2$ in toluene (0.0145 M , 0.580 mL, 0.00836 mmol). The vial was sealed with a PTFE-lined cap and maintained at 23 ^oC with stirring for 30 min.

This catalyst solution was then utilized in the following procedure: To a 7-mL vial equipped with a stir bar and containing triene **4.41**[21] (13.6 mg, 0.0376 mmol, 0.9 eq) was added the boronic acid as a solution in THF (estimated 0.6 mL, 0.0419 mmol, 1 eq), anhydrous Cs_2CO_3 (81.8 mg, 0.251 mmol, 6 eq), and the catalyst stock solution described above (0.290 mL, 0.00418 mmol Pd, 10 mol% Pd). The resulting mixture was sealed with a PTFE-lined cap and stirred at 45 ˚C for 3.5 hours. The reaction was then diluted with EtOAc (2 mL) and filtered throught a short pad of silica gel with copious amounts of EtOAc. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (50% → 75% EtOAc/hexanes) to yield pentaenyl MIDA boronate **4.43** (12.8 mg, 0.00644 mmol, 17%) as a pale yellow solid.



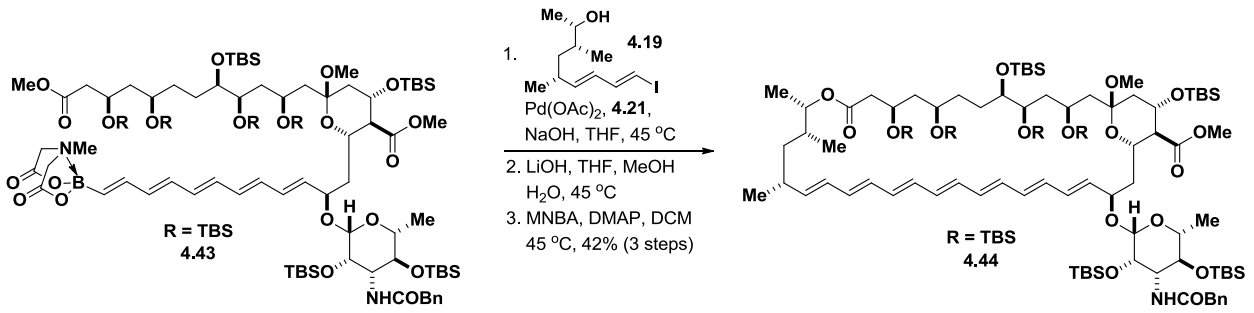
TLC (75% EtOAc/hexanes)

R_f = 0.43, stained by anisaldehyde.

^1H NMR (500 MHz, acetone-d_6)

δ 7.31-7.20 (m, 5H), 6.41-6.28 (m, 8H), 6.15-6.07 (m, 1H), 5.79-5.58 (m, 2H), 4.59 (s, 1H), 4.40-4.24 (m, 3H), 4.21 (d, *J* = 21.0 Hz, 2H), 4.03 (d, *J* = 21.5 Hz, 2H), 3.90-3.83 (m, 2H), 3.69 (s, 3H), 3.62 (s, 3H), 3.56-3.54 (m, 1H), 3.29 (d, *J* = 6.0 Hz, 1H), 3.15 (s,

3H), 2.99 (s, 3H), 2.26-2.21 (m, 2H), 1.82-1.63 (m, 13H), 1.60-1.49 (m, 2H), 1.48-1.39 (m, 2H), 1.30-1.11 (m, 13H), 0.95-0.84 (m, 72H), 0.18--0.02 (m, 48H).

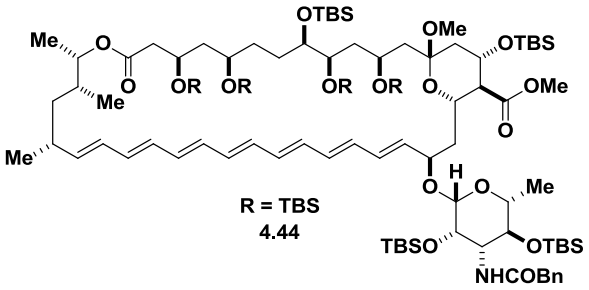


Macrolactone 4.44

A solution of the palladium catalyst was prepared as follows: To a 1.5 mL vial equipped with a stir bar and containing 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl ligand (1.5 mg, 0.0031 mmol) was added a solution of $Pd(OAc)_2$ in toluene (0.0073 M , 0.676 mL, 0.00057 mmol). The vial was sealed with a PTFE-lined cap and maintained at 23 ^{o}C with stirring for 15 min.

This catalyst solution was then utilized in the following procedure: To pentaenyl MIDA boronate **4.44** (12.8 mg, 0.00643 mmol, 1 eq) and dienyl iodide **4.19** (1.8 mg, 0.00611 mmol, 0.95 eq) was added the catalyst stock solution described above (0.045 mL, 0.000321 mmol Pd, 5 mol% Pd). The resulting mixture was sealed with a teflon-lined septum cap and 1 M NaOH (0.032 mL, 0.032 mmol, 5 eq) was added. The reaction was stirred at 23 ^{o}C for 30 min then at 45 ^{o}C for 2 hours. The reaction was diluted Et_2O (10 mL) and was quenched with 0.5 M pH 7 phosphate buffer (5 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic layers were filtered through a short plug of silica gel with Et_2O and concentrated. The residue was taken up in THF:MeOH:H_2O 3:1:1 (0.7 mL), LiOH (14.7 mg, 0.349 mmol, 50 eq) was added, and the vial was sealed under argon. The reaction was stirred at 35 ^{o}C for 1 h and then heated to 45 ^{o}C for 3 hours. The reaction was then diluted with EtOAc (10 mL) and was poured into water (10 mL). The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was dissolved in CH_2Cl_2 (1.5 mL) and was added dropwise over 5 h to a solution of MNBA (2.4 mg, 0.0070 mmol, 1.2 eq) and DMAP (1.7 mg, 0.0140 mmol, 2.4 eq) in CH_2Cl_2 (2.4 mL). The reaction was stirred an additional 10 hours and was then heated to 45 ^{o}C and stirred for 1 hour. The reaction was cooled to 0 ^{o}C and quenched with saturated $NaHCO_3$ (10 mL). The layers were

separated and the aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 5% → 10% EtOAc/hexanes) to provide macrolactone **4.44** (5.1 mg, 0.00259 mmol, 42% over 3 steps) in very low purity.

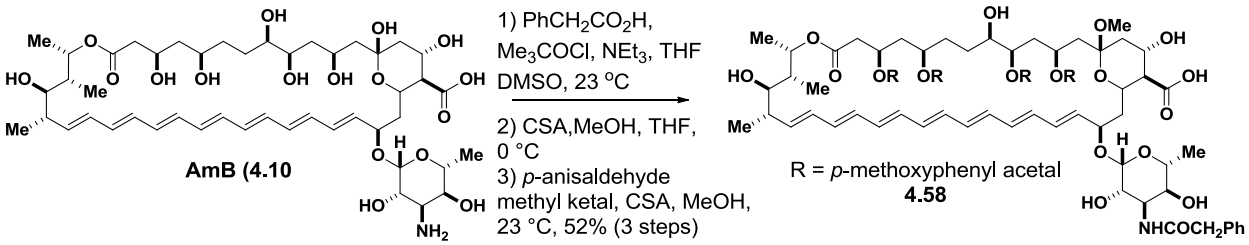


TLC (20% EtOAc/hexanes)

R_f = 0.54, stained by anisaldehyde.

HRMS (ESI)

Calculated for $C_{105}H_{195}NO_{17}Si_8$ $(M + Na)^+$:	1989.2477
Found:	1989.2449



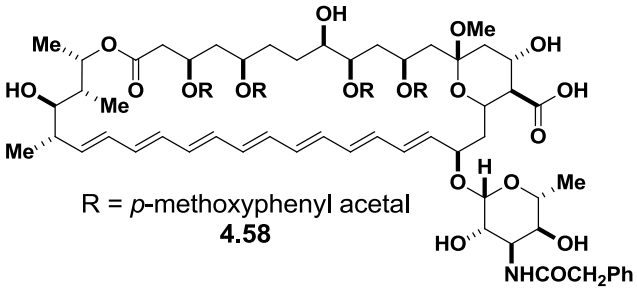
Acetal Protected 4.58

Trimethyl acetyl chloride (400 µL, 3.25 mmol, 2 eq) was added to a solution of phenyl acetic acid (662 mg, 4.86 mmol, 3 eq) in THF (30 mL). Triethylamine (900 µL, 6.46 mmol, 4 eq) was added to the reaction, and it was stirred for 6 hours at 23 °C. The reaction was placed in an ice bath, and DMSO (30 mL) was added over 2 minutes as the solution cooled. Once the reaction mixture reached 0 °C, AmB (1.50 g, 1.62 mmol, 1 eq) was added. The yellow-tan suspension was stirred for 90 minutes at 0 °C. The reaction was then poured into diethyl ether (1.8 L) with rapid stirring. After 15 minutes of stirring, the resulting yellow precipitate was vacuum filtered

and washed 3 times with diethyl ether (200 mL). The yellow powder was placed under vacuum for 8 hours prior to the next reaction.

Three 1.5 gram batches of N-phenyl acyl amphotericin B were pooled together for the succeeding reactions. The yellow solid (5.00 g, 4.80 mmol, 1 eq) was dissolved in a mixture of methanol (90 mL, 0.05 M) and THF (90 mL) and the solution was cooled to 0 °C. (±) Camphorsulfonic acid (223 mg, 0.96 mmol, 0.2 eq) was added to the cooled solution and the reaction was stirred for one hour at 0 °C. The reaction was quenched at 0 °C with triethylamine (130 μL, 0.96 mmol, 0.2 eq) and the volume of the solvent was reduced *in vacuo* by approximately 50 percent. The solution was poured into 3.6 L of a 1:1 ether:hexane solution and the resulting precipitate was isolated via vacuum filtration. The yellow solid was taken forward to the next step without further purification.

The yellow solid (*ca* 5 g, 4.8 mmol, 1 eq) was dissolved in methanol (80 mL) and *p*-anisaldehyde methyl acetal (12 mL, 70 mmol, 146 eq) was added to the reaction. Subsequently, (±) camphorsulfonic acid (449 mg, 1.93 mmol, 0.4 eq) was added and the reaction was stirred at 23 °C for one hour. The reaction was quenched by the addition of triethylamine (270 μL, 1.92 mmol, 0.4 eq) and the solvent was removed *in vacuo*. The crude was purified via flash chromatography (SiO_2; 3% → 10% MeOH/DCM/0.15 AcOH) to yield **4.58** as an orange solid (3.20 g, 2.48 mmol, 52% over three steps) of approximately 70% purity which was carried forward without further purification.



R = *p*-methoxyphenyl acetal

4.58

TLC (10% MeOH/DCM/0.1% AcOH)

R_f = 0.15 stained by anisaldeyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 4H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.22 (app. t,

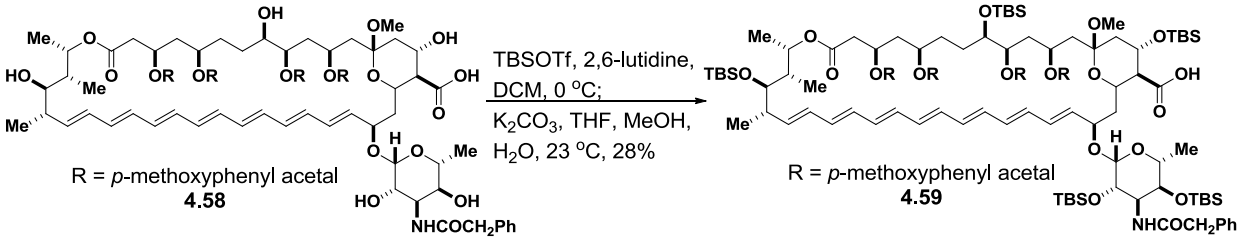
J = 7.5 Hz, 1H), 6.86 (dd, *J* = 3.0, 9.0 Hz, 4H), 6.44-6.19 (m, 12H), 5.87 (dd, *J* = 5.5, 15.0 Hz, 1H), 5.56 (dd, *J* = 9.5, 13.5 Hz, 1H), 5.51 (s, 1H), 5.46 (s, 1H), 5.28-5.25 (m, 1H), 4.67 (app. t, *J* = 6.0 Hz, 1H), 4.61 (s, 1H), 4.24-4.09 (m, 3H), 3.96-3.84 (m, 4H), 3.77 (s, 6H), 3.65 (s, 2H), 3.44-3.42 (m, 1H), 3.38-3.29 (m, 3H), 3.04 (s, 3H), 2.57 (dd, *J* = 6.0, 16.5 Hz, 1H), 2.42-2.37 (m, 1H), 2.32-2.27 (m, 2H), 2.21 (app. t, *J* = 10.0 Hz, 1H), 2.16-2.10 (m, 1H), 1.89-1.81 (m, 3H), 1.76-1.63 (m, 4H), 1.56-1.43 (m, 4H), 1.36-1.27 (m, 3H), 1.21 (d, *J* = 5.5 Hz, 3H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 169.8, 160.6, 160.5, 136.9, 134.2, 133.8, 133.0, 132.9, 132.7, 132.6, 130.1, 129.1, 128.3, 128.2, 127.3, 113.9, 101.1, 100.8, 100.6, 97.9, 81.1, 76.4, 74.4, 73.2, 72.9, 70.7, 70.5, 67.2, 67.0, 57.2, 56.4, 55.5, 48.7, 43.6, 43.3, 41.5, 37.9, 34.0, 33.3, 18.9, 18.2, 17.6, 11.9.

HRMS (ESI)

calculated for $C_{72}H_{93}NO_{20}$ $(M+Na)^+$:	1314.6189
found:	1314.6213

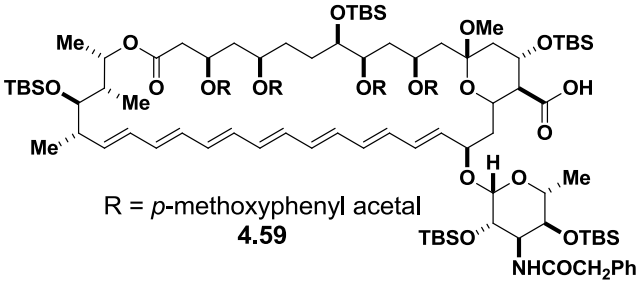


TBS Protected 4.59

Prior to the reaction, **4.58** was coevaporated with acetonitrile (3 x 25 mL) and left under vacuum for a minimum of eight hours. The resulting orange solid (2.98 g, 2.31 mmol, 1 eq) was dissolved in dichloromethane (70 mL) and 2,6-lutidine (3.5 mL, 30 mmol, 13 eq) was added to the solution. The reaction was subsequently cooled to 0 °C and *tert*-butyldimethylsilyl trifluromethane sulfonate (5 mL, 22 mmol, 9.5 eq) was added dropwise over approximately 15 minutes. The reaction was stirred for 1 hour at 0 °C and was then quenched by the addition of 50

mL saturated aqueous sodium bicarbonate. The biphasic mixture was transferred to a 2 L separatory funnel and was diluted with diethyl ether (1 L). The layers were separated and the organic phase was washed with saturated aqueous sodium bicarbonate (1 x 100 mL) and water (1 x 100 mL). The combined aqueous washings were back-extracted with diethyl ether (1 x 50 mL) and the combined organic extracts were washed with saturated aqueous copper sulfate (5 x 100 mL). The combined copper sulfate washings were back-extracted with diethyl ether (1 x 100 mL) and the combined organic extracts were washed with water (1 x 100 mL) and brine (1 x 100 mL), dried over sodium sulfate and concentrated *in vacuo*.

The resulting brown oil was taken up in THF:MeOH:H_2O (70 mL, 3:1:1 v/v/v) and potassium carbonate (3.2 g, 23 mmol, 10 eq) was added. Within approximately five minutes the reaction transitioned from turbid to clear. The reaction was stirred for 30 minutes at 23 °C and was then quenched by the addition of 50 mL potassium phosphate buffer (50 mL, pH 7.0). The mixture was transferred to a 1 L separatory funnel and was extracted with diethyl ether (3 x 250 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The crude was purified via flash chromatography (SiO_2; 30% → 100% EtOAc) to yield the title compound **4.59** as a yellow solid (1.21 g, 0.65 mmol, 28%).



R = *p*-methoxyphenyl acetal

4.59

TLC (30% EtOAc/hexanes)

R_f = 0.2 stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.37-7.27 (m, 4H), 7.24-7.22 (m, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.87-6.84 (m, 4H), 6.50 (d, *J* = 9 Hz, 1H), 6.44-6.30 (m, 8H), 6.28-6.18 (m, 2H), 6.06 (dd, *J* = 10, 15 Hz, 1H), 5.81 (dd, *J* = 6, 15 Hz, 1H), 5.66 (dd, *J* = 9.5, 15 Hz, 1H), 5.45 (s, 2H) 4.85 (bs, 1H), 4.66 (app t, 6 Hz, 1H), 4.58 (s, 1H), 4.25 (dt, 4.5, 10.5 Hz, 1H), 4.21-4.16 (m, 1H), 4.01-3.91(m, 2H), 3.92-3.87 (m, 3H), 3.79 (s, 3H), 3.71 (s, 3H),

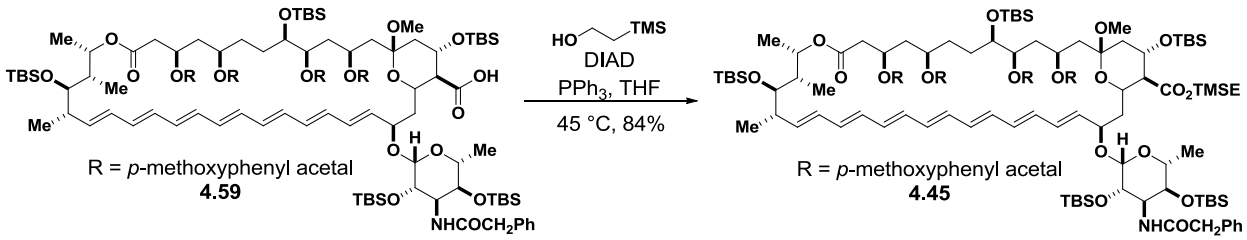
3.71-3.69 (m, 1H), 3.60 (s, 3H), 3.58-3.55 (m, 1H), 3.42-3.37 (m, 2H), 3.05 (s, 3H), 2.52 (dd, *J* = 7.5, 17.5 Hz, 1H), 2.41 (s, 2H), 2.27 (d, *J* = 5 Hz 1H), 2.28 (t, 3.5 Hz, 1H), 2.25-2.23 (m, 1H), 2.11 (dd, *J* = 4, 12 Hz, 1H), 1.92-1.84 (m, 2H), 1.73-1.69 (m, 1H), 1.66-1.61 (m, 1H), 1.59-1.47 (m, 2H), 1.44-1.40 (m, 1H), 1.34-1.27 (m, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6 Hz, 3H), 1.16-1.15 (m, 1H), 1.00 (d, *J* = 7 Hz, 3H), 0.95 (d, *J* = 7 Hz, 3H), 0.928, (s, 9H), 0.899 (s, 9H), 0.865 (s, 9H), 0.845 (s, 9H), 0.757 (s, 9H), 0.120 (s, 3H), 0.114 (s, 3H), 0.108 (s, 3H), 0.098 (s, 3H), 0.073 (s, 3H), 0.071 (s, 3H), 0.059 (s, 3H), 0.029 (s, 3H), -0.044, (s, 3H), -0.054 (s, 3H), -0.134 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 173.5, 170.2, 169.4, 160.1, 160.0, 157.5, 135.6, 134.1, 133.8, 133.2, 132.9, 132.5, 132.1, 132.0, 131.1, 130.6, 129.8, 129.7, 128.6, 128.1, 127.9, 127.8, 127.7, 120.4, 120.3, 113.4, 113.3, 101.0, 100.8, 100.6, 100.4, 100.2, 97.6, 75.5, 74.4, 73.0, 72.8, 72.3, 68.2, 67.0, 56.7, 56.0, 55.0, 54.9, 54.8, 43.2, 40.7, 26.2, 26.18, 26.05, 25.99, 25.91, 25.79, 25.72, 25.60, 25.40, 23.80, 18.44, 18.30, 18.11, 17.87, -3.65, -3.75, -3.93, -4.27, -4.42,-4.54, -4.63, -4.80, -5.22.

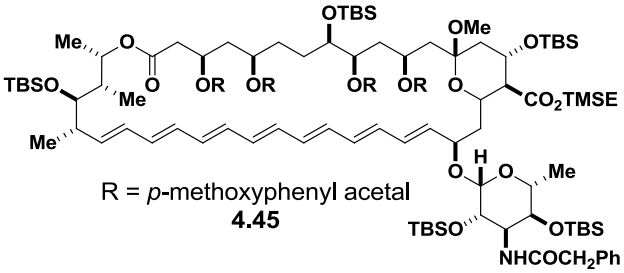
HRMS (ESI)

calculated for $C_{102}H_{163}NO_{20}Si_5$ $(M + Na)^+$:	1885.0513
found :	1885.0470



Trimethylsilyl ethyl ester 4.45

A 200 mL round bottom flask was charged with penta *tert*-butyldimethyl silyl **4.59** (1.2 g, 0.61 mmol, 1 eq) and THF (35 mL) was added. The solution was cooled to 0 °C and 2-(trimethylsilyl) ethanol (0.28 mL, 1.9 mmol, 3 eq) was added followed by triphenylphosphine (420 mg, 1.6 mmol, 2.5 eq). The reaction was stirred at 0 °C for approximately 10 minutes and then diisopropyl azodicarboxylate (0.28 mL, 1.4 mmol, 2.2 eq) was added dropwise. The reaction was then transferred to a 45 °C water bath and was stirred for 2 hours. After 2 hours the reaction was concentrated *in vacuo* and was subsequently dissolved in hexanes (100 mL). The hexanes solution was stirred for 10 minutes, the resulting precipitate was removed via vacuum filtration and the filtrate was concentrated *in vacuo*. The crude was purified via flash chromatography (SiO_2; 0% $\rightarrow$ 20% EtOAc/hexanes) to yield the trimethylsilyl ethyl ester **4.45** as yellow foamy solid (1.06 g, 0.539 mmol, 84%).



TLC (20% EtOAc/hexanes)

R_f = 0.32, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone d_6)

δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.37-7.27 (m, 6H), 7.23-7.20 (m, 1H), 6.87-6.83 (m, 4H), 6.42-6.30 (m, 9H), 6.25-6.18 (m, 2H), 6.07 (dd, *J* = 10, 15.5 Hz, 1H), 5.80 (dd, *J* = 6.5, 14.5 Hz, 1H), 5.67 (dd *J* = 9.5, 15.5 Hz, 1H) 5.45 (s, 2H), 4.86 (bs, 1H), 4.61 (app t *J* = 7 Hz, 1H), 4.57 (s, 1H), 4.24-4.15 (m, 4H), 4.02 (dt, *J* = 2, 6 Hz, 1H), 3.93-3.92 (m, 2H), 3.89-3.85 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.75-3.71 (m, 2H), 3.57 (s, 3H), 3.41-3.37

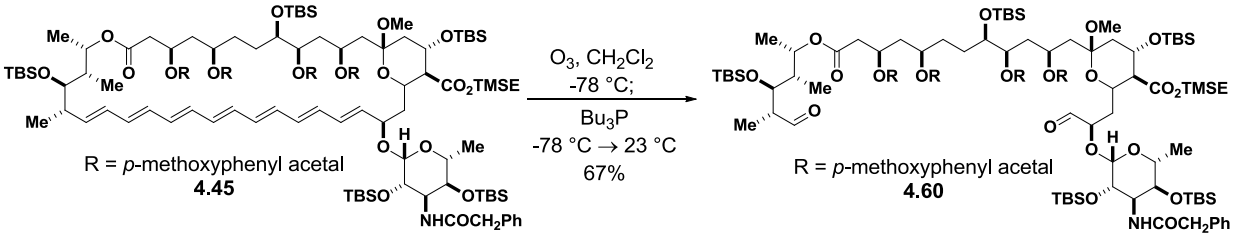
(m, 3H), 3.06 (s, 3H), 2.52 (dd, *J* = 7.5, 17.5 Hz, 1H), 2.44-2.40 (m, 1H), 2.31 (app t, *J* = 9.5 Hz, 1H), 2.28-2.24 (m, 3H), 2.00-1.95 (m, 1H), 1.89-1.85 (m, 1H), 1.81 (dd, *J* = 6.5, 13.5 Hz, 1H), 1.72-1.69 (m, 1H), 1.65-1.60 (m, 2H), 1.54-1.50 (m, 1H), 1.45-1.43 (app d, *J* = 12.5 Hz, 1H), 1.23 (d, *J* = 6 Hz, 3H), 1.21-1.20 (m, 1H), 1.18 (d, *J* = 9.5 Hz, 3H), 1.01 (app t, *J* = 7 Hz, 1H), 1.06-1.04 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.940 (d, *J* = 7 Hz, 3H), 0.928 (s, 9H), 0.916-0.912 (m, 1H), 0.900 (s, 9H), 0.888-0.885 (m, 1H), 0.864 (s, 9H), 0.842 (s, 9H), 0.749 (s, 9H), 0.118 (s, 3H), 0.107 (s, 3H), 0.099 (s, 3H), 0.069 (s, 3H), 0.055 (s, 9H), 0.038 (s, 3H), 0.020 (s, 3H), -0.002 (s, 3H), -0.046 (s, 3H), -0.084 (s, 3H), -0.169 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 172.7, 169.5, 169.4, 160.1, 160.0, 136.2, 135.7, 134.1, 133.7, 133.2, 133.1, 132.8, 132.5, 132.3, 132.1, 132.0, 130.6, 129.7, 128.5, 128.0, 127.7, 126.9, 113.4, 101.0, 100.5, 100.2, 98.1, 80.6, 75.4, 75.3, 74.3, 74.2, 72.9, 72.5, 72.3, 68.4, 67.2, 62.8, 58.8, 56.5, 55.8, 55.0, 54.9, 54.8, 47.9, 43.5, 42.8, 40.8, 37.4, 36.2, 32.8, 32.2, 27.5, 27.4, 26.1, 26.0, 25.9, 25.6, 25.3, 21.9, 21.8, 21.7, 19.3, 18.5, 18.3, 18.1, 17.9, 17.8, 17.7, -1.51, -1.72, -2.01, -3.73, -3.77, -3.93, -4.28, -4.38, -4.49, -4.62, -4.74, -5.33.

HRMS (ESI)

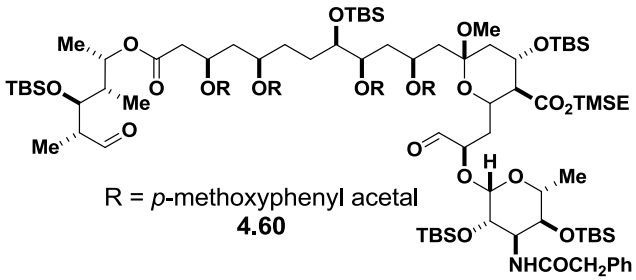
calculated for $C_{107}H_{175}NO_{20}Si_6$ $(M + Na)^+$:	1985.1221
found:	1985.1249



Bisaldehyde 4.60

TMSE ester **4.45** (1.65 g, 0.840 mmol, 1 eq) was dissolved in CH_2Cl_2 (65 mL) and MeOH (3.9 mL) and was cooled to -78 °C. Ozone was bubbled through the solution until a blue color persisted (~10 minutes) and then the excess ozone was bubbled out of the solution with a stream of argon. Tributylphosphine (2.1 mL, 8.40 mmol, 10 eq) was added at -78 ^{o}C with stirring, and

the cold bath was removed. The reaction was stirred for 30 minutes and then was poured into saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 0% → 30% EtOAc/hexanes) to furnish bisaldehyde **4.60** as a white foamy solid (1.028 g, 0.559 mmol, 67%). This material was taken on immediately to the next step as a precaution against decomposition.

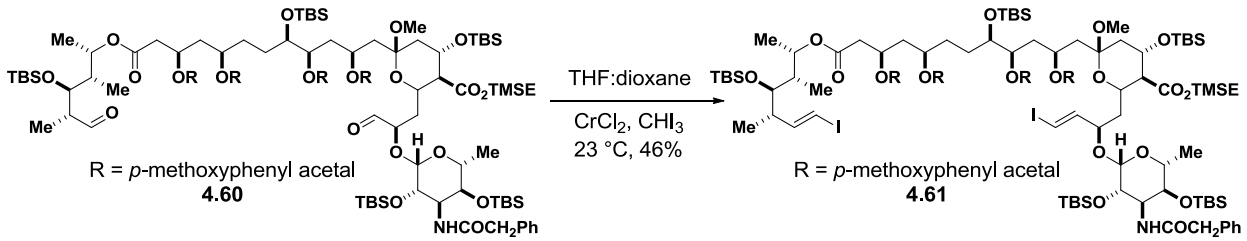


TLC (20% EtOAc/hexanes)

R_f = 0.27, stained by anisaldehyde.

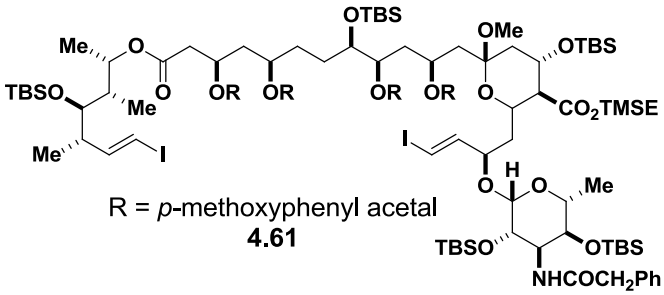
^{1}H NMR (500 MHz, acetone-d_6)

δ 9.67 (s, 1H), 9.53 (d, *J* = 1.5 Hz, 1 H), 7.39-7.21 (m, 9H), 6.86 (dd, *J* = 6.5, 8.5 Hz, 4H), 5.52 (s, 2H), 5.12 (p, *J* = 6.5 Hz, 1H), 4.75 (s, 1H), 4.37 (dd, *J* = 2.5, 7.0 Hz, 1H), 4.33-4.20 (m, 4H), 4.16-4.05 (m, 3H), 3.99 (t, *J* = 10.5 Hz, 1H), 3.92-3.88 (m, 2H), 3.84-3.78 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 1H), 3.59 (s, 2H), 3.49 (t, *J* = 6.5 Hz, 1H), 3.15 (s, 3H), 2.56-2.52 (m, 3H), 2.29 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.17 (t, *J* = 10.0 Hz, 1H), 2.01-1.95 (m, 3H), 1.77-1.61 (m, 7H), 1.50 (t, *J* = 11.0 Hz, 1H), 1.41-1.24 (m, 5H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85 (s, 9H), 0.76 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H), 0.06 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), -0.07 (s, 3H), -0.12 (s, 3H).



Bisvinyl iodide 4.61

A round bottom flask equipped with a stir bar was charged with $CrCl_2$ (2.11 g, 17.19 mmol, 31 eq) and THF (12.3 mL) and dioxane (3.1 mL) were added. Next, a solution of the bisaldehyde **4.60** (1.028 g, 0.559 mmol, 1 eq) and iodoform (1.79 g, 4.55 mmol, 8.2 eq) in THF (4.6 mL) and dioxane (3.1 mL) was added dropwise via syringe. The flask containing **4.60** was washed twice with a mixture of THF (2.3 mL) and dioxane (1.6 mL) and these washes were added to the reaction. The resulting dark red slurry was stirred at 23 °C for 2 hours before being poured into a 1L Erlenmeyer flask containing saturated aqueous $NaHCO_3$ (250 mL). The resulting green slurry was diluted with Et_2O (250 mL), agitated in a separatory funnel, and filtered through a pad of celite. The filtrate layers were separated and the aqueous layer was extracted with diethyl ether (2 x 100 mL), then the combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography (SiO_2; 0% → 20% EtOAc/hexanes) to furnish bisvinyl iodide **4.61** as a white solid (0.536 g, 0.257 mmol, 46%).



TLC (20% EtOAc/hexanes)

R_f = 0.37, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.40-7.37 (m, 4H), 7.33-7.28 (m, 3H), 7.24-7.22 (m, 1H), 6.87 (t, *J* = 8.0 Hz, 4H), 6.57 (d, *J* = 14.0 Hz, 1H), 6.56 (dd, *J* = 8.0, 14.0 Hz, 1H), 6.47 (dd, *J* = 8.0 Hz, 14.5Hz, 1H), 6.36 (d, *J* = 14.0 Hz, 1H), 6.20 (d, *J* = 14.5 Hz, 1H), 5.54 (s, 1H), 5.52 (s, 1H), 5.15 (p, *J* = 6.0 Hz, 1H), 4.60 (s, 1H), 4.38-4.14 (m, 6H), 4.02-3.97 (m, 2H), 3.94-3.87 (m, 3H),

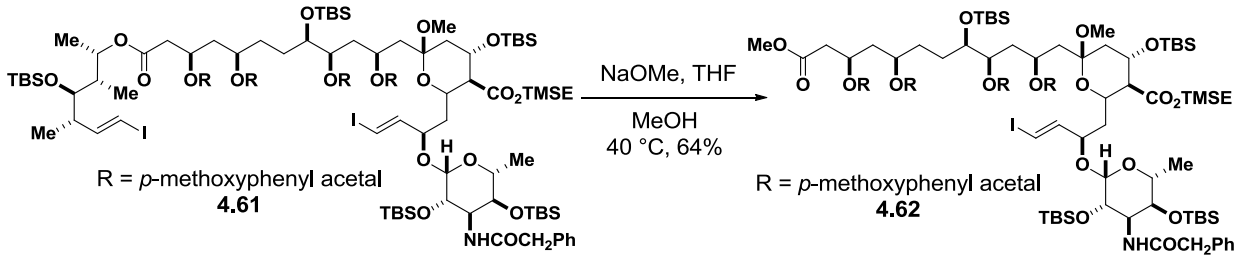
3.86-3.80 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68-3.65 (m, 2H), 3.58 (s, 2H), 3.55 (t, *J* = 8.5Hz, 1H), 3.33 (p, *J* = 6.0 Hz, 1H), 3.13 (s, 3H), 2.59-2.47 (m, 3H), 2.29 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.15 (t, *J* = 10.0 Hz, 1H), 2.10-2.07 (m, 2H), 1.96-1.88 (m, 3H), 1.78-1.61 (m, 8H), 1.50 (q, *J* = 12.5Hz, 1H), 1.43-1.28 (m, 3H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.04-0.99 (m, 2H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.77 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 18H), 0.02 (s, 3H), 0.01 (s, 3H), -0.07 (s, 3H), -0.11 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 172.8, 170.2, 170.1, 160.7, 160.6, 151.2, 147.7, 136.3, 132.5, 130.3, 129.1, 128.5, 128.2, 127.4, 126.0, 113.9, 101.4, 101.2, 101.0, 100.4, 80.4, 80.2, 79.8, 77.0, 76.7, 76.2, 74.8, 74.6, 74.1, 73.4, 71.7, 68.4, 67.6, 63.1, 58.3, 56.1, 55.5, 55.4, 48.5, 44.2, 44.0, 43.9, 43.1, 42.8, 42.0, 39.7, 37.3, 33.0, 32.3, 26.6, 26.5, 26.4, 26.3, 26.0, 19.7, 19.0, 18.9, 18.8, 18.8, 18.6, 18.3, 18.1, 16.5, 14.3, 11.2, -1.36, -3.25, -3.45, -3.57, -3.79, -3.87, -4.03, -4.20, -4.34, -4.90.

HRMS (ESI+)

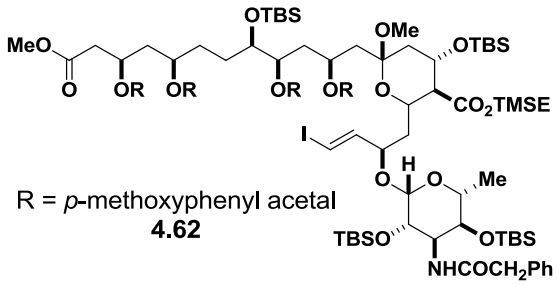
calculated for $C_{97}H_{165}NO_{20}Si_6I_2$ $(M+Na)^+$:	2108.8528
found:	2108.8557



Methyl ester 4.62

Prior to the reaction, bisvinyl iodide **4.61** was azeotropically dried via coevaporation with toluene (3 x 5 mL) and was left under vacuum for at least 1 hour. NaOMe (0.095 g, 1.75 mmol, 10 eq) in MeOH (4.6 mL) was added to a solution of bisvinyl iodide **4.61** (0.366 g, 0.175 mmol, 1 eq) in THF (2.3 mL). The reaction was stirred at 40 °C for 2 hours and was then quenched with potassium phosphate buffer (10 mL, pH 7.0). The mixture was diluted with Et_2O (20 mL) and

the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2; 0% $\rightarrow$ 20% EtOAc/hexanes) yielded methyl ester **4.62** (0.192 g, 0.112 mmol, 64%) and recovered bisvinyl iodide **4.61** (0.062 g, 0.030 mmol, 17%).



TLC (20% EtOAc/hexanes)

R_f = 0.18, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.40-7.35 (m, 4H), 7.33-7.28 (m, 3H), 7.25-7.22 (m, 1H), 6.87 (t, *J* = 8.0 Hz, 4H), 6.57 (d, *J* = 14.5 Hz, 1H), 6.47 (dd, *J* = 8.0, 14.5 Hz, 1H), 6.36 (d, *J* = 9.0 Hz, 1H), 5.52 (s, 2H), 4.60 (s, 1H), 4.38-4.34 (m, 1H), 4.30-4.13 (m, 4H), 4.06-3.97 (m, 2H), 3.95-3.85 (m, 3H), 3.84-3.80 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68-3.65 (m, 1H), 3.63 (s, 3H), 3.58 (s, 2H), 3.55 (t, *J* = 9.0 Hz, 1H), 3.33 (p, *J* = 6.5 Hz, 1H), 3.13 (s, 3H), 2.60-2.52 (m, 2H), 2.29 (dd, *J* = 4.5, 13.0 Hz, 1H), 2.15 (t, *J* = 10.0 Hz, 1H), 1.77-1.60 (m, 8H), 1.54-1.47 (m, 1H), 1.40-1.28 (m, 4H), 1.23 (d, *J* = 6.0 Hz, 3H), 1.08-1.00 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.77 (s, 9H), 0.09 (s, 3H), 0.07 (s, 18H), 0.02 (s, 3H), 0.01 (s, 3H), -0.07 (s, 3H), -0.11 (s, 3H).

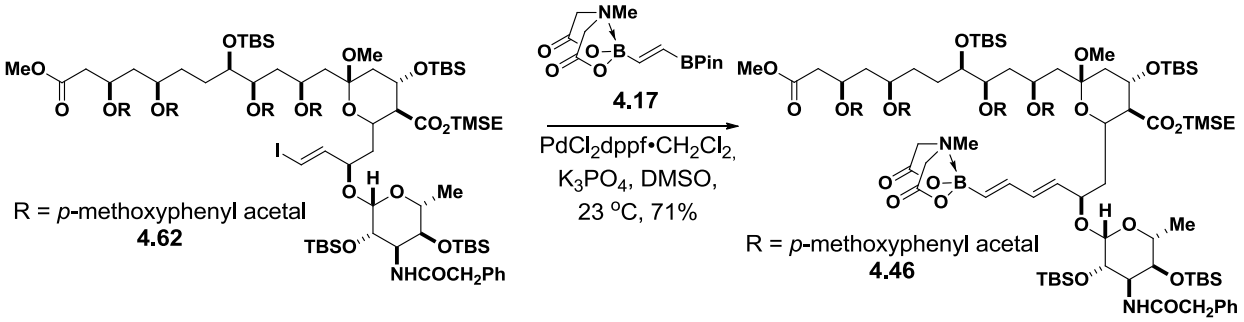
^{13}C NMR (125 MHz, acetone-d_6)

δ 172.2, 170.8, 169.7, 160.1, 147.1, 135.8, 133.9, 131.9, 129.7, 128.5, 127.9, 127.7, 126.8, 120.6, 117.3, 113.3, 79.8, 79.6, 79.3, 76.4, 74.2, 74.0, 73.3, 72.8, 71.9, 67.8, 67.0, 65.5, 62.5, 57.7, 55.6, 56.0, 54.9, 54.8, 51.1, 47.9, 43.4, 43.3, 42.2, 40.6, 39.1, 36.7, 32.4, 31.8, 19.1, 18.4, 18.2, 18.0, 17.7, 17.5, -2.00, -3.85, -4.07, -4.52, -4.65, -4.80, -5.01, -5.54.

HRMS (ESI)

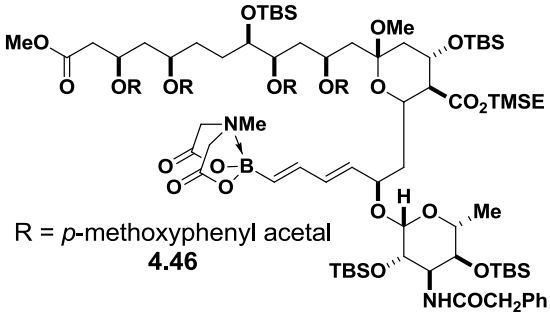
calculated for $C_{83}H_{138}NO_{19}ISi_5$ $(M + Na)^+$: 1742.7652

found: 1742.7677



Dienyl MIDA boronate 4.46

A 20 mL I-Chem vial equipped with a stir bar was charged with methyl ester **4.62** (0.219 g, 0.127 mmol, 1 eq) and bisborylated compound **4.17**[16,27] (0.082 g, 0.267 mmol, 2.1 eq), sealed under argon, and taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.021 g, 0.025 mmol, 0.2 eq) and K_3PO_4 as a finely ground powder (0.162 g, 0.763 mmol, 6 eq) were added, followed by DMSO (6.4 mL). The reaction was sealed with a PTFE-lined cap, removed from the glove box, and stirred at 23 °C for 24 hours. The solution was diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (100 mL). The filtrate was washed with water (3 x 50 mL) without agitation and brine (50 mL). The combined aqueous layers were back-extracted with EtOAc (1 x 75 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 30% → 80% EtOAc/hexanes) to furnish dienyl MIDA boronate **4.46** as a white solid (0.158 g, 0.089 mmol, 71%).



TLC (EtOAc)

R_f = 0.60, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.40-7.36 (m, 4H), 7.33-7.28 (m, 3H), 7.25-7.21 (m, 1H), 6.90-6.85 (m, 4H), 6.59 (dd, *J* = 10.0, 17.0 Hz, 1H), 6.37 (d, *J* = 9.5 Hz, 1H), 6.33 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.66 (d, *J* = 17.5 Hz, 1H), 5.63 (dd, *J* = 8.0, 15.5 Hz, 1H), 5.52 (s, 1H), 5.51 (s, 1H), 4.62 (d, *J* = 1.0 Hz, 1H), 4.41-4.37 (m, 1H), 4.30-4.12 (m, 6H), 4.04-3.96 (m, 4H), 3.92-3.86 (m, 3H), 3.84-3.79 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.64-3.59 (m, 1H), 3.63 (s, 3H), 3.57 (s, 2H), 3.55 (t, *J* = 8.0 Hz, 1H), 3.35 (p, *J* = 6.5 Hz, 1H), 3.10 (s, 3H), 2.95 (s, 3H), 2.60-2.52 (m, 2H), 2.28 (dd, *J* = 5.0, 13.5 Hz, 1H), 2.15 (t, *J* = 10.5 Hz, 1H), 2.00-1.94 (m, 1H), 1.77-1.61 (m, 8H), 1.50 (q, *J* = 11.5 Hz, 1H), 1.41-1.28 (m, 3H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.04-1.00 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.77 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.06 (s, 12H), 0.05 (s, 3H), 0.02 (s, 3H), -0.07 (s, 3H), -0.12 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

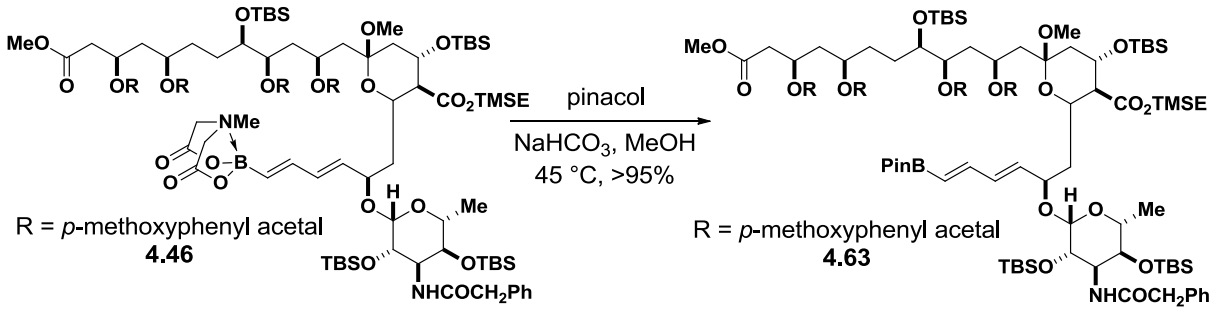
δ 172.9, 171.3, 179.1, 168.9, 168.8, 160.6, 142.7, 136.3, 135.9, 135.1, 132.5, 132.4, 130.2, 129.0, 128.4, 128.2, 127.4, 101.3, 101.1, 101.0, 100.0, 80.4, 78.0, 76.9, 74.8, 74.5, 73.9, 73.4, 73.3, 72.2, 68.4, 67.9, 63.0, 62.3, 62.2, 58.3, 56.1, 55.5, 55.4, 51.6, 48.5, 47.3, 44.0, 43.9, 42.7, 41.2, 40.3, 37.2, 32.9, 32.2, 31.4, 30.5, 28.4, 26.5, 26.3, 26.2, 25.9, 19.8, 18.9, 18.7, 18.5, 18.2, 18.0, -1.4, -3.4, -3.5, -3.9, -4.0, -4.1, -4.3, -4.4, -5.0.

^{11}B NMR (128 MHz, acetone-d_6)

δ 11.6.

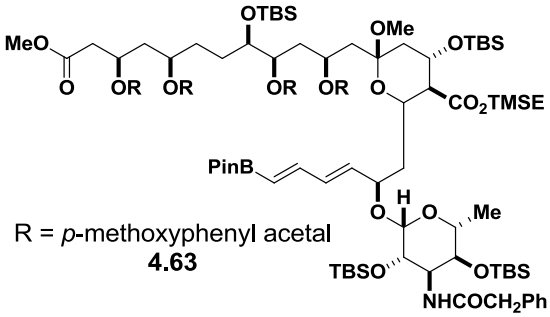
HRMS (ESI+)

calculated for $C_{90}H_{147}BN_2O_{23}Si_5$ $(M+Na)^+$:	1796.9268
found:	1796.9268



Dienyl pinacolboronic ester 4.63

A 20-mL I-Chem vial was charged with dienyl MIDA boronate **4.46** (0.257 g, 0.145 mmol, 1 eq), pinacol (0.052 g, 0.434 mmol, 3 eq), solid $NaHCO_3$ (0.061 g, 0.723 mmol, 5 eq) and MeOH (3 mL) was then added. The reaction was stirred at 45 °C for 3 hours and then was concentrated *in vacuo* and finely ground anhydrous $CaCl_2$ (0.064 g, 0.579 mmol, 4 eq), solid $NaHCO_3$ (0.024 g, 0.289 mmol, 2 eq), and toluene (4.3 mL) were added to the resulting residue. The mixture was stirred at 23 °C for 45 minutes, filtered through a pad of celite with toluene (50 mL) and concentrated to yield **4.63** (0.250 g, 0.143 mmol, >95%) as a white solid. The product was used directly in the next reaction without further purification.



TLC (75% EtOAc/hexanes)

R_f = 0.80, stained by anisaldehyde.

^{1}H NMR (400 MHz, acetone-d_6)

δ 7.40-7.36 (m, 4H), 7.33-7.28 (m, 4H), 7.15-7.11 (m, 1H), 6.97 (dd, *J* = 10.5, 17.5 Hz, 1H), 6.87 (app. t, *J* = 8.5 Hz, 4H), 6.39-6.34 (m, 2H), 5.81 (dd, *J* = 7.5, 15.5 Hz, 1H), 5.52 (s, 2H), 4.64 (s, 1H), 4.43-4.34 (m, 1H), 4.30-4.16 (m, 4H), 4.04-3.98 (m, 2H), 3.93-3.89 (m, 2H), 3.83-3.81 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67-3.61 (m, 1H), 3.63 (s, 3H), 3.57 (s, 2H), 3.56 (app. t, *J* = 8.5 Hz, 1H), 3.36 (p, *J* = 8.5Hz, 1H), 3.12 (s, 3H), 2.63-2.52 (m, 2H), 2.30-2.26 (m, 1H), 2.19-2.09 (m, 2H), 2.01-1.96 (m, 1H), 1.77-1.73

(m, 4H), 1.67-1.61 (m, 4H), 1.50 (q, J = 11.5 Hz, 1H), 1.43-1.28 (m, 3H), 1.24 (s, 12H), 1.19 (d, J = 6Hz, 3H), 1.04-1.00 (m, 2H), 0.91 (s, 9H), 0.89 (s, 9H), 0.85 (s, 9H), 0.77 (s, 9H), 0.11 (s, 3H), 0.07 (s, 12H), 0.06 (s, 6H), 0.03 (s, 6H), -0.07 (s, 3H), -0.11 (s, 3H).

^{13}C NMR (100 MHz, acetone-d_6)

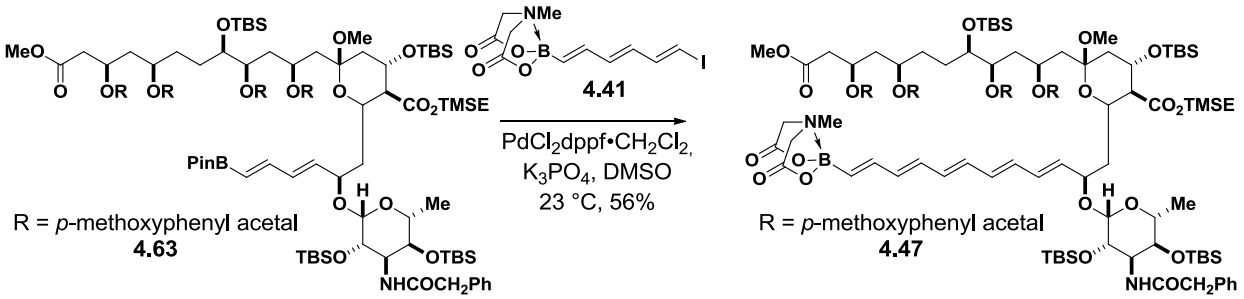
δ 172.8, 171.3, 170.2, 160.6, 149.8, 138.5, 138.4, 136.3, 134.9, 132.5, 132.5, 130.2, 129.1, 128.4, 128.2, 127.4, 113.9, 101.4, 101.2, 101.1, 100.2, 83.7, 80.4, 77.7, 77.0, 74.8, 74.5, 73.9, 73.4, 72.2, 68.4, 67.8, 63.0, 58.4, 56.1, 55.5, 55.4, 51.6, 48.5, 44.0, 43.9, 42.8, 41.2, 40.5, 37.2, 32.9, 32.3, 28.4, 26.6, 26.4, 26.3, 25.9, 25.2, 25.1, 19.8, 18.9, 18.8, 18.5, 18.3, 18.1, -1.4, -3.3, -3.4, -3.9, -4.0, -4.1, -4.3, -4.4, -4.9.

^{11}B NMR (128 MHz, acetone-d_6)

δ 31.7.

HRMS (ESI+)

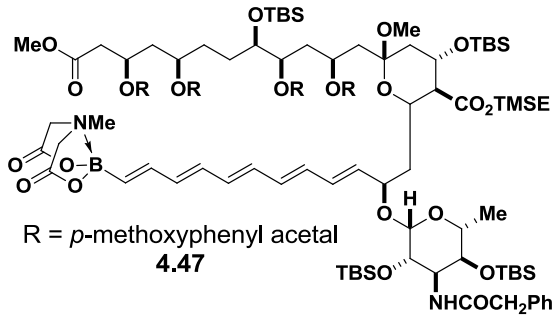
calculated for $C_{91}H_{152}BNO_{21}Si_5$ $(M+Na)^+$:	1768.9694
found:	1768.9722



Pentenyl MIDA Boronate 4.47

A 20 mL I-Chem vial equipped with a stir bar was charged with pinacolboronic ester **4.63** (0.253 g, 0.145 mmol, 1 eq) and triene **4.41**[21] (0.063 g, 0.174 mmol, 1.2 eq), sealed under argon, and taken into a glove box. $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.012 g, 0.014 mmol, 10 mol%) and K_3PO_4 as a finely ground powder (0.185 g, 0.870 mmol, 6 eq) were added, followed by DMSO (7.25 mL). The reaction was sealed with a PTFE-lined cap, removed from the glove box and stirred at 23 °C for 8 hours. Then, the reaction was taken back into the glove box and additional trienyl iodide

4.41 (0.063 g, 0.174 mmol, 1.2 eq) and $PdCl_2dppf{\cdot}CH_2Cl_2$ (0.012 g, 0.014 mmol, 10 mol%) were added. The reaction was sealed with a PTFE-lined cap, removed from the glovebox stirred at 23 °C for an additional 16 hours. The solution was diluted with EtOAc (10 mL) and filtered through a pad of silica gel, washing with EtOAc (100 mL). The filtrate was washed with water (3 x 50 mL) and brine (50 mL) without agitation. The combined aqueous layers were back-extracted with EtOAc (1 x 75 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified via flash chromatography (SiO_2; 50% → 100% EtOAc/hexanes) to furnish pentenyl MIDA boronate **4.47** as a white solid (0.150 g, 0.081 mmol, 56%).



TLC (75% EtOAc/hexanes)

R_f = 0.25, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

δ 7.38 (app. t, *J* = 8.5 Hz, 4H), 7.32-7.28 (m, 3H), 7.25-7.22 (m, 1H), 6.87 (dd, *J* = 8.5, 11.5 Hz, 4H), 6.63 (dd, *J* = 9.5, 17.5 Hz, 1H), 6.42-6.31 (m, 8H), 5.72 (d, *J* = 17.5 Hz, 1H), 5.64 (dd, *J* = 8.0, 14.0 Hz, 1H), 5.52 (s, 1H), 5.51 (s, 1H), 4.61 (s, 1H), 4.41-4.37 (m, 1H), 4.30-4.12 (m, 6H), 4.06-3.99 (m, 4H), 3.91-3.89 (m, 3H), 3.84-3.81 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.67-3.60 (m, 1H), 3.63 (s, 3H), 3.57 (s, 2H), 3.54 (t, *J* = 8.0 Hz, 1H), 3.36-3.32 (m, 1H), 3.11 (s, 3H), 2.98 (s, 3H), 2.61-2.52 (m, 2H), 2.28 (dd, *J* = 4.5, 13.5 Hz, 1H), 2.15 (t, *J* = 10.5 Hz, 1H), 1.99-1.95 (m, 1H), 1.78-1.73 (m, 4H), 1.70-1.59 (m, 4H), 1.50 (app. q, *J* = 11.5 Hz, 1H), 1.40-1.28 (m, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.03-1.00 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.84 (s, 9H), 0.77 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.06 (s, 12H), 0.05 (s, 3H), 0.02 (s, 3H), -0.07 (s, 3H), -0.11 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 172.9, 171.4, 170.2, 168.9, 160.7, 148.6, 143.3, 136.4, 136.0, 135.0, 134.6, 134.2, 134.1, 134.0, 133.6, 132.6, 132.5, 130.2, 129.1, 128.5, 128.2, 127.4, 113.9, 101.4, 101.2, 101.1, 100.1, 80.4, 78.1, 77.0, 74.8, 74.5, 73.9, 73.5, 73.4, 72.3, 68.5, 67.9, 66.0, 63.0, 62.4, 62.2, 58.5, 56.1, 55.5, 55.4, 51.7, 48.5, 47.3, 44.1, 44.0, 42.8, 41.3, 40.5, 37.3, 33.0, 32.3, 29.3, 28.4, 26.6, 26.4, 26.3, 26.0, 19.8, 19.0, 18.8, 18.6, 18.3, 18.1, 9.2, 5.0, -1.4, -3.3, -3.4, -3.9, -4.0, -4.1, -4.3, -4.4, -4.9.

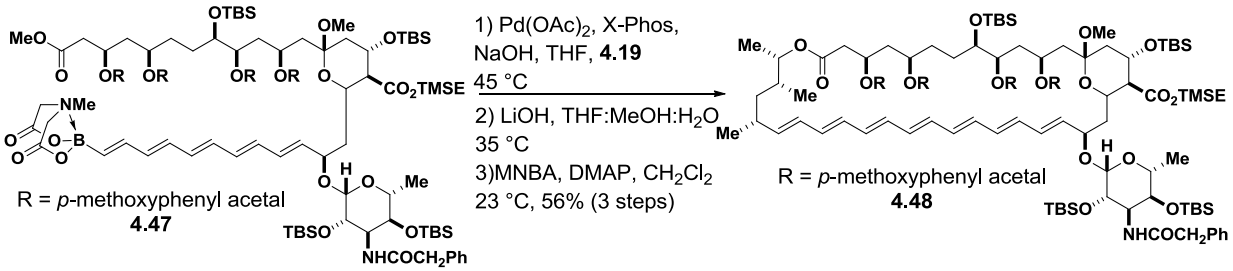
^{11}B NMR (128 MHz, acetone-d_6)

δ 11.4.

HRMS (ESI+)

calculated for $C_{96}H_{153}BN_2O_{23}Si_5$ $(M+Na)^+$: 1876.9736

found: 1876.9712



Macrolactone 4.48

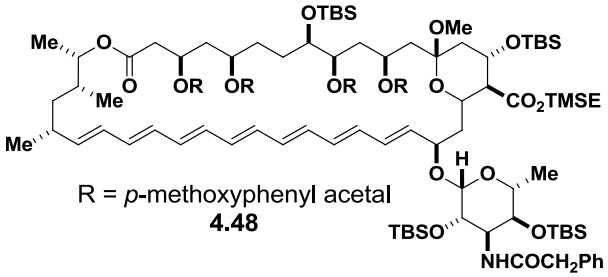
A solution of the catalyst was prepared as follows: A 20 mL Wheaton vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (2.2 mg, 0.0098 mmol) and 2-cyclohexylphosphino-2',4',6'-isopropyl-1,1'-biphenyl (X-Phos, 9.3 mg, 0.0196 mmol). Toluene (1.35 mL) was added and the vial was sealed with a PTFE lined cap. The resulting mixture was stirred at 23 °C for 45 minutes resulting in a yellow catalyst stock solution (0.00725 M in Pd).

The above catalyst solution was then used in the following procedure: A 20 mL Wheaton vial with a PTFE cap was charged with pentenyl MIDA boronate **4.47** (100 mg, 0.0539 mmol, 1 eq), and dienyl iodide **4.19** (15 mg, 0.0512 mmol, 0.95 eq). THF (2.7 mL, 0.02 M) was then added. Subsequently, the catalyst stock solution (372 μL, 5 mol% Pd) was added and the resulting mixture was sealed with a teflon-lined septum cap. NaOH (1M aqueous, degassed, 270

μL, 5 eq) was added and the reaction was stirred at 23 °C for 30 minutes. Then, the reaction was placed in a 45 °C aluminum heating block and was stirred for an additional 3 hours. The crude reaction mixture was filtered through a pad of silica gel and washed with ethyl acetate (50 mL). The solvent was removed *in vacuo* and the product was carried immediately forward to the saponification without further purification.

To a 20 mL Wheaton vial with a PTFE cap containing the product of the Suzuki coupling was added THF:MeOH:H_2O (5.12 mL, 3:1:1 v/v/v) and lithium hydroxide (107 mg, 2.56 mmol, 50 eq). The reaction was stirred at 35 °C in an aluminum heating block for 40 minutes. The reaction was quenched with potassium phosphate buffer (10 mL, pH 7.0) and the product was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed, dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude reaction product was carried immediately forward to the macrolactonization without further purification.

CH_2Cl_2 (12.8 mL) was added to a 100 mL round bottom flask containing the product of the saponification. Then, a mixture of 2-methyl-6-nitrobenzoic acid (21.2 mg, 0.0614 mmol, 1.2 eq) and DMAP (15 mg, 0.123 mmol, 2.4 eq) in DCM (20.5 mL) in a gastight glass syringe was added via dropwise addition over the course of 13 hours at 23 °C with a syringe pump. At the end of the addition, the syringe was filled with CH_2Cl_2 (10 mL), and this solution was added to the reaction, which was then stirred for an additional hour. The reaction was then quenched with saturated aqueous sodium bicarbonate (25 mL) and the product was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The crude was purified via flash chromatography (SiO_2; 0 → 15% EtOAc/hexanes) to yield macrolactone **4.48** as a yellow solid (52.3 mg, 0.0285 mmol, 56% over 3 steps).



TLC (15% EtOAc/hexanes)

R_f = 0.67, stained by anisaldehyde.

^{1}H NMR (500 MHz, acetone-d_6)

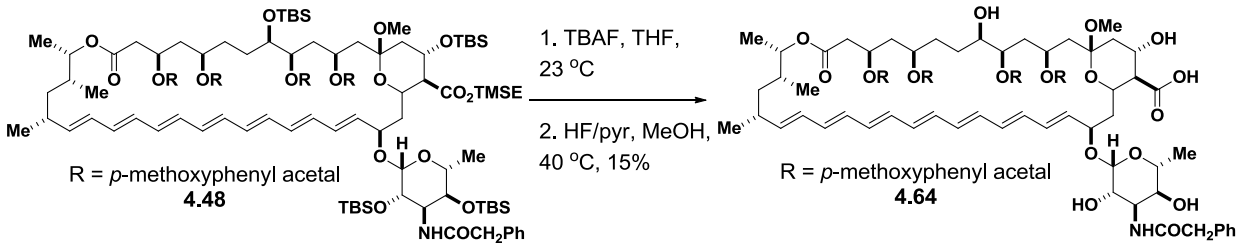
δ 7.41-7.36 (m, 4H), 7.34-7.27 (m, 4H), 7.23-7.21 (m, 1H), 6.90-6.865 (m, 4H), 6.36-6.15 (m, 12H), 5.79 (dd, *J* = 7, 14.5 Hz, 1H), 5.48 (s, 1H), 5.45 (s, 1H), 5.40 (dd, *J* = 9, 15 Hz, 1H), 5.17 (app t, 6.5 Hz, 1H), 4.60 (app t, *J* = 7.5 Hz, 1H), 4.55 (s, 1H), 4.23-4.16 (m, 3H), 4.04-4.00 (m, 2H), 3.91-3.85 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73-3.71 (m, 2H), 3.57 (s, 4H), 3.36 (dd, *J* = 10, 13.5 Hz, 1H), 3.07 (s, 3H), 2.61 (m, 1H), 2.40-2.28 (m, 2H), 2.26-2.24 (m, 1H), 2.04-1.88 (m, 2H), 1.79-1.55 (m, 4H), 1.47-1.40 (m, 2H), 1.38-1.28 (m, 2H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.15-1.11 (m, 1H), 1.12-1.11 (m, 1H), 1.07 (d, *J* = 6 Hz, 3H), 1.04-1.02 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 9 Hz, 3H), 0.896 (s, 9H), 0.858 (s, 9H), 0.847 (bs, 18H), 0.750 (s, 9H), 0.109 (s, 3H), 0.067-0.057 (m, 15H), 0.042 (s, 3H), -0.033 (s, 3H), -0.081 (s, 3H), -0.168 (s, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 173.2, 170.2, 169.9, 160.7, 160.6, 139.6, 136.8, 134.5, 133.8, 133.5, 133.0, 132.6, 132.3, 131.1, 130.3, 129.1, 129.0, 128.7, 128.3, 127.4, 114.0, 113.9, 101.6, 101.1, 100.9, 98.9, 81.5, 76.4, 76.3, 74.8, 73.5, 73.4, 71.1, 69.0, 68.1, 63.4, 56.7, 56.3, 55.5, 55.4, 48.3, 43.9, 41.9, 41.5, 37.9, 37.3, 35.4, 35.3, 33.1, 26.6, 26.5, 26.3, 26.0, 22.1, 19.8, 19.0, 18.6, 18.3, 18.2, 14.8, 13.5, -1.34, -3.29, -3.34, -3.55, -3.90, -4.02, -4.89.

HRMS (ESI)

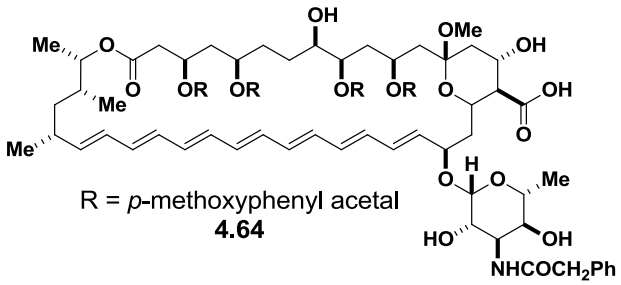
calculated for $C_{101}H_{161}NO_{19}Si_5$ $(M + Na)^+$:	1855.0407
found:	1855.0337



Bisketal 4.64

To macrolactone **4.48** (70 mg, 0.0382 mmol, 1 eq) in THF (3.6 mL) was added dropwise TBAF (1.0M in THF, 0.19 mL, 5 eq). The reaction was stirred for 30 min. at 23 °C and then was diluted with EtOAc (20 mL) and poured into a mixture of saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; CH_2Cl_2:MeOH:AcOH 96.4:3.5:0.1) to furnish 60 mg of a mixture partially desilylated derivatives. Prior to the next reaction, this material was transferred to a Teflon vial and placed under vacuum with P_2O_5 for 4h to remove water.

The solid was dissolved in MeOH (3.1 mL) and 2.3 mL of HF·4 pyridine complex (prepared by adding 0.684 mL 70% HF·pyridine complex to 4 mL pyridine at 0 ^oC) was added dropwise. The resulting reaction mixture was heated to 40 ^oC and stirred for 14h. The reaction was quenched with TMSOMe (1 mL) and was stirred at 23 ^oC for 10 min. The solution was concentrated and purified by preparative RP-HPLC (Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm; 25 mL/min flow rate; gradient of 5 $\rightarrow$ 95% MeCN in 25 mM aqueous ammonium acetate over 5 min) to furnish **4.64** as a yellow solid (7.5 mg, 0.0059 mmol, 15%) and a mixture of monosilylated derivatives (6.9 mg, 0.0050 mmol, 13%) that were resubjected to the HF·pyridine conditions.



R = *p*-methoxyphenyl acetal

4.64

HPLC

t_R = 10.3 min; flow rate = 25 mL/min, Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm column gradient of 5 → 95% MeCN in 25 mM aqueous ammonium acetate over 5 min.

^{1}H NMR (500 MHz, acetone-d_6)

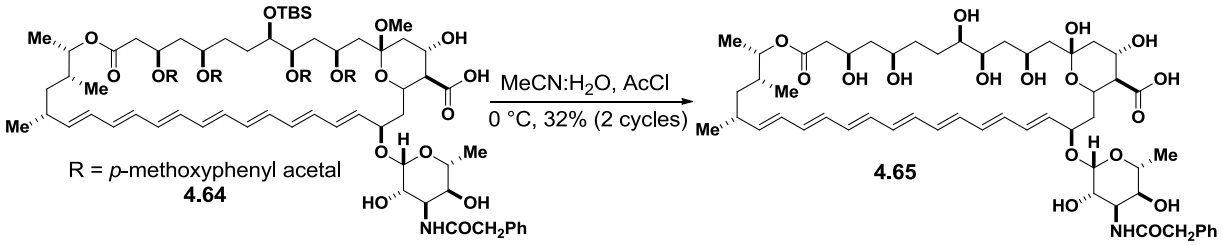
δ 7.42-7.34 (m, 5H), 7.30 (t, *J* = 8.0 Hz, 3H), 7.24-7.20 (m, 1H), 6.89-6.84 (m, 4H), 6.42-6.20 (m, 12H), 5.86 (dd, *J* = 5.0, 15.0 Hz, 1H), 5.49 (s, 1H), 5.48 (dd, *J* = 9.0, 14.5 Hz, 1H), 5.46 (s, 1H), 5.12 (dq, *J* = 5.0, 6.5 Hz, 1H), 4.67 (app t, *J* = 5.5 Hz, 1H), 4.61 (s, 1H), 4.24-4.18 (m, 1H), 4.16-4.08 (m, 1H), 3.91 (app t, *J* = 10.5 Hz, 2H), 3.85-3.80 (m, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.71-3.66 (m, 1H), 3.64 (s, 2H), 3.59-3.56 (m, 1H), 3.50-3.41 (m, 1H), 3.28 (broad s, 1H), 3.03 (s, 3H), 2.63 (dd, *J* = 5.5 Hz, 1H), 2.59 (s, 1H), 2.38 (dd, *J* = 7.5, 11.0 Hz, 1H), 2.36-2.29 (m, 1H), 2.22-2.18 (m, 1H), 1.95-1.80 (m, 4H), 1.78-1.58 (m, 5H), 1.52-1.42 (m, 3H), 1.38-1.22 (m, 6H), 1.20 (d, *J* = 4.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (125 MHz, acetone-d_6)

δ 173.1, 169.9, 160.7, 160.6, 140.0, 137.0, 136.1, 134.1, 134.0, 133.9, 133.7, 133.6, 133.5, 133.0, 132.7, 132.6, 131.9, 130.1, 129.9, 129.1, 128.6, 128.4, 128.3, 127.3, 113.9, 101.2, 100.9, 100.8, 98.0, 81.3, 76.5, 74.5, 74.4, 73.6, 73.3, 73.2, 71.3, 70.7, 68.9, 67.2, 56.5, 55.5, 55.4, 48.6, 44.0, 43.3, 43.2, 41.6, 30.5, 28.7, 26.5, 26.1, 22.4, 21.9, 18.4, 18.1, 14.9, 14.0, -4.1, -4.8.

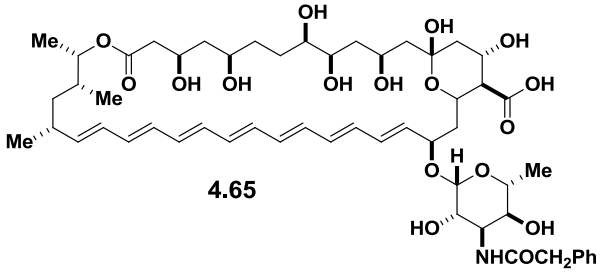
HRMS (ESI+)

calculated for $C_{72}H_{93}NO_{19}$ $(M+H)^+$:	1276.6420
found:	1276.6448



N-phenylacyl C35-deoxyamphotericin B 4.65

Prior to the reaction, acetyl chloride was freshly distilled from quinoline (20% v/v) and used immediately. The distillation apparatus was set up immediately before the distillation and was used only once per reaction. A 20 mL I-Chem vial was charged with acetonitrile (5 mL), water (250 μL) and acetyl chloride (50 μL). The vial was enclosed with a PTFE-lined cap and was stirred for 30 minutes at 23 °C and then was cooled to 0 °C and stirred for an additional 15 minutes. Subsequently, the cooled acetonitrile:water solution (1.1 mL) was added to a 7 mL Wheaton vial containing **4.64** (10 mg, 7.8 μmol). The vial was enclosed with a PTFE-lined cap and stirred at 0 °C for 30 min. The reaction was quenched with triethylamine (50 μL) and the resulting hazy solution was solubilized with the minimal amount of methanol. The crude was immediately purified by preparative RP-HPLC (Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm 25 mL/min flow rate 5% → 95% MeCN in 25 mM aqueous ammonium acetate over 17 minutes) to yield the title compound **4.65** as a yellow solid (2.6 mg, 2.5 μmol, 32% over 2 cycles).



HPLC

t_R = 16.6 min; flow rate = 25 mL/min, Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm column gradient of 5 → 95% MeCN in 25 mM aqueous ammonium acetate over 17 min.

^{1}H NMR (500 MHz, pyridine-d_5 : CD_3OD 1:1)

δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.24-7.19 (m, 1H), 6.65 (dd, *J* = 11.0, 14.0 Hz, 1H), 6.61 (dd, *J* = 10.0, 14.5 Hz, 1H), 6.55-6.25 (m, 12H), 4.90-4.81 (m, 2H), 4.72 (broad s, 2H), 4.64 (t, *J* = 10.5 Hz, 1H), 4.43-4.38 (m, 1H), 4.29-4.25 (m, 1H), 4.14 (s, 1H), 4.02-3.98 (m, 1H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.77-3.65 (m, 2H), 3.57-3.46 (m, 1H), 3.36-3.32 (m, 1H), 3.28-3.25 (m, 1H), 2.54 (dd, *J* = 9.0, 17.0 Hz, 1H), 2.39 (dd, *J* = 4.0, 16.5 Hz, 1H), 2.36-2.26 (m, 2H), 2.13-2.05 (m, 1H), 2.00-1.49 (m, 10H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.35-1.22 (m, 6H), 1.17-1.11 (m, 1H), 1.08 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H).

HRMS (ESI+)

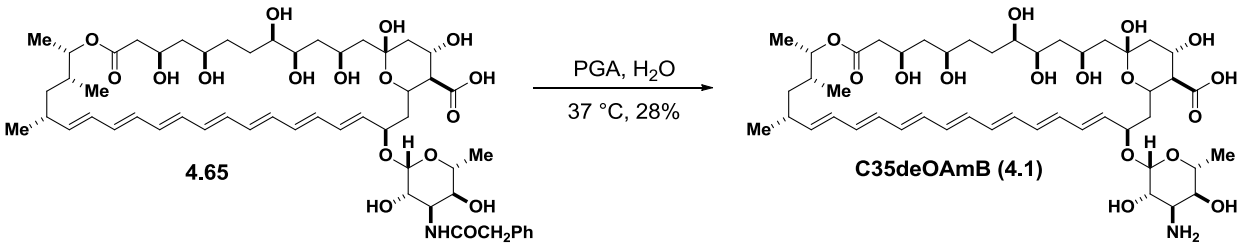
calculated for $C_{55}H_{79}NO_{17}$ (M+Na):	1048.5246
found:	1048.5238

Purification of Penicillin G Amidase

Penicillin G amidase (PGA) was purchased from Clea Technologies (Delft, The Netherlands) as a crude solution and was purified within one month of use using the following procedure. 2.5 mL of the crude PGA solution and 1.6 mL of saturated aqueous ammonium sulfate were each added to twelve individual 15 mL centrifuge tubes. The tubes were inverted several times to mix and were then left to stand for 5 minutes. Subsequently, the PGA/$(NH_4)_2SO_4$ solutions were centrifuged at 4500xg for 20 minutes at 23 °C and after centrifugation the supernatants were transferred to fresh 15 mL centrifuge tubes and the brown pellets were discarded. To each supernatant was added 6 mL of saturated $(NH_4)_2SO_4$ and the tubes were inverted several times to mix and then let stand for 5 minutes. Next, the samples were again centrifuged at 4500xg for 20 minutes at 23 °C. The supernatants were discarded and the pellets were dissolved in 1.1M $(NH_4)_2SO_4$ 50 mM TRIS (pH 7.5). The samples were then purified using a 15 x 5 cm phenyl sepharose 6 (Sigma-Aldrich, St. Louis, MO) gel column. The sepharose column was pre-equilibrated with 2 column volumes of 1.1M $(NH_4)_2SO_4$ 50 mM TRIS (pH 7.5) and the samples were then loaded. The protein was then eluted with one column volume each of 50 mM TRIS (pH 7.5) buffer of decreasing ionic strength in the order: 1.1M $(NH_4)_2SO_4$, 0.9M $(NH_4)_2SO_4$, 0.7M $(NH_4)_2SO_4$, 0.45M $(NH_4)_2SO_4$, 0.25M $(NH_4)_2SO_4$ and then two column volumes of MilliQ

H_2O. Fractions were collected beginning with the 0.25M $(NH_4)_2SO_4$ eluent and were analyzed for the presence of PGA using SDS-PAGE.

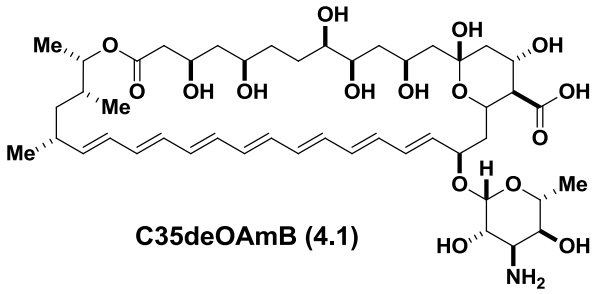
The loading buffer was prepared by dissolving 20 mg of dithiothreitol in 500 μL Laemmli sample buffer (Bio-Rad, Hercules, CA). Then, 15 μL of each fraction and 15 μL of the loading buffer were added to individual 0.6 mL microcentrifuge tubes, mixed and then incubated at 95 °C for 5 minutes. The samples were cooled by incubating at 23 °C for 15 minutes and then 12.5 μL of each sample was loaded onto precast Mini-PROTEAN TGX (Bio-Rad) gels. The gels were run at 190V for 35 minutes using TRIS/glycine running buffer (125mM TRIS, 1.92M glycine, 0.5% SDS, pH 8.3). The gels were then stained with Brillant Blue staining solution (Sigma-Aldrich) for 30 minutes with gentle shaking. The stain was decanted and the gels were destained by three successive 30 minute destaining cycles using H_2O:MeOH:AcOH (45:45:10, v/v/v). Fractions containing PGA were then concentrated using Amicon Ultra centrifugal filter units (Sigma-Aldrich). PGA containing fractions were added to the filter units and centrifuged at 4500xg for 20 minutes at 4 °C. Once all the samples had been concentrated, the collected PGA was suspended in 12 mL MilliQ H_2O and stored at 4 °C.



C35-deoxy amphotericin B (C35deOAmB)

N-phenylacyl C35-deoxy AmB **S23** (8 mg, 7.8 μmol) was dissolved in MeOH (4 mL) and 0.25 mL of this solution was added to 16 separate 7 mL Wheaton vials, each containing a magnetic stir bar. The MeOH was removed under a stream of N_2 and the samples were left under vacuum overnight. The next morning, 0.5 mL of PGA solution was added to each vial, which was then vortexed for 30 seconds and enclosed under an atmosphere of argon with a PTFE-lined cap. The samples were incubated with stirring at 37 °C for 96 hours to reach >90% conversion as measured by analytical HPLC (the time required to reach >90% conversion varied by experiment from 72 to 120 hours). Once >90% conversion had been reached, the samples were removed to individual 15 mL centrifuge tubes, washing with MeOH. The total volume of each sample was

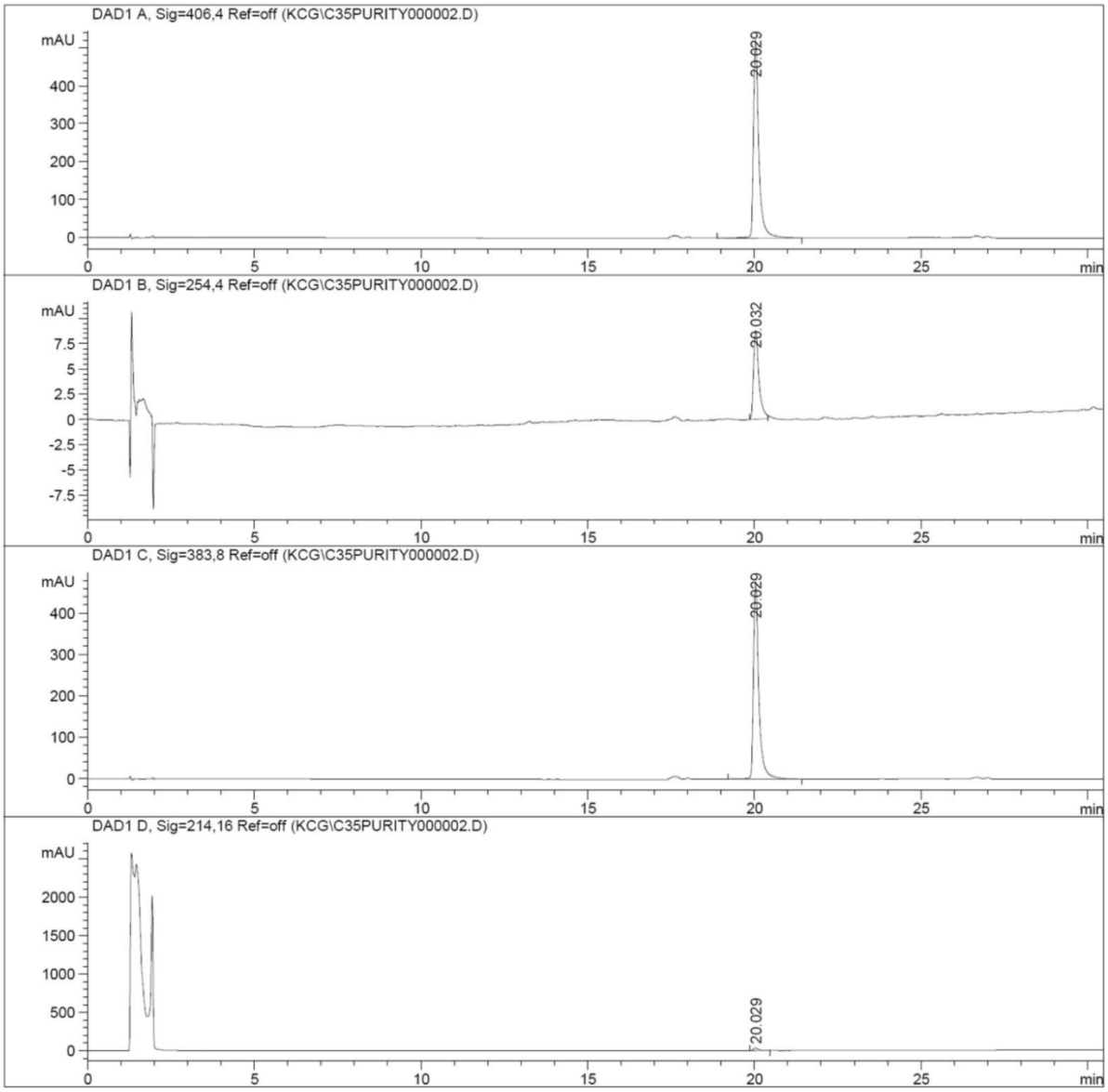
diluted to 5 mL with MeOH and the samples were centrifuged at 4500xg for 30 minutes at 23 °C. Following centrifugation, the supernatants were collected and the pellets were resuspended in 5 mL MeOH and reexposed to the same centrifugation conditions. The supernatants from this second round to centrifugation were added to the initial supernatants and the volume of the solution was reduced to approximately 10 mL *in vacuo*. The reduced solution was then filtered through a small plug of celite, washing with copious amounts of MeOH. The solvent was then completely removed and the resulting yellow solid was taken up in 0.5 mL DMSO and diluted to 1 mL with MeOH. The crude was purified *via* preparative RP-HPLC (Waters Sunfire prep C_{18} ODB 5 micron 30 x 150 mm, 25 mL/min flow rate, gradient of 5% $\rightarrow$ 95% MeCN in 25 mM aqueous ammonium acetate over 30 minutes) to yield C35deOAmB as a yellow solid (2.00 mg, 0.0022 mmol, 28%).



C35deOAmB (4.1)

HPLC

t_R = 20.0 minutes; flow rate = 1.2 mL/min through a Waters Sunfire C_{18} ODB 5 micron 4.6 x 150 mm column, gradient of 5 $\rightarrow$ 95% MeCN in 25 mM aqueous ammonium acetate over 30 minutes.



^{1}H NMR (500 MHz, pyridine-d_5 : CD_3OD 1:1)

δ 6.68 (dd, *J* = 11.0, 14.5 Hz, 1H), 6.63 (dd, *J* = 10.5, 14.5 Hz, 1H), 6.56-6.38 (m, 9H), 6.35-6.25 (m, 3H), 5.01 (s, 1H), 4.89-4.85 (m, 1H), 4.78-4.72 (m, 2H), 4.67 (t, *J* = 9.5 Hz, 1H), 4.56 (s, 1H), 4.45-4.40 (m, 1H), 4.04-3.99 (m, 1H), 3.89-3.81 (m, 2H), 3.74-3.62 (m, 2H), 2.55 (dd, *J* = 9.5, 17.5 Hz, 1H), 2.40 (dd, *J* = 3.5, 17.0 Hz, 1H), 2.36-2.28 (m, 2H), 2.14-2.06 (m, 3H), 1.99-1.87 (m, 2H), 1.84-1.74 (m, 2H), 1.71-1.64 (m, 3H), 1.60-1.53 (m, 3H), 1.45 (d, *J* = 5.5 Hz, 3H), 1.36-1.22 (m, 6H), 1.08 (d, *J* = 6.5 Hz, 3H),

1.00 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H).

HRMS (ESI+)

calculated for $C_{47}H_{73}NO_{16}$ (M+H):	908.5008
found:	908.5012

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[17] For the development of the MIDA boronate to iodine exchange see the synthesis of **3.25** in chapter 3.

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[29] See chapter 3 for the synthesis of this intermediate.