University of Alberta

Synthetic Methods Towards the Core Tricyclic Ring System of Pradimicin A

by

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ABSTRACT

The pradimicins are natural products that are both structurally intriguing to a synthetic chemist and possess biological activity as antifungal and antiviral agents. Our interest towards designing a synthetic route for these compounds and various analogues was sparked by the potential to produce a library of efficient carbohydrate receptors. The initial synthetic approach towards pradimicin A involved a model study of the synthesis of the core tricyclic ring system. This route featured an alkoxyallylboration, ring closing enyne metathesis and Diels-Alder cycloaddition. Chapter 2 describes the efforts towards synthesizing starting materials and the enyne metathesis precursor, which includes a mono-protected *trans*-diol. Chapter 3 focuses on the reaction conditions and various substrates that were tested for the ring closing enyne metathesis reaction. The optimal route found for the synthesis of the tricyclic ring system featured a one-pot palladium catalyzed cycloisomerization, Diels-Alder reaction and aromatization.

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LIST OF ABBREVIATIONS

AMPB	amphotericin B
AcOH	acetic acid
BBEDA	*N,N*-bis-(benzylidene)ethylenediamine
BBN	borabicyclononane
BHT	butylated hydroxytoluene
Bn	benzyl
*t*Bu	*tert*-butyl
Calcd	calculated
CBA	carbohydrate binding agent
CV-N	cyanovirin N
Cy	cyclohexyl
d	doublet
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
dr	diastereomeric ratio
dt	doublet of triplets
EA	ethanolamine
EC_{50}	half maximal effective concentration
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
equiv	equivalent
FLU	fluconazole

HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPLC	high performance liquid chromatography
HQ	hydroxyquinoline
HRMS	high resolution mass spectrometry
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
m	multiplet
MBL	mannose-binding lectin
MEM	methoxyethoxymethyl
MFC	minimum fungicidal concentration
MIC	minimum inhibitory concentration
MOM	methoxymethyl
MOMCl	methyl chloromethyl ether
NMR	nuclear magnetic resonance
OMe	methoxy
OTf	trifluoromethanesulfonate
Ph	phenyl
PMP	*p*-methoxyphenyl
PRM	pradimicin
RCEM	ring closing enyne metathesis
Rf	retardation factor
rt	room temperature
SARS	severe acute respitory syndrome
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl

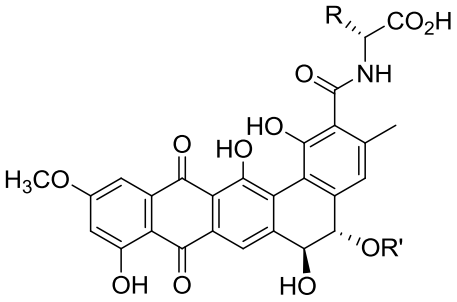
CHAPTER 1

INTRODUCTION

1.1 Pradimicins and Benanomicins

Efforts to discover novel microbial metabolites led to the isolation of a new class of natural products called pradimicins and benanomicins in 1988 by two different groups, Oki and Takeuchi.[1-7] Oki and coworkers found that a cultured broth of *Actinomadura hibisca* bacteria, isolated from a Fiji Island soil sample, contained red pigments that precipitated from the broth at a pH of 5 and were purified by column chromatography.[4] The components were later identified and characterized to be pradimicins A, B, and C and were shown to be active against various fungi, yeasts, and viruses.[6] Takeuchi and coworkers isolated benanomicin A and B from a cultured broth of *Actinomadura species* in the same year.[3, 8] The unique biological activity that this class of compounds exhibits and the ongoing need for antifungal and antiviral treatments makes this compound a desired target in the synthetic community.

The structure of pradimicins and benanomicins consists of an amino acid, a disaccharide and a benzo(α)naphthacenequinone core.[9] There are approximately twenty congeners in this family to date, eleven are illustrated in *Table 1.1*, and they vary based on the amino acid and disaccharide functional groups.[9] Pradimicin A, one of the first and most abundant congeners isolated, was initially subjected to biological testing, but was claimed to have limited solubility in water, ≤ 50 μM.[9, 10] To overcome this issue, biological testing has also been done using the analogues BMY-28864, BMS-181184 and more recently, PRM-S, which have different and more water soluble amino acid and disaccharide functionalities.[10-15]



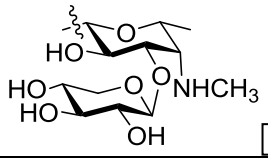
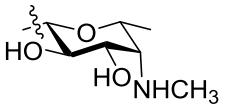
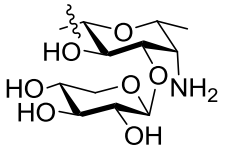
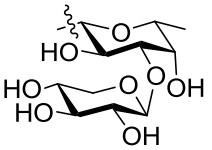
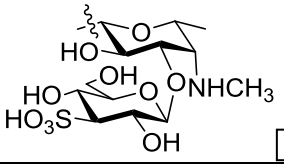
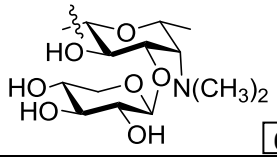
Name	***R***	***R' Sugar Moiety***
Pradimicin A	CH_3	 **1**
Pradimicin B	CH_3	 **2**
Pradimicin E	H	 **3**
Benanomicin A	CH_3	 **4**
Pradimicin S	CH_3	 **5**
BMY-28864	CH_2OH	 **6**
Pradimicin D	H	**1**
Pradimicin FA-1	CH_2OH	**1**
Pradimicin FA-2	CH_2OH	**3**
Benanomicin B (Pradimicin C)	CH_3	**3**
BMS-181184	CH_2OH	**4**

Table 1.1: Pradimicin and benanomicin analogues[9, 16]

1.2 Carbohydrate Binding Agents

Pradimicins and benanomicins exhibit their antifungal and antiviral biological activities by acting as Carbohydrate Binding Agents (CBA's). There is a large variety of CBA's that are derived from various sources in nature such as prokaryotics, plants, fungi, invertebrates and vertebrates.[17] Two main types of CBA's exist: the majority being lectins, which are carbohydrate-binding proteins, and low molecular weight non-peptidic CBA's such as the pradimicins.[18] As low molecular weight natural products, the ability for the pradimicins to bind to carbohydrates is very rare, proving them to be extremely unique with great potential in regards to its antifungal and antiviral applications. CBA's are categorized according to the particular carbohydrate for which they have a binding affinity, targeting such sugars as glucose, mannose or galactose.[17] A known peptidic CBA is cyanovirin-N (CV-N), a 101 amino acid protein isolated from the cyanobacterium *Nostoc ellipsosporum*.[17, 19, 20] The carbohydrate recognition sites on CV-N are selective towards mannose oligomers and it has been shown to inhibit HIV infection in cell cultures at EC_{50}'s of 0.1 and 0.3 nM.[18] The mammalian immune system uses CBA's as well, an example being the mannose-binding serum lectin (MBL), one of the most studied lectins in the immune system that targets pathogens in the body.[8, 17, 18]

Since pradimicins are non-peptidic, the advantages to applying pradimicins as antibiotics compared to protein CBA's are numerous. The main advantage is their low molecular weight, which would be beneficial in scale-up, purification and production.[17] Other pitfalls of the peptidic CBA's include bioavailability and the potential side effects such as inflammatory activity, cellular toxicity and mitogenic stimulation of human lymphocyte cells.[17] The low molecular weight CBA's also have the potential to bind to multiple glycan sites on one HIV molecule, whereas the peptidic CBA's have less access to binding sites due to greater steric hindrance.[8] Research efforts towards gaining more insight into the

low molecular weight CBA's could result in the avoidance of these undesired immunologic responses.[17]

The pradimicins are CBA's that have the same carbohydrate specificity as CV-N, which is towards high-mannose type glycans. This trait, along with their ability to form a chemical complex with the carbohydrate and calcium, can classify these compounds as 'lectin mimics'.[21] In 1993, Oki and coworkers showed that an analogue of pradimicin, BMY-28864, could form complexes when reacted with either the α or β anomer of D-mannopyranoside and calcium.[15, 21] Complex formation was indicated by the presence of a precipitate as well as a shift in the absorption peaks in a spectrophotometric study.[21] Lack of precipitation with other carbohydrates, such as glucose, altrose and talose, revealed that the configuration at the C-2, C-3 and C-4 positions of the sugars are crucial for successful binding and subsequent complex formation.[21] This was supported by the positive results obtained for the sugars D-arabinose, D-lyxose and D-mannose (*Figure 1.1)*.[21]

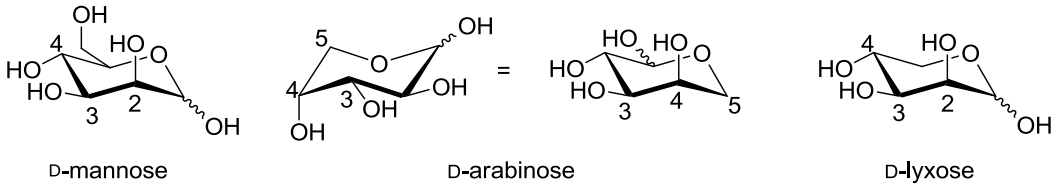


Figure 1.1: Saccharides that form a complex with BMY-28864 and calcium[21]

During their investigations towards BMY-28864's antifungal activity, Oki and coworkers confirmed that the binding mechanism was calcium dependent and this idea was further proven by Balzarini and coworkers during antiviral investigations.[11, 15] Although the mechanism is not well understood, it is proposed to involve the formation of a ternary complex between the CBA, calcium and mannose residue.[15, 17, 21] Oki and coworkers

proved that the complex consisted of two molecules of BMY-28864, four molecules of D-mannopyranoside, and one Ca^{2+}.[15, 17, 21] The requirement of calcium in the binding mechanism classifies the pradimicin family as a 'C-type lectin' mimic.[11] From spectrophotometric studies, they also found that the ternary complex is formed only when BMY-28864 binds first to D-mannopyranoside and then to calcium.[21] The reverse sequence, on the other hand, resulted in no complex formation.[21]

The molecular architecture of pradimicin was proposed to be crucial, where the aglycon core, the amino acid and the disaccharide are all involved in the binding mechanism.[21] According to the study conducted by Oki and coworkers, it is known that the calcium is coordinating to two molecules of pradimicin A (PRM-A) at the carboxylic acid position and the other two moieties are involved in binding to the target sugar as shown in the cartoon model *Figure 1.2.*[21] This correlates with the finding that when the carboxylic acid is methylated, PRM-A loses its biological activity.[10, 22] It is unclear whether the function of calcium is solely to bridge two PRM-A molecules or if it plays a role in coordinating mannose to the antibiotic.[10] In addition, it was also shown that derivatives that did not possess the sugar moiety were biologically inactive against fungi.[23]

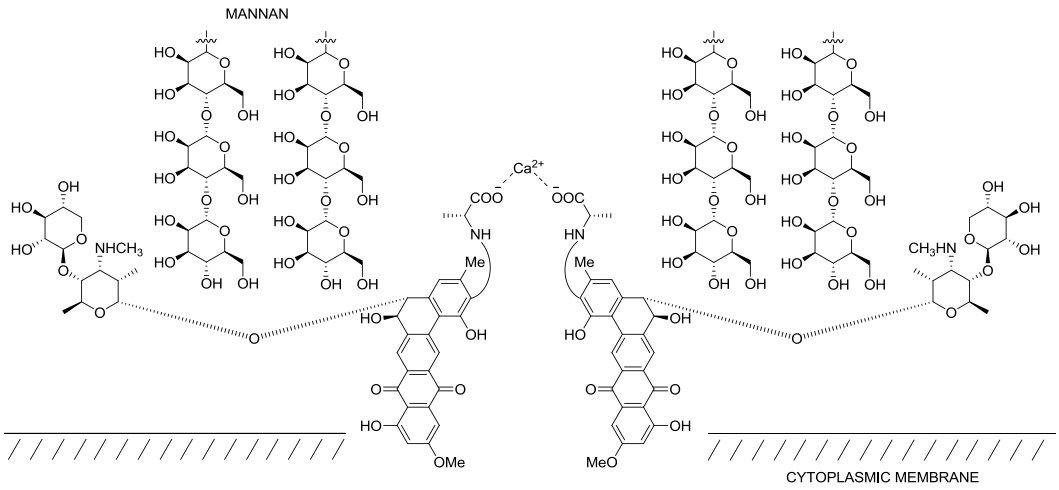


Figure 1.2: Proposed binding model of pradimicins/benanomicins by Oki and coworkers[21]

1.3 Antiviral Activity

Pradimicins have shown activity against numerous pathogens, including systemic fungal infections and potentially more importantly against the human immunodeficiency virus (HIV).[1, 7, 11, 17, 20, 24-26] 2.6 million new infections of HIV occurred in the year 2009 and each year this number is rapidly increasing.[27] The ongoing efforts to produce a vaccine for HIV have so far been inadequate and the pathogen still remains as a prominent issue in many countries, particularly in developing countries where treatment is not easily accessible.[27]

Many viral cells contain glycoproteins on their cellular envelope and are therefore recognized by the immune system as 'self' and escape destruction or neutralization.[18] The glycans on the viral surface are also critical in the transmission of the pathogen and entry into its host cell.[18] This type of cellular machinery is present in many other viruses such as the influenza virus, SARS coronavirus and hepatitis C virus (HCV).[17, 20] Therefore, it would be beneficial to target these glycans as a newfound approach in the development of a therapeutic resolution.[17, 18] CBA's are the first type of chemotherapeutics with a novel and potential dual mechanism of action against pathogens involving: 1) the initial binding to the glycans on the viral envelope to prevent entry into the host cell and 2) deletions on the glycan shield as a result of the binding and the potential to initiate an immune response towards the previously hidden pathogen.[18]

The glycoproteins present on the HIV envelope that mediate entry into the host cell are gp120 and gp41, gp120 being the outermost glycoprotein.[20] Upon infection, gp120 first binds to cellular receptor CD4, undergoes a conformational change and then binds to a coreceptor.[8] The binding triggers other conformational changes leading to insertion of gp41 to the cell membrane and eventual fusion of the virus with the cell.[8] Enfuvirtide, which targets gp41, is the first and so far the only entry inhibitor officially approved for

HIV treatment.[11] Pradimicin, on the other hand, has been shown to target gp120.[11] The glycans that make up gp120 have been found to contain a high amount of mannose and, as previously mentioned, pradimicins have a specific binding affinity towards mannose.[10, 20] Mammalian cells have a significantly less amount of high-mannose type glycans on the cell surface, which results in little to no binding with mannose-targeting CBA's.[11] This implies pradimicin CBA's could be selective towards the viral cells with little toxicity towards the host.[11] It is estimated that 11 out of approximately 24 glycosylation sites on gp120 contain high-mannose type glycans and the Balzarini group reported that PRM-A is selective for these sites.[10] Once bound to gp120, although not proven it can be assumed that the CBA prevents the conformational changes required in gp120 for gp41 to be exposed to and fuse to the cell membrane.[20] Upon subjection to CBA drug pressure, the virus then faces the dilemma of eventual elimination from the host after continual suppression or escape of drug pressure by progressive deletion of glycosylation sites.[11] In 2007, Balzarini and coworkers illustrated the glycosylation sites present in gp120 as shown in *Figure 1.3.*[11] The sites shown in red were deleted under PRM-A pressure, the sites that were not mutated are green and the site that was created during the drug selection process is blue.[11] With deletion of these sites comes the potential to activate the second mode of antiviral action, which is the production of antibodies by the immune system that will target the mutated virus after its glycan shield is no longer intact.[18] This phenomenon has yet to be proven, but seems highly plausible and would have a great impact on future drug development.[18] There have been no indications that glycoprotein gp41 is affected by PRM-A drug pressure, but higher drug concentrations might produce a different result.[11]

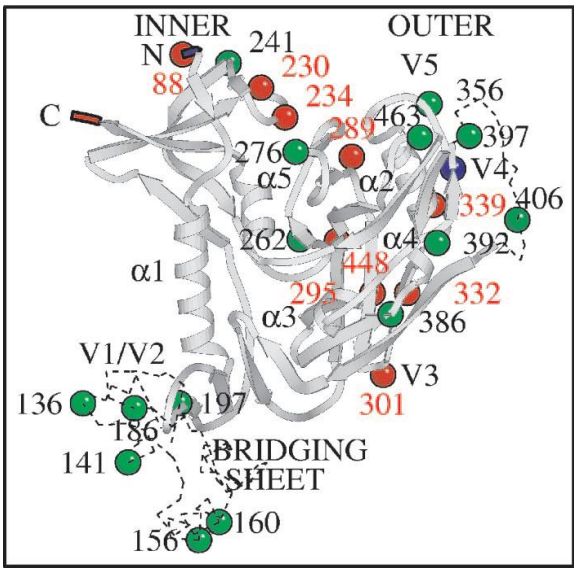


Figure 1.3: Map of the glycosylation sites in gp120 of HIV-1 strains isolated under escalating PRM-A concentrations by Balzarini and coworkers[11]

As previously mentioned, the ternary complex formed during binding involves two molecules of PRM-A and therefore would require two mannose binding sites for each PRM-A molecule.[10] To allow for multiple glycan binding, these sites are required to be a defined distance from one another, suggesting that PRM-A may possess a 'cross-linking' ability that creates a network of cross-linked and immobilized glycoproteins between the gp120 viral envelope and the target cell membrane.[11] The prevention of virus entry into the host cell may be due to these 'cross-linked' glycans that are immobilized and therefore cannot adopt the desired conformation for attack on the host cell.[11] Binding to multiple sites on the gp120 envelope results in PRM-A having the ability to bind non-stoichiometrically, unlike other HIV treatments available.[11] Balzarini and coworkers revealed that gp120 exists in a 1:33 molar ratio with the drug, allowing for a high number of PRM-A molecules to bind to the viral envelope, which may hinder the potential for drug resistance.[11] In comparison, the peptidic CBA CV-N has been reported to bind in a 1:5 stoichiometric ratio.[11, 28] This difference may be due to the size of the CBA's, CV-N having a molecular weight of 11,000 D, while PRM-A has a weight of 838 D.[11] The

smaller molecule is likely able to bind to multiple sites on the gp120 envelope because of less steric hindrance.[11]

In 2010, Balzarini and coworkers reported that PRM-A inhibited the cytopathic effects of HIV on various cell lines with an EC_{50} ranging from 5.2 to 5.9 µg/mL.[10] This group also proved that the drug was not toxic to cell cultures at a concentration of 50 µg/mL, which was the highest concentration tested due to PRM-A's low solubility.[11] The more soluble PRM-A derivative, PRM-S whose structure is shown in *Table 1.1*, had comparable EC_{50} values ranging from 5.1 to 8.9 µg/mL.[10] PRM-S was also capable of withstanding harsh conditions, tolerating 50 °C for 4 days and a pH of 4.0 for 4 days without impacting its antiviral potency.[10] Since the antiviral activity of these low molecular weight CBA's is in the low micromolar range, it is not as pronounced as the lectin CBA's and other potential therapeutics for HIV.[10] However, the pradimicins do have a biological activity comparable to the drug tenofovir, which is currently one of the methods used for HIV treatment.[10] It should be noted that since the pradimicins' mode of action is outside the cells, they do not require cellular uptake and metabolism before undergoing antiviral activity.[10]

1.4 Antifungal Activity

Along with the potential as antiviral agents, pradimicins have also shown antifungal activity against a number of different fungi, including *Candida*, *Cryptococcus*, and *Aspergillus* species.[2, 7, 29-33] This property proves to be beneficial since most humans who are immunodeficient are more susceptible to fungal infections.[23] It was reported in 2000 that over 80% of HIV infected patients suffer from oropharyngeal candidiasis, caused by the yeast *Candida albicans*.[23] In this case, there is potential for pradimicin to act as both an antiviral and antifungal resolution against HIV as well as fungal infections likely present in the same immunodeficient individual. Amphotericin B (AMPB/Fungizone) is one of the most well-known fungicidal treatment, along with flucytosine, itraconazole and

fluconazole (FLU), but the demand for new drugs is still urgent.[34] Disadvantages associated with current treatments include toxicity, limited spectrum of activity, and the emergence of resistant fungal strains.[34] Pradimicins are associated with an entirely different mode of action that may be an alternative to current treatments or used as a co-administered drug.

The three species, *Candida, Cryptococcus*, and *Aspergillus*, that the pradimicins target are the cause of the most frequently diagnosed fungal infections.[35] *Candida albicans* is thought to be the major fungal infection in humans, and usually colonizes the skin and mucosal surfaces.[35] They are capable of a number of escape mechanisms and can adapt easily to a change in environment, eventually becoming drug resistant.[35] *Cryptococcus neoformans* inhabits pigeon droppings and contaminated soil and its yeast cells can be easily inhaled by humans.[35] Although less prevalent than the *Candida* species, contraction of this fungus usually results in a higher mortality rate.[35] Lastly, *Aspergillus fumigatus* is the fungus primarily responsible for mould and can be found in certain foods such as pepper, tea and tap water.[35] The immune system as well as known antifungal treatments usually suffice in eliminating infections, but more invasive versions such as pulmonary aspergillosis can be more fatal.[35]

The pradimicins' mode of antifungal action is similar to that of its antiviral action such that it targets the mannose rich glycoproteins on the fungal cell wall. Mannan is a major cell wall component of most yeasts and functions in cell-to-cell recognition and cell reproduction.[36] Its outer chain is notably rich in α-mannose residues, which is again not as prevalent in mammalian cells, allowing for the CBA to selectively attack the invading fungal cells.[36] Unlike most fungicidal treatments currently available, the potential for a pradimicin-resistant strain of fungi to develop is highly unlikely, due to the fact that there has not been yeast isolated that does not contain mannan within its cellular envelope.[36]

The mechanism of binding again involves an initial ternary complex formation between pradimicin, D-mannopyranoside and calcium, noted by the red pigment of pradimicin associating with fungal cells in cultures.[23] At this stage, the ternary complex is transported from the cell wall to the cytoplasmic membrane, where it was suggested that the complex causes cell surface alterations, eventually leading to cell death.[21, 23, 33] In 1993, Oki and coworkers performed a scanning electron microscopy experiment that demonstrated morphological changes to the cell wall, including aberrations, invaginations and swollen bud scars, when *Candida albicans* cells were subjected to 100 µg/mL of BMY-28864 after 4 hours.[14, 21] *Figure 1.4* shows the cells prior (3a and 3b) and after drug pressure (3c and 3d), illustrating the morphological changes such as uneven cell surface, swollen bud scars (single arrow) and budding collars (double arrow).[14, 21] The sites of budding scars are known to contain a thinner layer of mannan, resulting in a more rapid saturation of the drug and disintegration of the cell wall at that site.[14, 21] After the formation of the aberrations on the cell wall, Oki and coworkers attribute the cytocidal effect of the drug to potassium leakage from the cell.[21]

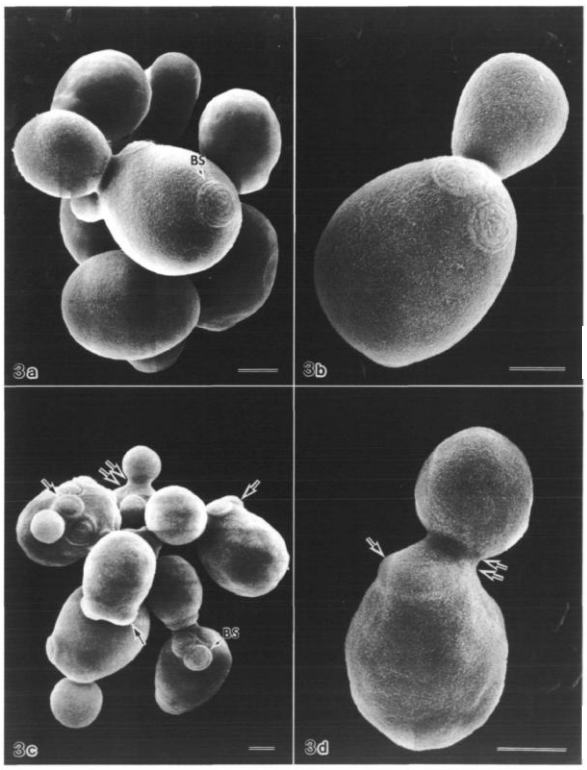


Figure 1.4: Scanning electron microscope images of Candida albicans cells before and after BMY-28864 drug pressure by Numata et al.[14]

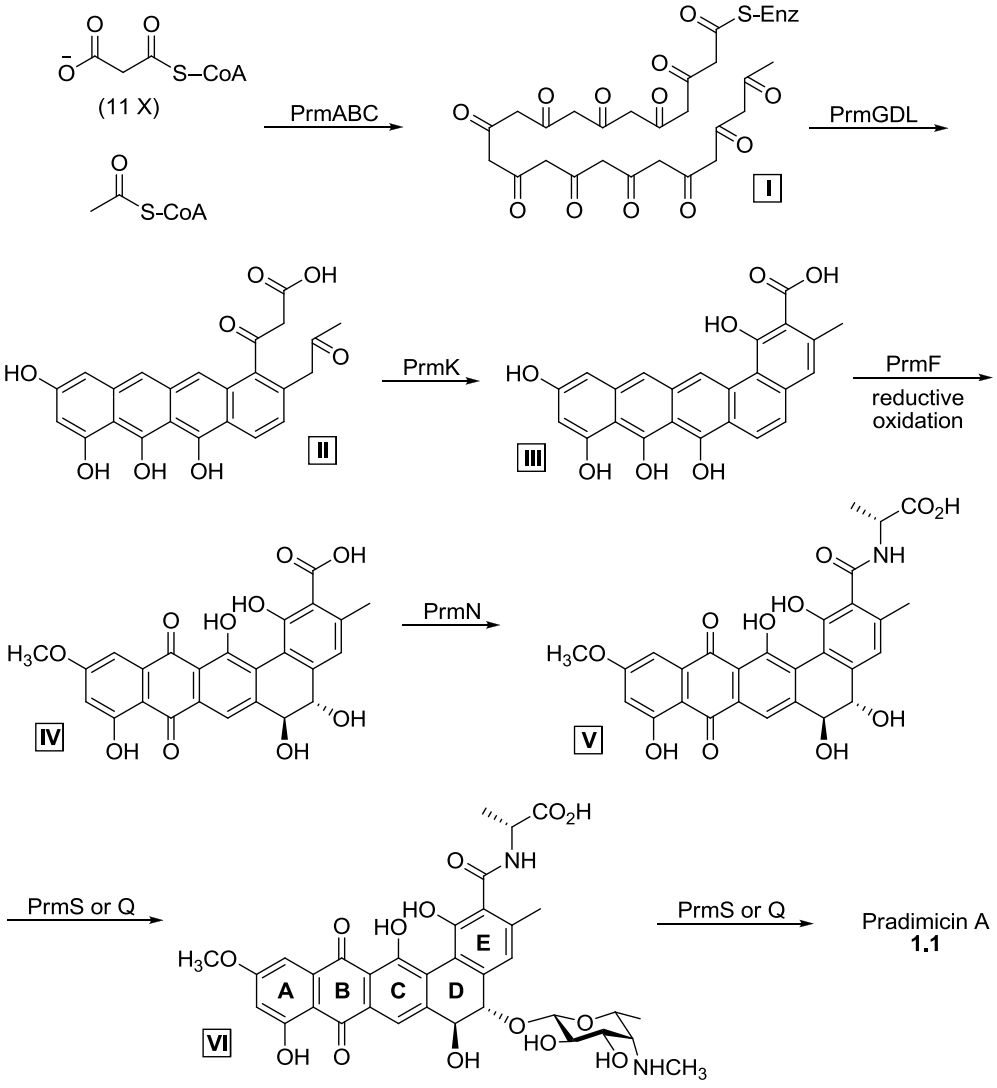
In 1996, Denning and coworkers reported the effect that analogue BMS-181184 had on *Candida* species *in vitro* compared to two other fungicidal drugs, AMPB and FLU.[37] The minimum inhibitory concentration (MIC) determined for BMS-181184 towards 64 *Candida* species had a range of 0.78 to 6.25 µg/mL with one isolate having a value of 12.5 µg/mL.[37] The majority of MIC values for AMPB were < 0.5 µg/mL and for FLU ranged from 0.09 to > 100 µg/mL.[37] The minimum fungicidal concentration (MFC) for BMS-181184 was no more than two-fold greater than the MIC value, indicating that the drug is indeed fungicidal and was active against species resistant to both AMPB and FLU.[37] Oki and coworkers reported that another more soluble pradimicin derivative, BMY-28864, showed similar results in terms of antifungal activity with both *in vitro* and *in vivo* testing on mice.[32]

In 1998, Walsh and coworkers investigated the *in vivo* activity of BMS-181184 against pulmonary aspergillosis in immunodeficient rabbits and compared its effectiveness with AMPB.[38] The results indicated that the drug possessed potent antifungal activity and was just as effective as AMPB in terms of survival rates.[38] BMS-181184 required a higher dosage compared to AMPB, due to its higher MIC of 8 μg/mL, but had no toxicity.[38, 39] Fung-Tomc and coworkers also confirmed this minimum inhibitory concentration in vitro with 90% of the 35 fungal species that were tested.[39] The drug proved to be 40 to 50-fold less active compared to AMPB, but at least 130-fold less toxic when administered on a mg/kg scale.[38] Although not as potent as AMPB, pradimicins are said to be a more selective and safer alternative, with the capacity to prevent the development of resistant strains.[32]

1.5 Biological Synthesis

In 2007, the Kim group proposed an interesting biosynthetic pathway for the pradimicin natural products, as shown in *Scheme 1.1*.[6, 40, 41] The genes involved in the biosynthesis possess strong similarities to those involved in the synthesis of polycyclic antibiotics such as rubromycin.[42] Much like the biosynthesis of many polyketides, the backbone of pradimicin A was proposed to arise from a number of condensations between acetyl starter units and 11 malonyl CoA extender units.[40, 43] Malonyl CoA is usually required for chain elongation in the synthesis of most fatty acids and polyketides.[40] The enzymes *prmA, prmB* and *prmC* are polyketide synthases likely responsible for the biosynthesis of the backbone precursor **I** ready to undergo further regiospecific folding.[40] The cyclase genes, *prmD*, *prmL*, and *prmK* are proposed to be responsible for the subsequent intramolecular aldol reactions to form the pentacyclic core **II**.[40] Specifically, *prmD* initiates folding of the linear polyketide and, along with *prmL* and *prmK*, takes part in catalyzing the cyclizations to produce the aromatic rings.[40] Meanwhile, Kim and coworkers propose *prmG* is responsible for catalyzing the reduction of a ketone to an alcohol to drive the

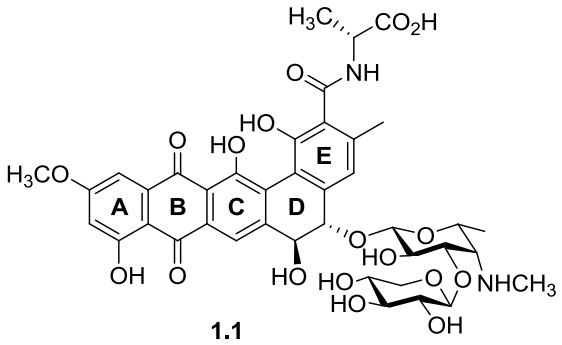
aromatization process.[40] Once the pentacyclic core **III** is formed, *prmF* is presumably the methyltransferase responsible for catalyzing the methylation of the alcohol in ring **A** and *prmN* is responsible for the amidation process to form diol **V**.[40] There were three monooxygenases found in the pradimicin gene cluster, *prmJ*, *prmW* and *PrmV,* which are likely responsible for installing the oxygens in the **B** and **C** rings that did not originate from the Malonyl-CoA precursor.[40] To complete the synthesis of the natural product, glycosyltransferases *prmS* and *prmQ* are two of the enzymes likely involved in the construction of the disaccharide moiety and final glycosylation.[40]



*Scheme 1.1: Proposed biosynthesis of pradimicin A **1.1** by Kim and coworkers[40]*

1.6 Chemically Synthetic Challenges of Pradimicin A

A number of factors must be taken into consideration when designing a synthetic route towards the pradimicin/benanomicin family of natural products. The main challenges associated with this molecule include a highly substituted pentacyclic core, a *trans*-1,2-diol and a disaccharide that requires regioselective introduction. As seen in *Figure 1.5*, the core **C**,**D**, and **E** rings of pradimicin A would therefore require the most consideration. In fact, most of the previous synthetic efforts by the Suzuki, Breit and Hauser groups, as well as efforts reported herein, are directed towards this tricyclic system.[40] The key to the synthesis lies within the formation and functionalization of the **D** ring. It would be ideal if the diol were introduced in a manner that would afford different protecting groups on each alcohol. Selective deprotection of the alcohol would allow glycosylation to occur chemoselectively and therefore dramatically increase the synthetic efficiency of the overall synthetic plan.



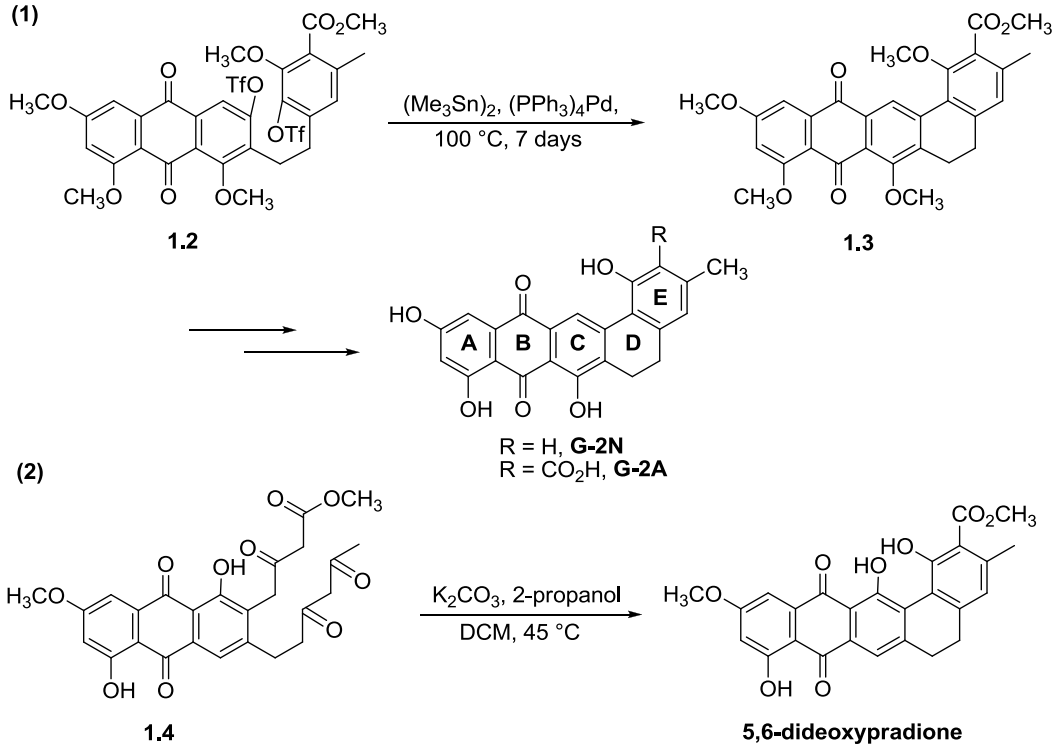
1.1

Figure 1.5: Structure of pradimicin A ***1.1***

1.7 Previous Synthetic Approaches Towards Related Aglycon Cores

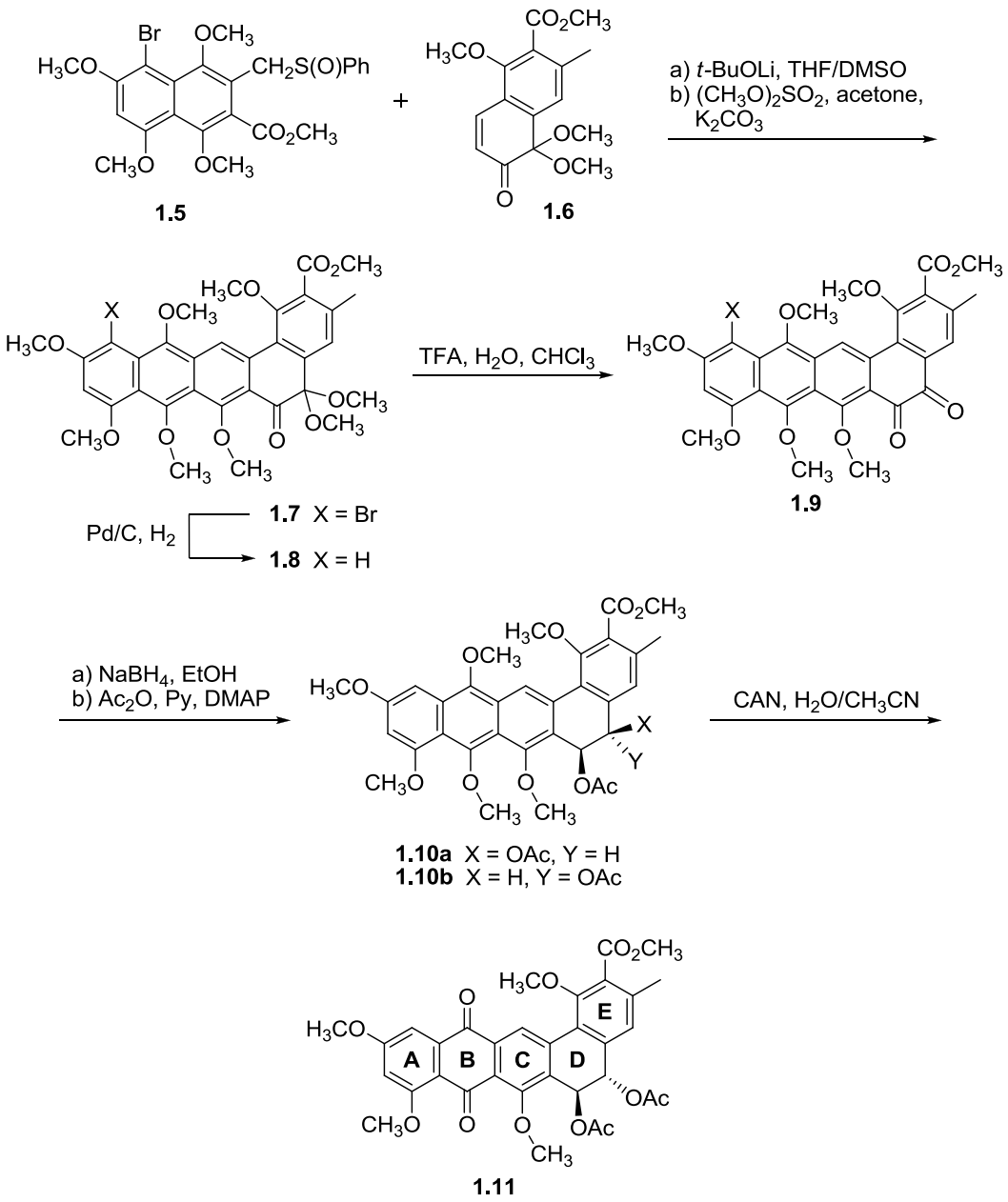
There is only one total synthesis to date of the pradimicin and benanomicin family, but there have been a few interesting partial syntheses that target variations of the aglycon core.[9, 44-47] These compounds include G-2N, G-2A, and 5,6-dideoxypradione,

which have similar core ring systems and are desired synthetic targets themselves due to their unique structures as well as their antibacterial and anticancer activity.[9, 44, 45, 47-49] In 1993, Kelly and coworkers reported a synthetic route towards pradimicin analogues G-2N and G-2A (*Scheme 1.2, equation **1***) that featured a palladium catalyzed intramolecular biaryl ring coupling of the two triflate substituted sp^2 centers in **1.2** to form ring **D** in pentacycle **1.3**.[44-46] The product was obtained in a 44% yield after one week.[46] In 1999, Krohn and coworkers developed a synthetic route towards G-2N and G-2A that mimicked the biosynthesis of pradimicin through a series of base catalyzed aldol reactions.[46] This method avoids the necessity of a biaryl ring coupling and forms ring **E** with the correct substitution pattern.[48] As seen in *Scheme 1.2, equation **2**,* the Krohn group later applied this chemistry to a system more similar to pradimicin to afford 5,6-dideoxypradione from precursor **1.4** using potassium carbonate.[48] This route provides access to the core ring system efficiently, but does not take into account the installation of the asymmetric diol functionality present in pradimicin A.



*Scheme 1.2: Synthetic strategies towards aglycon cores by the Kelly **(1)** and Krohn **(2)** groups* [45]

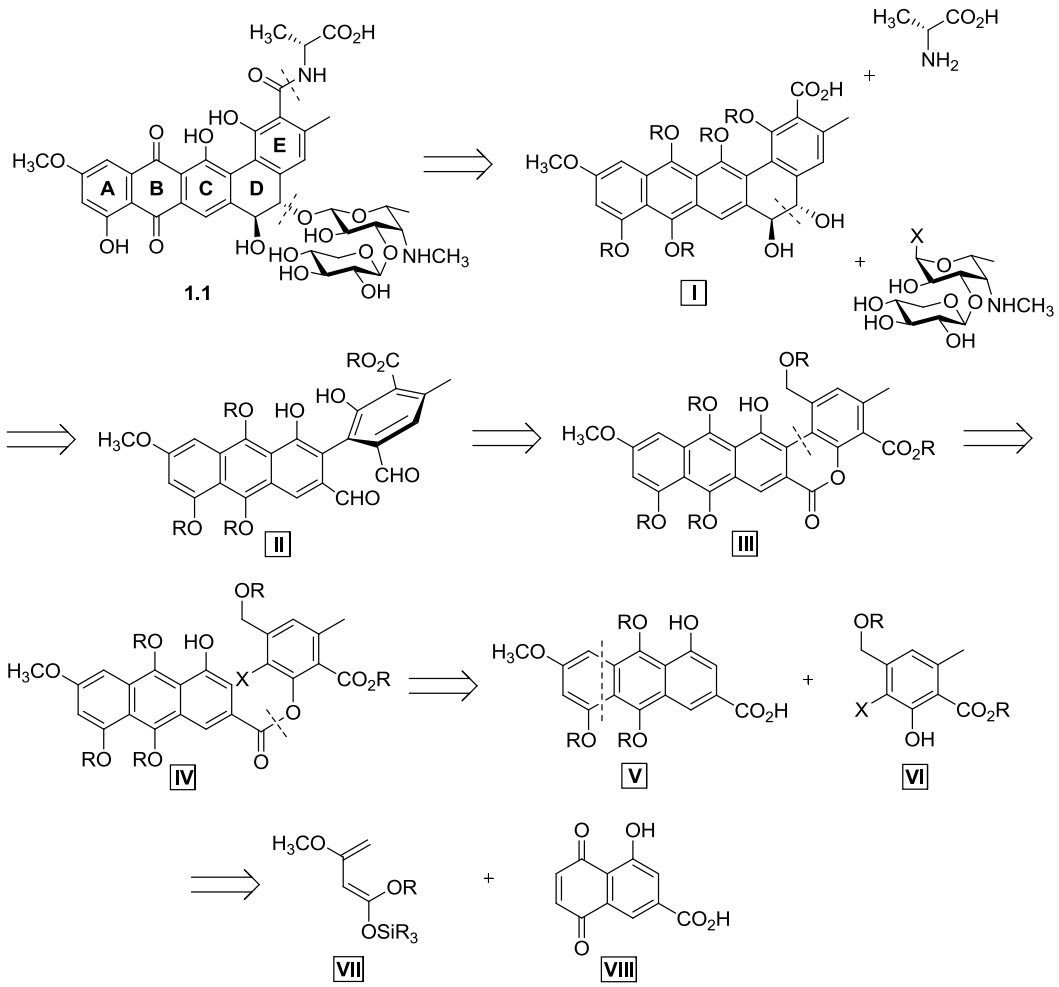
In 2002, Hauser and coworkers reported a synthesis of a pradimicinone/benanomicinone analogue diacetate **1.11**.[43, 46, 48] This synthetic route featured methodology previously developed in the group for the synthesis of naturally occurring aromatic ring systems.[44, 50] It featured the conjugate addition of the lithiated phthalide sulfone **1.5** with an *ortho*-quinone acetal **1.6** followed by an intramolecular enolate trapping to form the pentacyclic ring system **1.7** *(Scheme 1.3).*[44] Hydrolysis of compound **1.8** afforded diketone **1.9**, which was directly reduced to the diol and acetylated to afford a diastereomeric mixture of *cis*- and *trans*-diacetates **1.10a** and **1.10b**.[44, 50] The diastereomers formed in a 3:1 ratio, the major product being the trans isomer, and were separated by silica gel chromatography.[44] Despite the effectiveness of the key steps in constructing the pentacyclic core system, the synthesis is racemic and lacks the differentiation of the diol necessary for the selective glycosylation. As a result, further improvements would need to be made in order for this route to be applied towards the total synthesis.



*Scheme 1.3: Synthetic approach towards pradimicinone/benanomicinone analogue **1.11** by Hauser and coworkers*[44]

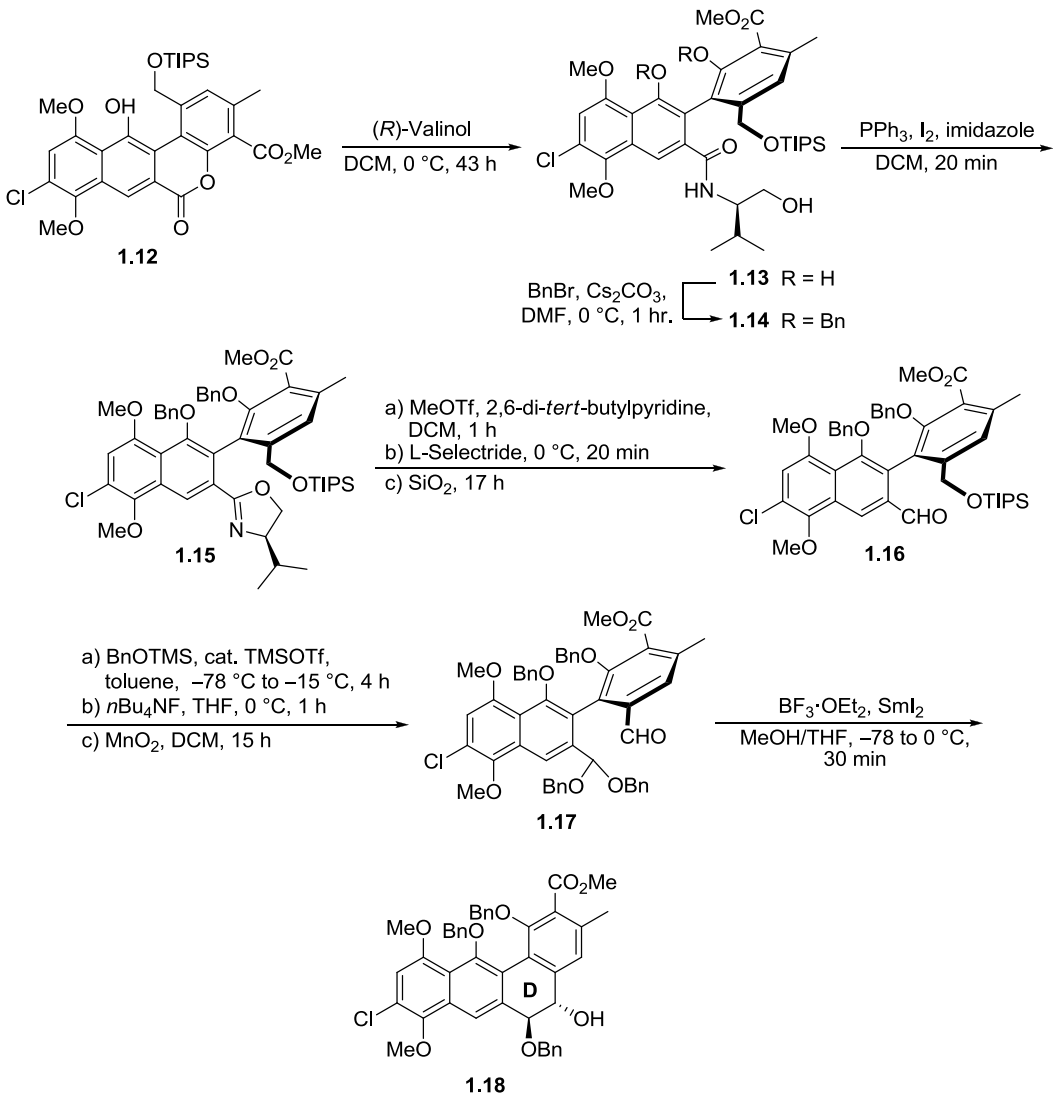
1.8 Total Synthesis of Pradimicin A by Suzuki and Coworkers

In 1999, the Suzuki group published the first synthesis of pradimicinone, an aglycon of the pradimicins and benanomicins that lacks the disaccharide moiety and contains a free *trans*-diol.[9, 44, 51] As seen in *Scheme 1.4*, the Suzuki group's retrosynthetic plan towards the total synthesis of the natural products initially involved the disconnections of the amino acid and disaccharide moieties leading to aglycon **I**.[9, 52] This pentacycle was produced from the featured pinacol cyclization of the two aromatic aldehydes in structure **II** to produce the *trans*-diol selectively, at the same time exploiting the transfer of axial to central chirality.[9] The dialdehyde **II** was proposed to derive from the biaryl lactone **III** via an asymmetric lactone ring opening, but this was not accomplished until the second generation synthesis.[9, 49, 52, 53] The biaryl bond was formed from a Pd-catalyzed cyclization of ester **IV**, which is derived from carboxylic acid **V** and phenol **VI** through an esterification reaction.[9] The Suzuki group later classified this route as their first generation synthesis and had to resolve two major issues in order to complete the first total synthesis of benanomicin B in 2005: 1) the synthesis of the axially chiral biaryl dialdehyde **II** was only obtained by optical resolution, producing the other enantiomer as a wasted byproduct and 2) the disaccharide moiety was introduced with a poor 3:2 regioselectivity favoring the desired regioisomer.[9]



Scheme 1.4: Retrosynthetic approach to pradimicins/benanomicins by Suzuki and coworkers[9, 49]

To overcome the first problem, Suzuki proposed using a Bringmann-type asymmetric ring opening of the biaryl lactone **III** instead of having to resort to optical resolution to acquire the enantioenriched biaryl aldehyde.[9] The original issue with the asymmetric lactone ring opening was the synthesis of the lactone itself, which was prone to hydrolysis during silica gel chromatography.[9] After successfully isolating lactone **1.12**, the Suzuki group screened various conditions and found the use of a chiral nucleophile was the ideal solution to afford the chiral amide **1.13** with a 91:9 diastereomeric ratio, as seen in *Scheme 1.5*.[9]



*Scheme 1.5: Synthetic route towards the differentiated trans-diol **1.18** by Suzuki and coworkers*[9]

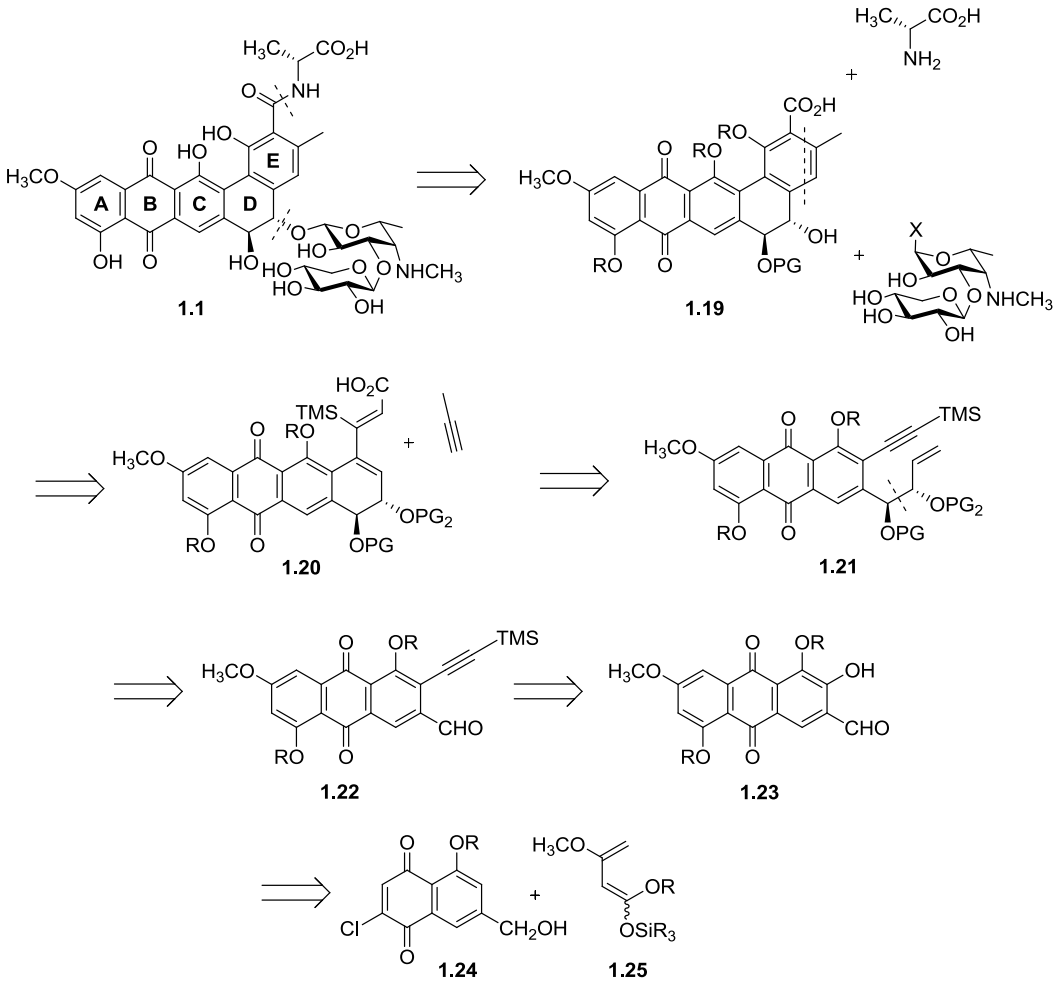
The Suzuki group then looked towards a semi-pinacol cyclization strategy to address the second issue of differentiating the alcohols in ring **D**.[9] Benzylation of the phenolic alcohols in amide **1.13** and cyclization of the hydroxy amide **1.14** afforded oxazoline **1.15** in a quantitative yield.[9] Intermediate **1.15** was subjected to N-methylation and the activated iminium was reduced with lithium tri-*sec*-butylborohydride (L-Selectride).[9] Hydrolysis of the resulting O-N acetal with silica afforded aldehyde **1.16**.[9] Formation of

the dibenzyl acetal, deprotection of the silyl protecting group and oxidation of the alcohol provided the precursor **1.17** for the key semi-pinacol cyclization.[9] After screening various conditions, $BF_3 \cdot OEt_2$ was chosen as the Lewis acid and SmI_2 as the reductant to access the *trans*-diol **1.18** in 95% yield and greater than 99% ee. Access to the monobenzylated diol **1.18** allowed for the synthesis of various analogues of pradimicin via the subsequent amidation and glycosylation, in which different functional groups can be installed. The Suzuki group successfully synthesized three naturally occurring congeners: benanomicin B, benanomicin A and pradimicin A through the installation of the appropriate amino acid and disaccharide functionalities.[9]

1.9 Hall Group Retrosynthetic Analysis

The goal of this project is to develop an alternative and more efficient synthetic route for the pradimicin/benanomicin natural products. This route would also enable easy access to analogues later on in order to design libraries of receptor CBA's. In particular, we hope to achieve a more direct enantioselective route towards the differentiated *trans*-diol, compared to the Suzuki group's synthesis that required several manipulations. A more direct route for the synthesis of the differentiated *trans*-diol would be ideal. *Scheme 1.6* illustrates our proposed retrosynthetic analysis. Similar to the Suzuki group's retrosynthesis, the installation of the amine and disaccharide were envisioned to occur in the later stages of the synthesis, allowing for an easily accessible route to analogues.[9] Pentacycle **1.19** can be derived from a Diels-Alder reaction involving diene **1.20** and a dienophile. We proposed diene **1.20** to be synthesized initially from a ruthenium catalyzed enyne metathesis using precursor **1.21**, followed by a cross metathesis to install the carboxylic acid onto the terminal alkene. The presence of the carboxylic acid allows for elimination of regioselectivity issues in the Diels-Alder reaction and also results in the desired functionalization of ring **E**. This enyne metathesis reaction followed by a Diels-Alder reaction to close rings **D** and **E** would be an interesting and new approach

towards the synthesis of these natural products. The enyne **1.21** was envisioned to be synthesized via a Brown alkoxyallylboration reaction with aldehyde **1.22**. This key reaction will potentially allow the chiral centers to be created asymmetrically, affording the monoprotected diol in one step. Alkyne **1.22** could be synthesized through a Sonogashira reaction with the triflated alcohol of fragment **1.23**. Another Diels-Alder reaction can be envisioned to occur between the two known substrates **1.24** and **1.25** in order to synthesize the tricyclic ring system **1.23**.[9]



Scheme 1.6: Hall group's initial retrosynthetic approach to pradimicins/benanomicins

1.10 Objectives

One of the interests within the Hall group involves the design and application of carbohydrate receptors. In 2008, our group reported on the ability of *o*-hydroxymethyl-benzoboronic acid (benzoboroxole) to coordinate to galactopyranosides through a *cis*-3,4-diol, as illustrated in *Figure 1.6*.[45] This approach relies on the Lewis acidity of benzoboroxoles and allows these compounds to act as low molecular weight carbohydrate receptors in an aqueous environment.[54, 55] Our group then elaborated on this project to synthesize a library of bis(benzoboroxole) peptidyl carbohydrate binding units to target a tumor-associated carbohydrate antigen. The most potent receptor was found to have a half maximum inhibitory concentration value of 20 μM and further investigations are underway to develop a broader application of this receptor.[55] The goal of this project is to study the synthesis of pradimicins and their corresponding analogues. An ideal route to stimulate the synthetic community would combine both the efficiency and flexibility in accessing libraries of structurally diverse analogues. The future application of these synthesized compounds is to measure their carbohydrate binding affinity in hopes of revealing an ideal carbohydrate receptor that is biologically active towards various pathogens.

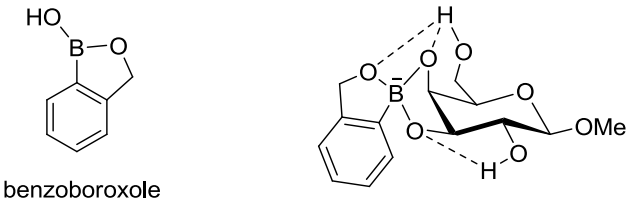


Figure 1.6: Benzoboroxole's carbohydrate binding ability with a galactopyranoside[56]

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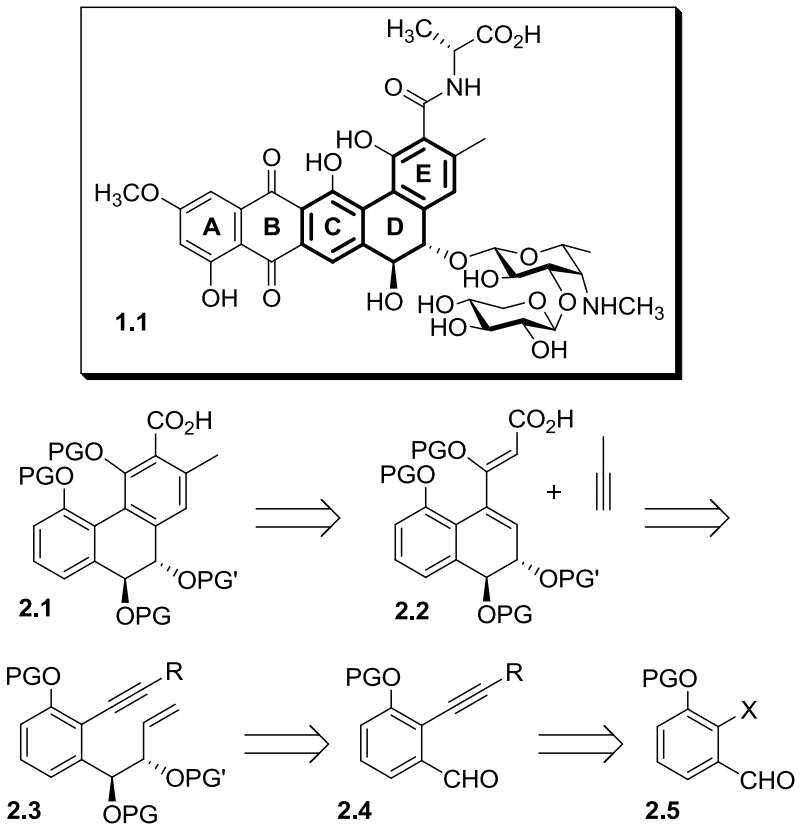
CHAPTER 2

MODEL STUDY TOWARDS THE CORE TRICYCLIC RING SYSTEM OF PRADIMICIN A

2.1 Design of a Model Study

Based on our retrosynthetic analysis, it was clear that the synthesis proposed for the core **C**, **D**, and **E** rings of pradimicin A **1.1** was going to be the most ambitious and challenging. The key reaction included the asymmetric Brown alkoxyallylboration to install the monoprotected diol and, more importantly, the enyne metathesis and Diels-Alder reactions to close rings **D** and **E**. We proposed that rings **A** and **B** could be generated either at the beginning or during the synthesis of the core tricyclic system by following similar synthetic routes previously employed by the Suzuki, Kelly and Krohn groups.[1-3] With that in mind, a model study was proposed in order to test the key reactions involved in the synthesis of the **C**, **D** and **E** ring systems from precursors **2.4** and **2.5**, as shown in the original retrosynthetic plan and *Scheme 2.1.* We believed that by testing these key reactions and developing an efficient synthetic route towards tricyclic ring system **2.1** would afford sufficient grounds to pursue the total synthesis of pradimicin A.

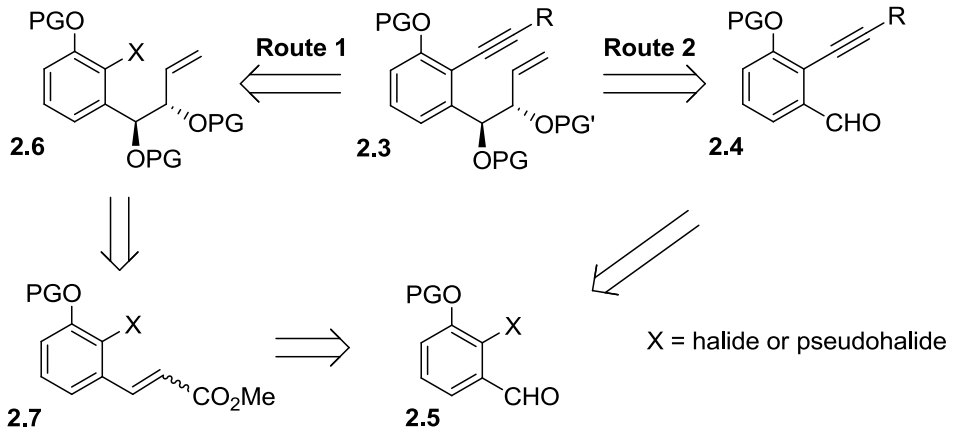


Scheme 2.1: Proposed retrosynthetic scheme for our model study

2.2 Synthesis of Enyne Precursor 2.3

Our efforts in this synthesis began with designing a route towards enyne precursor **2.3** from aldehyde **2.5**. Two options were contemplated to install the terminal alkene chain (*Scheme 2.2)*. **Route 1** involved a Wittig olefination of the aldehyde **2.5** to obtain alkene **2.7**, followed by a Sharpless asymmetric dihydroxylation. After protection of the diol, the ester would be reduced and reoxidized to form the aldehyde. A second Wittig olefination was proposed to install the terminal alkene to form precursor **2.6**. **Route 2** consisted of an alkoxyallylboration to directly install both the diol and terminal alkene functionalities from alkyne **2.4** in one step. The second route is more appealing, but both were explored in order to obtain access to **2.3** with optimal enantioselectivity. Since both routes were

envisioned to originate from trisubstituted benzene **2.5**, the initial goal in obtaining the key enyne precursor involved the synthesis of trisubstituted benzene derivatives.

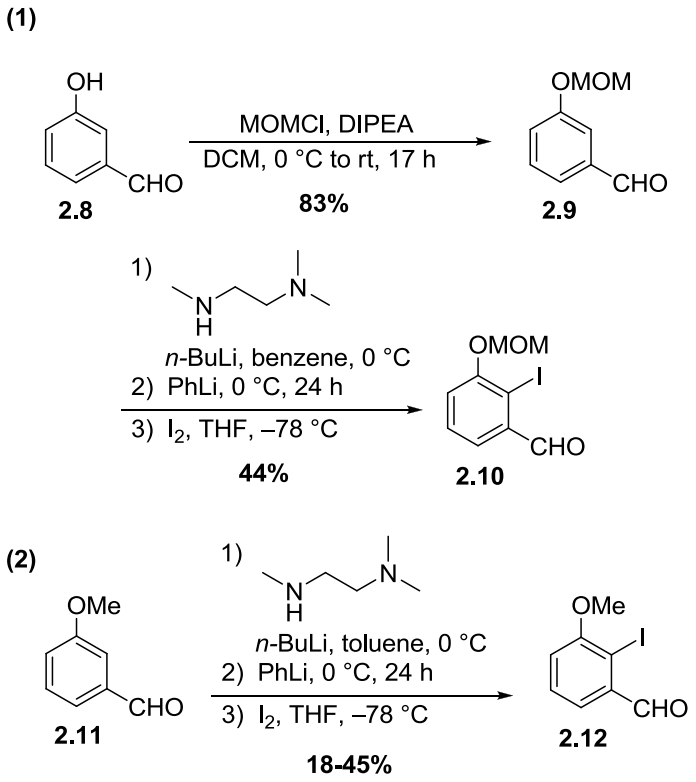


*Scheme 2.2: Proposed retrosynthetic scheme towards the synthesis of precursor **2.3***

2.2.1 Synthesis of Trisubstituted Benzene 2.5

The synthesis of starting material, aldehyde **2.5**, proved to be more troublesome than one would initially imagine. An inexpensive and high yielding synthetic route towards **2.5** was preferable in order to obtain the product on a large scale. Our initial synthesis of this starting material began with the use of commercially available 3-hydroxybenzaldehyde. Work published by Breit and coworkers illustrated a method involving an *in situ* protection of the aldehyde using N′,N,N-trimethylethylene aminoamide followed by an *ortho*-directed metallation with phenyllithium.[4] The metallation generated the 2-lithio aryl species which was then trapped using iodine to afford the desired product, aldehyde **2.10**. The Breit group used a methoxymethyl (MOM) protecting group for the alcohol to help direct the lithiation to the *ortho* position.[4] The directing effect is amplified through the coordination with the protected aldehyde. In light of their success, we employed a similar strategy to protect phenol **2.8** with a MOM group as well to afford aldehyde **2.9** (*Scheme 2.3 equation **1***).[5] This protection required a large excess of both MOMCl and DIPEA to the extent of 6 equivalents to obtain a yield of 83% of **2.9**, thus making this route difficult to

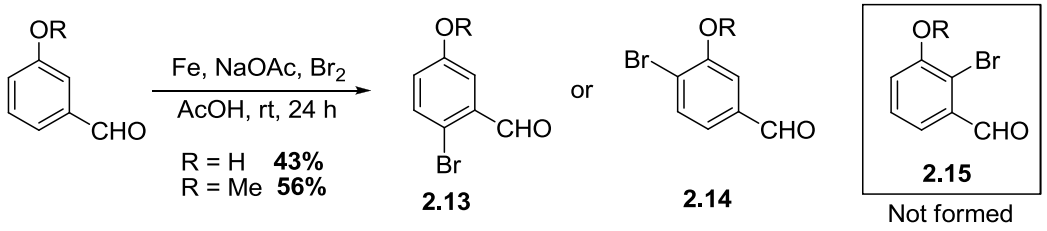
achieve on a large scale. Moreover, access to MOMCl is both costly and difficult due to its carcinogenic properties. As an alternative, we then looked into using commercially available 3-methoxybenzaldehyde **2.11** instead as the starting point (*Scheme 2.3 equation **2***).



*Scheme 2.3: Synthesis of trisubstituted benzene derivatives **2.10** and **2.12***

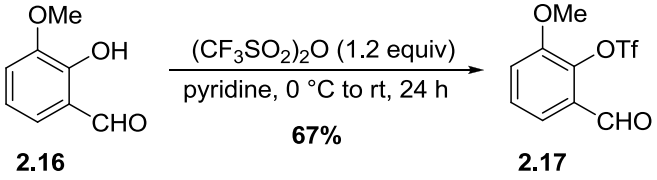
As seen in *Scheme 2.3*, the iodination of aldehydes **2.9** and **2.11** requires a number of relatively expensive reagents and takes approximately 48 hours to complete. Moreover, the yield was difficult to reproduce on a large scale. As a result, we looked towards using another approach found in the same publication by Breit and coworkers where a direct bromination of phenol **2.8** was performed to obtain 2-bromo-2-hydroxybenzaldehyde in a 50% yield.[4] Even though the reported yield is similar to the previous iodination, the bromination could be easier in terms of scale up and purification to produce the desired benzaldehyde **2.5**. However, efforts to reproduce this reaction resulted in brominated

aldehyde **2.13** or **2.14** forming instead of the desired product **2.15**. Based on coupling constants, it was clear that desired product **2.15** was not obtained and, upon comparison to ^{1}H-NMR literature data, **2.13** was suspected to be the product formed.[6, 7] At this stage, an alternative route towards the trisubstituted precursor **2.5** was required.



*Scheme 2.4: Bromination of aldehydes **2.8** and **2.11***

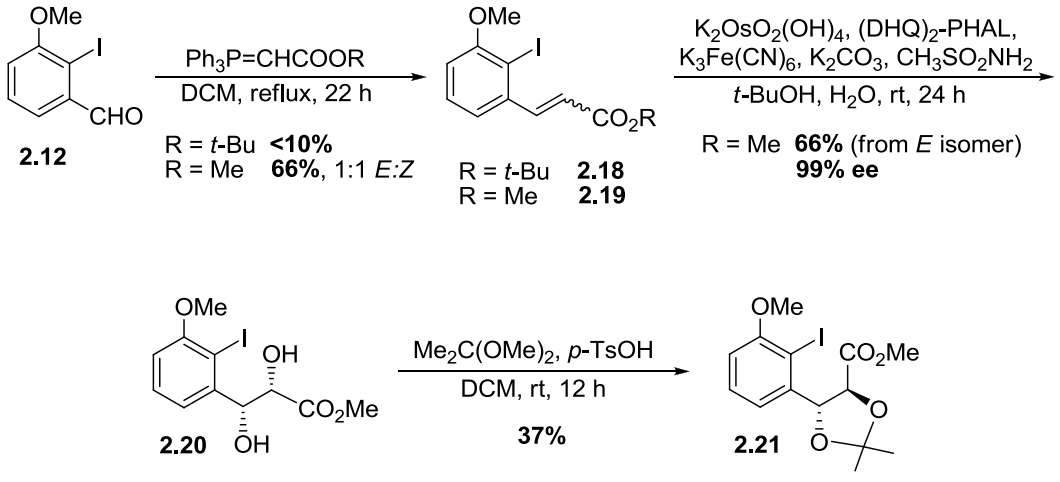
Taking into account the fact that a Sonogashira cross coupling reaction was to be done on the halogenated product, we looked towards installing a triflate group in the *ortho* position as a pseudohalide. Utilizing commercially available alcohol **2.16** and triflic anhydride, triflate protection on the alcohol afforded product **2.11** in a 67% yield.[8] This was the highest yield obtained thus far for the Sonogashira precursor with this particular substitution pattern. Therefore, this route was continuously used throughout the synthesis to obtain large scale amounts of starting material **2.17**.



*Scheme 2.5: Triflate protection of alcohol **2.16***

2.2.2 Route 1: Synthesis of Alkene 2.6

With the trisubstituted benzaldehydes in hand, synthetic ***Route 1*** *(Scheme 2.2)* towards the core tricyclic system **2.3** was first explored. It began with the Wittig olefination of aldehyde **2.12** using the ylide, methyl (triphenylphosphoranylidene)acetate, and reaction conditions reported by Harmata and coworkers.[9] The reaction resulted in approximately a 1:1 ratio of *E*:*Z* isomers in a 66% yield of methyl ester **2.19** (*Scheme 2.6*). A *tert*-butyl ester ylide was also tested to potentially increase the *E*:*Z* selectivity and indeed afforded an approximate *E*:*Z* ratio of 4:1 for product **2.18**. However, due to a low yield this product was not applied to further reactions in the synthesis. The *E* and *Z* geometric isomers of methyl ester **2.19** from the Wittig reaction could not be separated via column chromatography, but regardless the mixture was subjected to the next step in the synthesis. A Sharpless asymmetric dihydroxylation reaction was employed to produce diol **2.20**.[10] Fortunately, only the *E* isomer of **2.19** was dihydroxylated under these conditions and the unreacted *Z* isomer was visible in the crude ^{1}H-NMR of the product. The diol was obtained in a 66% yield from the *E* isomer with an excellent enantiomeric excess of 99% determined by chiral HPLC. The diol was then protected using 2,2-dimethoxypropane to afford acetal **2.21**, albeit with a lower 32% yield.[10]



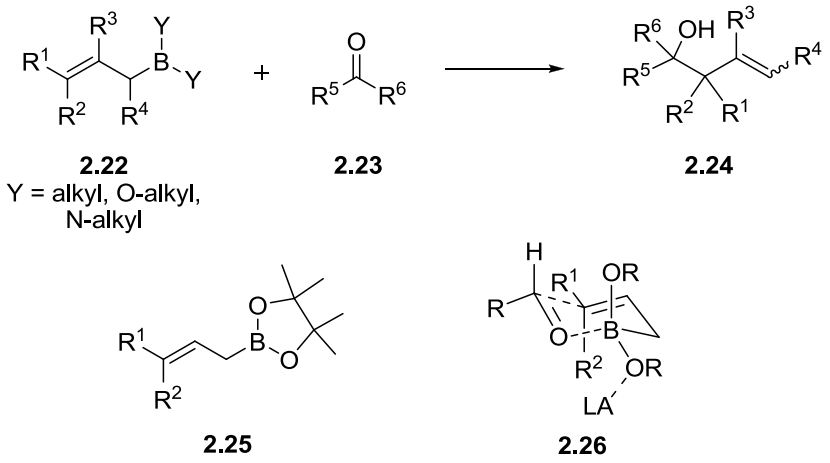
*Scheme 2.6: Preparation of protected diol **2.21***

At this point in the synthesis, the plan was to reduce the methyl ester to an alcohol, followed by a reoxidization to produce the aldehyde. From there, a second Wittig olefination would install the terminal alkene required for the enyne metathesis reaction to obtain precursor **2.6**. Despite the high enantiomeric purity obtained, the plan for **Route 1** involved multiple steps and a more direct preparation to precursor **2.3** was desired. Therefore, it was decided that **Route 1** should be abandoned. Also, simultaneous research efforts towards the **Route 2** approach to enyne **2.3** displayed more promising results and research hereon was focused in this direction.

2.2.3 Route 2: Alkoxyallylboration of Aldehyde 2.5

The main advantage associated with the preparation of precursor **2.3** via an alkoxyallylboration involves the installation of the monoprotected diol and terminal alkene in one step from the aldehyde. The allylboration reaction is a widely used reaction for the formation of homoallylic alcohols **2.24** through an allyl-transfer reaction between allylic borane or boronate **2.22** and carbonyls **2.23**.[11-24] It is a useful process because a new carbon-carbon bond is formed as well as up to two stereogenic centers.[11] Silicon[25-30], tin[30, 31] and chromium[32-37] are just some examples of other metals employed instead of boron for these reactions. Allylation reagents can be classified as type I, II or III based on their mechanism and stereoselectivity observed with substitution in the R^1 and R^2 positions (*Scheme 2.7).*[11, 38] Allylboration reagents belong to the class of Type I reagents that proceed through a rigid 6-membered Zimmerman-Traxler transition state. The benefit of this type is the predictability based on the *E* or *Z* starting material used and high stereoselectivity obtained.[11, 38] Furthermore, Type I allylations allow for the reaction to occur spontaneously without a need for external activators.[11, 38] The end byproduct of the allylboration is a boric acid salt that can be easily disposed of, compared to other toxic metal byproducts.[12] Lastly, the four points of substitution available on allylborane reagent **2.22** at the R^1 to R^4 positions make it to be a very versatile reaction.[11, 12] Types II and III

allylation reagents require the need for an external activator for the aldehyde and occur via an open transition state, resulting in products which stereochemistry cannot be as easily predicted by the olefin geometry of the substrates.[38]

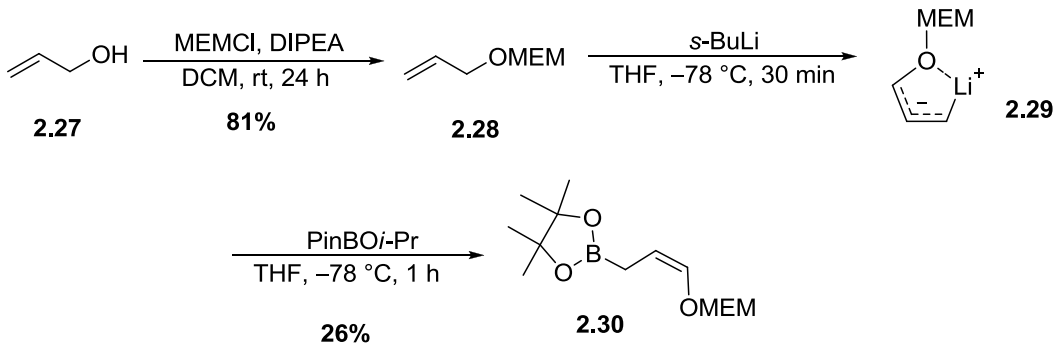


*Scheme 2.7: Allylboration reaction for the preparation of homoallylic alcohols **2.24** and the proposed transition state for Lewis acid-catalyzed additions of pinacol allylic boronates **2.25***[11, 38]

There have been many contributions to the development of stoichiometric chiral auxiliaries for the asymmetric allylboration, including extensive work by Hoffmann, Roush, Brown, Masamune and Yamamoto.[12] However, the option of a catalytic variation of this reaction has not shown precedent in the literature until recently. The Hall and Miyaura groups have made significant contributions to this area by directing research towards a Lewis acid catalyzed allylboration (*Scheme 2.7)*.[39, 40] It was previously proven by the Hall group that the role of the Lewis acid is to coordinate to one of the oxygens on the boronic ester, electophilically activating the boronate (**2.26**).[38, 41] In 2006, our group applied a catalytic system developed by Yamamoto and coworkers utilizing a chiral diol•$SnCl_4$ complex towards the enantioselective addition of stable and commercially available allylboronic acid pinacol esters **2.25** to aliphatic aldehydes.[38, 42] In this system, the use of a small proton from the diol as an activator is ideal to bind to the hindered pinacolate

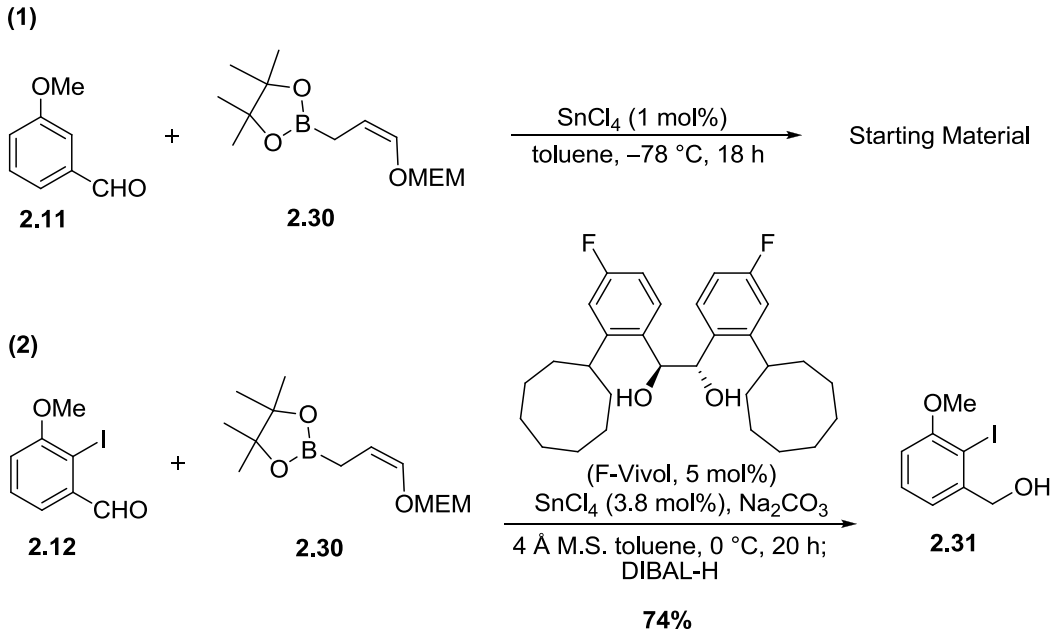
oxygen.[42] Indeed, under Yamamoto's chiral diol•$SnCl_4$ system, homoallylic alcohol products were obtained with high diastereoselectivities and moderate enantioselectivities.[42] Afterwards, an improved chiral alcohol was sought out to optimize this reaction and lead to the development of a novel second generation diol, Vivol, which as a complex with $SnCl_4$ efficiently catalyzed the allylboration of aliphatic aldehydes with pinacol allyl- and crotyl-boronates.[38] Optimization of the diol included introducing *ortho*-cycloalkyl groups as well as *para*-fluoro groups to increase the acidity, eventually resulting in the catalyst F-Vivol (*Scheme 2.9*).[38, 43] We envisioned testing our group's methodology on aldehyde **2.5** to see if this type of catalytic variation of the allylboration reaction was applicable towards a novel aromatic substrate. If successful, a broader substrate scope for the diol•$SnCl_4$ system could be attainable as well as access towards precursor **2.3** by means of a catalytic allylboration compared to the stoichiometric variant. However, it was not previously known for an alkoxyallylboration reaction to occur with an aromatic substate under this system.

The catalyzed alkoxyallylboration began with the preparation of starting material pinacol boronate **2.30**. Initially, allyl alcohol **2.27** was protected with a MEM group using 2-methoxyethoxymethyl chloride and the product **2.28** was obtained in a good yield of 81%. Upon treatment with *sec*-butyllithium, the protected alcohol **2.28** was deprotonated forming allyl anion **2.29**, where the lithiated intermediate coordinates to the oxygen in the 5-membered deprotonation transition state, preferentially forming the Z isomer.[12] Treating the intermediate **2.29** with *iso*-propoxyboronic acid pinacol ester followed by a work-up using a pH 7 buffer resulted in the formation of 2,3-alkoxyallylboronate **2.30**. The yield of 26% was not ideal, however, efforts towards optimization were not performed since only a small amount of product was needed in order to test the catalytic alkoxyallylboration.



*Scheme 2.8: Preparation of pinacol (Z)-3-alkoxyallylboronate **2.30***

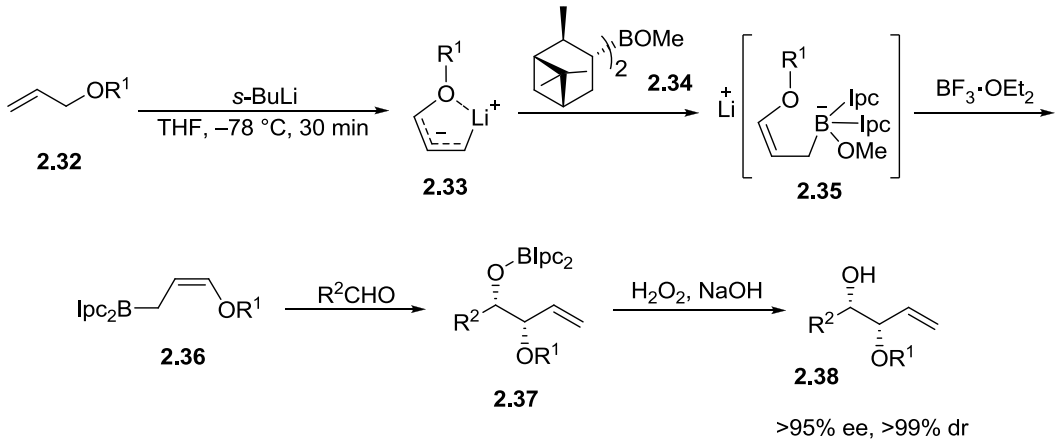
With precursor **2.30** in hand, the acid catalyzed alkoxyallylboration was ready to be tested (*Scheme 2.9*). Using conditions from previous work,[43] an initial background reaction was performed using only tin tetrachloride as a catalyst at –78 °C with aldehyde **2.11** (*Equation 1)***.** After 18 hours, the reaction resulted in only starting material and possible decomposition of the pinacol boronate. Also, another uncatalyzed neat reaction between aldehyde **2.11** and boronate **2.30** run at room temperature for 36 hours produced a new spot visible by TLC with a lower Rf value, potentially indicating positive alcohol formation. From this observation, it appeared that a higher temperature is necessary for the background reaction to occur. With this information in mind, the second attempt that was carried out utilized aldehyde **2.12** and the catalytic system F-Vivol•$SnCl_4$ at 0 °C for 20 hours. This attempt, however, resulted in no reaction and the aldehyde starting material was reduced to benzylic alcohol **2.31** during the DIBAL-H work-up with a 74% yield (*Equation 2*). As a result, it was concluded that this acid catalyzed alkoxyallylboration was not compatible with the aromatic aldehyde substrate and the higher temperatures needed would most likely have a negative impact on the enantioselectivity.



Scheme 2.9: Acid catalyzed alkoxyallylboration attempts

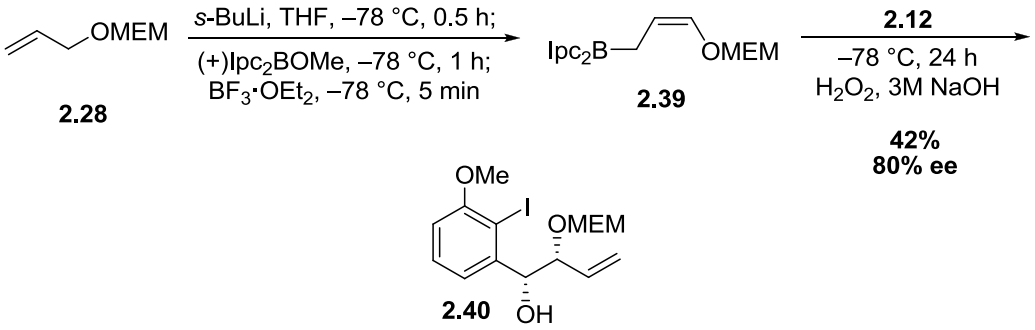
Once the Hall group methodology proved to be unsuccessful with this particular aldehyde, we proposed to utilize the stoichiometric chiral allylborane derived from α-pinene developed by Brown and coworkers.[12] This alkoxyallylboration is applicable towards a wide range of aldehyde substrates and the syntheses of several higher order alkoxyallylboranes *in situ* are well known.[12] The general preparation of the allylboration reagent (*B*)-(*Z*)-ɣ-[alkoxyallyl]diisopinocampheylborane followed by the *in situ* addition to the aldehyde is shown in *Scheme 2.10.*[12] Similar to the synthesis of boronate **2.30**, the preparation begins with the addition of *sec*-butyllithium to protected allyl alcohol **2.32** to form *Z*-allyl anion **2.33**.[12] Addition of borinate **2.34** to the anion results in the intermediate **2.35**, which retains the *Z*-olefin geometry.[12] The strong Lewis acid then releases the alkoxyallylboration reagent **2.36** and immediate addition of the aldehyde forms product **2.38** after oxidative workup using alkaline hydrogen peroxide.[12] The 1,2-*syn*-alkoxy homoallylic alcohol products are obtained in high ee and dr.[12] The absolute configuration of the homoallylic alcohol produced is governed by the borane reagent used, (+)-

Ipc_2BOMe or (–)-Ipc_2BOMe.[12] Various protecting groups have been employed for the alcohol, including methoxymethyl (MOM) and *p*-methoxyphenyl (PMP), allowing for milder deprotection conditions compared to methoxy.[12]



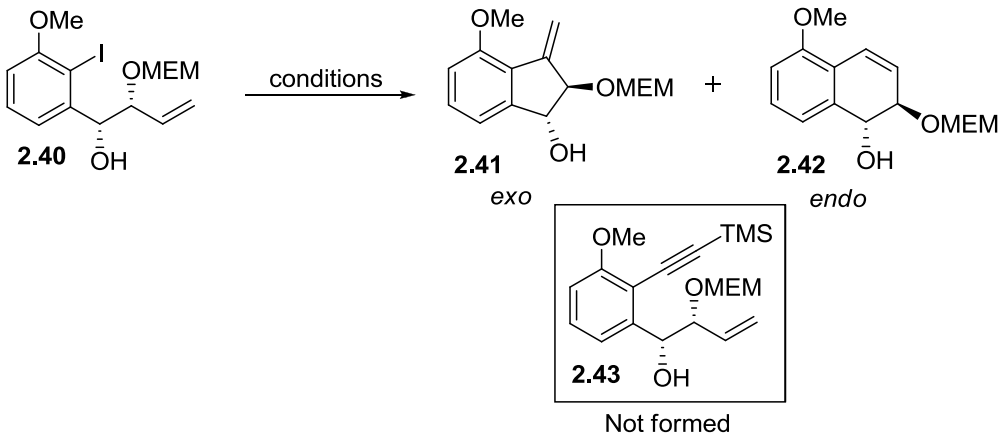
Scheme 2.10: Sequence Details of the Brown alkoxyallylboration[12]

In 2002, Ramachandran and coworkers reported an alkoxyallylboration between olefin **2.39** and the most related substrate, benzaldehyde, to produce the α-alkoxy homoallylic alcohol product in a 71% yield and 98% ee.[44-46] Application of this alkoxyallylboration methodology towards trisubstituted benzene **2.12** has not been previously reported. Using the same reaction conditions, homoallylic alcohol product **2.40** was obtained in a 42% yield and 80% ee (*Scheme 2.11*). Various reaction conditions were altered including increasing the equivalents of borane and Lewis acid used, but did not significantly impact the outcome of the reaction.



*Scheme 2.11: Brown alkoxyallylboration of aldehyde **2.12***

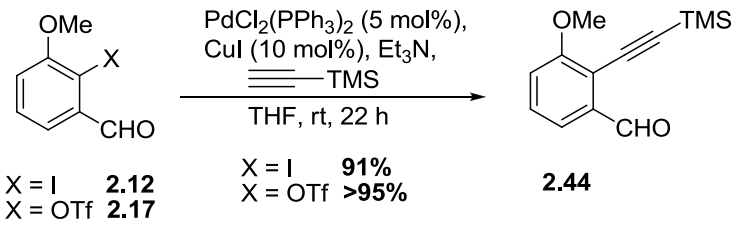
With a plan to later optimize the yield and ee for the alkoxyallylboration reaction, the product **2.40** was directly applied to further reactions in the synthesis. The next step was the installation of the alkyne via the Sonogashira coupling reaction between aryl iodide **2.40** and trimethylsilylacetylene *(Table 2.1)*. Despite using standard conditions such as Schmalz and coworkers reported in 2009,[47] the expected alkyne product **2.43** was not observed. Instead, it was found that a Heck-type reaction occurred cyclizing the aryl group onto the external alkene to produce a 3:1 ratio of *exo* product **2.41** to *endo* product **2.42** (*Entry 1*). From this result, the possibility of optimizing the formation of cyclohexene product **2.42** and using it in an alternate synthesis towards pradimicin A became another option. Various conditions that were tried are listed in *Table 2.1.* It was found that when using $Pd(PPh_3)_4$ or $Pd(Cl)_2(PPh_3)_2$ in 10 mol% in the presence of triethylamine, the *exo* pentacyclic product **2.41** was formed in a higher 10:1 ratio, which is the more kinetically favored product (*Entry 2)*. It was intriguing to find that without the presence of TMS-acetylene under Sonogashira conditions that there was no reaction, meaning that this reagent could play a role in the cyclization (*Entry 3)*. The final entry shows that the copper iodide had no effect on the *exo* to *endo* ratio of products. Despite numerous attempts at optimizing the amount of cyclohexene **2.42** produced, none were successful at obtaining more than a 3:1 ratio of *exo:endo* isomers. Although an interesting result was obtained, the potential to use cyclohexene **2.42** in an alternate synthetic route was not looked into beyond this point.



Entry	***Conditions***	***Product***
1	$Pd(Cl)_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, TMS-acetylene, THF, rt, 24 h	**3:1 2.41:2.42**
2	$Pd(PPh_3)_4$ (10 mol%), Et_3N, THF, rt, 24 h	**10:1 2.41:2.42**
3	$Pd(Cl)_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N, THF, rt, 24 h	**No reaction**
4	$Pd(Cl)_2(PPh_3)_2$ (10 mol%), Et_3N, TMS-acetylene, THF, rt, 24 h	**3:1 2.41:2.42**

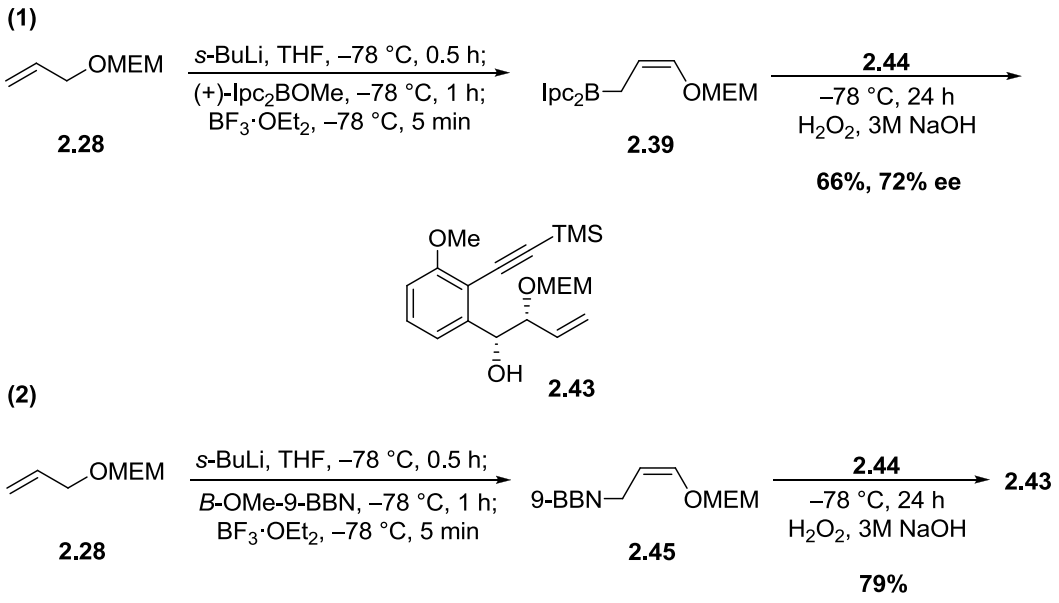
*Table 2.1: Attempted Sonogashira coupling reaction of aryl iodide **2.40** and TMS-acetylene*

In order to avoid formation of Heck products **2.41** and **2.42** and to obtain the desired enyne **2.43**, the option to install the alkyne prior to the Brown alkoxyallylboration was examined. Using the same conditions as previously mentioned, the Sonogashira reaction was performed on both aldehydes **2.12** and **2.17** to obtain alkyne **2.44** in excellent yields (*Scheme 2.12)*.[47]



*Scheme 2.12: Sonogashira coupling reaction to yield TMS alkyne **2.44***

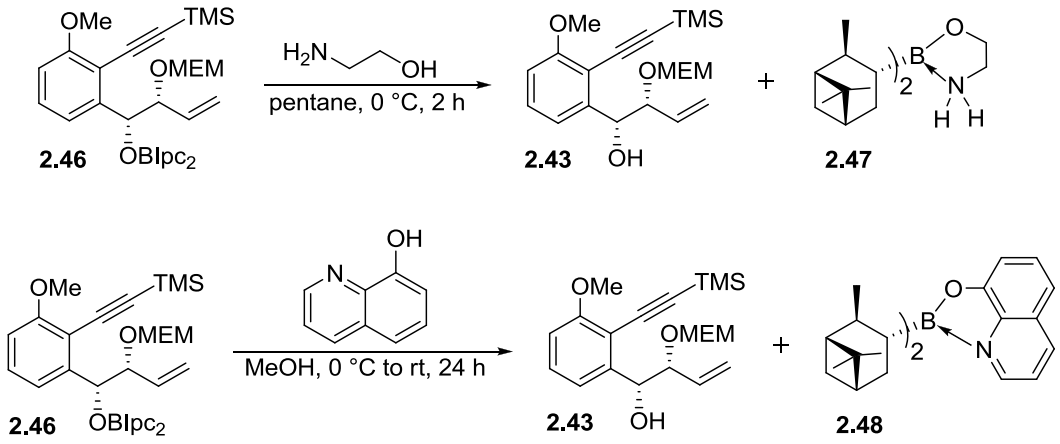
The next step in the synthesis was to see if the Brown alkoxyallylboration reaction was successful with substrate **2.44** where the TMS-alkyne is already installed in the *ortho* position. Aldehyde **2.44** was subjected to the same alkoxyallylboration conditions to obtain α-alkoxy homoallylic alcohol **2.43** in a 66% yield and 72% ee (*Scheme 2.13, equation **1***). This ee was lower than expected, potentially due to the substrate used or the source of borane. This reaction yield and ee could have been optimized more and this issue remains a future goal for this project. (*B*)-Methoxy-9-borabicyclo-[3.3.1]nonane (B-OMe-9-BBN) was used to form the racemic homoallylic alcohol product **2.43** for an HPLC standard to determine the ee (*Scheme 2.13, equation **2**)* This reaction proceeded with a better yield of 79%, potentially illustrating the source of borane as the factor that was detrimental to the yields of the enantiomerically pure product. This racemic product was also used to test future cyclization reactions, due to access to greater quantities.



*Scheme 2.13: Brown alkoxyallylboration reaction for the preparation of α-alkoxy homoallylic alcohol **2.43***

Throughout the preparation of Brown alkoxyallylboration product **2.43**, other work-up conditions were tried in order to optimize the yield. Previously, an oxidation of borinate **2.37** was employed using alkaline hydrogen peroxide to form the α-alkoxy homoallylic alcohol products. A publication in 1992 by Brown and coworkers illustrated alternate methods for work-up conditions stating the advantages of recycling the chiral auxiliary and overcoming purification issues.[48, 49] The first method that was tried was the reaction of borinate intermediate **2.46** with ethanolamine (EA), which is supposed to precipitate out the corresponding EA-BIpc_2 adduct **2.47** at 0 °C from pentane (*Scheme 2.14)* After multiple attempts, the adduct did not precipitate out of pentane and resulted in an oil that was a complex mixture. A second procedure was tested that utilized an 8-hydroxyquinoline (8-HQ) work-up to theoretically form a similar adduct, **2.48,** that precipitated out as a bright yellow solid in methanol. Despite the observed formation of this adduct precipitate, the reaction yield of the alcohol **2.43** obtained after column chromatography was still low at around 10%. The use of these various work-up

techniques was tested in hopes of increasing the yields, but they were not successful. Therefore, the alkaline hydroxide work-up continued to be used in future alkoxyallylboration reactions throughout the synthesis.



Scheme 2.14: Alternate Brown alkoxyallylboration work-up conditions

2.3 Conclusion – Optimal Route Towards Enyne 2.3

At this point, the Sharpless asymmetric dihydroxylation route towards enyne precursor **2.3** was abandoned due to low yields and multiple steps. It was proven that the Brown alkoxyallylboration route provided access to enyne **2.43** in one step and allowed for differentiation of protecting groups on the diol unit. The sequence of performing the Sonogashira reaction prior to the alkoxyallylboration reaction may have led to erosion of the ee and could be investigated further if the model study proved to be successful. With enyne **2.44** in hand, the key enyne metathesis cyclization step was ready to be tested.

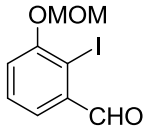
2.4 Experimental

2.4.1 General

Unless otherwise noted, all reactions were performed under an atmosphere of either argon or nitrogen using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. THF, toluene, dichloromethane, and methanol were also used that were treated by Fisher Scientific-MBraun MB SPS* solvent system prior to use. Molecular sieves were prepared by heating under vacuum at 130 ºC (overnight) and then stored inside an oven maintained at 125 ºC. Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F254 plates and, visualized with UV light and $KMnO_4$. NMR spectra were recorded on Varian INOVA-300, INOVA-400, INOVA-500 or Unity 500 instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm upfield towards tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; app dt, apparent doublet of triplets; m, multiplet. High-resolution mass-spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory, using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared-spectra and optical rotations were recorded by University of Alberta Spectral Services. Optical purities of α-alkoxy homoallylic alcohol products were measured by Chiral HPLC (Daicel OD Column, 0.46 X 25 cm) or by formation of Mosher esters and subsequent ^1H or ^{19}F NMR analysis of the crude product. Specific details are indicated in the experimental section for each individual product. Compounds **2.9**[5], **2.12**[4], **2.13**[4], **2.17**[8], and **2.44**[47] were synthesized according to procedures found in the literature. Catalyst F-Vivol was synthesized and donated by a former Hall group member, Dr. Vivek Rauniyar.

2.4.2 Preparation of Trisubstituted Benzene 2.10

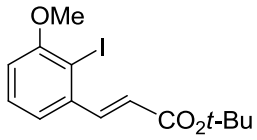
2-iodo-3-(methoxymethoxy)benzaldehyde (2.10)



N′,N,N-trimethylethylene aminoamide (1.1 mL, 8.8 mmol, 1.1 equiv.) was added to a round bottom flask containing 22 mL of benzene and cooled to 0 °C. *n*-BuLi (3.8 mL, 8.8 mmol, 1.1 equiv.) was added dropwise to the flask, warmed to room temperature and then stirred for 15 minutes. The flask was again cooled to 0 °C at which point aldehyde **2.9** (1.3 g, 8.0 mmol, 1.0 equiv.) was added dropwise and stirred at room temperature for 15 minutes to form a dark brown solution. PhLi (13 mL, 24 mmol, 3.0 equiv) was added dropwise at 0 °C and the flask was warmed to room temperature and stirred for 24 hours. Next, the solution was diluted with 20 mL of THF and the flask was cooled to – 78 °C. A solution of iodine (10.1 g, 40.0 mmol, 5.0 equiv) in 20 mL THF was added dropwise, warmed to room temperature and stirred for another 24 hours. A volume of 40 mL of 1 M HCl was added to the reaction flask and the organic layer was extracted with diethyl ether (3 times, 25 mL). The combined organic layer was washed with $Na_2S_2O_3$ (2 times, 30 mL), dried with $MgSO_4$, gravity filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography (50% toluene:DCM) to yield 1.13 g of an orange oil in a 44% yield. IR (cast film) 2957, 2848, 1693, 1565, 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.54 (dd, *J* = 1.6, 7.5 Hz, 1H), 7.36 (dt, *J* = 0.6, 8.1 Hz, 1H), 7.30 (dd, *J* = 1.6, 8.1 Hz, 1H), 5.30 (s, 2H), 3.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 196.3, 156.3, 136.8, 129.5, 123.6, 120.1, 95.3, 94.8, 56.6; HRMS (ESI) Calcd. $C_9H_9IO_3$: 291.95966. Found: 291.96030.

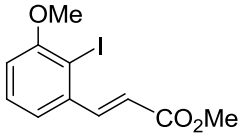
2.4.3 Synthesis of Route 1 Diol

(*E*)-tert-butyl 3-(2-iodo-3-methoxyphenyl)acrylate (2.18)



Aldehyde **2.12** (0.26 g, 1 mmol, 1 equiv) and *t*-butyl (triphenylphosphoranylidene)acetate (0.41 g, 1.1 mmol, 1.1 equiv) were added to a round bottom flask, followed by 5 mL of DCM. The solution was refluxed for 22 hours and concentrated *in vacuo*. The crude material was purified by column chromatography (30% ethyl acetate:hexane) and the light yellow solid product was obtained in a < 10% yield as a 4:1 mixture of *E*:*Z* isomers. Spectral data reported includes only the major *E* isomer. IR (cast film) 3003, 2976, 2935, 1701, 1633, 1581, 1563, 1466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 15.7 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 1.4, 7.8 Hz, 1H), 6.78 (dd, J = 1.3, 7.8 Hz, 1H), 6.25 (d, *J* = 15.7 Hz, 1H), 3.88 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 165.6, 158.4, 147.3, 139.9, 132.4, 130.2, 128.3, 123.4, 119.9, 111.4, 56.6, 28.2; HRMS (EI) Calcd. $C_{14}H_{17}INaO_3$: 383.0115. Found: 383.0111.

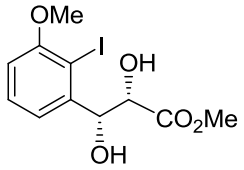
methyl 3-(2-iodo-3-methoxyphenyl)acrylate (2.19)



Following the previous procedure used for the preparation of **2.18**, using methyl (triphenylphosphoranylidene)acetate (0.74 g, 2.2 mmol, 1.1 equiv) and aldehyde **2.12** (0.52 g, 2.0 mmol, 1.0 equiv). A volume of 6 mL of DCM was used and the reaction was stirred for 24 hours. 0.84 g of the yellow solid product was obtained in a 66% yield of a 1:1 mixture of *E*:*Z* geometric isomers. IR (cast film) 3066, 2948, 2837, 1719, 1584, 1563, 1466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (*E*, d, *J* = 15.8 Hz, 1H), 7.30 (*E*, t, *J* = 8.1

Hz, 1H), 7.28 (*Z*, t, *J* = 8.1 Hz, 1H), 7.16 (*Z*, dd, *J* = 1.0, 7.6 Hz, 1H), 7.01 (*Z*, d, *J* = 12.0 Hz, 1H), 6.99 (*Z*, d, *J* = 7.6 Hz, 1H), 6.82 (*E*, dd, *J* = 1.2, 8.1 Hz, 1H), 6.76 (*E*, d, *J* = 8.1 Hz, 1H), 6.30 (*E*, d, *J* = 15.8 Hz, 1H), 6.02 (*Z*, d, *J* = 12.0 Hz, 1H), 3.91 (*E*, s, 3H), 3.90 (*Z*, s, 3H), 3.83 (*E*, s, 3H), 3.63 (*Z*, s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.7, 165.9, 158.5, 157.9, 148.5, 147.1, 141.6, 139.8, 129.3, 128.5, 122.4, 121.1, 120.7, 119.9, 111.6, 110.2, 93.6, 90.0, 56.7, 56.5, 51.9, 51.4; HRMS (ESI) Calcd. $C_{11}H_{11}IO_3$: 317.97531. Found: 317.97540.

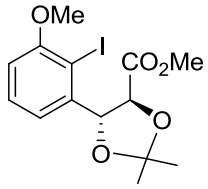
(2*S*,3*R*)-methyl 2,3-dihydroxy-3-(2-iodo-3-methoxyphenyl)propanoate (2.20)



To a stirred solution of $K_2OsO_2(OH)_4$ (1.0 mg, 2.8 µmol, 0.004 equiv), $(DHQD)_2$-PHAL (0.5 mg, 0.7 µmol, 0.001 equiv), $K_3Fe(CN)_6$ (0.69 g, 2.1 mmol, 3.0 equiv), K_2CO_3 (0.29 g, 2.1 mmol, 3.0 equiv) and $CH_3SO_2NH_2$ (66 mg, 0.7 mmol, 1.0 equiv) in 2.5 mL of H_2O and 2.5 mL of *t*-BuOH in a round bottom flask, the *E*:*Z* mixture of alkene **2.20** (0.24 g, 0.7 mmol, 1.0 equiv) was added in one portion to form a yellow slurry. The reaction was stirred at room temperature for 24 hours. A portion of $Na_2S_2O_3$ (0.5 g) was added and the solution was stirred for another hour and then extracted with ethyl acetate (2 times, 5 mL). The organic layer was washed with brine (2 times, 5 mL) and dried with $MgSO_4$. The solution was filtered, concentrated *in vacuo* and purified by column chromatography (20% ethyl acetate:hexane) to yield 0.16 g (66% yield from *E* isomer) of a white solid. $[\alpha]_D^{25}$ 24.9 (*c* 0.13, DCM); IR (cast film) 3509, 3401, 2952, 2939, 1751, 1568, 1465; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.9 Hz, 1H), 7.14 (dd, *J* = 1.2, 7.7 Hz, 1H), 6.81 (dd, *J* = 1.2, 8.1 Hz, 1H), 5.44 (dd, *J* = 1.5, 6.2 Hz, 1H), 4.52 (dd, *J* = 2.1, 5.7 Hz, 1H), 3.90 (s, 6H), 3.04 (d, *J* = 5.8 Hz, 1H), 2.71 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) 173.1, 157.7, 143.4, 129.2, 120.7, 110.6, 89.7, 72.4, 56.7, 53.2; HRMS (ESI) Calcd. $C_{11}H_{13}IO_5$: 351.98077. Found: 351.98085.

(4*S*,5*R*)-methyl 5-(2-iodo-3-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (2.21)

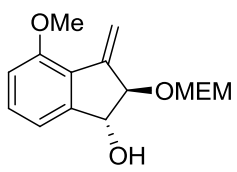


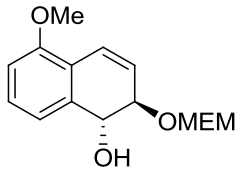
To a solution of diol (89 mg, 0.25 mmol, 1.0 equiv.) **2.20** and *p*-TsOH•H_2O (0.48 mg, 2.50 µmol, 0.01 equiv) in 1 mL DCM in a round botton flask was added $Me_2C(OMe)_2$ (0.15 g, 1.2 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 15 hours. A saturated solution of $NaHCO_3$ (2 mL) was added and the aqueous layer was extracted with DCM (2 times, 2 mL). The organic layer was washed with brine (2 times, 2 mL), dried with $MgSO_4$, and filtered. The solution was concentrated *in vacuo* and purified by column chromatography (40% ethyl acetate:hexane) to produce 31.7 mg of a yellow oil in a 32% yield. $[\alpha]_D^{25}$ 10.5 (*c* 0.19, DCM); IR (cast film) 2989, 2937, 1757, 1588, 1569, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 1.3, 7.8 Hz, 1H), 6.80 (dd, *J* = 1.3, 8.1 Hz, 1H), 5.59 (d, *J* = 7.8 Hz, 1H), 4.25 (d, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.2, 157.9, 141.3, 129.7, 120.3, 111.9, 110.9, 91.4, 84.2, 56.6, 52.6, 27.1, 26.0; HRMS (ESI) Calcd. $C_{14}H_{17}IO_5$: 392.01208. Found: 392.01252.

2.4.4 Synthesis of Cyclized products 2.41 and 2.42

(1*R*,2*R*)-4-methoxy-2-((2-methoxyethoxy)methoxy)-3-methylene-2,3-dihydro-1H-inden-1-ol (2.41)

(1*R*,2*R*)-5-methoxy-2-((2-methoxyethoxy)methoxy)-1,2-dihydronaphthalen-1-ol (2.42)





Procedure 1: Sonogashira conditions to obtain a 3:1 *exo*:*endo* mixture

In a round bottom flask, aryl iodide **2.40** (0.16 g, 0.4 mmol, 1.0 equiv) was dissolved in 2 mL of THF. $PdCl_2(PPh_3)_2$ (11 mg, 26 µmol, 0.04 equiv), CuI (9.0 mg, 48 µmol, 0.12 equiv), TMS acetylene (0.11 mL, 0.8 mmol, 2 equiv) and 0.4 mL of triethylamine were then added sequentially to the reaction. The mixture was stirred at room temperature for 24 hours at which point it was dissolved in diethyl ether and filtered through a pad of celite. The crude solution was concentrated *in vacuo* and resulted in an approximate 3:1 ratio of *exo* **2.41** : *endo* **2.42** isomers with approximately 50% conversion based on ^{1}H-NMR.

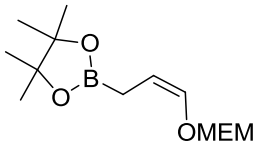
Procedure 2: Heck conditions to obtain a 10:1 *exo*:*endo* mixture

In a round bottom flask, aryl iodide **2.40** (0.3 g, 0.7 mmol, 1.0 equiv) was dissolved in 3 mL of THF. Catalyst $Pd(PPh_3)_4$ (0.12 g, 0.11 mmol, 15 mol%) was added to the solution followed by 1 mL of triethylamine. The reaction was stirred at room temperature for 24 hours. The solution was then dissolved in diethyl ether and filtered through a celite pad and concentrated *in vacuo*. The crude product afforded a 10:1 ratio of *exo* **2.41** : *endo* **2.42** isomers as a brown liquid with 100% conversion based on ^{1}H-NMR.

IR (cast film) 3436, 2937, 2897, 2839, 1727, 1590, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (*endo*, d, *J* = 7.6 Hz, 1H), 7.26 (*exo*, t, *J* = 7.9 Hz, 1H), 7.23 (*endo*, t, *J* = 7.8 Hz, 1H), 7.07 (*exo*, d, *J* = 7.5 Hz, 1H), 6.82 (*endo*, dd, *J* = 2.6, 10.4 Hz, 1H), 6.79 (*endo,* d, *J* = 7.8 Hz, 1H), 6.78 (*exo*, d, *J* = 8.2 Hz, 1H), 5.92 (*exo*, dd, *J* = 1.6, 2.7 Hz, 1H), 5.86 (*endo*, dd, *J* = 2.2, 10.1 Hz, 1H), 5.32 (*exo*, d, *J* = 1.9 Hz, 1H), 5.02 (*exo*, d, *J* = 7.0, 1H), 4.96 (*endo*, d, *J* = 7.3 Hz, 1H), 4.93 (*endo*, dd, *J* = 3.3, 10.8 Hz, 1H), 4.92 (*exo*, d, *J* = 7.0, 1H), 4.89 (*endo*, d, *J* = 7.3 Hz, 1H), 4.53 (*exo*, d, *J* = 3.8 Hz, 1H), 4.46 (*endo*, dt, *J* = 2.3, 10.9 Hz, 1H), 4.41 (*exo*, app dt, *J* = 3.0, 5.2 Hz, 1H), 4.03 (*exo*, m, 1H), 4.03 (*endo*, d, *J* = 3.6 Hz, 1H), 3.89–3.92 (*endo*, m, 1H), 3.87 (*exo*, s, 3H), 3.83 (*endo*, s, 3H), 3.77–3.81 (*endo*, m, 1H), 3.58–3.65 (*exo*, m, 4H), 3.61 (*endo*, m, 2H), 3.43 (*exo*, s, 3H), 3.42 (*endo*, s, 3H), 3.38 (*exo*, d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *exo:* 156.2, 144.3, 143.6, 129.9, 124.5, 116.7, 109.9, 108.8, 96.6, 92.1, 78.4, 71.5, 66.9, 59.0, 55.2, *endo:* not visible on spectrum. HRMS (ESI) Calcd. $C_{15}H_{20}O_5$: 280.13107. Found: 280.13108.

2.4.5 Synthesis of Route 2 Enyne

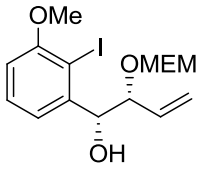
(Z)-2-(3-((2-methoxyethoxy)methoxy)allyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.30)



MEM protected allyl alcohol **2.28** (0.73 g, 5.0 mmol, 1.0 equiv) and 10 mL THF were added to a round bottom flask and cooled to – 78 °C. *s*-BuLi (3.4 mL, 5.0 mmol, 1.0 equiv) was added dropwise to the solution which was stirred for 30 minutes. Isopropoxyboronic acid pinacol ester (1.5 mL, 7.5 mmol, 1.5 equiv) was added dropwise to the reaction mixture and was stirred for another 1 hour at – 78 °C. The solution was then poured over a 0 °C pH 7 buffer (10 mL) at which point it turned cloudy and was diluted with ether (10 mL) The aqueous layer was extracted with ether (2 times, 5 mL)

and dried with $MgSO_4$. The solution was then filitered and concentrated *in vacuo* to produce the crude material that was purified by column chromatography (30% ethyl acetate:hexane). The final product was 0.36 g of a colorless liquid obtained in a 26% yield. IR (cast film) 2978, 2930, 2892, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (dt, *J* = 1.6, 6.1 Hz, 1H), 4.85 (s, 2H), 4.55 (app dt, *J* = 6.2, 7.8 Hz, 1H), 3.69 (m, 2H), 3.51 (m, 2H), 3.34 (s, 3H), 1.63 (dd, *J* = 1.2, 7.7 Hz, 2H), 1,21 (s, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) 142.1, 103.5, 95.1, 83.1, 71.6, 67.1, 58.9, 24.7; HRMS (ESI) Calcd. $C_{13}H_{25}BO_5$: 272.17950. Found: 272.17897.

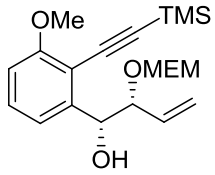
(1*R*,2*R*)-1-(2-iodo-3-methoxyphenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-ol (2.40)



MEM protected allyl alcohol **2.28** (0.29 g, 2 mmol, 1 equiv.) was added to a neck round bottom flask along with 3 mL of THF. The solution was cooled to – 78 °C and *s*-BuLi (1.8 mL, 2.2 mmol, 1.1 equiv.) was added dropwise and stirred for 30 minutes to form a yellow mixture. (+)-Ipc_2BOMe (0.76 g, 2.4 mmol, 1.2 equiv.) dissolved in 1 mL of THF was added dropwise forming a colorless solution that was stirred for 1 hour. BF_3•OEt_2 (0.38 mL, 3 mmol, 1.5 equiv.) was then added dropwise, followed directly by aldehyde **2.12** (0.52 g, 2 mmol, 1 equiv) dissolved in 1 mL THF. The reaction mixture was stirred for 24 hours at – 78 °C at which point it was quenched with 2.5 mL of 30% H_2O_2 and 2.5 mL of 2M NaOH and warmed to room temperature. The reaction was stirred at room temperature for 12 hours. The aqueous layer was washed with diethyl ether (2 times, 3 mL) and the combined organic layers were washed with brine (5 mL) and dried with $MgSO_4$. The solution was filtered, concentrated *in vacuo* and purified by column chromatography (20% ethyl acetate:DCM) to produce 0.34 g of the solid yellow product in 42% yield and 80% ee. $[\alpha]_D^{25}$ 61.5 (*c* 3.57, DCM); IR (cast film) ; ^1H NMR (400 MHz,

$CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 7.11 (dd, *J* = 1.3, 7.7 Hz, 1H), 6.73 (dd, *J* = 1.3, 8.1 Hz, 1H), 5.84 (ddd, *J* = 7.2, 10.4, 17.5 Hz, 1H), 5.18–5.24 (m, 2H), 5.10 (d, *J* = 5.1 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.33 (m, 1H), 3.87 (s, 3H), 3.47–3.50 (m, 1H), 3.34–3.40 (m, 3H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.7, 144.7, 134.2, 128.9, 121.1, 119.2, 110.1, 93.2, 91.4, 80.8, 79.0, 71.7, 67.2, 58.9, 56.6; HRMS (EI) Calcd. $C_{15}H_{21}IO_5$: 431.0326. Found: 431.0325.

(1*R*,2*R*)-1-(3-methoxy-2-((trimethylsilyl)ethynyl)phenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-ol (2.43)



Following the procedure used for the preparation of **2.41** for the synthesis of **2.43** with the use of aldehyde **2.44** (1.1 g, 4.9 mmol, 1.0 equiv). The crude material was purified via column chromatography (10% ethyl acetate:DCM). 1.22 g of the yellow oil product was obtained in a 66% yield and 72% ee. $[\alpha]_D^{25}$ 139.5 (*c* 0.28, DCM); IR (cast film) 3448, 2957, 2893, 2151, 1596, 1574, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.1 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.72 (dd, *J* = 0.8, 8.3 Hz, 1H), 5.75–5.82 (m, 1H), 5.17 (m, 2H), 5.15 (m, 1H), 4.66 (d, *J* = 6.9 Hz, 1H), 4.54 (d, *J* = 6.9 Hz, 1H), 4.26 (m, 1H), 3.81 (s, 3H), 3.44 (m, 1H), 3.31–3.37 (m, 3H), 3.29 (s, 3H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.3, 145.3, 134.4, 129.2, 118.9, 110.7, 109.3, 104.5, 98.9, 93.1, 81.2, 73.6, 71.6, 67.0, 58.9, 55.9, 0.1; HRMS (EI) Calcd. $C_{20}H_{30}NaO_5Si$: 401.1755. Found: 401.1750.

2.5 References

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CHAPTER 3

FORMATION OF THE D AND E RINGS

3.1 Introduction to Enyne Metathesis

In olefin chemistry, the word metathesis refers to the redistribution of carbon-carbon double bonds between two alkenes.[1] The metathesis that can occur between an alkene and alkyne (enyne metathesis) in an intramolecular, ring closing fashion is most often catalyzed by metal carbenes.[1] The olefin metathesis reaction was for many years limited to simple substrates until the 1990's, which oversaw new catalyst development allowing this reaction to be useful in organic synthesis. The first enyne metathesis was reported by Katz and coworkers in 1985 using a tungsten Fisher carbene catalyst.[2] Hoye[3, 4] and Mori[5] followed with studies involving molybdenum and chromium Fischer carbene complexes, but catalysts later produced by Grubbs[6-8] and Schrock[9] proved to be the most useful.[1] The potential to utilize a transition-metal-induced cycloisomerization of a 1,7-enyne would be both a unique and attractive method for the construction of the D ring in pradimicin A. This process generates access to 1,3-dienes that would be beneficial in the construction of the E ring via an intermolecular Diels-Alder reaction.

Enyne metathesis can be grouped into two separate catalyst systems; the metal-carbene complexes and the low-valent transition metals including palladium(II),[10] platinum(II),[11, 12] ruthenium(II)[13] and iridium(I)[14].[1] Our initial attempts towards the enyne metathesis of precursor **2.44** applied the Grubbs ruthenium carbene system. The first enyne metathesis using a ruthenium carbene complex was reported by Kinoshita and Mori in 1994, where they obtained good yields of five-, six- and seven-membered heterocycles through a ring-closing enyne metathesis (RCEM) using catalyst **A** *(Figure 3.1)*.[6, 15] Grubbs and coworkers also reported a dienyne metathesis reaction in that same year using the same catalyst.[16] Catalyst **A** was later replaced with catalyst **B** (Grubbs catalyst,

1st generation), which was both more reactive and easily made. The reactivity of these catalysts was further improved by the generation of catalysts **C**[17] (Grubbs catalyst, 2nd generation) and **D**[18-20] in 1999 based on work by Herrmann and coworkers on *N*-heterocyclic carbene ligands.[1, 21, 22] The second generation Grubbs catalyst **C** proved to be just as air and water stable as catalyst **B** but exhibited higher Lewis basicity that translated into increased catalytic activity.[17] The saturation of the N-heterocyclic carbene ligand in catalyst **C** compared to **D** also resulted in increased basicity due to lack of π-interactions.[17] Hoveyda contributed to the ruthenium carbene system with the introduction of Hoveyda-Grubbs (**E**) and Hoveyda-Grubbs II (**F**) catalysts, which are useful due to their recoverability.

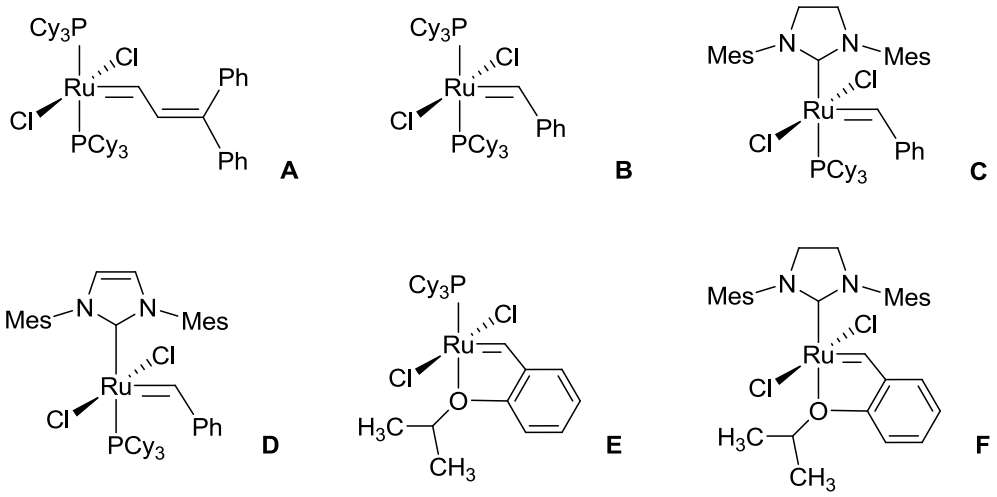
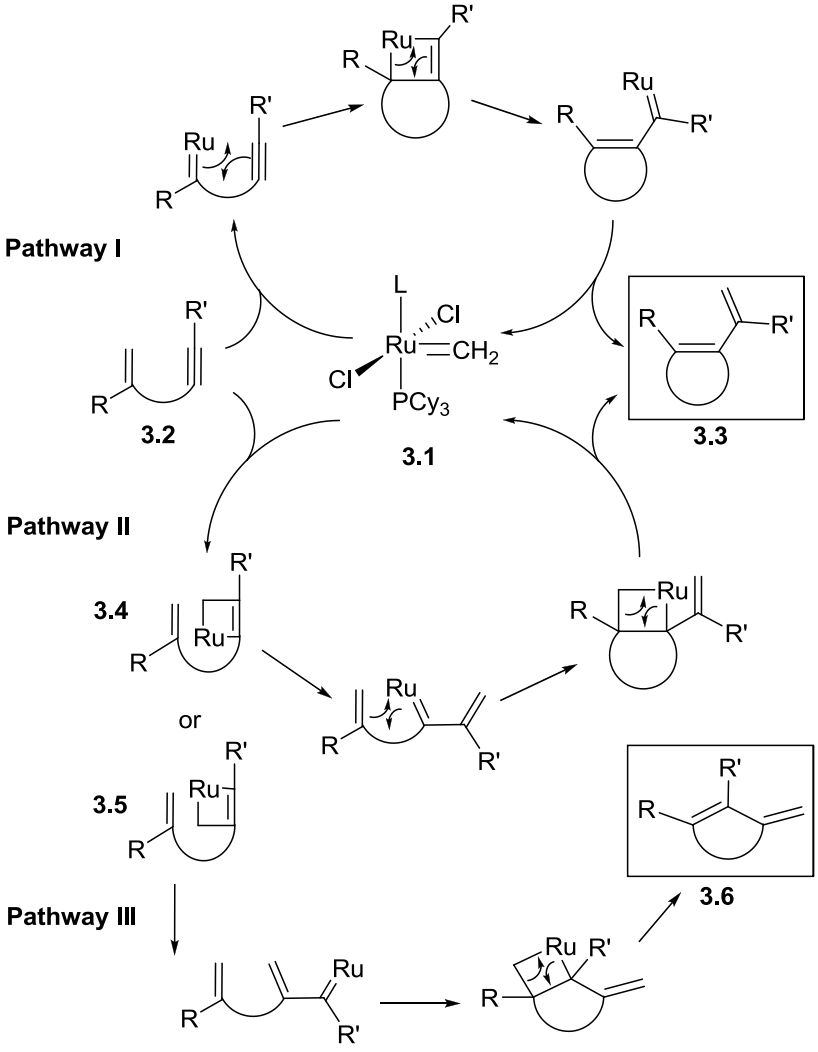


Figure 3.1: Ruthenium carbene catalysts for enyne metathesis[1]

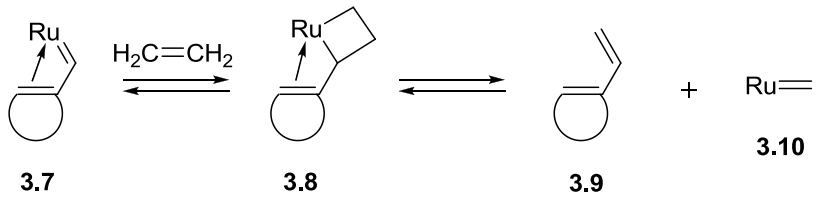
The mechanism for the enyne metathesis is not as well studied compared to that of the diene metathesis.[1] Both the low-valent transition metal catalyzed or metal carbene catalyzed systems operate with individual mechanisms.[1] The option for the ruthenium to complex to either the alkene or alkyne results in two different mechanistic pathways.[1] Pathway **I** (*Scheme 3.1)* involves the active carbene catalyst **3.1** reacting with the alkene of enyne **3.2**, followed by a series of [2 + 2] cycloadditions that lead to 1,3-diene product **3.3**.[1] On the other hand, if catalyst **3.1** initially reacts with the alkyne of enyne **3.2**, then

two possible ruthenacyclobutene regioisomers, **3.4** and **3.5**, are capable of forming, leading to products **3.3** and **3.6**, via pathways **II** and **III**. Enyne metathesis usually proceeds through both pathways **I** and **II** and is more likely to proceed through pathway **I** via initial coordination to the alkene when it is monosubstituted.[1] Hoye monitored an enyne metathesis by NMR and conferred that the carbene formed is compatible with pathway **I**.[23] Nevertheless, Mori obtained products from pathway **III**, indicating initial catalyst coordination to the alkyne.[24] The exact mechanism seems to be substrate and condition dependent and likely involves multiple pathways operating for one system.



Scheme 3.1: Proposed mechanistic pathways of enyne metathesis with a ruthenium carbene catalyst[1]

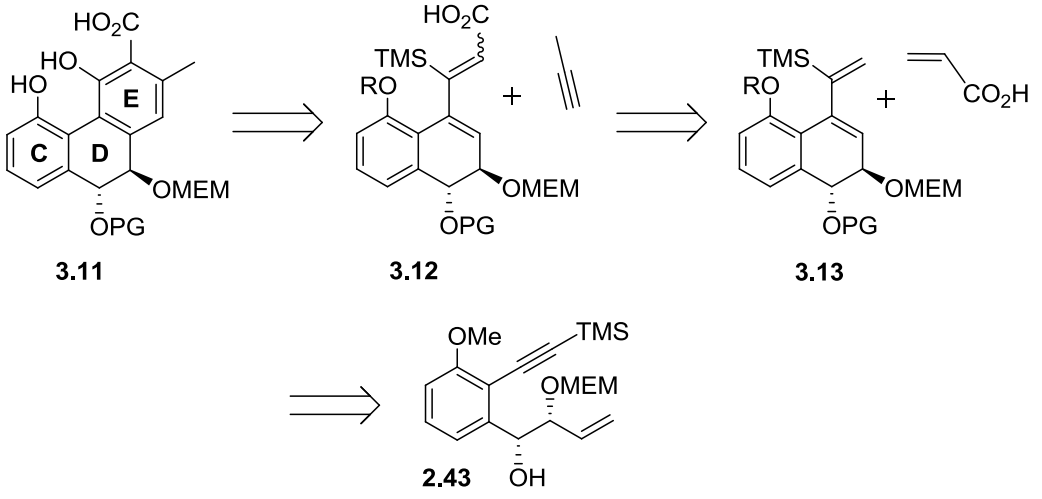
The substitution on the alkene, whether it is mono-, di- or tri-substituted, affects the product distribution as well as the reactivity of the enyne, with monosubstituted ones being the most reactive.[1] The substitution on the alkyne has more of an impact on the yield and rate of the reaction.[1] The cyclization is known to proceed successfully with alkyl groups on the alkyne and particularily well with esters of boronic acids, silyl ethers and silyl groups.[25-28] Electron withdrawing groups present on the alkyne tend to have a negative impact on the reaction and RCEM involving a terminal alkyne can sometimes be a sluggish reaction.[1] In these cases, the cyclization can potentially be accelerated by performing the reaction in the presence of ethylene gas.[1, 29] The effect of ethylene is not completely understood, but it could promote the generation of the ruthenium methylene species **3.10** as depicted in *Scheme 3.2.* If carbene intermediate **3.7** is generated through pathway **I** in the mechanism, it can be stabilized through olefin coordination, resulting in a slower catalyst turnover.[1, 29] The addition of ethylene gas would allow for the reaction to occur through metallocyclobutene **3.8** and therefore faster liberation of desired diene **3.9**.[1, 29] Various functional groups can be present in the enyne substrate, including esters, amides, ethers, and ketones, but amines and alcohols should be protected in order to obtain high yields.[1]



Scheme 3.2: Potential role of ethylene gas in the acceleration of enyne metathesis[1]

3.2 Enyne Metathesis for the Preparation of the D and E Rings

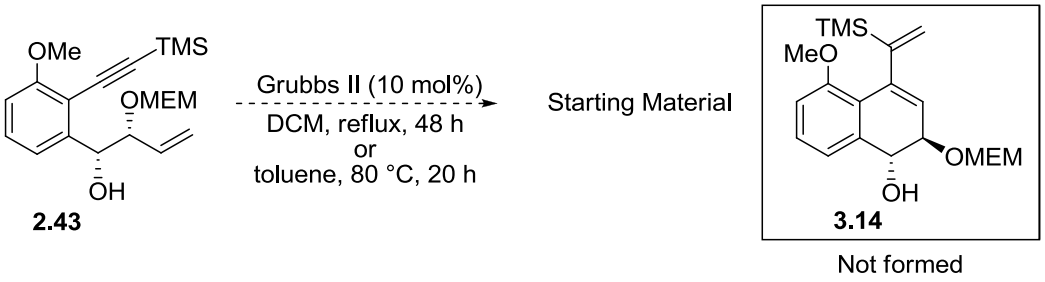
As seen in the previously proposed retrosynthesis (*Scheme 2.1*), tricycle **3.11** was to be obtained from enyne **2.43**. It was envisioned that the formation of the **E** ring would arise from a Diels-Alder cycloaddition of **3.12** and the dienophile, propyne. Diene **3.12** was designed to be more activated by installing a carboxylic acid on the terminal alkene of **3.13** via a cross metathesis that would lead to a more regioselective inverse demand Diels-Alder reaction with the dienophile. It also allowed for the desired substitution to occur on ring **E**. Diene **3.13** was envisioned to arise from an ruthenium carbene catalyzed enyne metathesis reaction with precursor **2.43**. The choice of installing a trimethylsilyl group on the alkyne arose from the idea to first test the tolerability of the silyl group and later replace it with a dimethylphenylsilyl group that is capable of undergoing a Fleming-Tamao oxidation to form an alcohol. Also, the TMS group was chosen due to its known compatability with the enyne metathesis.[30, 31] If this route proved to be unsuccessful, there was always the option of using alternative dienophiles, or the diene could be redesigned as need be.



Scheme 3.3: Retrosynthetic analysis of the D and E rings of pradimicin A

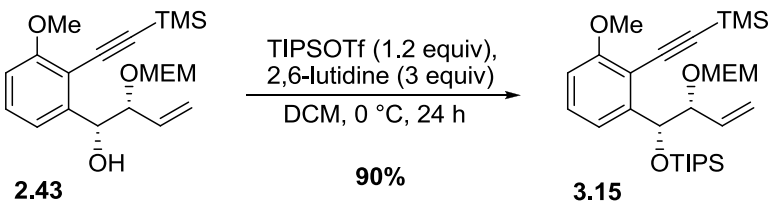
3.3 Enyne Metathesis with Substrate 2.43

Initial attempts towards the enyne metathesis of synthesized precursor **2.43** began first with the most often used Grubbs I (**B**) and Grubbs II (**C**) catalysts. Although previous evidence suggested that a free alcohol may hinder the enyne metathesis by coordinating to the catalyst, a publication by Granja and coworkers in 2001 showed a metathesis occurring in the presence of a free alcohol. [32] Therefore, with the alcohol **2.43** in hand the cyclization was tested despite the threat of a lower yield simply to determine if the desired diene product was attainable. The reaction is illustrated in *Scheme 3.4.* Dichloromethane is the most commonly used solvent for enyne metathesis, along with toluene if higher temperatures are necessary.[1] When the reaction was run in dichloromethane at reflux temperatures as well as toluene at room temperature and at 80 °C, no conversion was observed in both cases. It was therefore assumed that the enyne metathesis reaction was likely not tolerable to the free alcohol in enyne **2.43**.



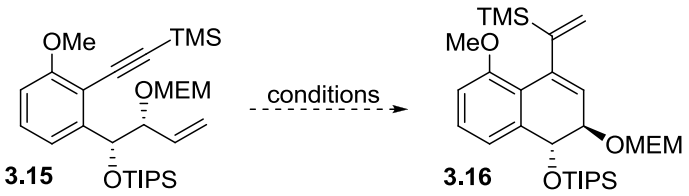
*Scheme 3.4: Enyne metathesis with substrate **2.43***

The next step was to protect the alcohol in **2.43** to eliminate it as a potential factor that prevented the metathesis from occurring. A silyl protecting group was chosen to differentiate the protecting group from the MEM group and to prevent any interference with the cyclization. The reaction occurred in an excellent 90% yield over 24 hours at 0 °C using conditions from a publication by Martin and coworkers in 2000 (*Scheme 3.5*).[33]



*Scheme 3.5: TIPS Protection of alcohol **2.43***

With the substrate in hand, enyne **3.15** was then subjected to various metathesis conditions with ruthenium carbene catalysts, Grubbs I, Grubbs II, and Hoveyda-Grubbs II (*Table 3.1*). Disappointingly, at temperatures ranging from 23 °C to 80 °C in both toluene and dichloromethane solvents, the enyne metathesis did not occur with substrate **3.15**. In all cases listed in *Table 3.1* where 20 mol% of catalyst was used, starting material was recovered at the end of the reaction as well as an undesired product later characterized as **3.17** *(Scheme 3.6)*, as opposed to the expected diene product **3.16**. *Entry 5* also illustrates that the reaction was performed under an ethylene atmosphere, but again did not produce the desired diene. These results were somewhat disappointing and indicated that alterations to the catalyst system or substrate needed to be done. A number of other catalysts were tested for the cyclization of substrate **3.15** as well, including $PtCl_2$ and $AuCl_3$, but produced complex mixtures and no indication of the diene product.



3.15 **3.16**

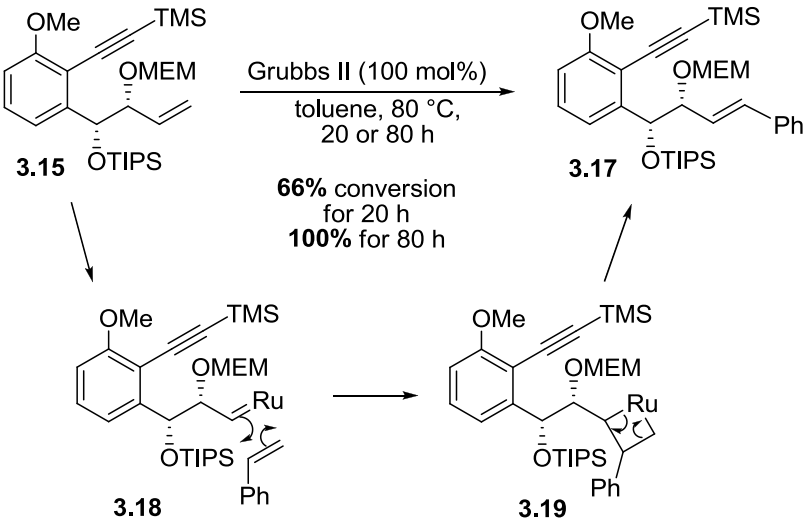
Entry	***Catalyst***	***Reaction Conditions (solvent, temperature, time)***
1	Grubbs I (20 mol%)	DCM, reflux, 17 h
2	Grubbs I (20 mol%)	Toluene, 80 °C, 20 h
3	Grubbs II (20 mol%)	DCM, reflux, 17 h
4	Hoveyda-Grubbs II (20 mol%)	Toluene, 80 °C, 20 h
5	Grubbs II (20 mol%)	Toluene, 80 °C, 20 h, ethylene atmosphere

Table 3.1: Reaction conditions tested for the ruthenium catalyzed enyne metathesis

3.3.1 Unexpected Product as a Result of Enyne Metathesis

As a last attempt utilizing the Grubbs catalyst system, 100 mol% of Grubbs II catalyst was employed in the metathesis reaction with substrate **3.15** at 80 °C in toluene for 20 hours (*Scheme 3.6*). Surprisingly, an alkene product was observed and, after confirmation by 2D NMR experiments and mass spectrometry, was found to most likely be *E* olefin **3.17**. With complete addition of the catalyst at the beginning of the reaction, approximately 66% of the starting material was converted to product based on ^{1}H-NMR data. In a separate experiment, the 100 mol% of catalyst was also added over 80 hours in 20 mol% increments and resulted in 100% conversion of starting material into product. The presumable mechanism for the formation of **3.17** is through ruthenium carbene intermediate **3.18**, which is normally formed during the enyne metathesis catalytic cycle. Instead of **3.18** cyclizing intramolecularly with the alkyne, it could potentially undergo a [2 + 2] reaction with the styrene that was previously formed in solution from the catalyst, since it is present in stoichiometric amounts. From there, ruthenacyclobutane

intermediate **3.19** opens up via another [2 + 2] retrocyclization to form product **3.17**. With this result and previous results, it was concluded that the alkyne was not in close enough proximity to the alkene to react or was sterically hindered by either the *ortho*-methoxy group or the TMS group. In 2004, Pérez-Castells also reported the possible formation of a benzylidene intermediate in a similar enyne metathesis system with a terminal benzylic alkyne, indicating that a reaction with styrene is possible.[34]

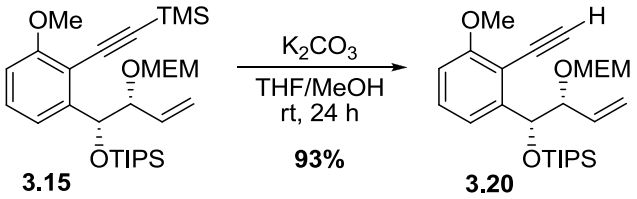


Scheme 3.6: Enyne metathesis with 100 mol% Grubbs II catalyst

3.3.2 Enyne Metathesis with Modified Substrate 3.20

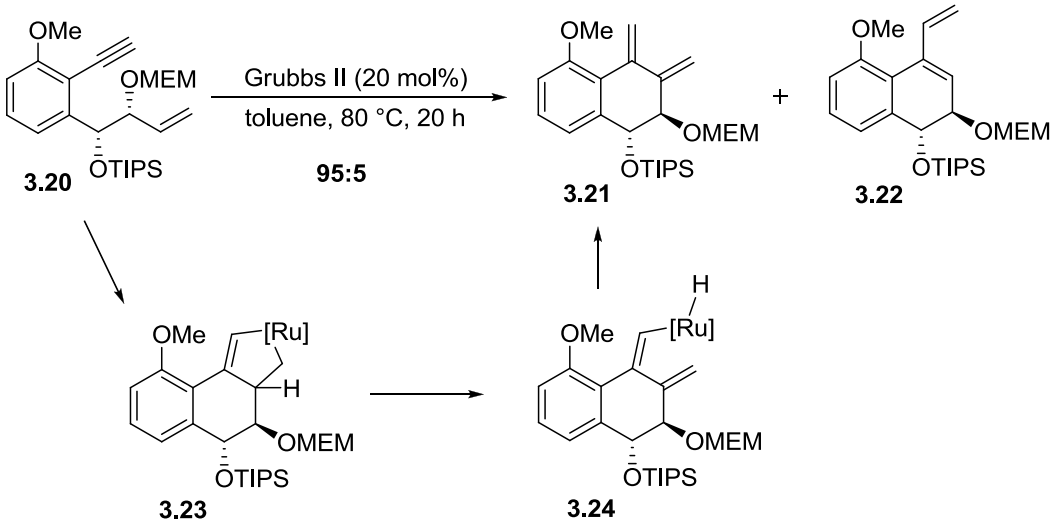
The next step was to test the enyne metathesis without the presence of the TMS group on the alkyne to see if that was the factor hindering the reaction. The alkyne was successfully deprotected using potassium carbonate in an 89% yield at room temperature as shown in *Scheme 3.7.* Although the removal of the TMS group was not ideal to form the desired substitution on ring E, we believed that the alcohol moiety could be installed at a later stage, potentially after the Diels-Alder reaction and aromatization where a carboxylic acid could serve as a directing group for *ortho*-lithiation. This could be

followed by the formation of a boronate and subsequent oxidation to obtain the alcohol in the desired position.



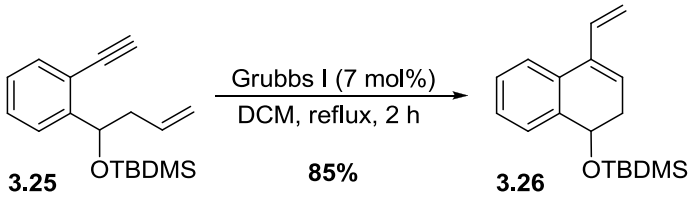
Scheme 3.7: Deprotection of TMS group

After obtaining terminal alkyne **3.20**, the enyne metathesis was conducted again under the previous conditions of toluene at 80 °C. What seemed to be an alkene had formed based on initial ^{1}H-NMR data and all starting material had reacted. Upon further analysis, it had appeared that alkene **3.21** was formed as opposed to the predicted **3.22** in a 95:5 ratio (*Scheme 3.8*). The mixture could not be isolated due to instability of the products after time and when subjected to column chromatography. Mechanistically, this was an unexpected product with this catalytic system. The formation of a ruthenacyclopentene intermediate is possible with a variety of transition metals and unsaturated partners and has been generated in the presence of a Ru(II) catalyst.[35, 36] In 1994, Murai observed the first example of a 1,7-enyne undergoing skeletal reorganization in the presence of the catalyst $[RuCl_2(CO_3)]_2$ to form a vinylcyclohexene product.[37] The publication however, did not postulate a mechanism. Granted the catalyst system is different, ruthenacyclopentene **3.23** was considered to be a possible intermediate in the formation of diene **3.21**. In this case, the metal would first undergo complexation with both points of unsaturation, followed by oxidative coupling to form ruthenacyclopentene complex **3.23**. A β-hydride elimination and reductive elimination would lead to the resultant 1,3-diene **3.21**.



*Scheme 3.8: Enyne metathesis with terminal alkyne **3.20***

To support the unprecedented formation of diene **3.21**, the enyne metathesis was compared to the previously mentioned publication by Pérez-Castells and coworkers in 2004.[34] This group illustrated a similar substrate **3.25** undergoing an enyne metathesis reaction to form diene **3.26** in an 85% yield using Grubbs I catalyst (*Scheme 3.9*).[34] The difference between our system and substrate **3.25** is the additional alkoxy substitution on the alkene chain and the presence of the methoxy group on the adjacent phenyl ring. Ultimately, the exact cause of the formation of diene product **3.21** over **3.22** is not known. Based on the results published by Pérez-Castells and coworkers, it was speculated that the methoxy group on the phenyl ring is sterically hindering the formation of diene **3.22**. If this were the case, then the ruthenium carbene intermediate similar to **3.18** may be prevented from reacting with the alkyne as was the likely explanation for the formation of the benzylidene product **3.17**. Another possible explanation is the cycloisomerization to form intermediate **3.23** may simply be kinetically favored.



*Scheme 3.9: Enyne metathesis to form diene **3.26** by Pérez-Castells and coworkers*[34]

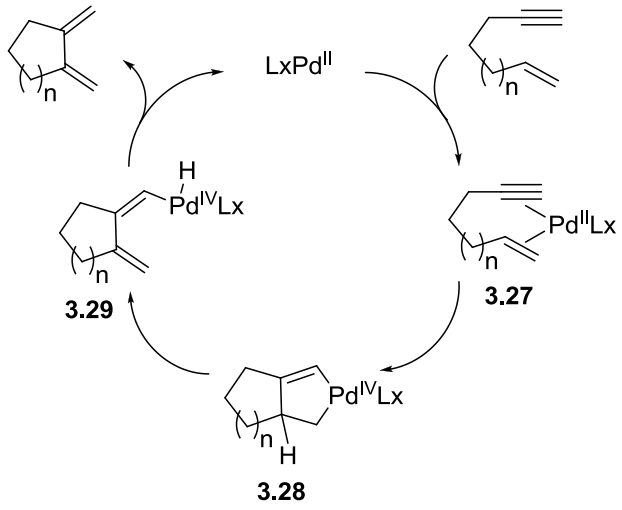
3.4 Alternative Synthetic Route with Diene 3.21

The previously proposed retrosynthesis illustrated in *Scheme 3.3* featured the use of diene **3.12** in the Diels-Alder reaction with the dienophile, propyne. However, as this diene was not successfully synthesized by the methods tested and a different route towards tricycle **3.11** needed to be investigated. Since diene **3.21** was synthesized successfully, we then looked towards potential routes that utilized this diene instead. The potential to perform the Diels-Alder cycloaddition with diene **3.21** and non-symmetric dienophile proved to be attractive for the formation of ring **E**. However, this theory is dependent on which regioisomer is formed from the Diels-Alder reaction since it would be hard to predict electron molecular orbital coefficients on the diene carbon atoms. In the previous retrosynthesis (*Scheme 3.3*), the installation of a carboxylic acid on the terminal diene minimized this factor. If methyl-2-butynoate was used as a dienophile, the methyl and ester groups would potentially be installed on ring **E** in the desired positions. A subsequent *ortho*-lithiation could result in the installment of the third substituent on the newly formed ring via coordination to the ester moiety.

3.5 Palladium Catalyzed Cycloisomerization with Substrate 3.20

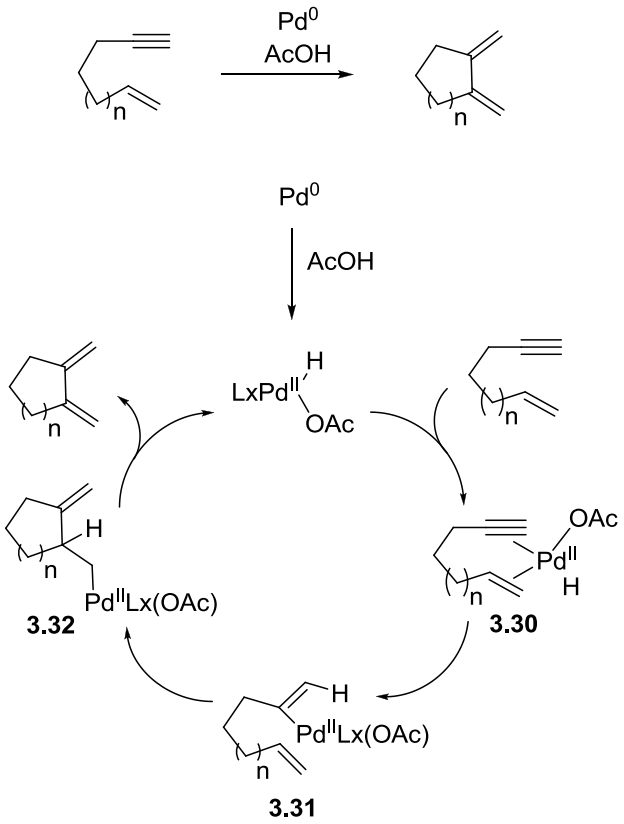
Due to the unexpected formation of diene **3.21**, we wanted to design a synthetic strategy that involved the use of diene **3.21** instead of diene **3.22** in the Diels-Alder reaction. We were also interested to see which diene would be favored with the use of low-valent

transition metal catalysts. We then looked towards various palladium catalysts as a less expensive and potentially yield increasing alternative to see if similar results could be obtained. Palladium catalyzed enyne metathesis has undergone extensive studies since the first Alder-ene reaction reported by Trost and coworkers in 1984.[35, 38] It has led to numerous useful cycloisomerization reactions as well as tandem transformations with cycloadditions.[35] In 1994, Trost and coworkers proposed a mechanism for the Pd-catalyzed cycloisomerization transformation, which included a palladacyclopentene intermediate **3.28** as shown in *Scheme 3.10*.[39, 40] The Pd(II) catalyst is believed to coordinate to the enyne substrate to form complex **3.27**, which then cyclizes to form pallada(IV)cyclopentene complex **3.28**. Next, β-hydride elimination and reductive elimination lead to expulsion of the diene product. If substrate **3.20** were to undergo this mechanism with a palladium catalyst to form diene **3.21**, it may help to support the postulated formation of the metallocyclopentene in the ruthenium catalyzed system as well.



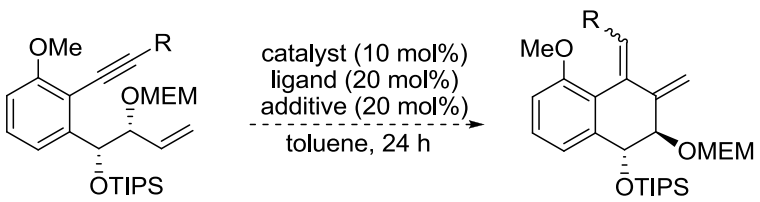
Scheme 3.10: Proposed mechanism for the Pd catalyzed enyne cycloisomerization by Trost and coworkers[39]

The Pd sources that were tested include $Pd(OAc)_2$ and $Pd_2(dba)_3$. Trost and coworkers had previously shown that the ligand, *N,N*-bis-(benzylidene)ethylenediamine (BBEDA), had increased catalytic activity for sluggish enyne cycloisomerization reactions, therefore this ligand was synthesized and employed here.[39] An alternative catalytic system was also employed where acetic acid is used to oxidatively add to a Pd(0) source to form a H–Pd(II)–OAc species.[40] In this case, the cycloisomerization occurs via a slightly different mechanism as illustrated in *Scheme 3.11*. The Pd-acetate complex then undergoes a hydropalladation on the triple bond to form vinyl-palladium intermediate **3.31**.[40] An intramolecular carbopalladiation of the double bond in **3.31** leads to alkyl palladium **3.32**, which can then undergo β-hydride elimination to produce the desired diene.[40]



Scheme 3.11: Proposed mechanism for the Pd catalyzed enyne cycloisomerization with acid additive by Trost and coworkers[40]

The palladium catalyzed cycloisomerization was initially tested on substrate **3.15** where the alkyne was TMS substituted to see if the reaction would proceed with a different catalyst. The conditions that were tried are listed in *Table 3.2*, *Entries 1-5* and include both sources of Pd and the use of the BBEDA ligand as well as the acetic acid additive. In all cases, only starting material was obtained, concluding that this alkyne substituted cycloisomerization does not proceed in the presence of the Pd catalysts tested or the previously tested Ru carbene catalysts. Next, substrate **3.20** was subjected to the same reaction conditions and actually provided more promising results. In the presence of the catalyst $Pd(OAc)_2$ at room temperature a minimal amount of starting material was converted to the desired diene **3.21**. At this stage, the temperature was raised to 60 °C and resulted in a 100% conversion of starting material into product based on ^{1}H-NMR. The reaction was also tested with $Pd(OAc)_2$, PPh_3, and the acetic acid additive at room temperature and resulted in a cleaner crude product compared to the higher temperature reaction (*Entry 8*). Therefore, these reaction conditions were utilized in all subsequent cycloisomerizations.



3.20 R = H
3.15 R = TMS

3.21 R = H
3.33 R = TMS

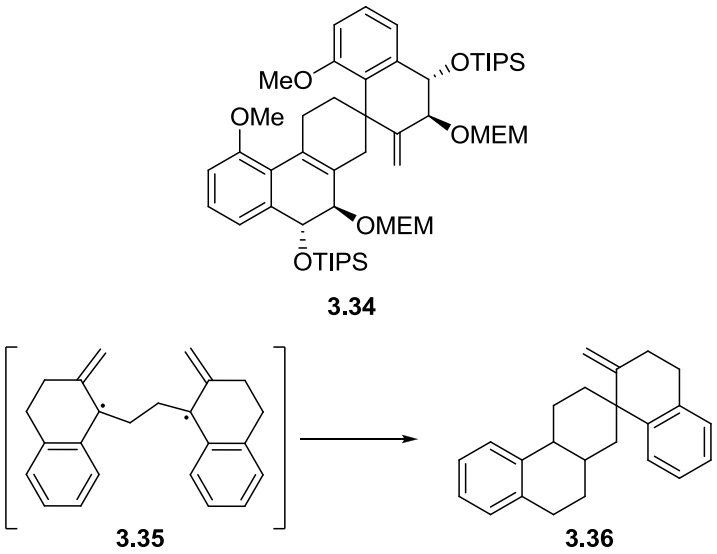
Entry	***Catalyst/Ligand***	***Additive***	***R***	***Temp (°C)***	***% Conversion (based on NMR)***
1	$Pd(OAc)_2$	–	TMS	rt	0
2	$Pd(OAc)_2$/BBEDA	–	TMS	60	0
3	$Pd(OAc)_2$/BBEDA	–	TMS	110	0
4	$Pd_2(dba)_3/PPh_3$	AcOH	TMS	rt	0
5	$Pd_2(dba)_3/PPh_3$	AcOH	TMS	80	0
6	$Pd(OAc)_2$	–	H	rt	< 10
7	$Pd(OAc)_2$	–	H	60	100
8	$Pd(OAc)_2/PPh_3$	AcOH	H	rt	100

*Table 3.2: Conditions for the Pd catalyzed cycloisomerization of enynes **3.20** and **3.15***

3.5.1 Isolation of Diene 3.21

Throughout the preparation of diene **3.21**, it was noted that when the product was subjected to purification via column chromatography a decomposed or alternative product seemed to be formed. Furthermore, after a period of approximately 24 hours, new peaks appeared in the ^{1}H-NMR spectra and eventually the product was all converted into the unknown compound. After the crude diene was completely converted to the unknown product based on ^{1}H-NMR, the unknown compound was purified via column chromatography and characterized. The ^{1}H-NMR and ^{13}C-NMR obtained of the final product were not entirely clean, however the mass spectrometry data revealed the

potential presence of dimer **3.34** forming under the previously described conditions (*Scheme 3.12*). The particular isomer formed was established based on findings by Vogel and coworkers in 2002.[41] This group reported the formation of dimer **3.36** as the sole isomer from the corresponding diene based on diradical intermediate **3.35**.[41] Provided the Diels-Alder reaction occurred via a radical intermediate, both radicals in **3.35** would be stabilized due to their allylic and benzylic positions.[41] Alternate isomers that could be formed do not have such stability of both radicals. Therefore, it was predicted that dimer **3.34** is the likely product. The stereochemistry at the spirocenter, however, is not known.



*Scheme 3.12: Proposed dimer formed from diene **3.21** based on previous results from Vogel and coworkers*[41]

3.5.2 Diels-Alder Cycloaddition with Crude Substrate 3.21

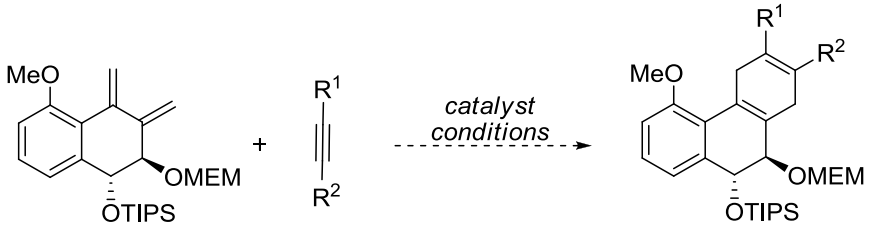
Due to the finding that diene **3.21** was unstable and dimerized easily after a short period of time, we then looked towards the potential of a one-pot or tandem Pd-catalyzed cycloisomerization and Diels-Alder cycloaddition. To further examine this, the Diels-Alder

reaction was first tested using the fairly pure crude diene **3.21** to determine if it would proceed and with which dienophiles. As previously mentioned, an asymmetric alkyne dienophile such as methyl-2-butynoate would be ideal to install a methyl group and ester group on the **E** ring. Therefore, during preliminary testing of the Diels-Alder reaction, various asymmetric dienophiles were tested.

The conditions that were first examined include thermal, Lewis acid catalyzed and boronic acid catalyzed Diels-Alder cycloadditions, as illustrated in *Table 3.3*. The Lewis acid catalyzed Diels-Alder reaction proved to be unsuccessful as shown in *Entries 1* to *4*. The scandium triflate catalyzed reaction (*Entry 1*) showed that at room temperature diene **3.21** dimerized after not reacting with the dienophile, illustrating the potential need for higher temperatures. The addition of an aluminum chloride catalyst (*Entries 2* and *3*) resulted in immediate decomposition, which proved that the diene did not tolerate acidic conditions as seen previously during purification.[42] The boronic acid catalyzed cycloaddition, a method previously published in the Hall group utilizing 2-alkynoic acids, may have been too acidic as well and only resulted in a complex mixture (*Entries 4* and *5*).[43] *Entry 6* illustrated that the thermal Diels-Alder reaction at 50 °C was not a high enough temperature and again resulted in the unreacted diene dimerizing to form **3.34**. As seen in *Entry 7*, a base additive was tested in hopes of acting as an acid scavenger, but only resulted in a complex mixture.

After many failed attempts, *Entry 8* shows the use of a cobalt catalyzed system developed by Hilt and coworkers which produced the desired tricycle **3.37** in a 22% yield at room temperature.[44] Also, results from a thermal Diels-Alder reaction at higher temperatures became more positive and produced yields of 32% and 29% of the desired product (*Entries 9* and *10*). Butylated hydroxytoluene (BHT) was added as a potential radical scavenger but showed no effect on the reaction. (*Entries 9* and *10*). Since the crude cycloisomerization product was used, the yields obtained were for both the

cycloisomerization and Diels-Alder cycloaddition steps. From these results, it was concluded that an acid catalyzed reaction was not achievable with this substrate and higher temperatures were necessary to obtain even a lower yield of 30%. Furthermore, the issue with the failed attempts could have also been due to the particular dienophile used in conjunction with diene **3.21**. This can be proven when comparing results from the diester substituted dienophiles to the monoester dienophiles.



3.21

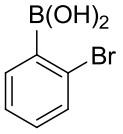
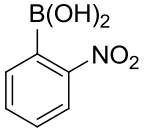
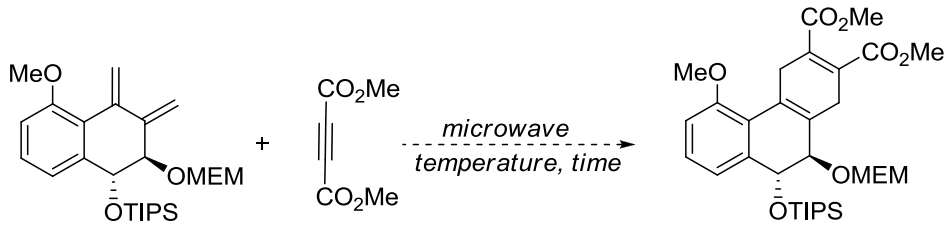
Entry	***Catalyst or Additive***	***R^1***	***R^2***	***Conditions***	***Result***
1	$Sc(OTf)_3$ (20 mol%)	CO_2Me	CO_2Me	THF, rt, 48 h	dimerization
2	$AlCl_3$ (2 equiv)	CO_2Me	CO_2Me	DCM, rt	decomposition
3	$AlCl_3$ (2 equiv)	H	CO_2Me	DCM, rt	decomposition
4	 (20 mol%)	H	CO_2H	DCM, rt, 26 h	complex mixture
5	 (20 mol%)	H	CO_2H	DCM, rt, 26 h	complex mixture
6	–	Me	CO_2Me	toluene, 50°C, 24 h	dimerization
7	Et_3N	CO_2Me	CO_2Me	toluene, 80°C, 24 h	complex mixture
8	$CoCl_2$dppe (10 mol%), ZnI_2 (20 mol%), Zn (10 mol%)	CO_2Me	CO_2Me	toluene, rt, 24 h	22% yield **3.37**
9	–	CO_2Me	CO_2Me	toluene, 80°C, 24 h	32% yield **3.37**
10	BHT	CO_2Me	CO_2Me	toluene, 80°C, 24 h	29% yield **3.37**

*Table 3.3: Diels-Alder cycloaddition reaction conditions with substrate **3.21***

In hopes of increasing the yield of the Diels-Alder cycloaddition step, microwave heating conditions were then considered. This would also allow for higher temperatures to be reached in a shorter reaction time, potentially resulting in less dimerization of the unstable diene. Some of the microwave conditions that were examined are shown in *Table 3.4*. Here, the cycloisomerization was performed in the microwave tube so as the dienophile could be directly added to the crude product to undergo the cycloaddition reaction. The reaction was also tested in DMF as a potentially better solvent for microwave conditions, but resulted in a complex mixture of products including dimerized product **3.34** and starting material. *Entries 2* and *3* showed that higher temperatures of 140°C for both 5 minutes and 30 seconds resulted in lower yields. *Entry 4* was chosen as the ideal microwave conditions of 120°C for 1 minute as it produced the highest yield over the two steps. Again, the BHT additive was applied in *Entry 5* to ensure that it did not have an effect on the reaction under microwave conditions, which was indeed the case.



3.21 **3.37**

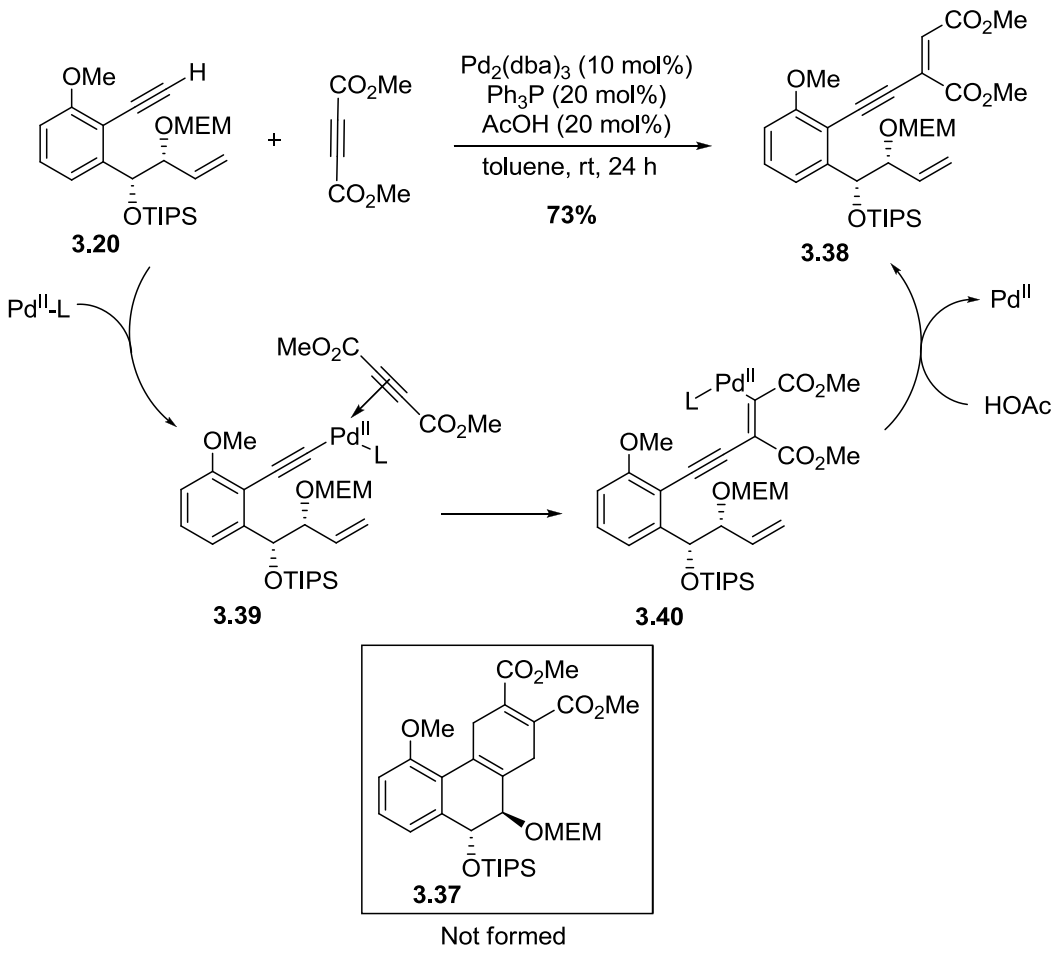
Entry	*Temp (°C)*	*Time (min.)*	*% Yield*
1	80	3	33
2	140	5	<10
3	140	0.5	22
4	120	1	44
5*	120	1	42

**with BHT additive*

Table 3.4: Diels-Alder cycloaddition under microwave reaction conditions with substrate ***3.21***

3.5.3 One-pot Cycloisomerization and Diels-Alder Cycloaddition

Throughout the synthetic studies towards the Diels-Alder reaction, a one-pot cycloisomerization and Diels-Alder cycloaddition was also examined. A tandem reaction where the enyne precursor, catalyst and dienophile are all present at the beginning of the reaction would be an elegant route towards the desired tricycle.[1] The use of a strongly electron deficient dienophile is necessary to minimize its reactivity with the catalyst and the potential for it to participate in cross metathesis.[1] Substrate **3.20** was combined with dimethyl butynedioate in the presence of catalyst $Pd_2(dba)_3$ in hopes of yielding tricycle **3.37** (*Scheme 3.13*). Instead, it was found that enynene **3.38** was produced in a 73% yield. Trost and coworkers have published related work where the C–H bond of a terminal alkyne is added to an activated internal alkyne in the presence of a palladium catalyst and ligand.[45] This proposed mechanism initially involves the displacement of hydrogen with Pd(II), oxidized from Pd(0) with acetic acid to form intermediate **3.39**. The internal alkyne then coordinates to the Pd(II) species and inserts into the triple bond to form vinylpalladium species **3.40**. This intermediate is then protonated to form the final product **3.38**. This result further illustrates that the cycloisomerization proved to be difficult with this particular enyne system, but produced an interesting result nonetheless.



Scheme 3.13: Attempted one-pot cycloisomerization and Diels-Alder cycloaddition reactions

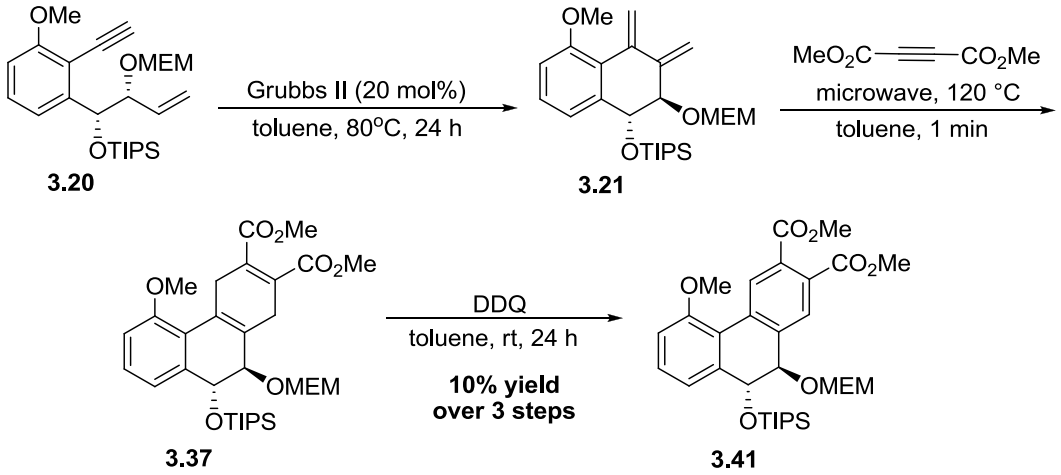
Regardless of the success of the one-pot reaction, the next step in the synthesis of the tricycle needed to be tested, which was the aromatization of the newly formed ring **E** in diene **3.37** (*Scheme 3.14*). Conditions using DDQ when reacting at room temperature overnight provided a 70% yield of tricycle **3.41**. As this reaction worked efficiently upon first try, no other conditions were attempted.

3.37 **3.41**

*Scheme 3.14: Aromatization of diene **3.37***

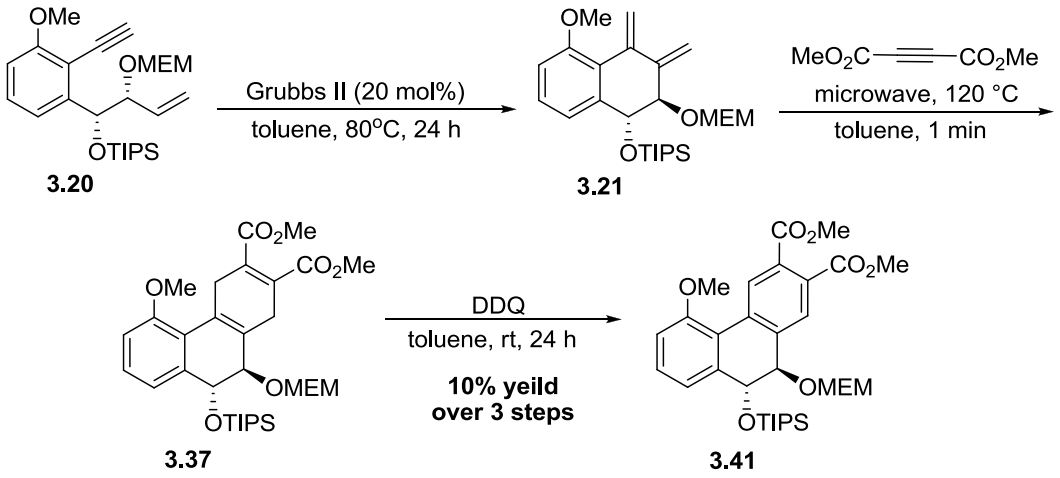
3.5.4 One-pot Cycloisomerization/Diels-Alder Cycloaddition/Aromatization

At this stage, diene **3.37** was purified prior to subjecting it to DDQ aromatization. Considering that the two step cycloisomerization and Diels-Alder cycloaddition reaction was performed in toluene, the potential to apply DDQ to the same crude mixture directly after the cycloaddition arose since it was proven to work in toluene as well. A one-pot reaction was tested where the DDQ was added at the same time as the reactants for the Diels-Alder cycloaddition step and subjected to the microwave conditions. However, this only resulted in a complex mixture and not the desired product. Therefore, an alternative one-pot procedure where the DDQ was added directly to the crude mixture after the Diels-Alder reaction was examined as illustrated in *Scheme 3.15*. This sequence worked out quite well and produced an overall yield of 45% for the three steps, in comparison to the 44% yield obtained previously for just the first two steps. This averaged out to approximately a 77% yield per step, with the Diels-Alder cycloaddition being the limiting factor. The benefits of this process included minimizing solvent waste, eliminating purification steps and maximizing the yield through use of the crude products. This one-pot procedure provides an efficient and unique route towards tricycle **3.41** and possesses the opportunity to be applied towards the synthesis of the core ring system of pradimicin A.



*Scheme 3.15: One-pot, three step reaction for the preparation of tricycle **3.41***

Keeping in mind that the original enyne metathesis approach utilizing the ruthenium Grubbs II catalyst produced diene **3.21** in an approximate 95:5 ratio, the one-pot procedure was tested with this catalyst to see if comparable yields could be obtained. The same conditions of 20 mol% catalyst at 80 °C to obtain diene **3.21** were applied for the enyne metathesis step, as shown in *Scheme 3.16*. Using the ruthenium carbene catalyst, the three step procedure only provided a 10% yield compared to the 45% obtained with the palladium catalyst. Therefore, it could be ruled out that this alternative route provided better results. Compared to the Grubbs II catalyst, the use of palladium acetate proved to be the less expensive option as well.

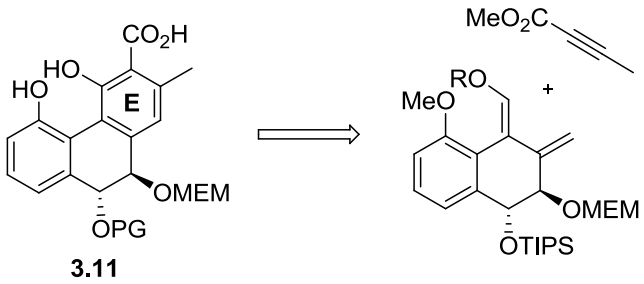


*Scheme 3.16: One-pot, three step reaction using Grubbs II catalyst for the preparation of tricycle **3.41***

3.6 Outlook: Application of the One-pot Route Towards Tricycle 3.11

Although the one-pot procedure provided an elegant route towards tricycle **3.41**, the application of the procedure towards tricycle **3.11** would have been more ideal for the construction of the core ring system in pradimicin A. However, the reactivity of diene **3.21** had to be taken into account, considering it was not shown to undergo cycloaddition with non-symmetric or monosubstituted alkyne dienophiles. Ideally, if this route were to be applied towards the synthesis of pradicimin A, an alternative dienophile would be required to provide access to the specific substitution on ring **E**. Another option would be to enhance the reactivity of the diene by substituting it with an electron donating group, providing access to the desired trisubstituted ring at the same time (*Scheme 3.17*). This would also allow for prediction of the regioselectivity of the Diels-Alder using an asymmetric alkyne so as to direct the ester and methyl groups to the correct positions. Installation of this electron donating group was envisioned to occur via the cycloisomerization with a different substituted alkyne or possibly a hydroboration followed

by an oxidation and protection. There is still the potential to utilize tricycle **3.41** towards the preparation of the natural product if one of the esters could be differentiated by reduction.



*Scheme 3.17: Alternative Diels-Alder route towards tricycle **3.11***

3.7 Conclusion

Efforts towards the total synthesis of carbohydrate binding agent, pradimicin A, lead to the synthesis of tricycle **3.41** via a one-pot palladium catalyzed cycloisomerization / Diels-Alder cycloaddition / aromatization in a 45% yield. The initial synthetic route involving a Grubbs II catalyzed enyne metathesis proved to be difficult with TMS-alkyne substrate **3.15**, forming benzylidene side product **3.17** when subjected to 100 mol% catalyst. Once the TMS group was removed the enyne metathesis proceeded effectively, but ended up yielding an unexpected diene **3.21** as the major product. With the formation of this new diene came an alternate synthetic route towards tricycle **3.11** to which **3.21** was applied. Other catalysts were tested as well to determine which product was produced under different catalyst systems. A palladium catalyzed cycloisomerization was the most efficient and clean reaction to yield diene **3.21**. Diene **3.21** proved to be difficult to work with when it spontaneously dimerized to product **3.34.** At this point, a one-pot process involving the cycloisomerization and Diels-Alder reaction was developed to ensure quick reaction of the crude diene. The first one-pot reaction where all reactants were initially added at the same time produced undesired enynene **3.38** in a good yield of 73%. A

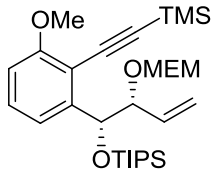
one-pot tandem process where each reaction was performed directly on the crude in the same reaction flask produced final tricycle **3.41** in a 45% yield over three steps.

3.8 Experimental

3.8.1 General: Refer to Chapter 2

3.8.2 Preparation of Enyne Metathesis Precursor 3.15

(8*R*,9*R*)-11,11-Diisopropyl-9-(3-methoxy-2-((trimethylsilyl)ethynyl)phenyl)-12-methyl-8-vinyl-2,5,7,10-tetraoxa-11-silatridecane (3.15*)*

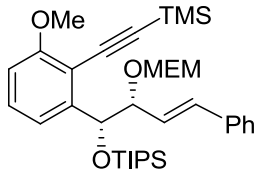


TIPS protection was performed according to the procedure published by Martin and coworkers.[33] In a round bottom flask, alcohol **2.43** (1.16 g, 3.06 mmol, 1.00 equiv) was dissolved in 7 mL of DCM. The solution was cooled to 0 °C and 2,6-lutidine (1.07 mL, 9.18 mmol, 3.00 equiv) was added slowly. TIPSOTf (1.00 mL, 3.76 mmol, 1.20 equiv) was then added dropwise to the solution and was allowed to stir for 24 hours at 0 °C. The solution was then warmed to room temperature and diluted with 5 mL of diethyl ether. The organic layer was washed with $NaHCO_3$ (2 times, 10 mL) and brine (1 time, 10 mL) and dried with $MgSO_4$. The solution was gravity filtered and concentrated *in vacuo* to produce the crude material that was purified via column chromatrography (20% ethyl acetate:hexane). 1.25 g of the product, a yellow oil, was obtained in a 90% yield. $[\alpha]_D^{25}$ 32.44 (*c* 0.27, DCM); IR (cast film) 2944, 2891, 2867, 2153, 1575, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (app t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 7.7, 0.9 Hz, 1H), 6.72 (dd, *J* = 8.0, 1.2 Hz, 1H), 5.68–5.80 (m, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 5.11 (m, 1H), 5.05–

5.08 (m, 1H), 4.74 (s, 2H), 4.18 (t, *J* = 6.5 Hz, 1H), 3.85 (s, 3H), 3.39–3.55 (m, 4H), 3.35 (s, 3H), 1.02–1.05 (m, 21H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.8, 146.5, 134.9, 128.8, 120.4, 118.3, 110.9, 108.8, 103.7, 99.2, 93.6, 81.7, 74.5, 71.7, 66.5, 58.9, 55.8, 18.1, 18.0, 17.9, 17.7, 12.4, 12.3, 0.0; HRMS (EI) Calcd. $C_{20}H_{30}NaO_5Si$: 557.3089. Found: 557.3084.

3.8.3 Preparation of Enyne Metathesis Benzylidene Side Product 3.17

(8*R*,9*R*)-11,11-Diisopropyl-9-(3-methoxy-2-((trimethylsilyl)ethynyl)phenyl)-12-methyl-8-styryl-2,5,7,10-tetraoxa-11-silatridecane (3.17)



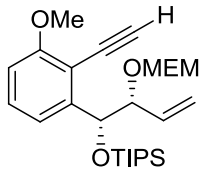
*The following procedure applies to product **3.17** synthesized by the addition of catalyst over 80 hours.* To a round bottom flask equipped with a condenser was added enyne **3.15** (23 mg, 48 µmol, 1.00 equiv) and Grubbs II ruthenium catalyst (7.3 mg, 9.6 µmol, 20 mol%). The mixture was then dissolved in 5 mL of toluene and heated to 80 °C for 12 hours. TLC was used to determine the completeness of the reaction. Another 20 mol% of catalyst was added to the reaction mixture and it was heated to reflux temperatures and stirred for another 17 hours. The process was repeated after 16, 18, and 17 hours until a total of 100 mol% catalyst was added and there was 100% conversion of starting material to product based on ^{1}H-NMR. The product was purified via column chromatography (10% ethyl acetate:hexane).

*The following procedure applies to product **3.17** synthesized by the addition of 100 mol% catalyst at the beginning of the reaction.* To a round bottom flask equipped with a condenser was added enyne **3.15** (49 mg, 92 µmol, 1.0 equiv) and Grubbs II ruthenium

catalyst (78 mg, 92 µmol, 1.0 equiv). The mixture was then dissolved in 2 mL of toluene and heated to 80 °C for 20 hours. The reaction resulted in a 66% conversion of starting material to product based on ^{1}H-NMR. IR (cast film) 2924, 2866, 2153, 1735, 1575, 1470 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27–7.37 (m, 7H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.25 (dd, J = 7.9, 16.0 Hz, 1H), 5.63 (d, *J* = 5.2 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.45 (t, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 3.56–3.67 (m, 2H), 3.42–3.51 (m, 2H), 3.40 (s, 3H), 1.02–1.10 (m, 21H), 0.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.0, 146.5, 137.0, 133.3, 128.8, 128.5, 127.4, 126.9, 126.6, 120.6, 110.9, 109.2, 103.6, 99.3, 93.4, 80.9, 74.7, 71.7, 66.5, 58.9, 55.9, 29.8, 18.1, 17.9, 12.5, 0.1; HRMS (EI) Calcd. $C_{35}H_{54}NaO_5Si_2$: 633.3402. Found: 633.3392.

3.8.4 Preparation of Terminal Alkyne 3.20

(8*R*,9*R*)-9-(2-Ethynyl-3-methoxyphenyl)-11,11-diisopropyl-12-methyl-8-vinyl-2,5,7,10-tetraoxa-11-silatridecane (3.20)

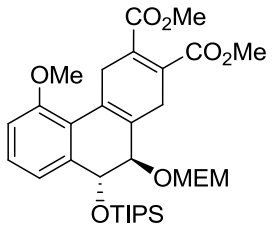


In a round bottom flask, enyne **3.15** (7.68 g, 14.4 mmol, 1.00 equiv) was dissolved in 50 mL of THF and 50 mL of MeOH. K_2CO_3 was then added to the solution and stirred at room temperature for 24 hours. The solution was then concentrated *in vacuo*, dissolved in 20 mL of diethyl ether and purified by a silica gel plug using diethyl ether as the eluent to obtain 6.19 g of a yellow oil as the product in a 93% yield. $[\alpha]_D^{25}$ 25.64 (*c* 0.45, DCM); IR (cast film) 3295, 2943, 2890, 2867, 2103, 1577, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.9 Hz, 1H), 7.17 (dd, *J* = 0.7, 7.7 Hz, 1H), 6.76 (dd, *J* = 1.0, 8.2 Hz, 1H), 5.70–5.82 (ddd, *J* = 7.5, 11.1, 16.7 Hz, 1H), 5.45 (d, *J* = 6.0 Hz, 1H), 5.11 (m, 1H), 5.07 (ddd, *J* = 0.9, 1.9, 8.1 Hz, 1H), 4.73 (s, 2H), 4.27 (t, *J* = 6.4 Hz, 1H), 3.88 (s, 3H), 3.54–

3.58 (m, 2H), 3.52 (s, 1H), 3.42–3.45 (m, 2H), 3.36 (s, 3H), 0.99–1.05 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.2, 146.5, 134.6, 129.0, 120.5, 110.7, 118.5, 109.9, 108.9, 93.4, 86.1, 81.3, 78.3, 71.7, 66.6, 58.9, 55.8, 16.0, 17.7, 12.4; HRMS (EI) Calcd. $C_{26}H_{42}NaO_5Si$: 485.2694. Found: 485.2689.

3.8.5 One-Pot Cycloisomerization / Diels-Alder Reaction for the Preparation of Diene 3.37

(9*R*,10*R*)-Dimethyl-5-methoxy-10-((2-methoxyethoxy)methoxy)-9-(triisopropylsilyloxy)-1,4,9,10-tetrahydrophenanthrene-2,3-dicarboxylate (3.37)

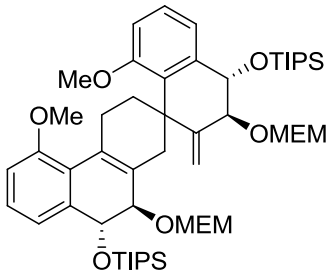


*The following procedure applies to the synthesis of diene **3.21** using the palladium catalyst followed by directly subjecting the crude product to the Diels-Alder reaction conditions.* Enyne **3.20** (0.10 g, 0.22 mmol, 1 equiv) was dissolve in 1.2 mL of toluene in a 2.5 mL microwave tube. To the reaction flask was added $Pd(OAc)_2$ (8.6 mg, 33 µmol, 15 mol%), PPh_3 (9.9 mg, 44 µmol, 20 mol%), and AcOH (5.3 µL, 88 µmol, 40 mol%). The reaction was stirred at room temperature for 24 hours at which point the dienophile, dimethyl butynedioate (0.27 mL, 2.2 mmol, 10 equiv), was added. The reaction vessel was sealed under nitrogen and subjected to the microwave conditions of 120 °C for one minute at a normal absorbance level. The solution was then concentrated *in vacuo* and purified via column chromatrography (30% ethyl acetate:hexane). The one-pot reaction yielded 58.5 mg and a 44% yield of a yellow oil.

*The following procedure applies to the synthesis of diene **3.21** using Grubbs II ruthenium catalyst followed by subjection of the crude product to the Diels-Alder reaction conditions.* Enyne **3.20** (0.20 g, 0.43 mmol, 1 equiv) was dissolved in 10 mL of toluene in a round bottom flask equipped with a condenser. Grubbs II catalyst (73 mg, 86 µmol, 20 mol%) was subsequently added to the reaction mixture. The solution was stirred at 80 °C for 24 hours at which point it was cooled to room temperature, transferred to a 2.5 mL microwave tube, and the dienophile, dimethyl butynedioate (0.55 mL, 4.3 mmol, 10 equiv), was directly added. The reaction vessel was sealed under nitrogen and subjected to the microwave conditions of 120 °C for one minute at a normal absorbance level. The solution was then concentrated *in vacuo* and purified via column chromatography (30% ethyl acetate:hexane). The one-pot reaction yielded 27.5 mg and a 10% yield of a yellow oil. IR (cast film) 2945, 2890, 2866, 1725, 1578, 1471 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 1H), 6.91 (dd, *J* = 0.9, 7.3 Hz, 1H), 6.84 (dd, *J* = 0.9, 8.4 Hz, 1H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.75, (d, *J* = 7.2 Hz, 1H), 4.72 (d, J = 4.1 Hz, 1H), 4.01–4.14 (m, 1H), 3.91–3.94 (m, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 3.48–3.60 (m, 6H), 3.37 (s, 3H), 3.05–3.15 (m, 1H), 0.93–1.07 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.5, 156.9, 138.1, 136.1, 128.9, 128.1, 127.1, 125.7, 121.9, 121.7, 112.7, 95.4, 78.5, 71.6, 67.1, 59.0, 55.5, 52.3, 52.1, 32.5, 31.9, 18.1, 18.0, 12.7; HRMS (EI) Calcd. $C_{32}H_{48}NaO_9Si$: 627.2960. Found 627.2941.

3.8.6 Dimerization of Diene 3.21

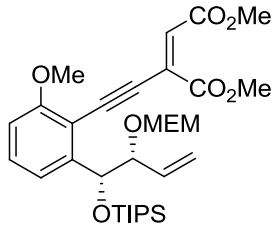
((3*S*,4*S*,9'*R*,10'*R*)-5',8-Dimethoxy-3,10'-bis((2-methoxyethoxy)methoxy)-2-methylene-3,3',4,4',9',10'-hexahydro-1'*H*,2*H*-spiro[naphthalene-1,2'-phenanthrene]-4,9'-diyl)bis(oxy)bis(triisopropylsilane) (3.34)



Diene **3.21** spontaneously dimerized after a period of approximately 24 hours at room temperature or when subjected to column chromatography purification. The ^{1}H-NMR and ^{13}C-NMR spectra were not clean enough to fully distinguish all the necessary peaks. IR (cast film) 2942, 2889, 2866, 1577, 1467 cm^{-1}; HRMS (EI) Calcd. $C_{52}H_{84}NaO_{10}Si_2$: 947.5495. Found 947.5488.

3.8.7 Preparation of Enynene Side Product 3.38

Dimethyl 2-((2-((8*R*,9*R*)-11,11-diisopropyl-12-methyl-8-vinyl-2,5,7,10-tetraoxa-11-silatridecan-9-yl)-6-methoxyphenyl)ethynyl)maleate (3.38)

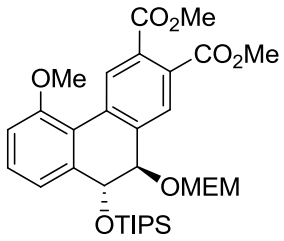


To a round bottom flask was added enyne starting material **3.20** (0.10 g, 0.22 mmol, 1.0 equiv) and 1.5 mL of toluene. $Pd_2(dba)_3$ (19 mg, 22 µmol, 10 mol%), PPh_3 (11 mg, 43 µmol, 20 mol%), AcOH (2.6 µL, 43 µmol, 20 mol%) and dienophile, dimethyl butynedioate (53 µL, 43 µmol, 2.0 equiv) were then added sequentially to the reaction flask. The

mixture was stirred at room temperature for 24 hours. The solution was concentrated *in vacuo* and purified via column chromatography (20% ethyl acetate:hexane). The product was obtained as 95.5 mg of a yellow oil in a 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.28 (s, 1H), 5.67 (ddd, J = 7.4, 10.5, 17.4 Hz, 1H), 5.29 (d, *J* = 5.2 Hz, 1H), 5.10 (d, *J* = 8.8 Hz, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.68 (d, *J* = 6.9 Hz, 1H), 4.20 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.53 (m, 2H), 3.41 (m, 2H), 3.33, (s, 3H), 1.04–0.98 (m, 12H), 0.90–0.94 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.6, 160.1, 146.5, 134.4, 130.5, 130.3, 126.8, 120.5, 118.6, 109.4, 109.1, 93.7, 93.4, 92.6, 81.3, 71.7, 66.6, 58.9, 55.8, 52.9, 52.2, 17.9, 17.8, 12.3.

3.8.8 Aromatization to form Tricycle 3.41

(9*R*,10*R*)-Dimethyl 5-methoxy-10-((2-methoxyethoxy)methoxy)-9-(triisopropylsilyloxy)-9,10-dihydrophenanthrene-2,3-dicarboxylate (3.41)



In a round bottom flask, diene **3.37** (0.10 g, 0.16 mmol, 1.0 equiv) was dissolved in 2 mL of toluene. DDQ (44 mg, 0.19 mmol, 1.2 equiv) was then added to the solution and the reaction was stirred for 24 hours at room temperature. The crude material was concentrated *in vacuo* and was purified via column chromatography to produce 67.5 mg of a yellow oil in a 70% yield. IR (cast film) 2944, 2892, 2866, 1729, 1612, 1598 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.82 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 4.5 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 4.75 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.67–3.71 (m, 1H), 3.52–3.58 (m,

3H), 3.40 (s, 3H), 0.98–1.06 (sep, *J* = 7.6 Hz, 3H), 0.88–0.96 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 167.5, 157.3, 135.6, 132.6, 129.7, 129.0, 128.6, 119.9, 112.4, 71.5, 67.1, 59.0, 55.7, 52.6, 52.5, 18.0, 17.9; HRMS (EI) Calcd. $C_{32}H_{47}O_9Si$: 603.2984. Found. 603.2984.

3.8.9 One-pot Cycloisomerization / Diels-Alder / Aromatization for the Preparation of 3.41

The following procedure was all performed in the same reaction vessel and the same solvent. No evaporation or purification was performed between steps. To a 2.5 mL microwave tube was added enyne **3.20** (0.10 g, 0.22 mmol, 1 equiv) and 1.2 mL of toluene. Next, $Pd(OAc)_2$ (8.6 mg, 33 µmol, 15 mol%), PPh_3 (9.9 mg, 44 µmol, 20 mol%), and AcOH (5.3 µL, 88 µmol, 40 mol%) were added to the reaction, which was allowed to stir for 24 hours. Dienophile, dimethyl butynedioate (0.27 mL, 2.2 mmol, 10 equiv), was added to the reaction and subjected to the microwave conditions of 120 °C for 1 minute (not including pre-heating time) at normal absorbance. Once cooled to room temperature, DDQ (59 mg, 0.26 mmol, 1.2 equiv) was added to the reaction flask and stirred for 24 hours. Upon completion, the solution was concentrated *in vacuo* and purified via column chromatography (30% ethyl acetate:hexane) to yield 59.7 mg of a light yellow oil in 45% over the three steps.

3.9 References

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