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Studies in the Asymmetric Synthesis of the C21-C34 Fragment of the Natural Product, Antascomicin B

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

by

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Abstract

This dissertation describes studies in the asymmetric synthesis of the C21 – C34 fragment of the natural product, antascomicin B. Antascomicin B is structurally related to FK506, binds strongly to FKBP12, yet does not show immunosuppressive activity. Small ligand FKBP12 binding complexes were shown to have potent neuroprotective and neuroregenerative properties in mouse models of Parkinson's disease. The highlighted chemical reactions include an asymmetric transfer hydrogenation (ATH), Ireland-Claisen rearrangement (ICR), directed hydrogenation and allylic diazene rearrangement.

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Thank you to my mom for your love, encouragement and support. Thank you to my children, Kasia and Landon. You are my inspiration and I love you more than you will ever know. Lastly, thank you to my lovely wife Juliette. Juliette, you came in to my life as a coworker and then friend. Stopping there I would have been privileged. To have you as my wife and to share this journey with has given me more than I could ever ask for, te amo.

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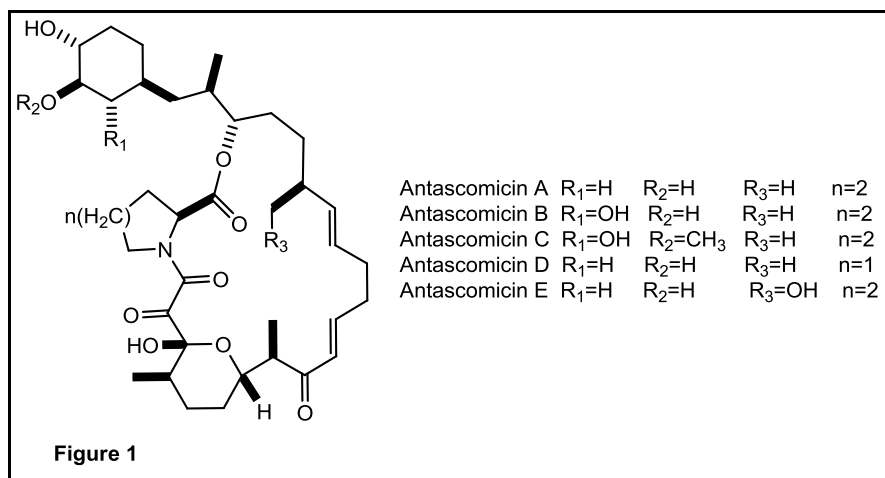
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Chapter 1

1.1 Background and significance

The antascomicins (A-E) are a small family of macrolides (Figure 1). These compounds were first isolated by Sandoz Pharma in 1996 by fermenting a strain of the genus *Micromonospora*, that had been isolated from soil samples collected in China.¹ This discovery was the result of an effort to uncover



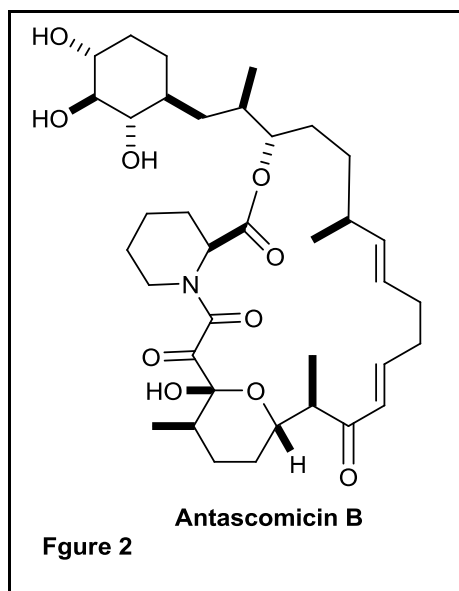
novel immunosuppressive metabolites from actinomycetes that might elicit similar biological activity to that of the macrolides rapamycin, ascomycin, FK506 and meridamycin.^{2,3} These macrolides, such as rapamycin and FK506, are known to be a powerful group of drugs that bind with high affinity to the abundant intracellular binding protein FKBP12. The 12 kDa FK506-binding protein, FKPB12, is a *cis-trans* peptidyl-prolyl isomerase that catalyzes the *cis-trans* interconversion around peptidyl prolyl amide bonds in peptides and accelerates protein folding in proline containing proteins.⁴ Alone, rapamycin and FK506 are not responsible for immunosuppression, but rather the complex formed between the respective macrolide and FKBP12 are believed to be responsible for the immunosuppressive activity. For example, both FK506 and rapamycin bind to FKBP12 in a similar fashion but they differ in activating the mechanism for undermining T-cell function, which results in different modes of immunosuppressive action. The FK506/FKBP12 complex binds to calcineurin, which is responsible for T-cell proliferation, and this ternary complex prevents the transcription of genes responsible for coding interleukin-2 (IL-2) and its receptor.⁵ The target of the rapamycin/FKBP12 complex is mTOR, a protein responsible for controlling cell growth and proliferation. This ternary complex blocks entry of the lymphocytes into the cell by

interfering with a signaling pathway that is mediated by a lymphokine receptor, thus inhibiting cell proliferation.⁶

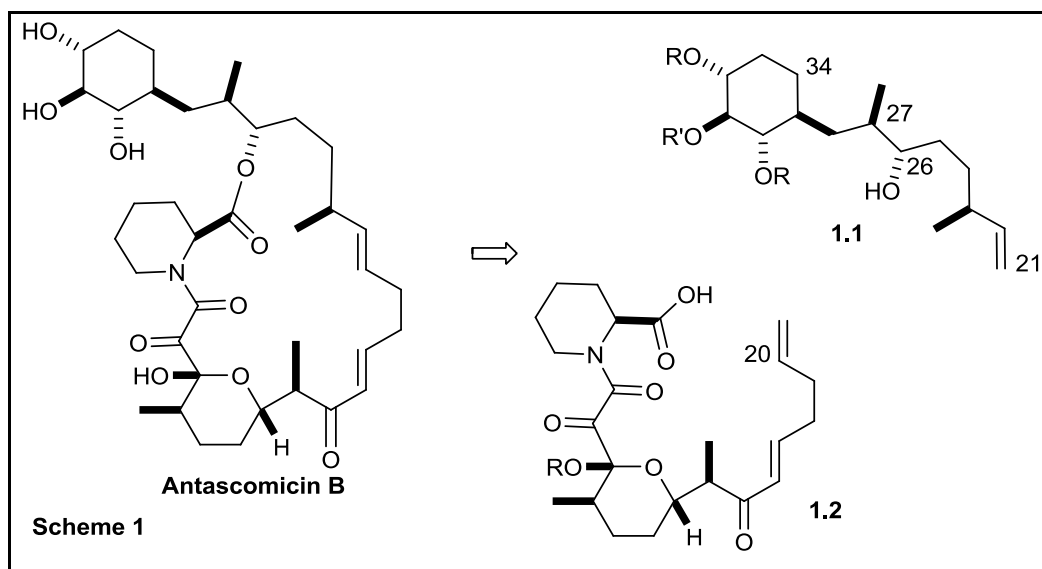
Immunophilins are endogenous cytosolic peptidyl-prolyl isomerases that interconvert between the *cis* and *trans* positions of proline containing proteins. Based on the activity of the known immunophilin-binding compounds, FK506 and rapamycin, a binding assay was conducted to identify active metabolites from actinomycetes. The immunophilin FKBP12 was used and the degree of binding to substrates in competition with FK506 were measured. Over 12,000 strains of bacteria were measured and the binding affinity was compared to the known immunophilin-binding compounds rapamycin and FK506. From this assembly, only one strain displayed a binding affinity for FKBP12 to a comparable degree that FK506/rapamycin bind to FKBP12. This strain produced five novel macrolides and were named antascomicins A-E.¹ The antascomicins were found to bind FKBP12 to the same degree as FK506 and rapamycin (1.1 and 0.6 nM, respectively). The antascomicins are structurally related to FK506, bind strongly to FKBP12, yet do not show immunosuppressive activity or inhibit proliferation of T-cells.¹ In a 1992 study published in *Nature*, it was discovered that FKBP12 exists at extraordinarily high levels in the brain, even more so than in the immune system.⁷ This evidence led researchers to investigate the roles of immunophilins in various areas of neural function. It was shown that the FKBP12/rapamycin and FKBP12/FK506 complexes do in fact show neuroprotective properties in neuronal systems.⁸ However, the immunosuppressive characteristics of these compounds limited their usefulness in the treatment of damaged nerves. This encouraged research to find non-immunosuppressive FKBP12 binding ligands.⁹ The small molecules that bind FKBP12 and do not cause immunosuppression lack the domain responsible for binding to calcineurin or mTOR, the effector domain. The antascomicins are among the few naturally occurring molecules that lack the effector domain and have been identified to bind FKBP12, but not show immunosuppressive tendencies.¹⁰ Small ligand FKBP12 binding complexes that lack an effector domain were shown to have potent neuroprotective and neuroregenerative properties in mouse models of Parkinson's disease.¹¹

1.1.1 Retrosynthesis of antascomicin B

Synthetic studies toward antascomicin A were published in 2004 by Fuwa¹² *et al*, Chakraborty *et al* published two fragments of antascomicin A in 2006¹³ and most recently, the Ghosh group published the C17-C34 fragment of antascomicin A in 2014.¹⁴ The first total asymmetric synthesis of antascomicin B (Figure 2) was reported by Stephen Ley's research group at Cambridge University in 2005.¹⁵

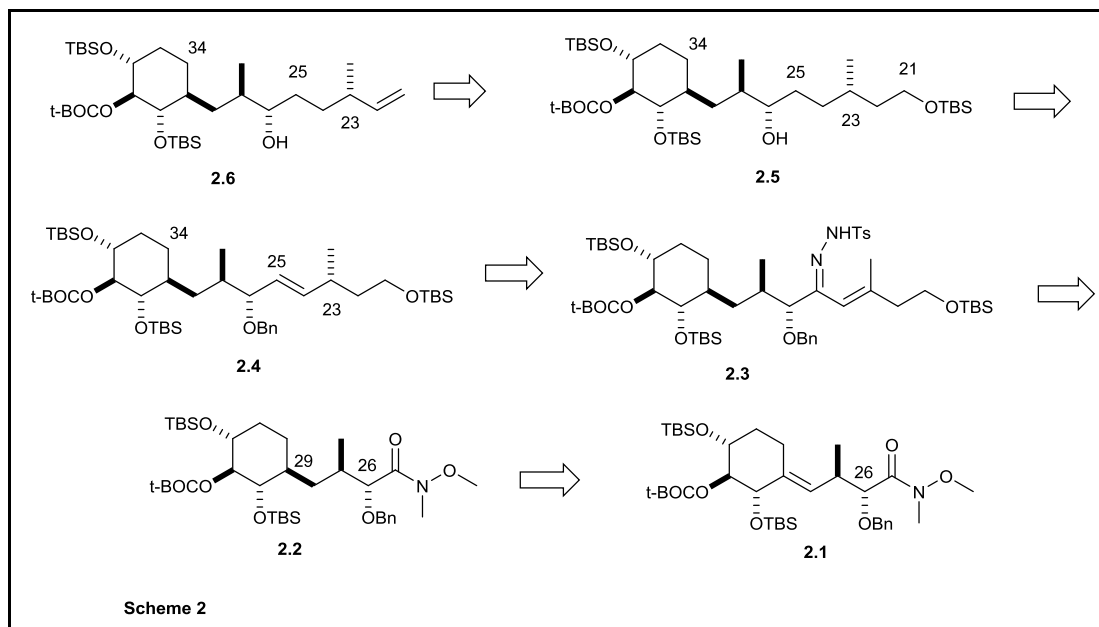


In 2008, our group published a model study¹⁶ of the C22 - C34 fragment of antascomicin B, and later published the synthesis of the racemic fragment in 2011.¹⁷ For our studies, the planned synthesis of antascomicin B will conclude with esterification at C1 and the hydroxyl group of C26 of the late stage intermediates **1.1** and **1.2** (Scheme 1). This will be followed by ring closing metathesis at C20-C21, and conclude with global deprotection. The synthesis of the C1-C21 fragment **1.2** of antascomicin B has been studied in our lab and its synthetic route includes an amino-Claisen rearrangement and an acid mediated lactonization.¹⁸ Efforts to construct the C21-C34 fragment **1.1** will be the focus of this thesis and the retrosynthesis is outlined below.



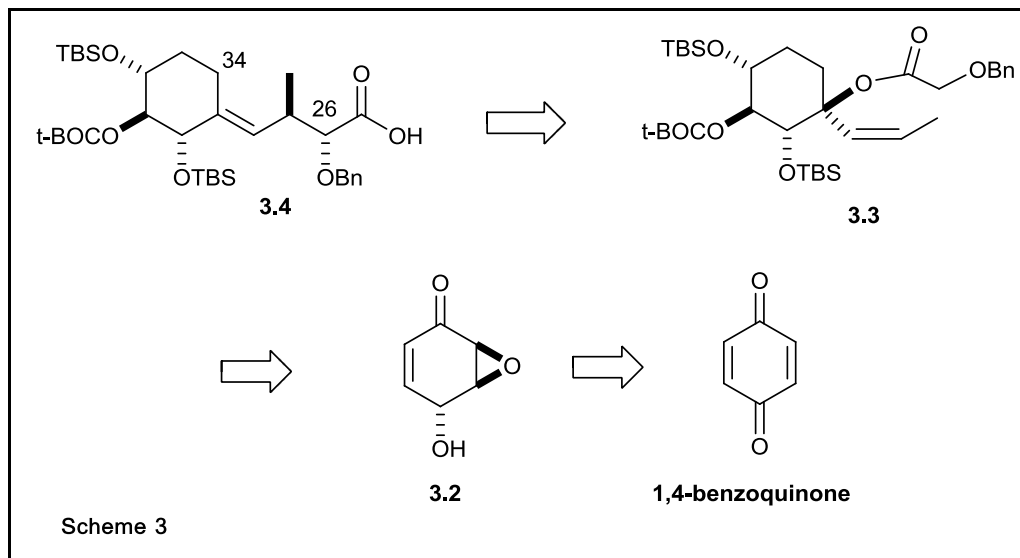
1.2 Retrosynthesis of the C21 – C34 fragment of antascomicin B

Initially, our plan for the asymmetric synthesis of the C21–C34 fragment of antascomicin B (Scheme 2). The final stage of fragment **2.6** was to be completed by selective removal of the silyl protecting group at C21 of **2.5** to give the alcohol. Grieco olefination would then be used to furnish the terminal alkene of **2.6**.¹⁹ This would follow simultaneous reduction of the C24–C25 alkene and removal of the C26 benzyl protecting group of compound **2.4** by catalytic hydrogenation. Compound **2.4** would



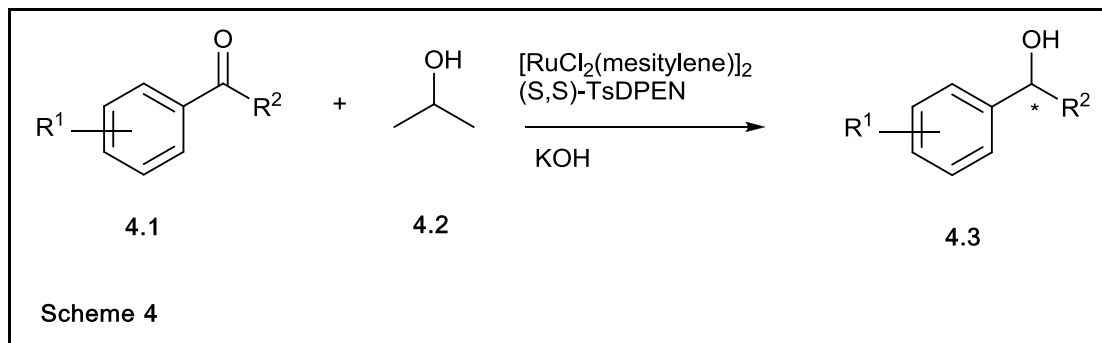
be the result of a substrate controlled 1,3-reductive transposition reaction to install the remote C23 stereocenter by way of an allylic diazene rearrangement from hydrazone **2.3**. To this end, compound **2.2**

would be obtained via directed hydrogenation using Crabtree's iridium catalyst to install the stereocenter of C29 from Weinreb amide **2.1**. The pentenoic acid **3.4** (Scheme 3) would come from the highly congested allylic ester **3.3** by way of an Ireland-Claisen rearrangement. Epoxy quinol **3.2** was envisioned to arise from an asymmetric transfer hydrogenation reaction in four steps from 1,4 –benzoquinone. The following sections are intended to inform the reader of the recent literature of these highlighted reactions discussed in the retrosynthesis for the asymmetric C21–C34 fragment of antascomicin B.

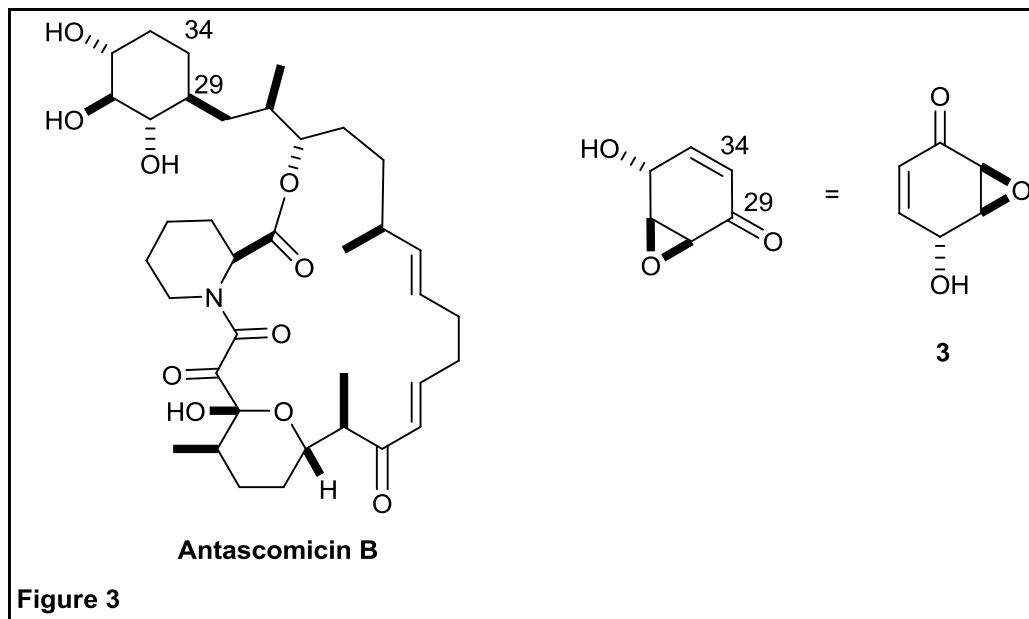


1.3 Asymmetric transfer hydrogenation

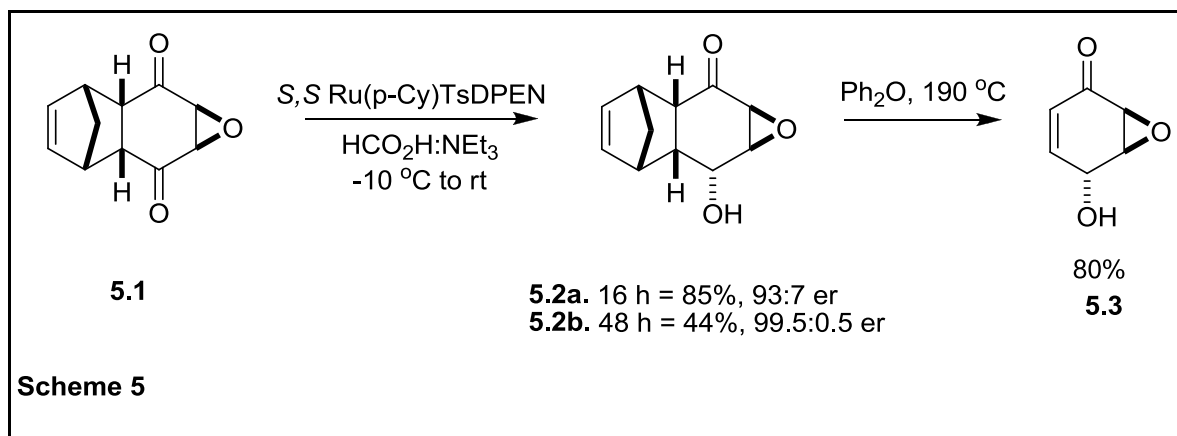
Transfer hydrogenation reactions consist of the transfer of hydrogen to a molecule from a source other than gaseous hydrogen.²⁰ A common example and widely used asymmetric transfer hydrogenation reaction in organic chemistry was developed by Noyori for the reduction of aromatic prochiral carbonyl compounds **4.1** to form chiral alcohols, **4.3** (Scheme 4).²¹ This approach offers advantages over other



reduction methods, such as molecular hydrogen under catalytic conditions or metal hydride reductions, by the ease of reaction set up and safer reaction conditions. Asymmetric transfer hydrogenation (ATH) for the reduction of carbonyls played a pivotal role in the efforts toward the asymmetric synthesis of the C21 – C34 fragment of antascomicin B. In 2011, the McIntosh group reported using Noyori transfer hydrogenative desymmetrization in route to an early intermediate **3** contained in the C29–C34 fragment of antascomicin B (Figure 3).²² This effort was significant in that the reported asymmetric route to the corresponding silyl ether of **3** required eight steps from benzoquinone, high enzyme loading and long reaction times (16 days). The success of this method shortened the synthesis to four steps to epoxy quinol, **3**.



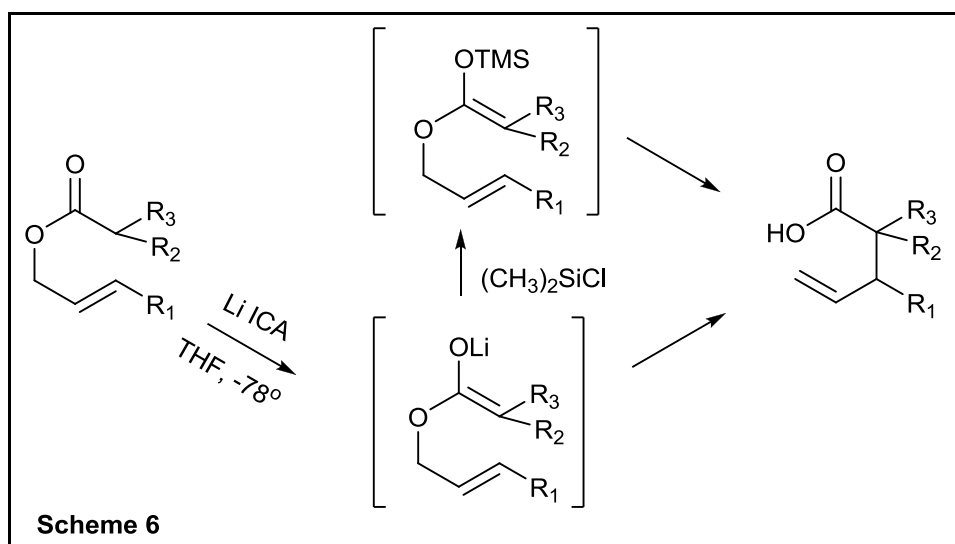
It was found that the precursor to the epoxyquinol **5.2a** could be produced in 93:7 *er* at 85% yield on a 60 mmol scale from the *meso*-epoxy diketone **5.1** (Scheme 5). Furthermore, a 99.5:0.5 *er* could be achieved for **5.2b** by way of a kinetic resolution of the minor enantiomer with longer reaction times, albeit with diminished yields. The intrinsic enantioselectivity for the reaction was 82:18 at 4% conversion and was in agreement with other dialkyl ketone transfer hydrogenations.^{23, 24}



The route to the epoxyquinol was completed using Taylor's variation²⁵ of the Lubineau procedure²⁶ for the *retro*-Diels-Alder reaction to complete the synthesis of **5.3**. In 2012, this epoxyquinol and several other examples of ATH reactions and mechanistic details were reviewed in a thesis by a former McIntosh group member.²⁷ For the interested reader, a review on the advances of asymmetric transfer hydrogenation of ketones was published by the Yus group that covers the most recent literature.²⁸

1.4 Ireland-Claisen rearrangement

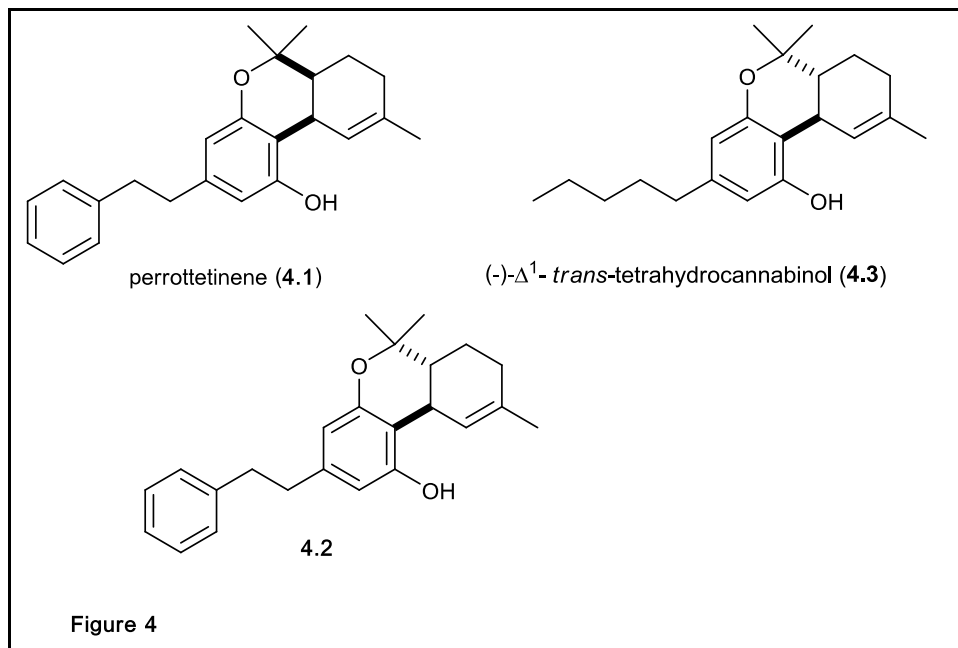
In 1972, the utility of the newly introduced [3,3] sigmatropic rearrangement that converts an allylic ester to a γ,δ -unsaturated carboxylic acid came to be known as the Ireland-Claisen rearrangement (Scheme 6).²⁹ The Ireland-Claisen rearrangement (ICR) advantages include the ease of preparation of the allylic esters, (the ability to perform reactions at low temperatures) and the capacity to induce stereochemical control due to the well-defined and highly ordered transition structure leading to the product. The ICR has been extensively reviewed.³⁰⁻³⁴ The following sections are intended to bring the reader up to date on some of the more recent (2008-2016) aspects of the ICR used in synthetic chemistry.



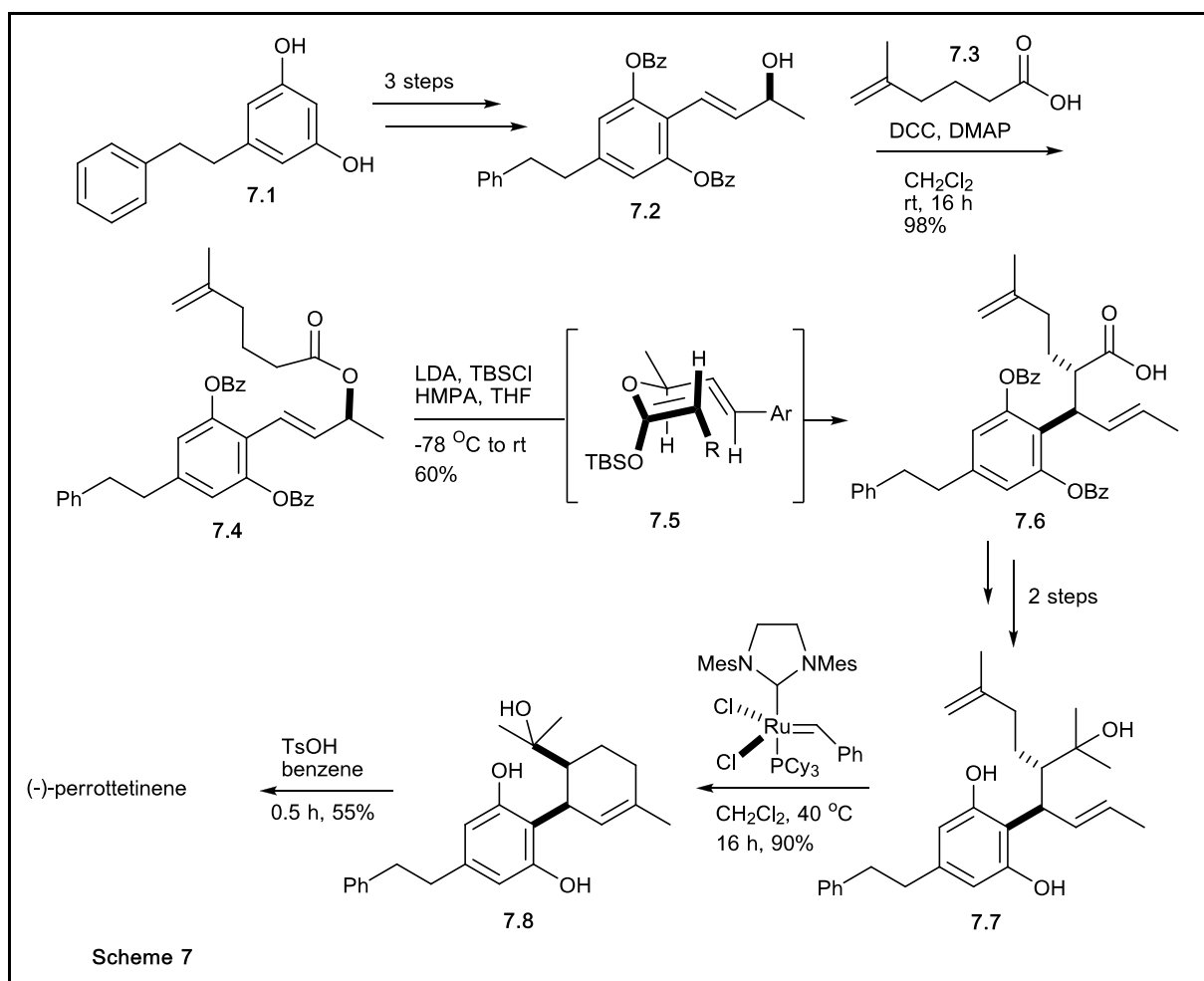
1.4.1 Ireland Claisen rearrangement in total synthesis

1.4.1.1 (-)-Perrottetinene

In 1994, the bibenzyl cannabinol (-)-perrottetinene **4.1** was isolated as a natural component in the ether extract from a liverwort *Radula perrottettii*, by Asakawa and coworkers.³⁵ The structure of **4.1** was elucidated by comparison to a synthesized bibenzyl *trans*-fused ring system **4.2** made by Crombie and coworkers, similar to (-)- Δ^1 -*trans*-tetrahydrocannabinol (Δ^1 -THC, **4.3**) or commonly known as (Δ^9 -THC), the principal psychoactive constituent of marijuana.³⁶ The synthesis of the *trans*-**4.2** and other cannabinoid analogs were made in part due to a connection between the bibenzyl and cannabinoid natural products at an early biogenetic stage.^{36, 37}



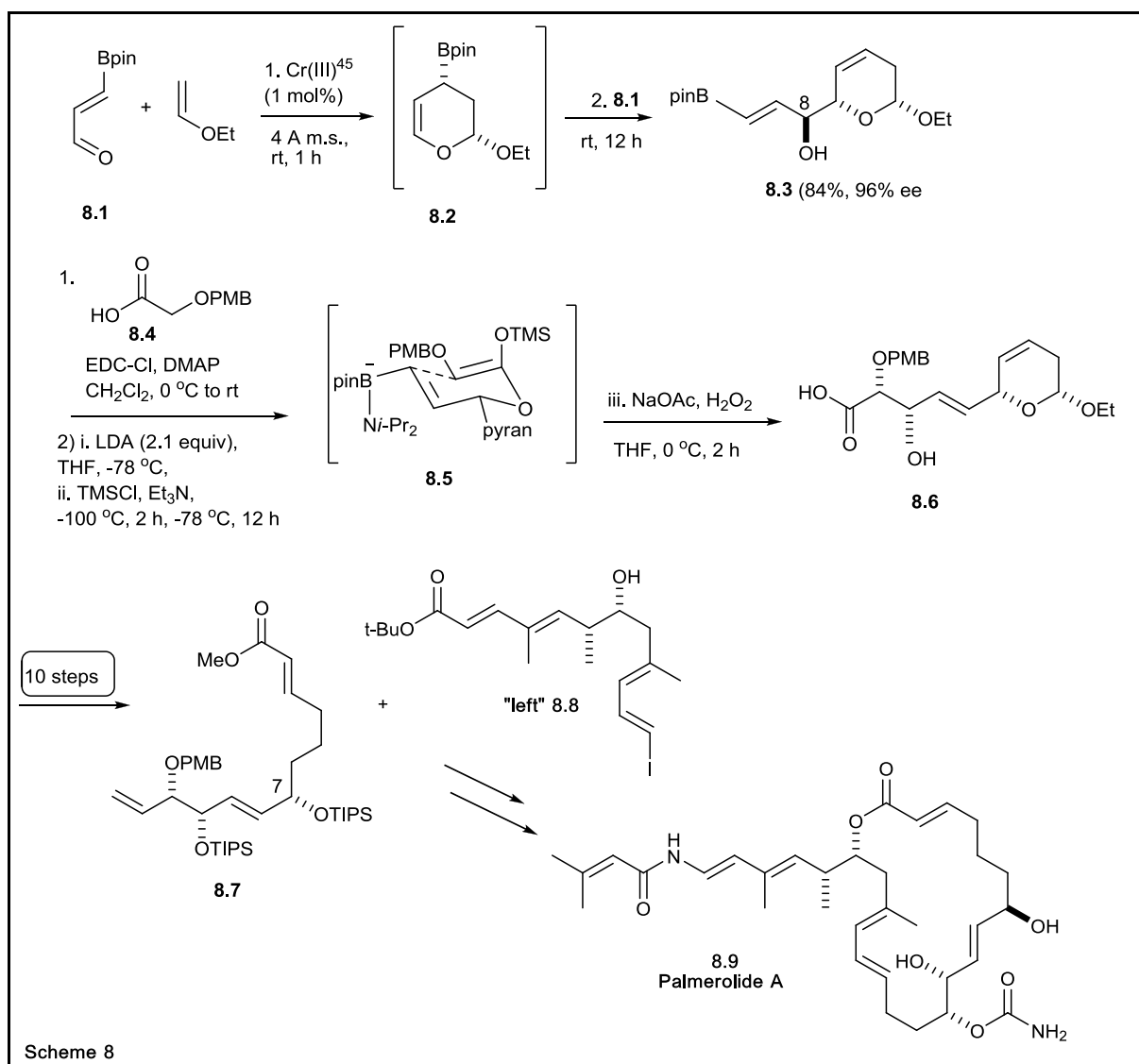
Though the *trans*-THC compounds have garnered the most attention from the synthetic community,³⁸⁻⁴⁰ sparse consideration has been given to the *cis*-THC analogs. This trend is likely due to the lack of psychoactivity in the *cis*-compounds.^{41, 42} Nevertheless, the stereoselective synthesis of (-)-perrottetinene is worth noting due to the key reaction of the *cis*-disubstituted cyclohexene ring by the diastereoselective Ireland-Claisen rearrangement (Scheme 7).⁴³ Allylic alcohol **7.2** was made in three steps from commercially available 3,5-dimethoxybenzaldehyde (**7.1**). Acylation of the secondary alcohol **7.2** with the known 5-methylhex-5-enoic acid **7.3** as the chiral building block gave the Ireland-Claisen ester precursor



7.4 in 98% yield. The (Z)-silyl ketene acetal was required to achieve the desired stereoisomer of **7.6**, if it occurred through the expected chair-like transition state **7.5** (Scheme 7). It was found that treatment of **7.4** under the standard Ireland-Claisen conditions for Z-enolate stereoselectivity (LDA and TBSCl in 20% HMPA/THF at -78 °C), followed by gradual warming to room temperature resulted in the desired product **7.6** in 60% yield with >20:1 diastereoselectivity. Ring closing metathesis using Grubbs' catalyst gave the desired cyclohexene derivative **7.8**. Catalytic amounts of TsOH in refluxing benzene gave the desired product in 55% isolated yield.

1.4.1.2 Palmerolide A

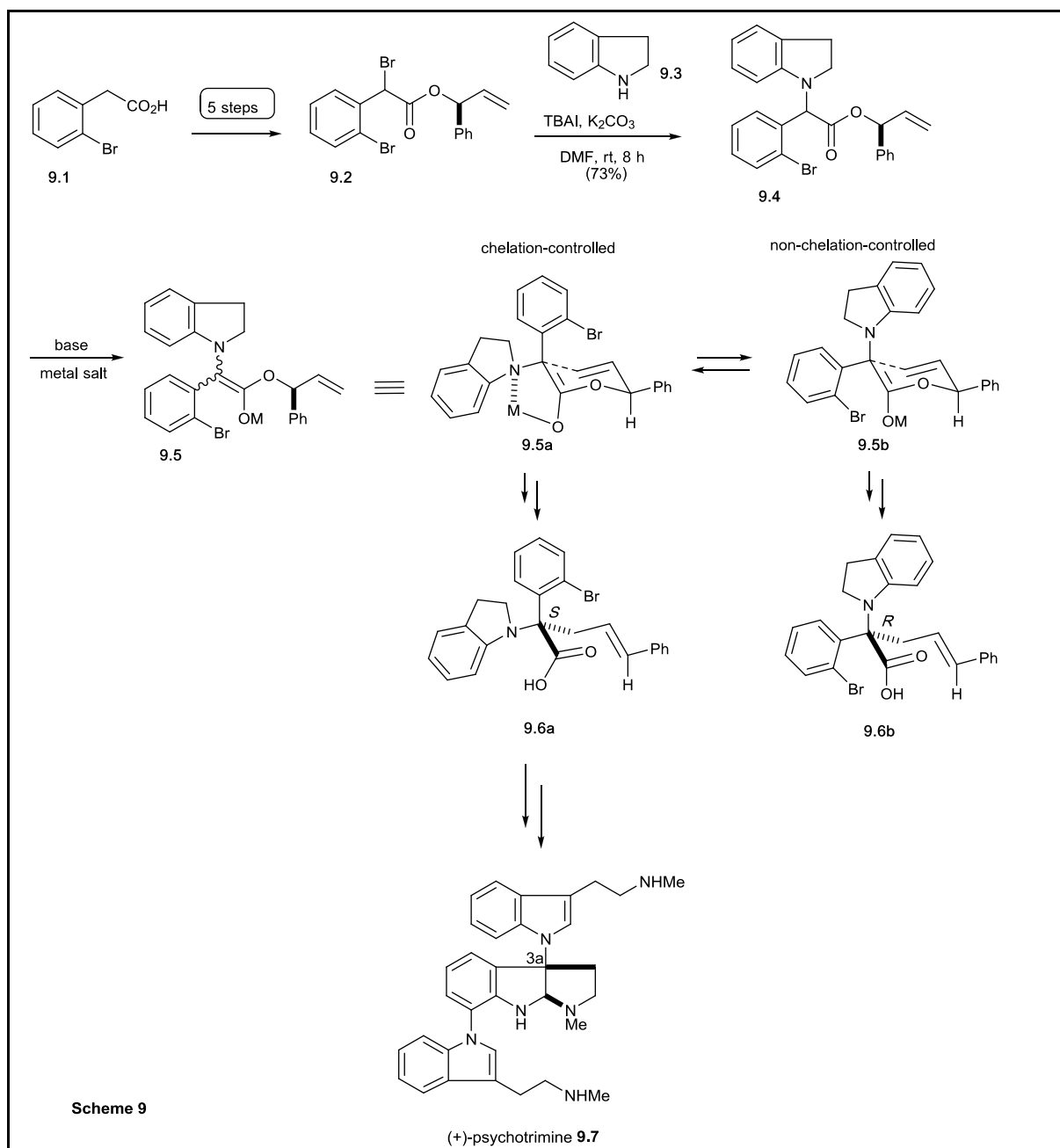
Palmerolide A is a complex polyunsaturated macrolide isolated from a marine invertebrate (*Synoicum adareanum*) found in the Antarctic Ocean. This compound contains five stereogenic centers and seven double bonds, figure 5. It has been shown to have potent and selective antitumor activity toward melanoma cell lines relative to other cell lines tested. An unprecedented variant of the Ireland Claisen rearrangement using an alkenylboronate as a masked hydroxyl forms the basis for a strategy for this synthesis.⁴⁴ The design for this synthesis concluded with a macrolactonization and sp^2 - sp^3 β -alkyl Suzuki cross coupling reaction of the fragments, **8.7** and **8.8** (Scheme 8). This convergent plan began with the construction of fragment **8.8**, but the highlight of this asymmetric total synthesis came from the construction of the fragment **8.7** of palmerolide A. The synthesis began with a catalytic enantioselective hetero[4+2] cycloaddition catalyzed by Jacobsen's chiral chromium complex, followed by *in situ* allylboration.⁴⁵ Compound **8.1** conveniently served the dual functions of heterodiene, and the substrate for allylboration with the intermediate cycloadduct **8.2** to give the secondary alcohol, **8.3**. Acylation of the alcohol leads to the Ireland-Claisen precursor and formation of the *Z*-enolsilane **8.5** initiates the rearrangement to give **8.6** as the pentenoic acid. The excess of LDA (2.1 equivalent) was likely needed due to coordination of the lithium to the boron. The diastereoselectivity of the product was controlled by the conformation of the pyran ring at C8 in the chairlike transition structure shown (**8.5**). Suzuki coupling of **8.7** and the left fragment **8.8**, followed by Yamaguchi macrolactonization led to the asymmetric total synthesis of palmerolide A.



1.4.1.3 (+)-Psychotrimine

The Malaysian rubiaceae plant is the source of psychotrimine **9.7**, a trimeric tryptamine-related alkaloid (Scheme 9). This alkaloid is the first known to have a tryptamine and a pyrrolidinoindoline unit contained in the same compound. The compound was first isolated by Takayama *et al.* and they later completed the first total asymmetric synthesis by using an ICR as a key step in the synthesis.⁴⁶ This work also allowed them to determine the absolute configuration of the natural product. The synthetic plan for psychotrimine was derived from earlier efforts to construct the racemic natural product. The key step in the asymmetric synthesis however, came from a chirality transfer process of the chiral allylic ester **9.4**. The chiral ester was prepared by esterification of 2-bromophenylacetic acid **9.1** followed by radical

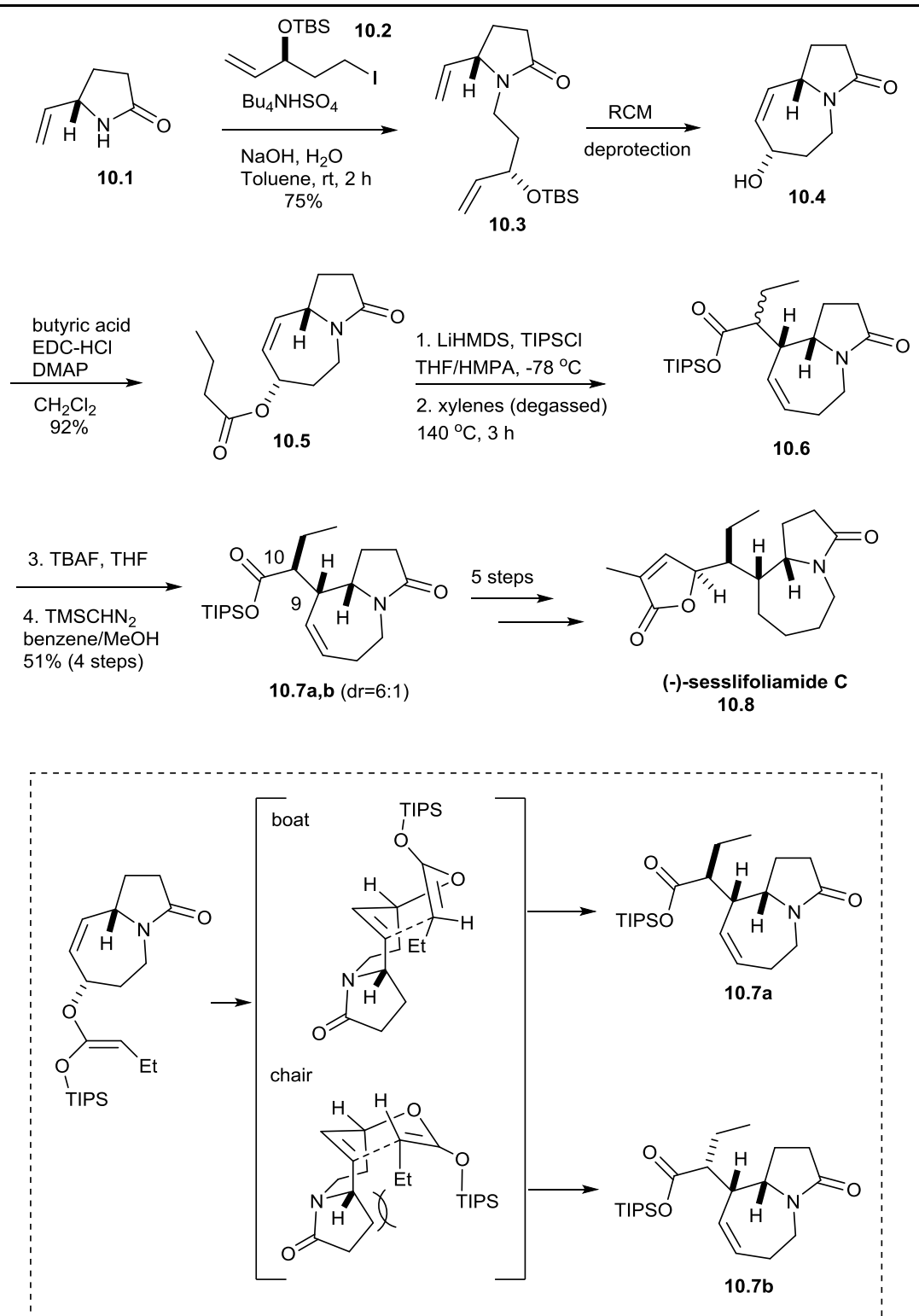
bromination at the benzylic position, alkaline hydrolysis and coupling to a chiral allylic alcohol in 5 steps gave **9.2** in 65% overall yield. With a point of chirality established, the indoline **9.3** was then installed to give the ICR precursor **9.4** as a diastereomeric mixture. Based on extensive earlier work by Kazmaier in the Ireland-Claisen rearrangement to prepare substituted α -amino acids,⁴⁷ studies found using ZnI_2 and the combination of KHMDS/THF as base and solvent were optimal and provided 79% yield in 74% ee. Ketene acetal **9.5** produced by treating ester **9.4** with base and metal salt would have two chair-like transition states, (*Z*)-enolate **9.5a** and (*E*)-enolate **9.5b**, both which favor the pseudo-equatorial position for the phenyl group. Using Zn salts, it was presumed chelation between the nitrogen of the indoline and the oxygen of the (*Z*)-enolate takes place, which led to the new chiral center (*S*) in good optical purity of the pentenoic acid **9.5a**. The absolute configuration was determined by converting the ICR product to a nitrile derivative that could be recrystallized to enantiomeric purity (99.9% ee, determined by chiral HPLC). X-ray crystallographic analysis revealed the compound had the (*S*)-configuration at the quaternary carbon center. The first asymmetric total synthesis of (+)-psychotrimine was then completed by following a route that was developed in the racemic synthesis in 18% overall yield from the pentenoic acid product. The spectral data ($[\alpha]_D$, NMR, mass) of the synthetic compound was compared to that of the natural one and found to be identical and the absolute configuration was thus established.



1.4.1.4 (-)-Sessilifoliamide

This natural product, **10.8** (Scheme 10), was isolated from the roots of the perennial herb, *Stenona sessilifolia* in 2003. Extracts from these plants have been used for centuries for the treatment of various respiratory problems, such as bronchitis and tuberculosis. These alkaloids possess a characteristic pyrrolo[1,2-a]azepine core attached to a butenolide substituent. In this synthesis the Ireland-Claisen rearrangement was used to install the adjacent C9-C10 stereocenters. It was found the

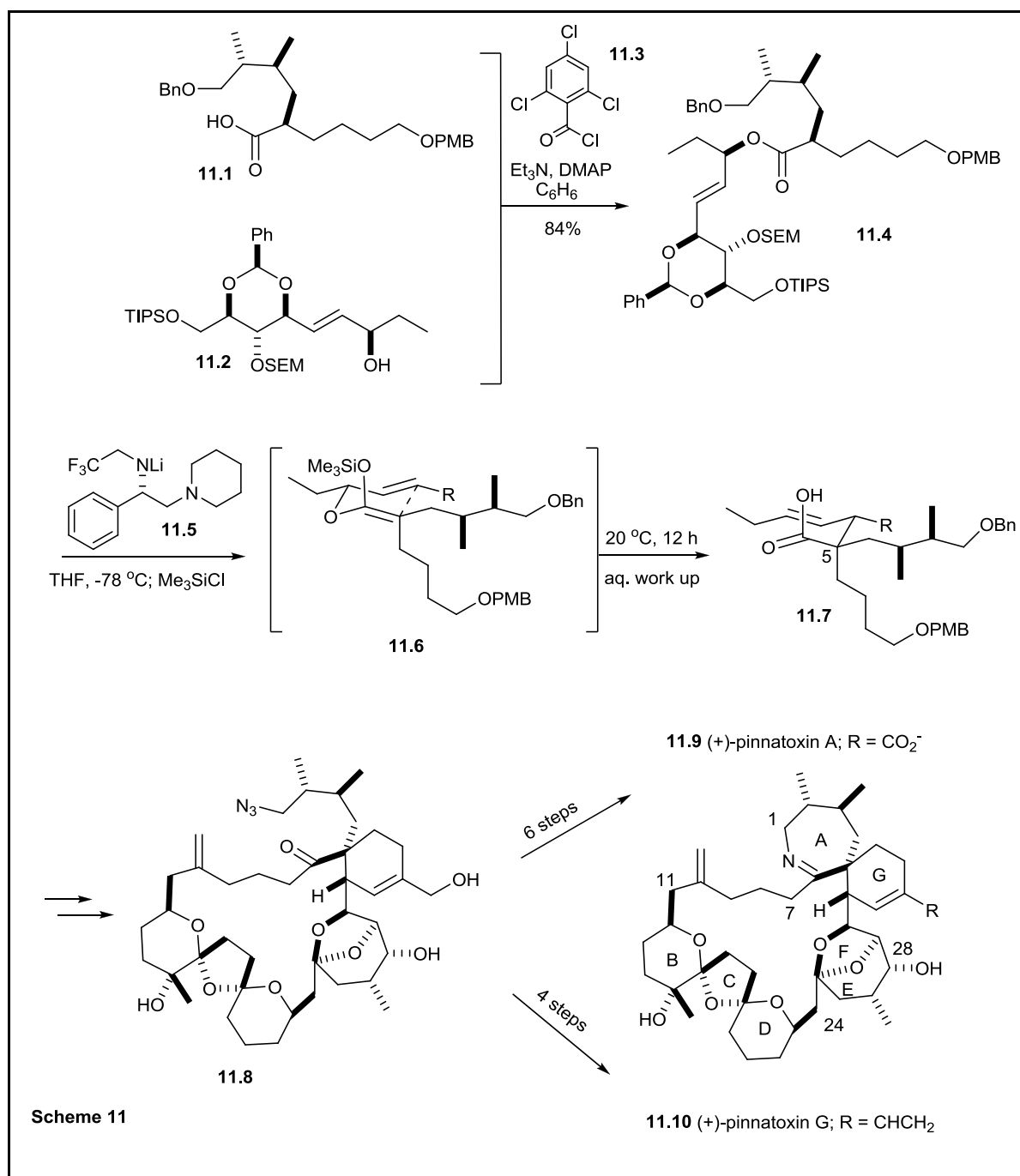
diastereoselectivity of the reaction could be improved by increasing the steric bulk in the silyl ketene acetal substituent in the ICR.⁴⁸ This convergent synthesis began with the construction of **10.1** from (S)-pyroglutamic acid in five steps. An enzymatic resolution strategy produced an allylic alcohol which was followed by iodination to give fragment **10.2**. The ICR precursor **10.5** was achieved by ring closing metathesis and acylation of the allylic alcohol **10.4**. It was discovered that changing the silyl group from TBS to TIPS increase the diastereoselectivity from a 2:1 to 6:1 (insert Scheme 10). It was postulated that the silyl group would be positioned underneath the 7-membered ring during the C-C bond formation and prefer the boat transition state leading to the desired rearrangement product, **10.7a**. The natural product was completed in five additional steps that included Swern oxidation, addition of vinyl magnesium bromide and another ring closing metathesis to give (-)-sessilifoliamide C, **10.8**.



Scheme 10

1.4.1.5 (+)-Pinnatoxin A and G

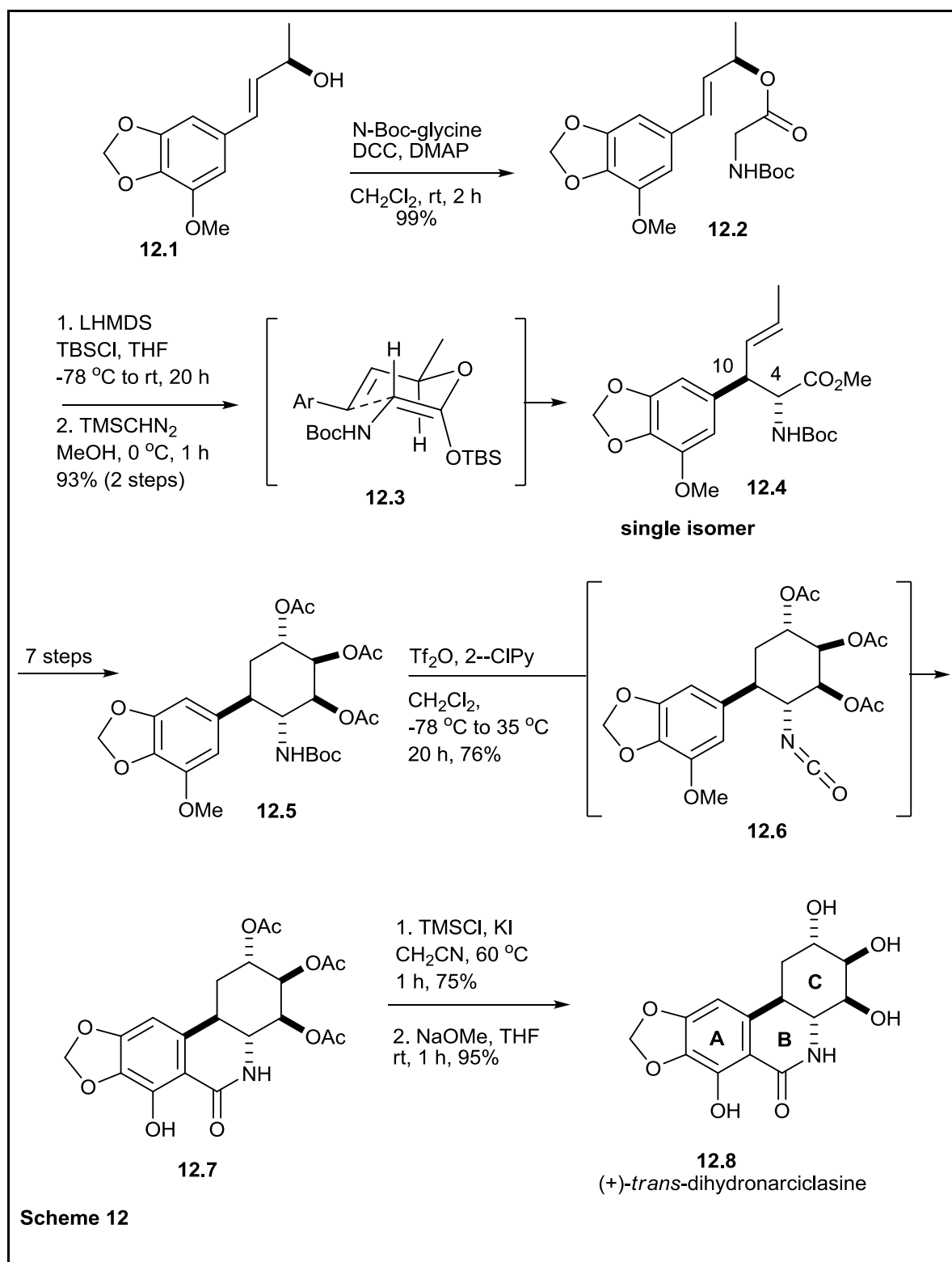
The 27-membered carbocycle core structure of pinnatoxins A and G (**11.9** and **11.10**) contains an AG-spiroimine and BCD-dispiroketal fragment connected by an alkyl chain (C7-C11) and a bridged EF-ketal ring (Scheme 11). The ICR was chosen to install the quaternary stereocenter at C5 of the AG rings in this total asymmetric synthesis of the (+)-pinnatoxin A and G.⁴⁹ The precursor of the ICR **11.4** came from the coupling of intermediates **11.1** and **11.2**, which were prepared in 9 steps from (*S*)-citronellic acid and 10 steps from *D*-ribose, respectively. The diastereoselective rearrangement was achieved using the chiral lithium amide base, *N*-trifluoroethyl lithium amide (**11.5**). The chirality transfer in the rearrangement is enabled by the stereoselective enolization of the acyclic α,α -disubstituted ester **11.4** leading to the stereodefined (*Z*)-enolate, **11.6**. The chiral base controls the conformation in the transition state between the substrate and the chiral reagent before the proton transfer. It is this conformational control that translates into the geometrical selectivity for the (*Z*)-enolate formation. This work marked the first general method for stereoselective generation of acyclic α,α -disubstituted ester enolates according to the report. The fragment was further elaborated to an advanced intermediate **11.8** where both Pinnatoxin A and G could be accessed in six and four steps, respectively.



Scheme 11

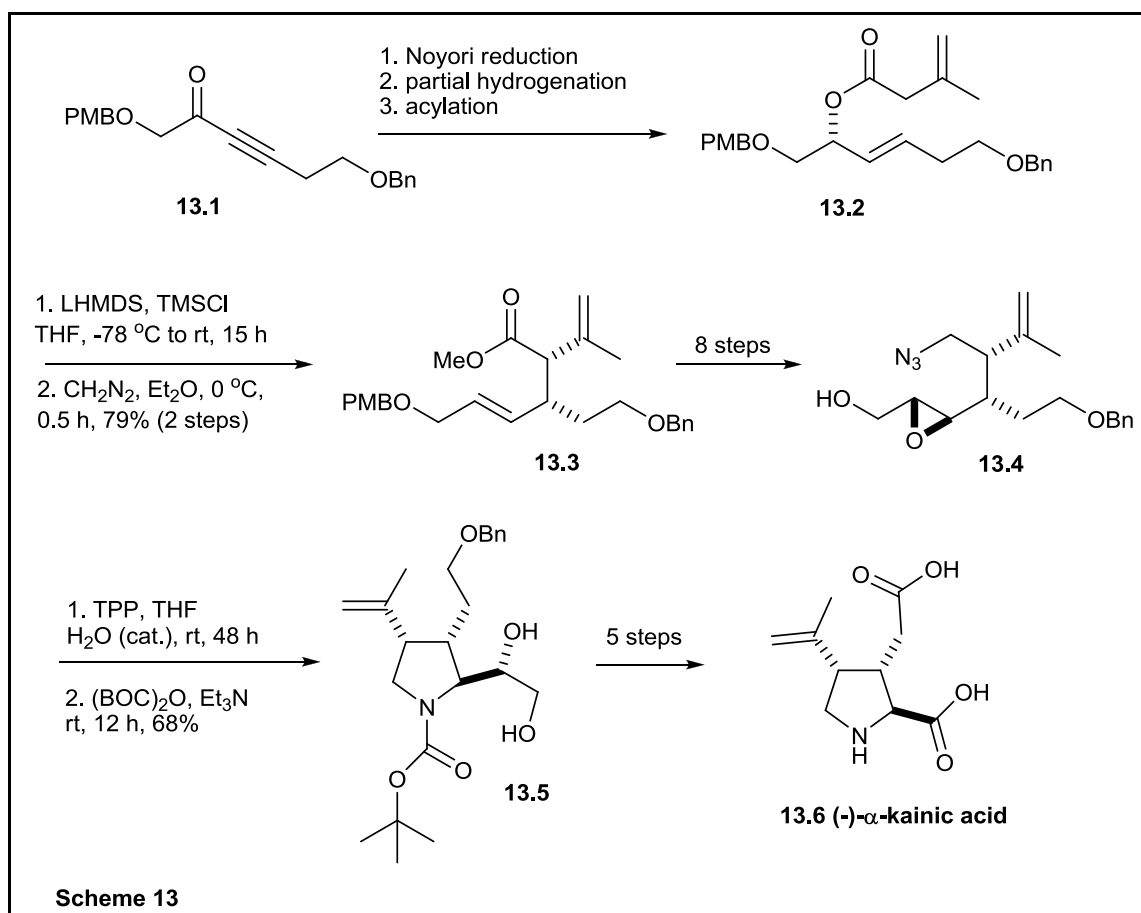
1.4.1.6 (+)-*trans*-Dihydronarciclasine

This natural product **12.8** (Scheme 12) comes from the Chinese medical plant, *Zephyranthes candida* and has shown potent and selective anticancer activity. The following asymmetric total synthesis includes the use of a *N*-Boc protecting group for both directing the stereochemical outcome of the ICR and to facilitate a highly selective Friedel-Crafts cyclization reaction to form the B ring of *trans*-dihydronarciclasine.⁵⁰ The precursor to the ICR was prepared by Stille coupling of an aryl bromide and chiral vinylstannane to give the allylic alcohol, **12.1**. Acylation of the allylic alcohol with *N*-Boc protected glycine gave the chiral allylic amino ester **12.2** in excellent yield and set the stage for the ICR. This was initiated by deprotonation with LHMDS and then formation of the (*Z*)-silyl ketene acetal intermediate, **12.3**. Trapping with TBSCl at -78 °C and gradual warming to room temperature was followed by treatment with TMS-diazomethane to give methyl ester **12.4** in excellent yield as a single diastereomer. The two new adjacent stereocenters were assumed to be 4*R* and 10*R* by invoking the chair transition state, **12.3** (Scheme 12). The assumption was ultimately confirmed upon completion of the natural product and comparing the spectral data. Progress to complete the asymmetric total synthesis of (+)-*trans*-dihydronarciclasine included an intramolecular Friedel Crafts-type cyclization of the *N*-Boc carbamate. It was found the final B ring could be formed with high regioselectivity and good yield via an isocyanate intermediate, **12.6**. Demethylation and deprotection of **12.7** led to the completion of the total synthesis with spectral data matching those reported for the natural product.



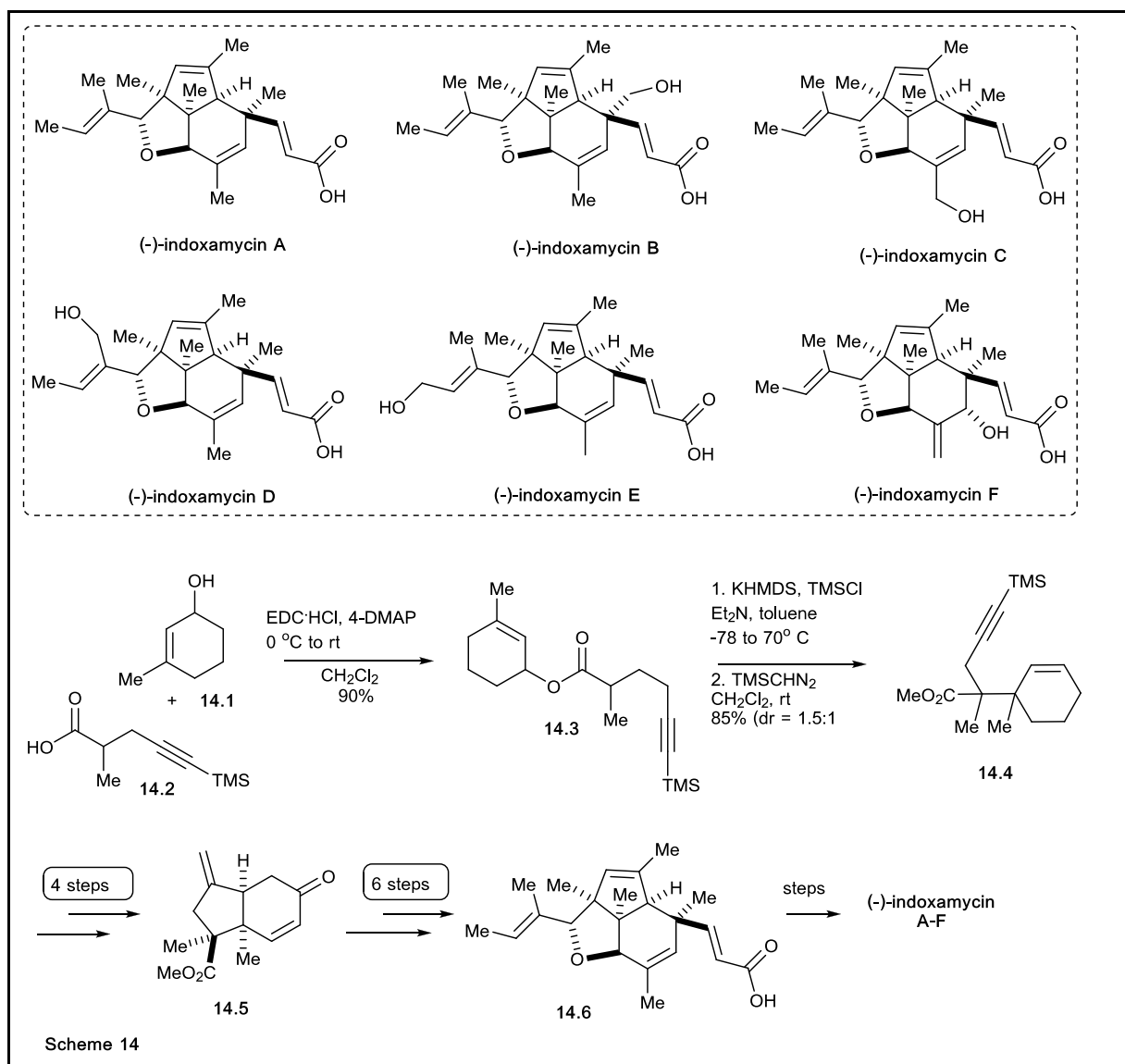
1.4.1.7 (-)- α -Kainic acid

Kainic acid **13.6** (Scheme 13) is a natural marine acid found in algae and is categorized in the kainoid family of non-proteinogenic amino acids. This compound has been used in animal models for its neuroexcitotoxic and epileptogenic properties for screening CNS disorders such as Alzheimer's disease and epilepsy. This, and others in the kainoid family of amino acids, share the same relative configuration of *trans*-C2/C3, *cis*-C3/C4 around the common pyrrolidine framework. The approach to this synthesis began with the differentially protected ynone, **13.1**.⁵¹ Through a sequence which included a Noyori asymmetric reduction (>95% ee), partial reduction of the triple bond and an acylation, the Ireland Claisen precursor **13.2** was obtained in 57% overall yield for the three steps. The allylic ester was then subjected to ICR conditions for the (*E*)-enolate and the rearrangement proceed with the expected chirality transfer to install the continuous C2-C3 stereocenters of the pentenoic acid. This step was followed by methylation with diazomethane to give the ester, **13.3** in 79% yield for the two steps. Further elaboration led to the azido epoxy alcohol **13.4** as a single diastereomer. The 5-exo-tet cyclization was furnished by reduction to the amine that was trapped as the carbamate **13.5** as the final stereocenter was installed. A series of oxidations and deprotections completed this asymmetric total synthesis in 47% yield over the next five steps.

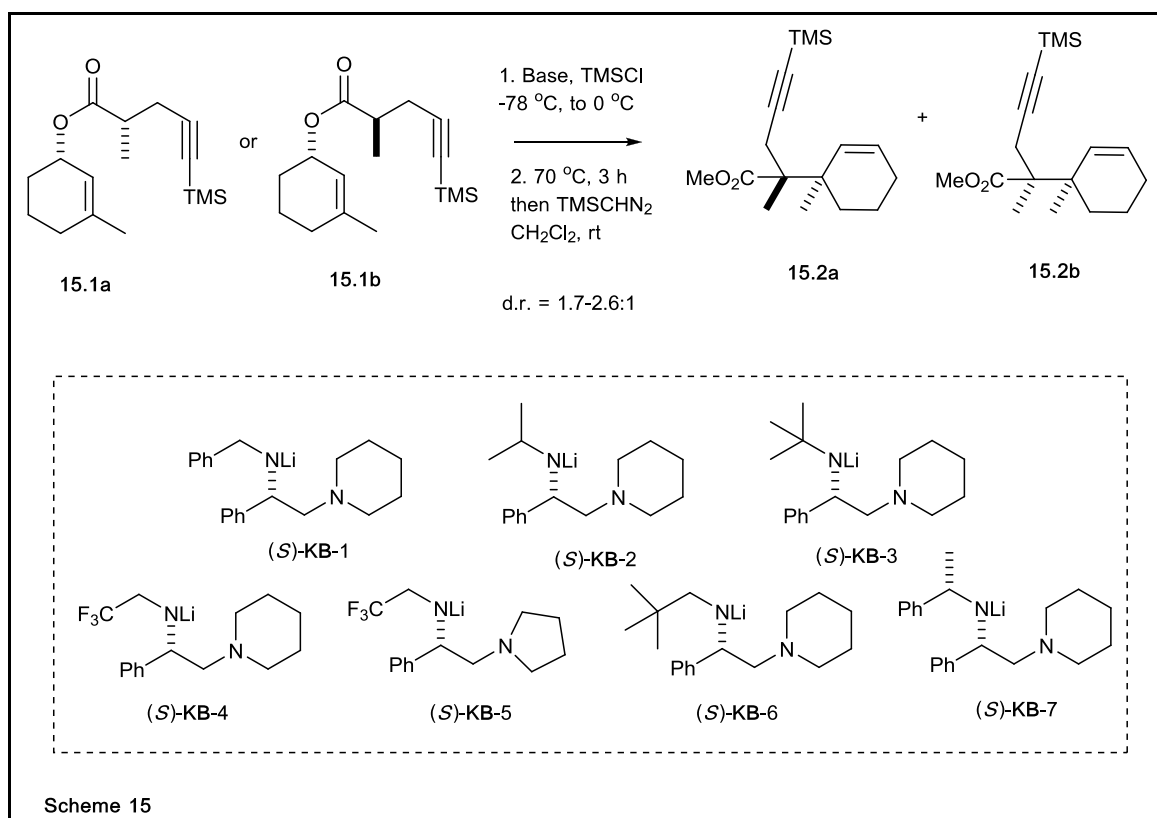


1.4.1.8 (-)-Indoxamycins A - F

This marine derived class of natural products was isolated in 2009 (see insert **A - F** Scheme 14) and introduced a highly congested and unique [5,5,6] tricyclic carbon framework. Among this family, indoxamycins A and F showed growth inhibition of the HT-29 tumor cell line with IC values of 0.59 and 0.31, respectively. The asymmetric total synthesis and structure elucidation of these natural products were completed in 2014 by Ding and coworkers.⁵² The ICR was used to introduce two vicinal quaternary stereocenters at C(2a) and C(7b) from the allylic ester, **14.3**. However, under the conditions shown (scheme 14), the rearrangement produced a modest 1.5:1 diastereoselectivity for the reaction. The two new quaternary carbons of **14.4** were the consequence of a reductive cyclization carried out over the next four steps to give **14.5** as a single diastereomer. The remaining three stereocenters were installed over

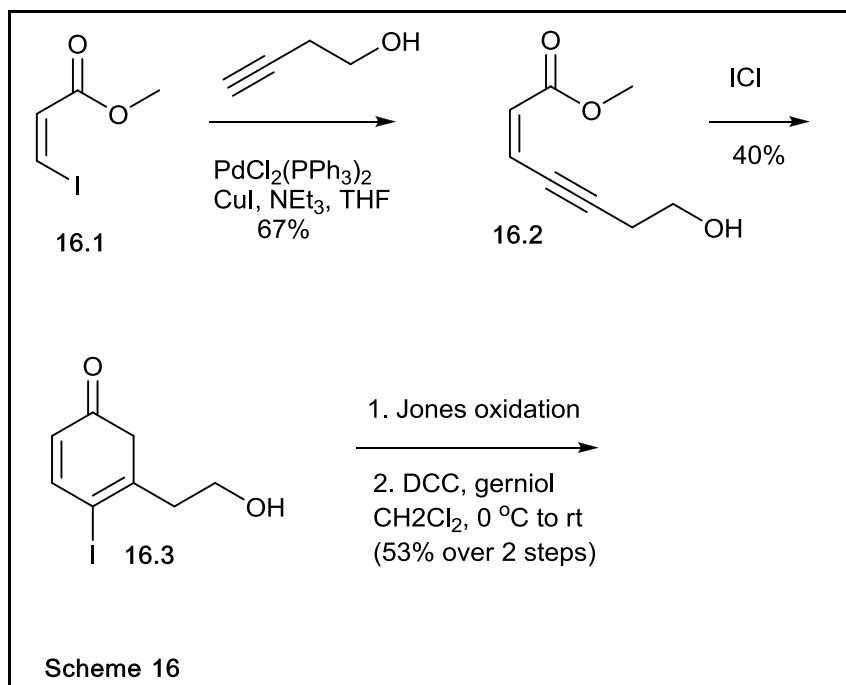


the next 6 steps to complete the highly congested core structure **14.6** of the indoxamycins. Efforts to achieve a complete asymmetric total synthesis included the use of chiral Koga-type bases (see insert Scheme 15) used in the ICR developed by Zakarian and coworkers.⁴⁹ However, only slight improvements in diastereoselectivity (2.6:1) were achieved under these conditions for **15.2a** and **15.2b**. Unlike the excellent acyclic stereocontrol, moderate results in similar cyclic esters were also reported by Zakarian et al.⁵³



1.4.1.9 Transtaganolides C and D

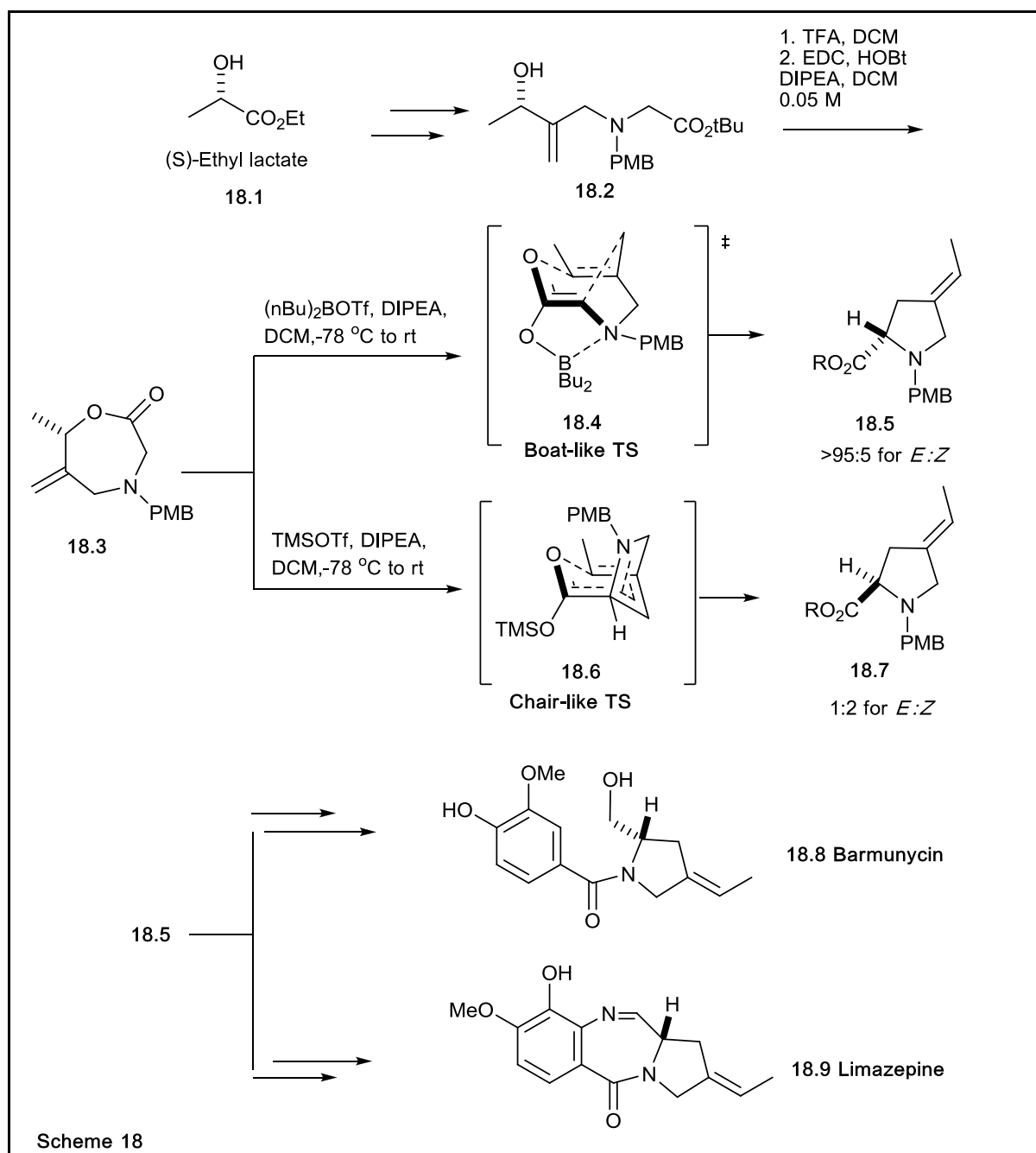
Ongoing synthetic studies by the Stoltz group and others have focused on the total synthesis of the natural products transtaganolides A-D.^{54, 55} Initial biological evaluation suggests that these natural products may inhibit SERCA, SERCA (**sarcoendoplasmic reticulum** Ca²⁺-ATPase), and is considered to be a target for new anticancer drugs. The central theme to these synthetic endeavors has been utilizing an Ireland-Claisen/Diels-Alder cascade reaction. Recent developments by Stoltz and coworkers have established a one-pot synthesis of transtaganolides C and D from an alkynyl pyrone.⁵⁶ The synthesis of the ICR precursor began with coupling (Z)-methyl iodoacrylate **16.1** with commercially available 3-butyne-1-ol to provide methyl ester **16.2** (Scheme 16). Treatment of the ester with ICl gave the desired cyclization product, 2-pyranone **16.3**.



Jones oxidation followed by direct coupling with geraniol provided allyl ester, **17.1** (Scheme 17). Earlier reports by Stoltz et al. used the allyl ester **17.1** at this point as the Ireland-Claisen/Diels-Alder precursor in studies for the synthesis of the transtaganolides, which would then require protection of the free pentenoic acid and coupling with stannylmethoxy acetylide. It was found that coupling to the allyl ester first was much more accessible, and the enyne could be purified on silica gel without hydration or decomposition of the product. This allowed for direct access to the transtaganolides C and D (**17.6** and **17.7**) in a single step from the alkynyl pyrone ester **17.3** in 14% yield and as a 2:1 mixture of diastereomers. Although the ICR product could be isolated, it was found to be susceptible to decomposition. It's postulated that the excess of transtaganolide C (2:1) is due to the preferential formation of the (Z)-enolate (**17.3a**) that places pyrone ring in the pseudo-equatorial position. Lack of complete selectivity in the enolization could be due to the gauche interaction between the pyrone ring and the silyl ether. This one-pot procedure forms three rings, two all carbon quaternary centers and four tertiary stereocenters from a simple monocyclic, achiral allylic ester precursor.

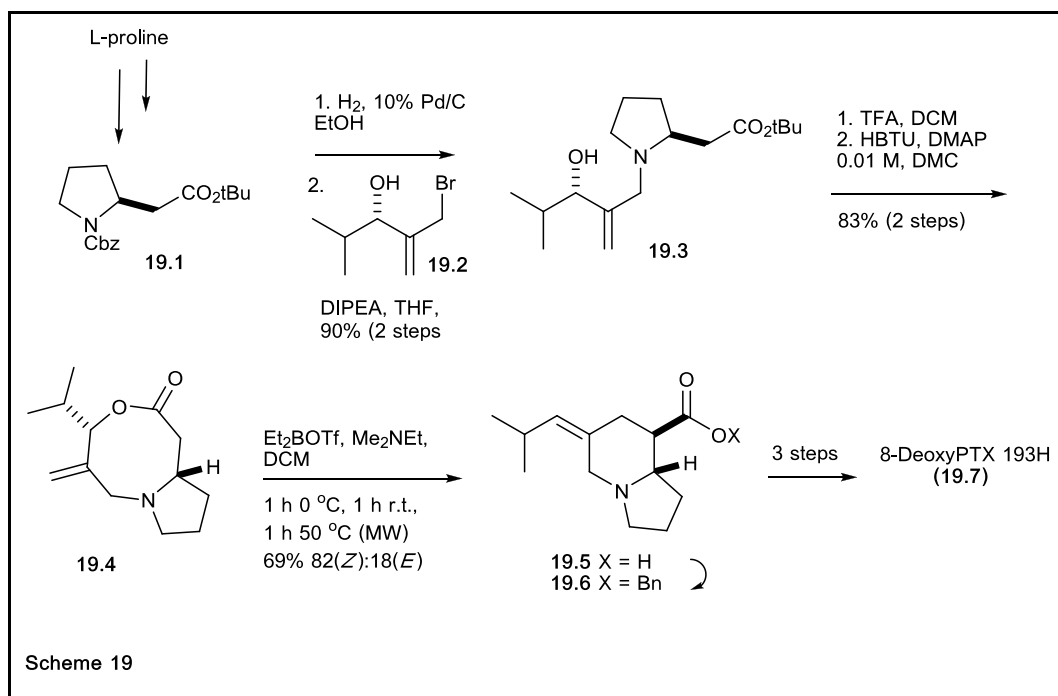
1.4.1.10 Barmumycin and Limazepine E

Both of these natural products were isolated from marine bacteria. Barmumycin was found to be cytotoxic against various human tumor cell lines and limazepine E is from a class of natural products whose antitumor antibiotic properties are due to their ability to covalently bind to the minor groove of DNA. The total synthesis of barmumycin has been reported.⁵⁷ However, this example illustrates the ability to control the geometry of the olefin ((*E*)-isomer) common to both Barmumycin **18.8** and Limazepine **18.9** by the ICR (Scheme 18). The seven membered lactone **18.3** was derived in four steps from (*S*)-ethyl lactate by bromination, alkylation with PMB-protected glycine, deprotection and macrolactonization to give the ICR precursor **18.3**. After screening reagents for the ICR, it was found the dibutylboron triflates showed excellent selectivity (95:%) for desired (*E*)-isomer. In contrast, the silyl triflates tested gave no selectivity and poor yields for the rearrangement. The rationale offered by the authors suggested a boat-like transition state, **18.4** was responsible for the selectivity. In this instance, they invoke coordination by the boron to the lone pair of electrons on the nitrogen atom that stabilizes the boat-like transition state leading to the (*E*)-isomer. In the case of the silyl ketene acetal the coordination does not occur and the transition state is believed to have a slight preference for the boat-like transition state, **18.6**. However, the precedence offered for chelation control with boron enolates offer a chairlike transition state.⁵⁸ A simple analysis of a boat transition state with a model shows an unlikely distance that would allow for chelation to nitrogen. If a boat transition state is responsible for the stereoselectivity, it seems unlikely boron chelation occurs. With this core structure in hand, **18.5**, both Barmumycin **18.8** and limazepine E **18.9** were accessed in three and five steps, respectively.

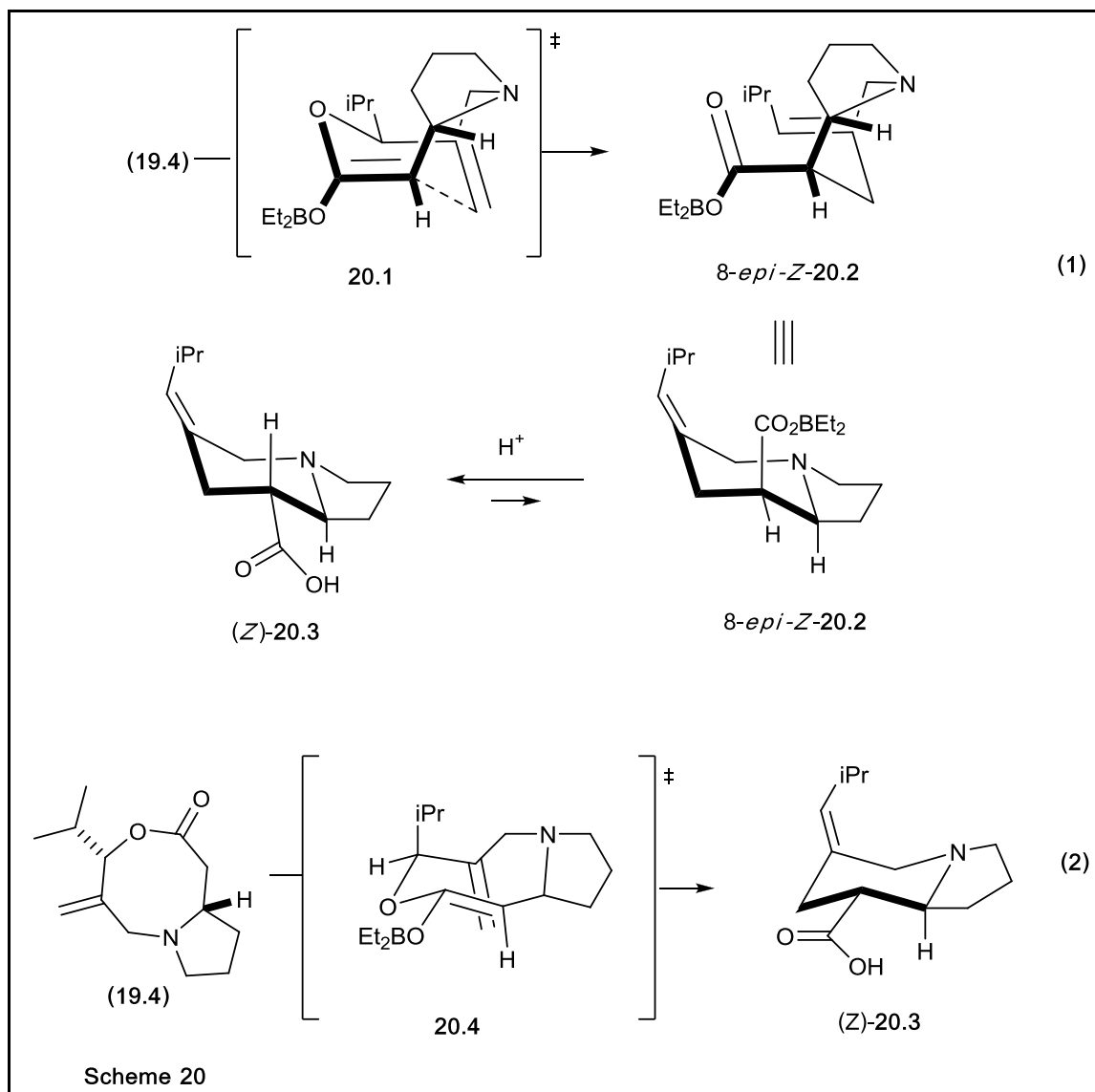


1.4.1.11 Deoxypumiliotoxin 193H

Pumiliotoxins are a class of dendrobatid alkaloids and are compounds primarily found in skin secretions of amphibians. This compound **19.7** (Scheme 19) was found in the extracts of the *Scheloribates azunensis* species of mites. Many of the pumiliotoxins share the common structural features of a stereochemically defined alkylidene substituent at C6 and an octahydroindolizine core. The utility of the boron enolate ICR to control the geometry of the exocyclic Z-double bond and the configuration of the chiral center in the 4-ethylidene proline moiety is demonstrated in this synthesis.⁵⁹ The starting point for this synthesis began with L-proline and was transformed in three steps to the homoproline *tert*-butyl ester **19.1** (Scheme 19). Alkylation to the fragment came after deprotection of the nitrogen by addition of **19.2**, which was derived from L-valine. The eight-membered lactone ring **19.4** was formed by cleavage of the ester group and macrolactonization with the alcohol to form the ICR precursor on a multigram scale. Several combinations of boron triflate and base were surveyed to carry out the ICR and give the desired ester **19.6**. It was found that the less hindered reagents Et₂BOTf and Me₂NEt gave the desired product with good stereoselectivity and yield. After converting to the benzyl ether for column separation, the ester was converted to Deoxypumiliotoxin 193H, **19.7**, in three steps. It was postulated the ICR

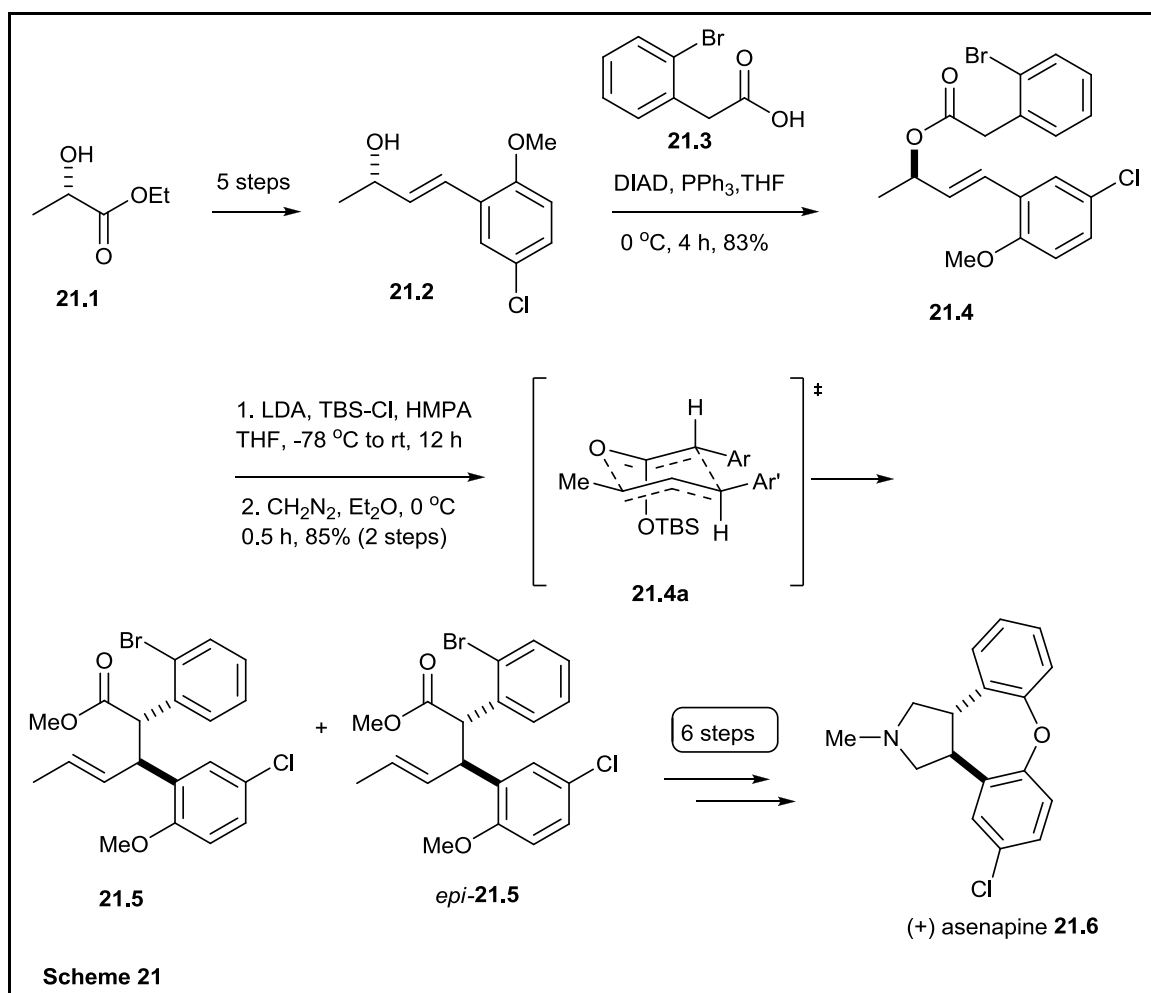


product was a result of the chair-like transition state **20.1** (Scheme 20) that provided 8-*epi*-(*Z*)-**20.2** with the correct double bond geometry, but opposite configuration at the chiral center. Although no precedence was provided, the authors speculated the final product was a consequence of an epimerization upon acidic workup to give the more thermodynamically stable isomer (*Z*)-**20.3** shown in equation 1 (Scheme 20). On the other hand, the transition state suggested in equation 2 could also lead to the desired (*Z*)-isomer without epimerization of the carboxylic acid. In any event, after the benzyl protecting group was added the stereochemistry was assigned by 2D and NOE experiments.



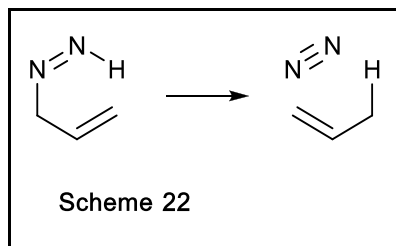
1.4.1.12 (+)-Asenapine

(±)-Asenapine is an FDA approved drug sold under the trade names Saphris and Sycrest. It is used for the treatment of schizophrenia and acute mania associated with bipolar disorder. The chemical structure of asenapine (Scheme 21) includes a tetracyclic framework with an N-methylpyrrolidine ring fused at the 3 and 4 positions. The 3 and 4 positions are substituted with a chlorophenyl and phenyl ether in a *trans*-geometry. The (+)-isomer has been reported to have a higher plasma concentration even though the FDA has approved the racemic version of the drug. The basis of the synthesis was to make one of the desired isomers and uncover a route to all four stereoisomers from an appropriate starting material that employs the same synthetic sequence.⁶⁰ The synthesis begins with conversion of the commercially available (S)-ethyl lactate **21.1** to the allylic alcohol **21.2** in five synthetic steps (scheme 21). The Ireland Claisen precursor was made using the Mitsunobu reaction between the allylic alcohol and the *o*-bromophenylactic acid **21.3** in the presence of DIAD and PPh₃ to give the ester **21.4** in 83% yield. The ICR was achieved with the addition of LDA, TBSCl and HMPA followed by esterification to give a mixture of diastereomers **21.5** and epi-**21.5**. The additive HMPA is known to stabilize the (Z)-transition state, **21.4a**, to furnish the anti-product. The diastereomers were separated by column chromatography, in a 9:1 ratio and 85% yield. The asymmetric synthesis of (+)-asenapine **21.6** was completed in 13% overall yield for the next six steps with 93.8% ee.



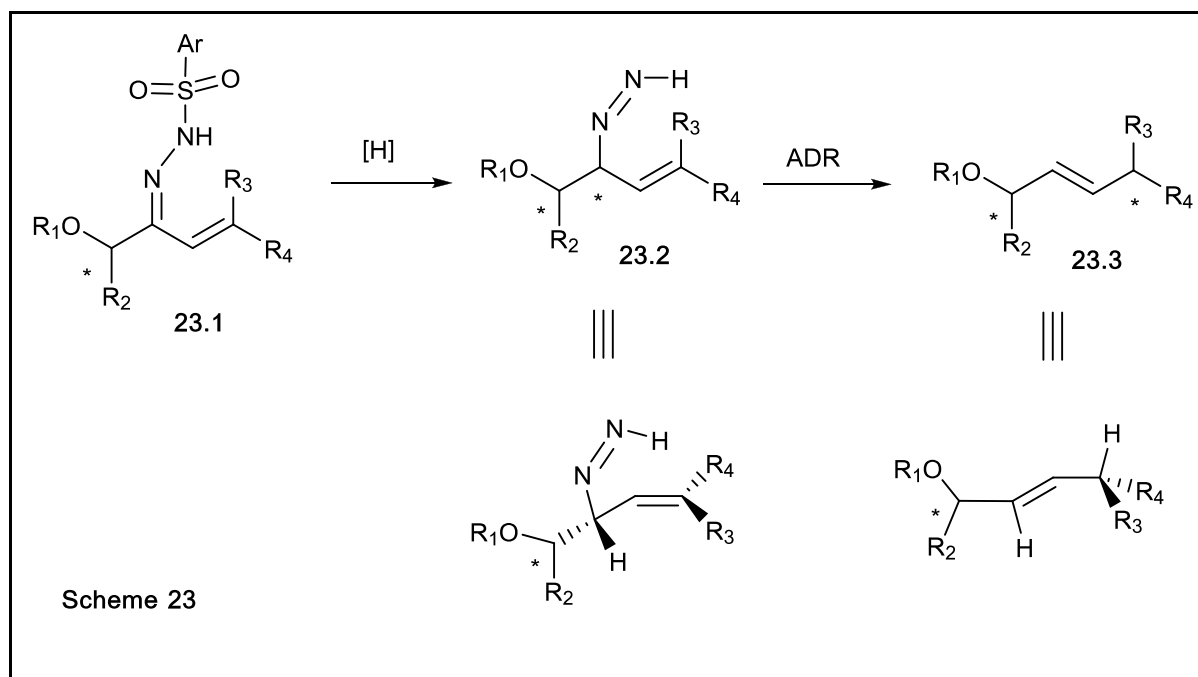
1.5 Allylic diazene rearrangement

The parent allylic diazene rearrangement (ADR) is the retro-ene reaction of *cis*-1-diazo-2-propene to produce propene and molecular nitrogen (Scheme 22).⁶¹



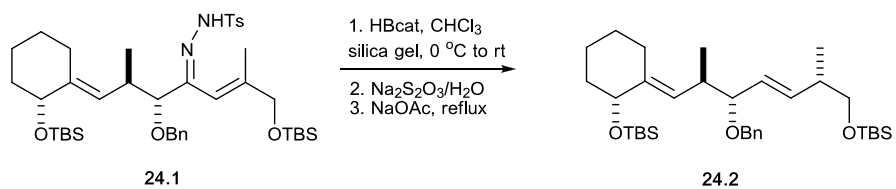
If the terminal carbon of the alkene of the allylic diazene is prochiral, a stereocenter can be installed via the ADR. This reaction has been applied to many cyclic systems to establish an sp^3 stereocenter.⁶²

However, this had not been applied to acyclic systems until the McIntosh group reported the diastereoselective reduction of an α, β -unsaturated tosylhydrazone under the influence of an α -alkoxy stereocenter (Scheme 23).⁶³

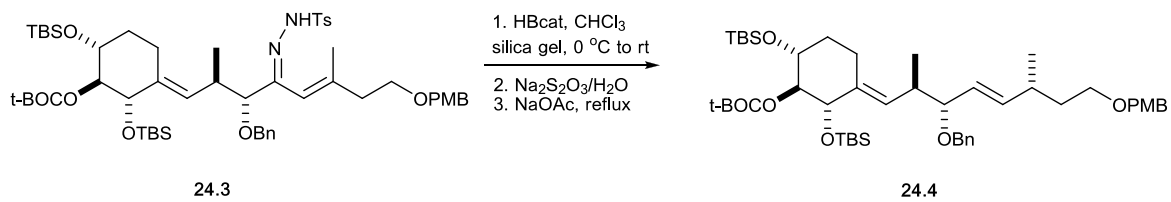


McIntosh et al. also applied this methodology to the model system¹⁶ and racemic synthesis¹⁷ of antascomycin B (Scheme 24).

model synthesis



racemic synthesis

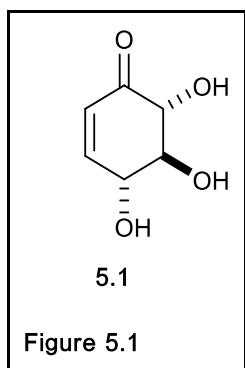


Scheme 24

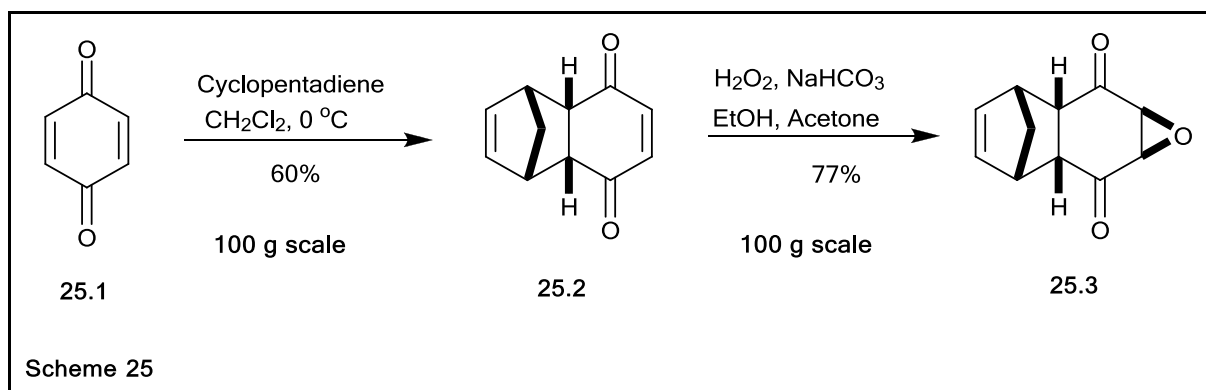
Chapter 2

2.1 Synthesis toward asymmetric transfer hydrogenation

Ongoing efforts in our lab have been devoted to the synthesis of antascomicin B.^{16, 17, 22} Our most recently published synthesis of the C21-C34 fragment was limited by the lack of an efficient asymmetric route to one of the key early intermediates, trihydroxy cyclohexenone **5.1**, Figure 5.¹⁷ At the time, the asymmetric routes available to make trihydroxy enone **5.1** included several steps, high enzyme loading, long reaction times and limited scale.⁶⁴⁻⁶⁶

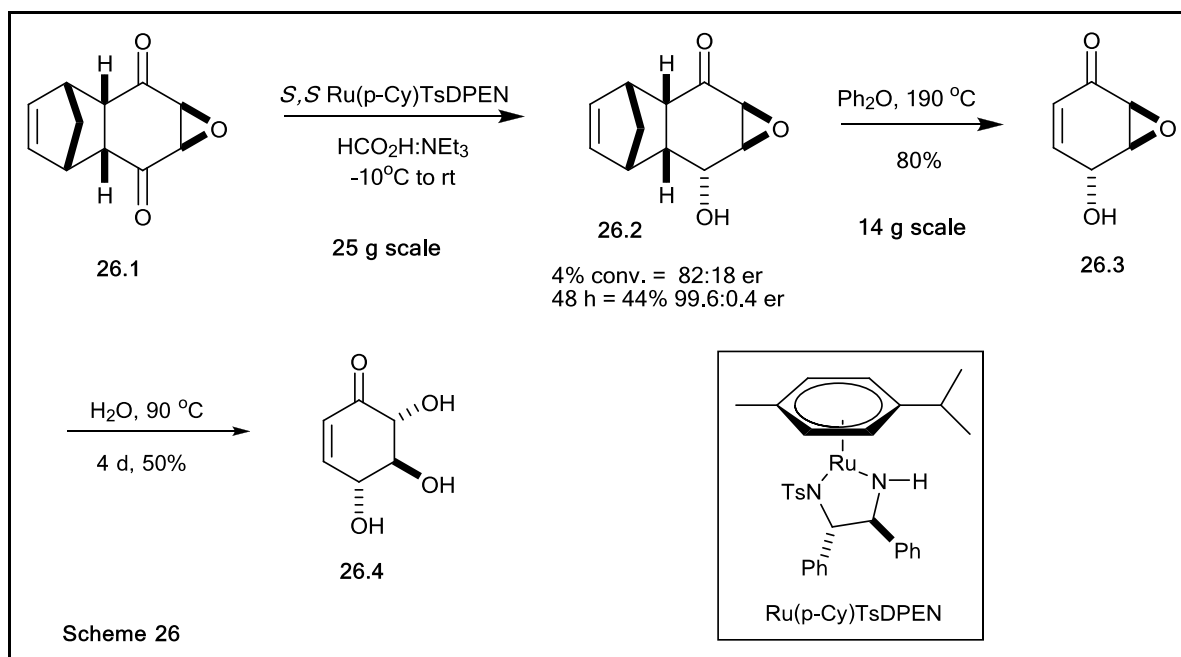


With that in mind, our group set out to develop an efficient asymmetric synthesis to mimic the racemic route to the trihydroxy cyclohexenone.^{25, 26} Our 2011 publication²² for the asymmetric synthesis of an early intermediate allowed us to apply the methodology of asymmetric transfer hydrogenation to the asymmetric synthesis of the C21-C34 fragment of antascomicin B. Our asymmetric synthesis began with the large scale Diels-Alder reaction between 1,4-benzoquinone **25.1** and freshly cracked cyclopentadiene (Scheme 25). The *meso* diketone product was then subjected to epoxidation conditions on a large scale to give the epoxy diketone **25.2**. The ability to execute this sequence on a large scale (100 grams) without suffering reduced yields allowed for the development of the large scale (25 grams) asymmetric transfer hydrogenation reaction that had been developed on a smaller scale in our lab.



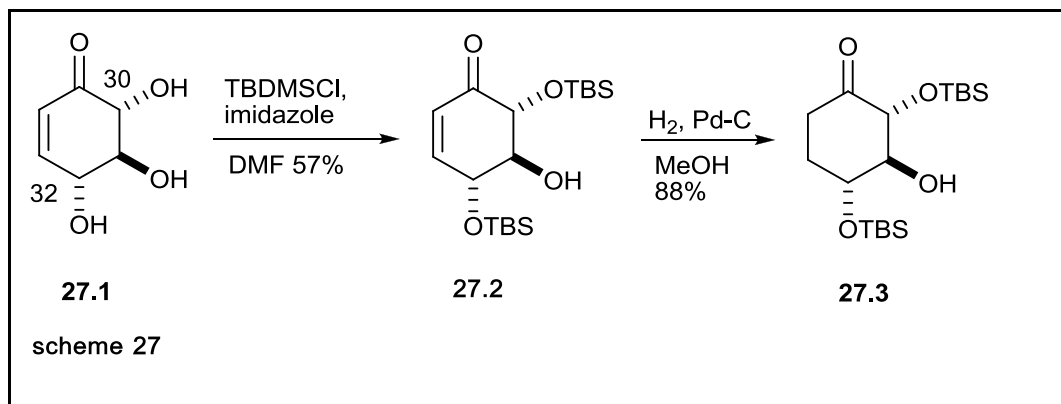
2.2 Application of asymmetric transfer hydrogenation

Using Noyori's Ru(*p*-cymene)[(S,S)-TsDPEN] catalyst and a 1:1 mixture of formic acid and triethylamine we converted epoxy diketone **26.1** to the epoxy keto alcohol **26.2** in moderate yield (44%), but high enantiopurity (99.6:0.4) (Scheme 26). The intrinsic enantioselectivity of the reaction was 82:18 *er* at 4% conversion of the starting material under optimized conditions, and a 93:7 *er* on a 60 mmol scale could also be achieved in 16 hours with 85% yields. Longer reaction time (48 hours) resulted in a still greater kinetic resolution of the minor enantiomer and increased the *er* to 99.6:.4, albeit with diminished yields. From there, we implemented Taylor's variant²⁵ of the Lubineau procedure²⁵ for the *retro* Diels-Alder to free epoxyquinol **26.3** in 80% yield on a 14 gram scale. This step was also optimized to decrease the amount of diphenyl ether by half needed for the reaction compared to our earlier reports. The ring opening of the epoxide was carried out in water at 90 °C and gave the trihydroxy cyclohexenone **26.4** in 44 - 50% yields consistently.⁶⁷

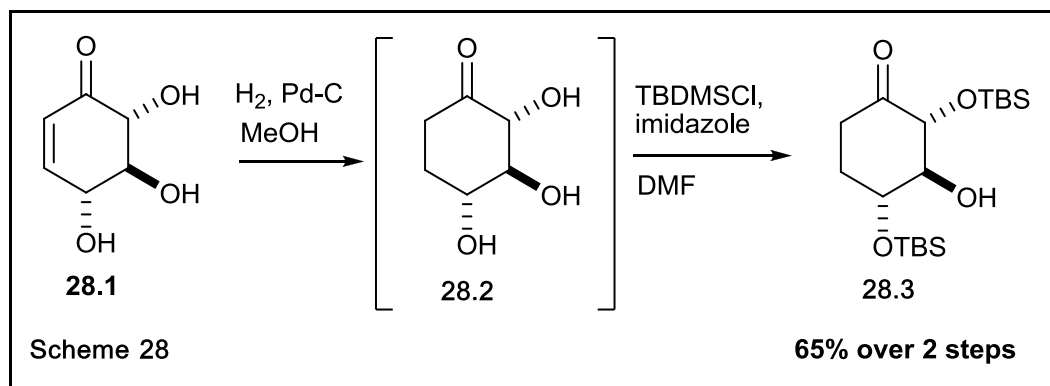


2.3 Synthesis toward Ireland Claisen rearrangement

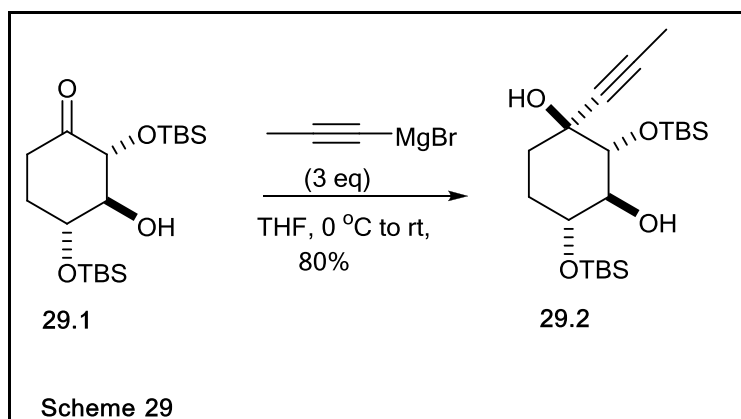
With an efficient asymmetric route to the trihydroxy cyclohexenone established, we turned our attention to the Ireland-Claisen rearrangement (ICR). Following the course from our racemic synthesis of the C21-C34 fragment, we next set out to protect the C30 and C32 hydroxyl groups of the triol to give **27.2**, followed by alkene hydrogenation to give **27.3** (Scheme 27). After attempts to repeat this sequence on a multi-gram scale, we were met with diminished yields compared with the racemic synthesis



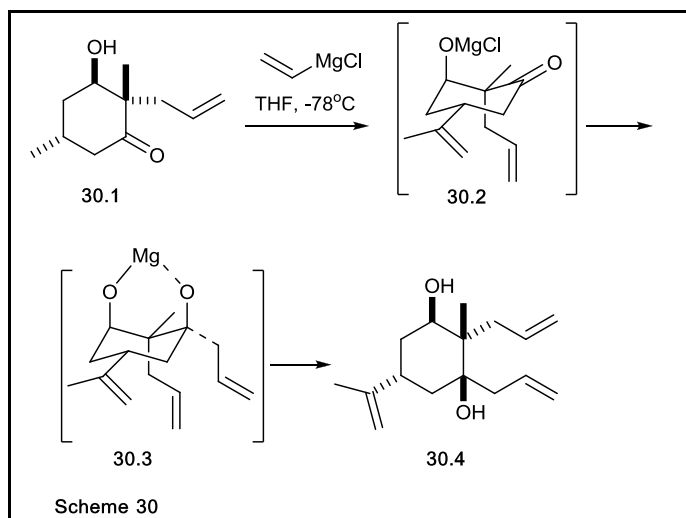
(50% vs. 59% over two steps). It was found that by reversing the hydrogenation and protection steps, we were able to improve the yield to 65% over the two steps without purification of the trihydroxy cyclohexanone intermediate (scheme 28). Doing so, we eliminated a purification step and improved the overall yield by about 15%.



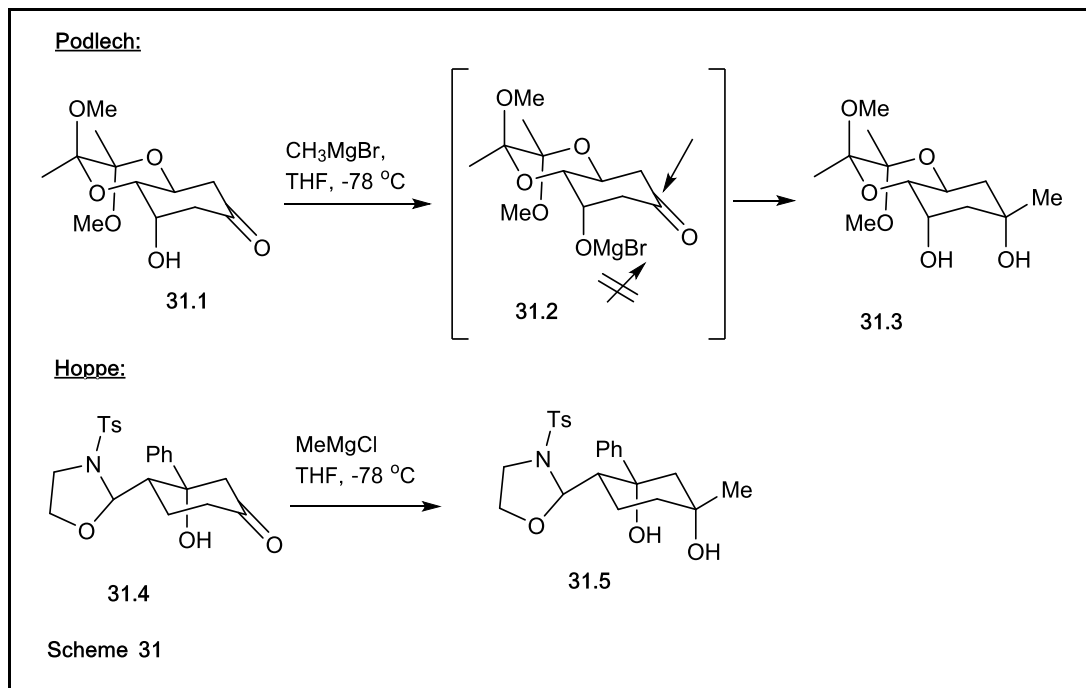
The addition of the propynyl Grignard to the β -hydroxy ketone gave compound **29.2** in 80% yield (Scheme 29). Examples of highly diastereoselective reactions with organometallic nucleophiles to cyclohexanones bearing unprotected β -hydroxyl groups have been reported.⁶⁸⁻⁷¹



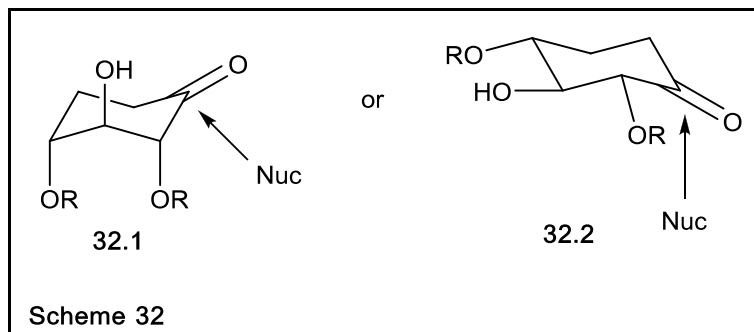
Mehta et al. made a 1,3-*syn* diol by allyl Grignard addition to a substituted cyclohexanone and suggested chelation by the magnesium, β -hydroxyl and carbonyl oxygen, **30.3** (Scheme 30).⁷²



Other examples from the literature showed selectivity for the *syn*-diol, but were substituted in such a way that the β -hydroxy group was axial and the larger groups were in the equatorial position (Scheme 31).^{69, 73} In the Podlech example, they suggested attack from the bottom did not occur due to steric hindrance

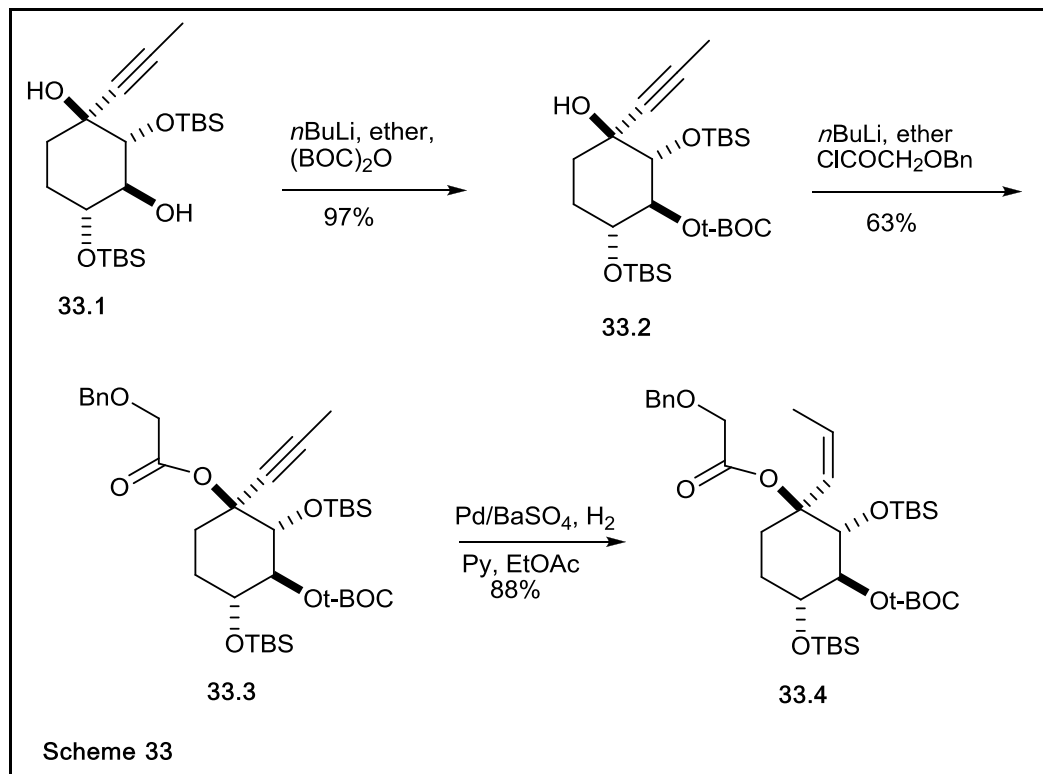


and they did not invoke chelation by the magnesium. During the racemic synthesis of the C21-C34 fragment it was found that protection of the β -hydroxyl group was unselective. Indicating the all equatorial configuration is unselective. In our case the unprotected β -hydroxyl was selective to afford the *syn*-diol, presumably through an all axial conformation (Scheme 32).



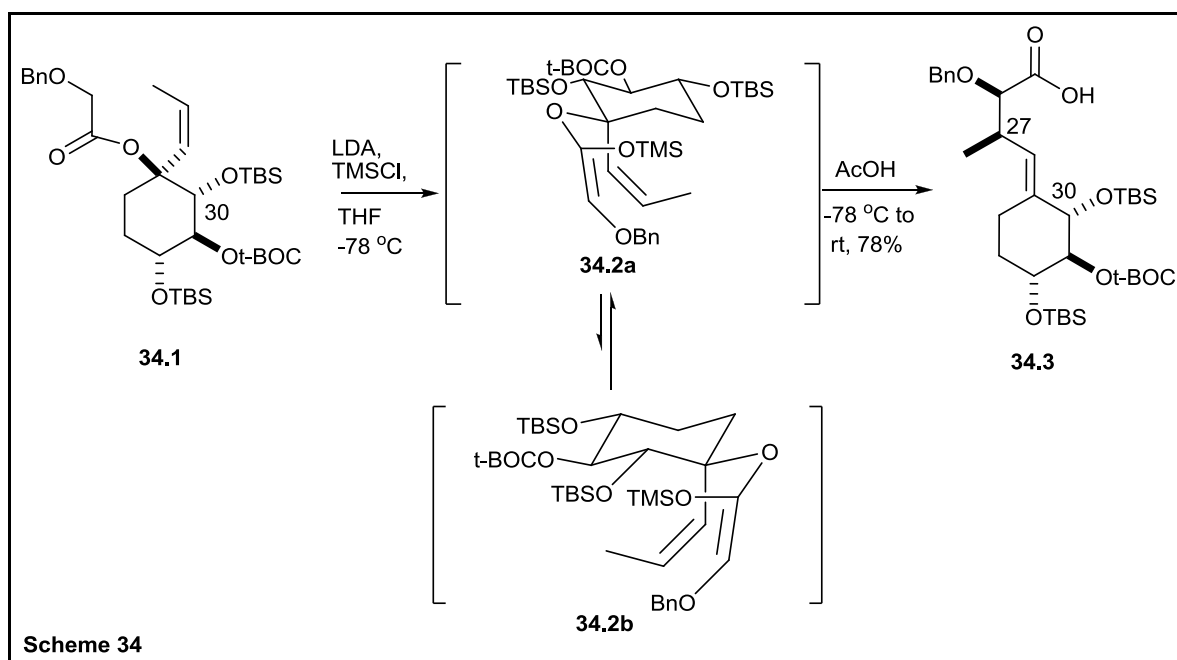
Regioselective protection of the secondary alcohol with *t*-Bu carbonate followed the Grignard addition in high yield to give **33.2** (Scheme 33) and allowed us to differentiate the protecting groups around the cyclohexyl ring for later manipulation of selective deprotection and directed hydrogenation. This was

followed by acylation of the highly congested tertiary alcohol in a similar fashion with *n*-BuLi to make propargyl ester **33.3**. Partial reduction of the triple bond to the (*Z*)-alkene was carried out using Pd/BaSO₄ to give the allylic ester **33.4**.



2.4 Application of Ireland Claisen rearrangement

The Ireland-Claisen rearrangement (Scheme 34) gave the desired anti-configuration at the C26-C27 carbons (extended conformation) of the pentenoic acid product and is believed to proceed through the chair like transition state **34.2a**. This transition state is believed to be favored because the C30 carbon bearing the protected α -hydroxyl adjacent to the quaternary carbon is in the pseudoequatorial position and avoids the 1,3-diaxial interaction with the silyl ketene acetal.⁷⁴ After the addition of acetic acid, used to protonate any unused base and prevent enolization of the product, **34.3** was produced in good yield as a single diastereomer based on ^1H NMR and ^{13}C NMR analysis.

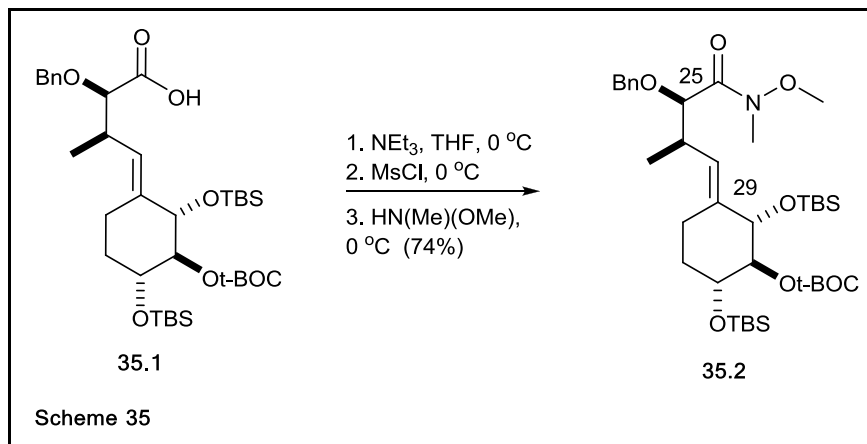


Scheme 34

2.5 Synthesis toward allylic diazene rearrangement

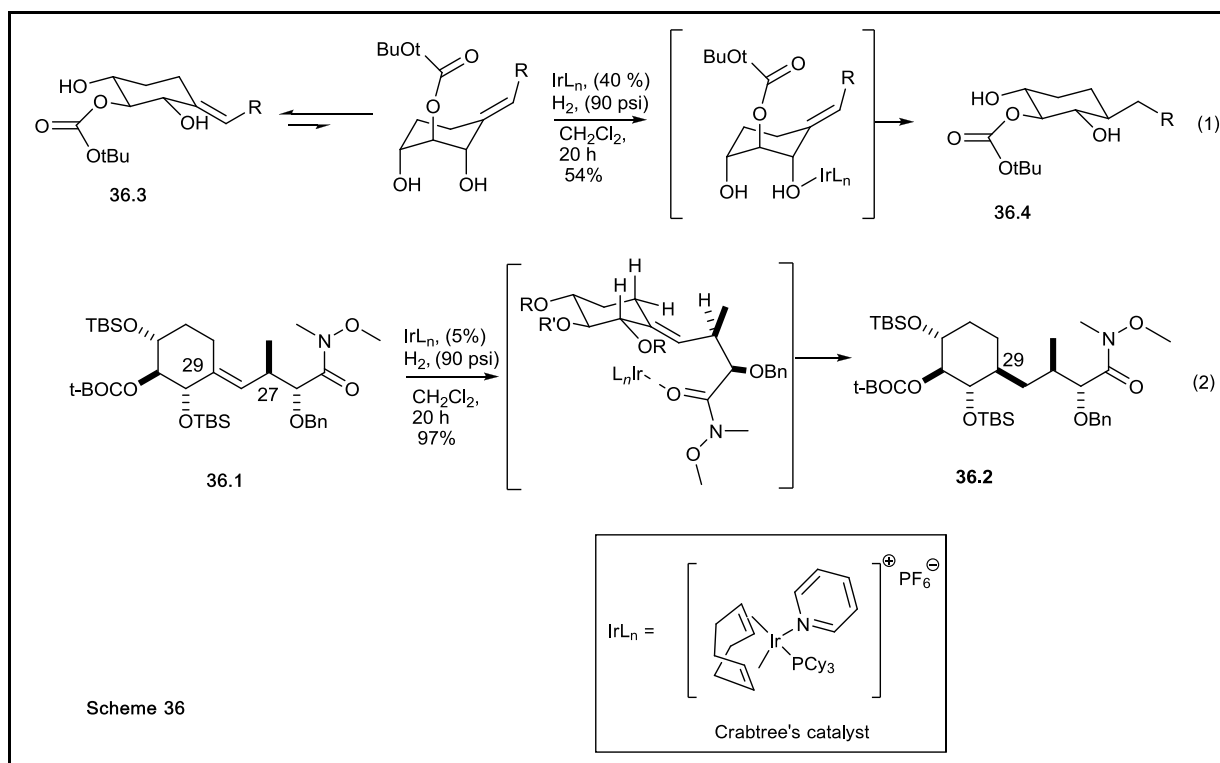
2.5.1 Initial approach

The next step in our asymmetric synthesis toward the allylic diazene rearrangement was to convert the acid product **35.1** to the Weinreb amide **35.2** (Scheme 35).

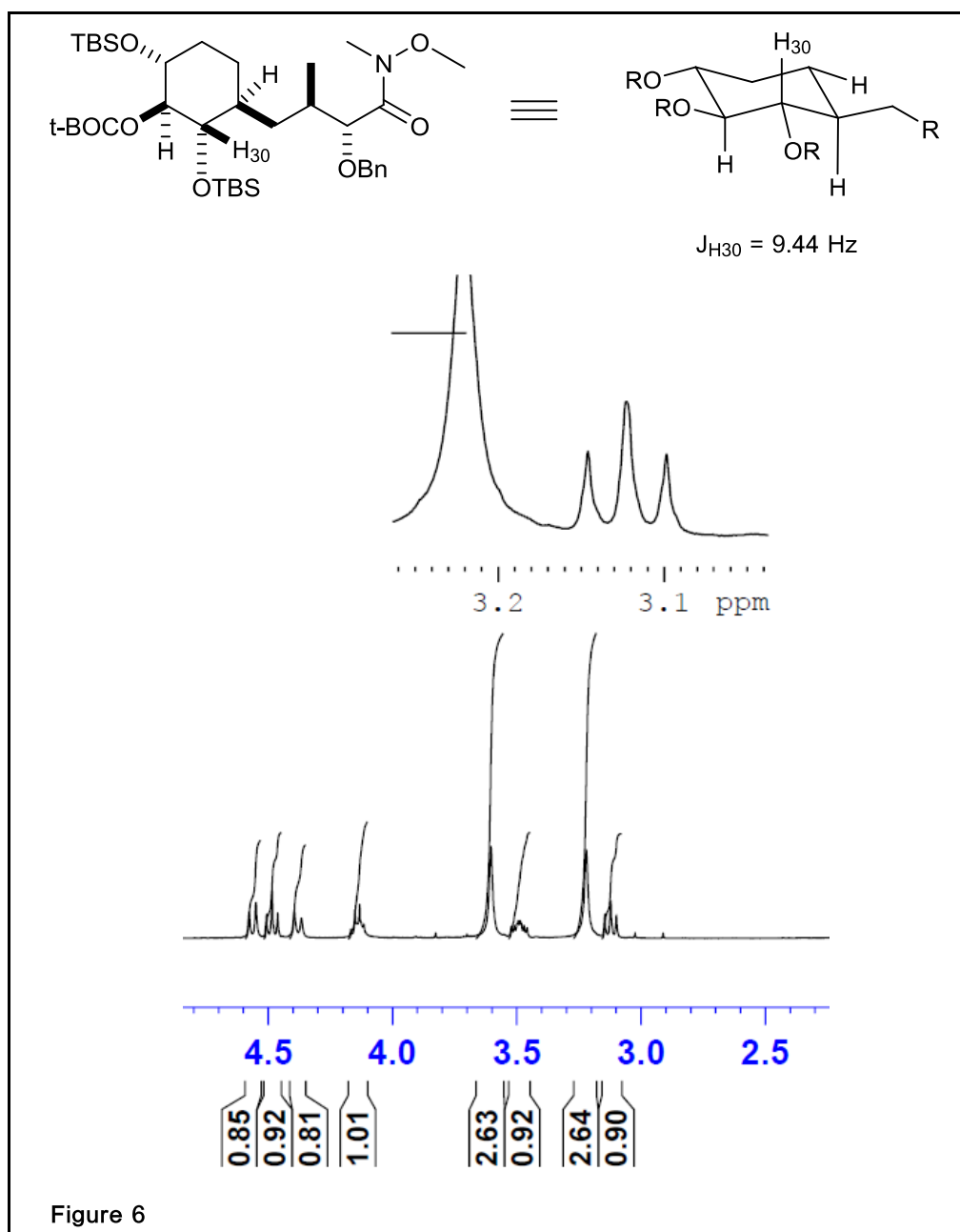


In the racemic synthesis of the C21-C34 fragment we used directed hydrogenation after homologation of the remaining C21 – C24 carbons (Scheme 36, equation 1). The problems we encountered were, 1) the yield for the reduction in the racemic synthesis was a modest 54%. 2) The racemic synthesis required an inefficiently high 40% catalyst loading, And 3) tedious protection/deprotection steps were required.

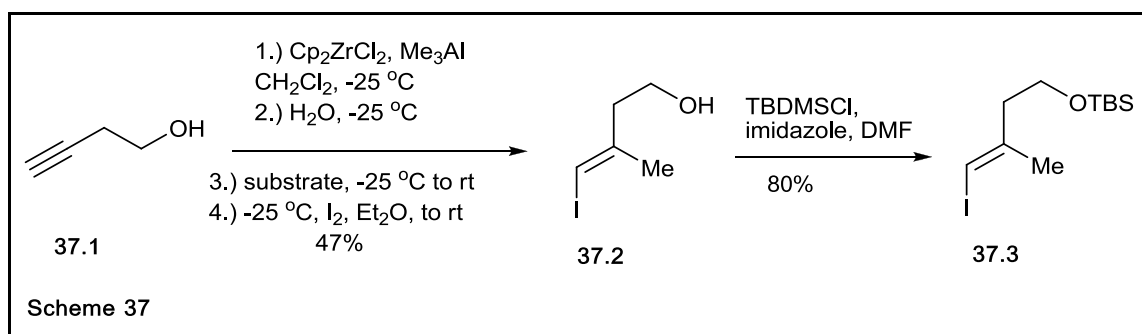
Differing from the racemic synthesis however, in our asymmetric synthesis we decided to exploit the amide functionality of the Weinreb amide for directed hydrogenation using Crabtree's catalyst.⁷⁵ It has been shown that amides are good directing groups for homogeneous hydrogenation reactions.⁷⁶ We believed the selectivity of the hydrogenation would be controlled by the stereocenter at C27, directing the coordination of the iridium catalyst to the desired face to avoid allylic 1,3 strain (Scheme 36, equation 2). By executing the reduction at this stage we gained several advantages, 1) we improved the yield to 97% for the hydrogenation. 2) we reduced the catalyst loading to 5%, and 3) we eliminated the need for the tedious protection/deprotection sequence. In order to confirm the selectivity of the directed hydrogenation



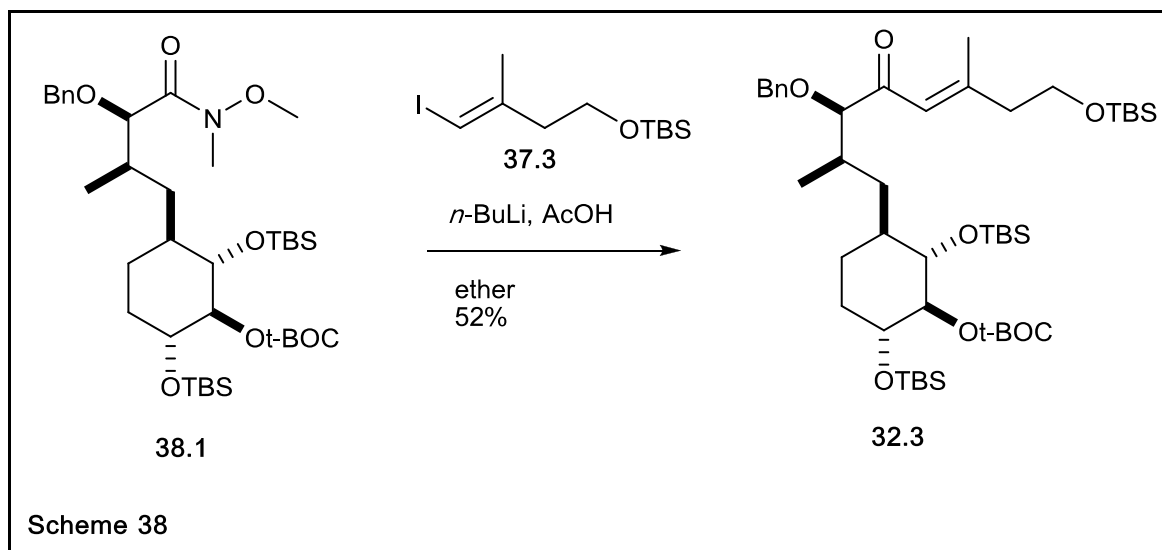
reaction, we identified the proton of C30 as a diagnostic peak. The directed hydrogenation reaction using Crabtree's catalyst gave a single product in excellent yield. Evidence for the expected *trans*-diaxial coupling ($J = 9.44$) between the C29-C31 protons were found at 3.1 ppm by ^1H NMR (Figure 6).



Next, with the four stereocenters set around the cyclohexyl moiety and the desired *anti*-relationship between the C26-C27 carbon substituents, we turned our attention to homologation of the remaining carbons for the fragment. The additional carbons would come by way of the synthesis described by Hall et al. (Scheme 37).⁴⁴ Starting from commercially available 3-buten-1-ol (**37.1**), carbometalation

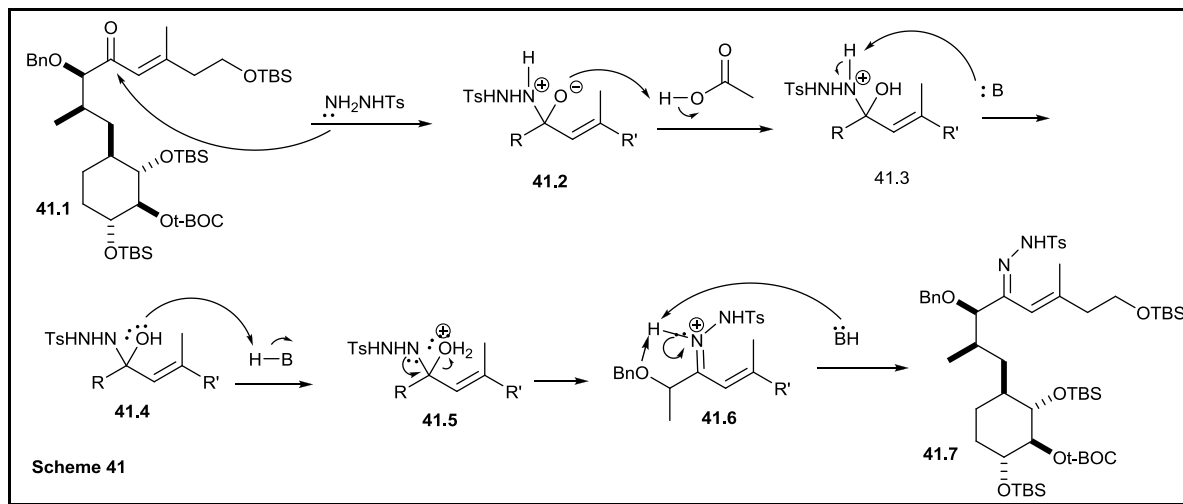


followed by iodination gave (*E*)-4-iodo-3-methylbut-3-en-1-ol **37.2** as a single product. Silylation of the hydroxyl group was then carried out with imidazole in DMF to give the silyl ether **37.3** in good yield. The vinyl iodide compound **37.3** was then converted to the organolithium and added to Weinreb amide **38.1** (Scheme 38).

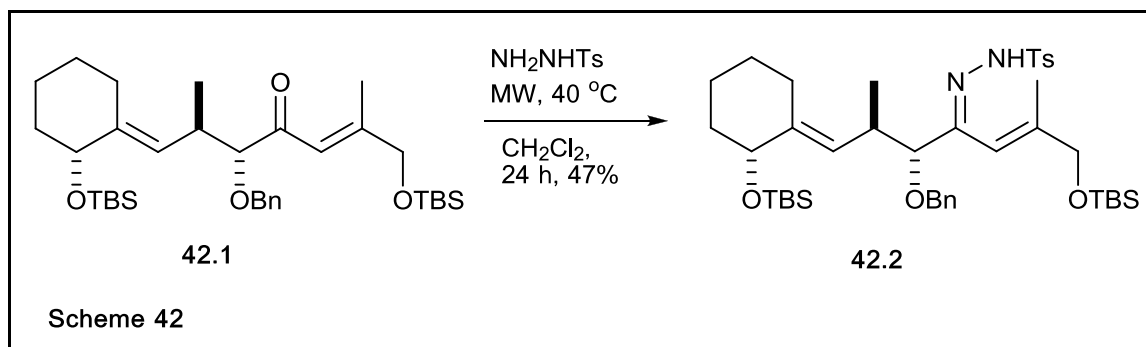


Our task following homologation was intended to lead to the 1,3-reductive transposition reaction by way of the allylic diazene rearrangement in order to set the remote stereocenter of the methyl group of C23 by our previously reported methodology. Initially, we attempted the conditions (NH_2NHTs , HOAc , CH_2Cl_2 , rt) used for the hydrazone formation in the racemic synthesis for the C21-C34 fragment of antascomycin B (Scheme 39).¹⁷

catalyzed reaction would likely follow a similar path (Scheme 41). One possible mechanism starts with nucleophilic attack of hydrazine to the carbonyl carbon of substrate **40.1** to form the tetrahedral zwitterionic intermediate **40.2**. Proton transfer leads to the carbinolamine intermediate **41.4**. Dehydration leads to **41.6**, which is stabilized by hydrogen bonding to the neighboring oxygen of the benzyl ether. Deprotonation leads to the (*E*)-hydrazone, **41.7**. However, no hydrazone formation occurred under these conditions in our experiments for the asymmetric synthesis.

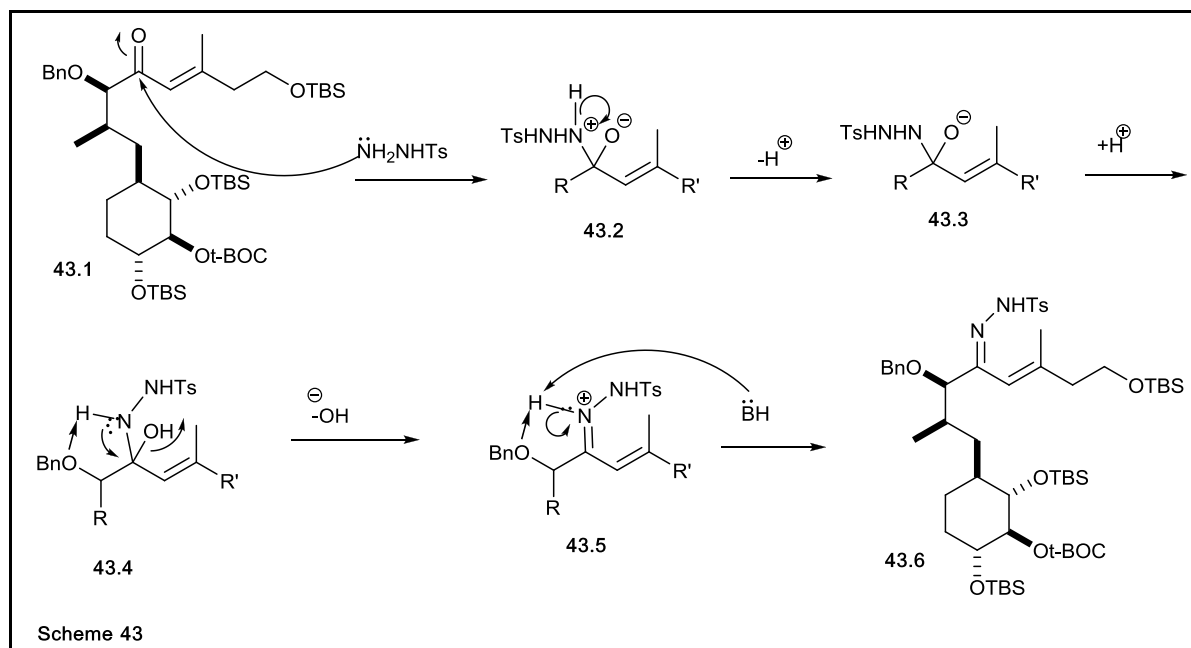


Next, we attempted the formation of the tosyl hydrazone using microwave radiation without the use of any catalyst. This method was used with moderate success (47% yield) to form exclusively the *E*-hydrazone in our model study (scheme 42).¹⁶



The mechanism we expected the microwave reaction would follow is outlined in Scheme 43. Under neutral conditions the nucleophilic hydrazine attacks the carbonyl carbon of substrate **43.1** to form the zwitterionic tetrahedral intermediate **43.2**. Proton transfer leads to the hemiacetal **43.4** which is stabilized by hydrogen bonding to the neighboring oxygen of the benzyl ether. The loss of hydroxide in **43.4** is

believed to be the rate-determining step under these conditions.⁷⁷ Hydrazone formation is preceded by deprotonation which leads to the (*E*)-hydrazone, **43.6**.



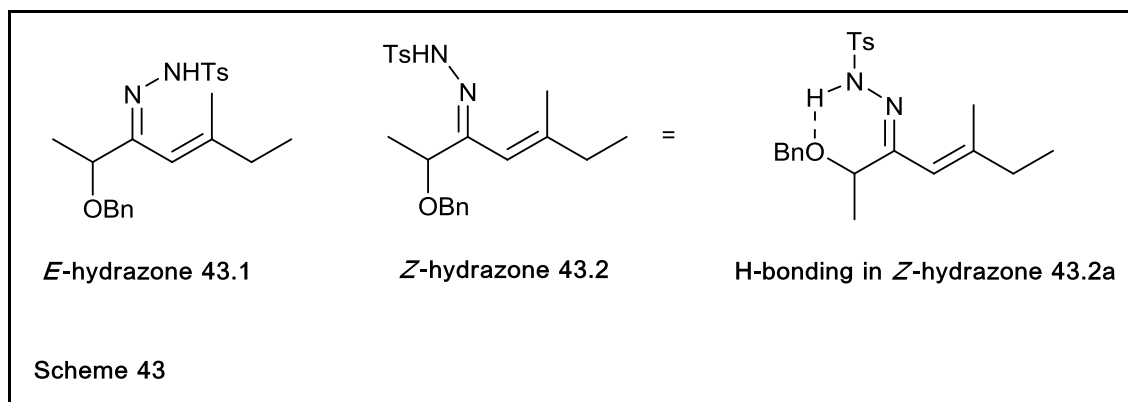
We surveyed reaction conditions for the formation of the hydrazone from the enone (Table 1). The CW pulse variable refers to a constant power and temperature throughout the experiment, similar to a conventional domestic microwave oven. Dynamic pulse refers to a maximum temperature, maximum power, and maximum pressure the reaction will reach in short pulses of microwave energy.⁷⁹ Once one of the maximum parameters is attained, the system will cool and vent, and then repeat the cycle

Entry	TsNHNH ₂ (equiv)	Power (watts)	Time (h)	Temp (°C)	Pressure (psi)	Pulse	result
1	2	100	16	40	105	CW	rsm
2	2	200	25	100	110	CW	Trace
3	2	300	8	105	110	CW	rsm
4	2	125	16	60	247	dynamic	rsm
5	4	250	15	250	247	dynamic	rsm
6	4	250	15	250	247	dynamic	55% rsm
7	4	250	15	250	247	dynamic	0
8	8	50	20	100	247	CW	0

Table 1: Microwave reaction conditions. *indicates addition of 4 Å molecular sieves **indicates addition of 0.5 equiv. AcOH and addition of 4 Å molecular sieves.

when a minimum parameter is attained. The dynamic pulse variable was explored based on a rate enhancement found by Ley et al. on the Claisen rearrangement of a propargylic enol ether.⁸⁰ The dynamic pulse effect was studied in more detail by Stiegman et al. and they compared conventional

thermal heating to dynamic pulse heating by microwave. In at least one instance, thermal conditions were ineffective while microwave heating was successful.⁷⁹ However, the authors were unable to determine the source of the microwave rate enhancement. Despite the precedence from our model study and attempts to vary reaction conditions, we were unable to form the hydrazone using microwave irradiation. Various attempts at microwave heating seemed to have no effect on the hydrazone formation (Table 1, entries 1-5). The ¹H NMR of the crude reaction mixture of entry 2 showed evidence of the sulfonamide diagnostic proton at ca. 8.0 ppm. The analysis of differentiating the NH proton was based on earlier work by our group in determining the E/Z geometry of α,β -unsaturated trisubstituted Hydrazones (Scheme 43). It was found the sulfonamide proton of *E*-hydrazone **43.1** is found at ca. 8 ppm



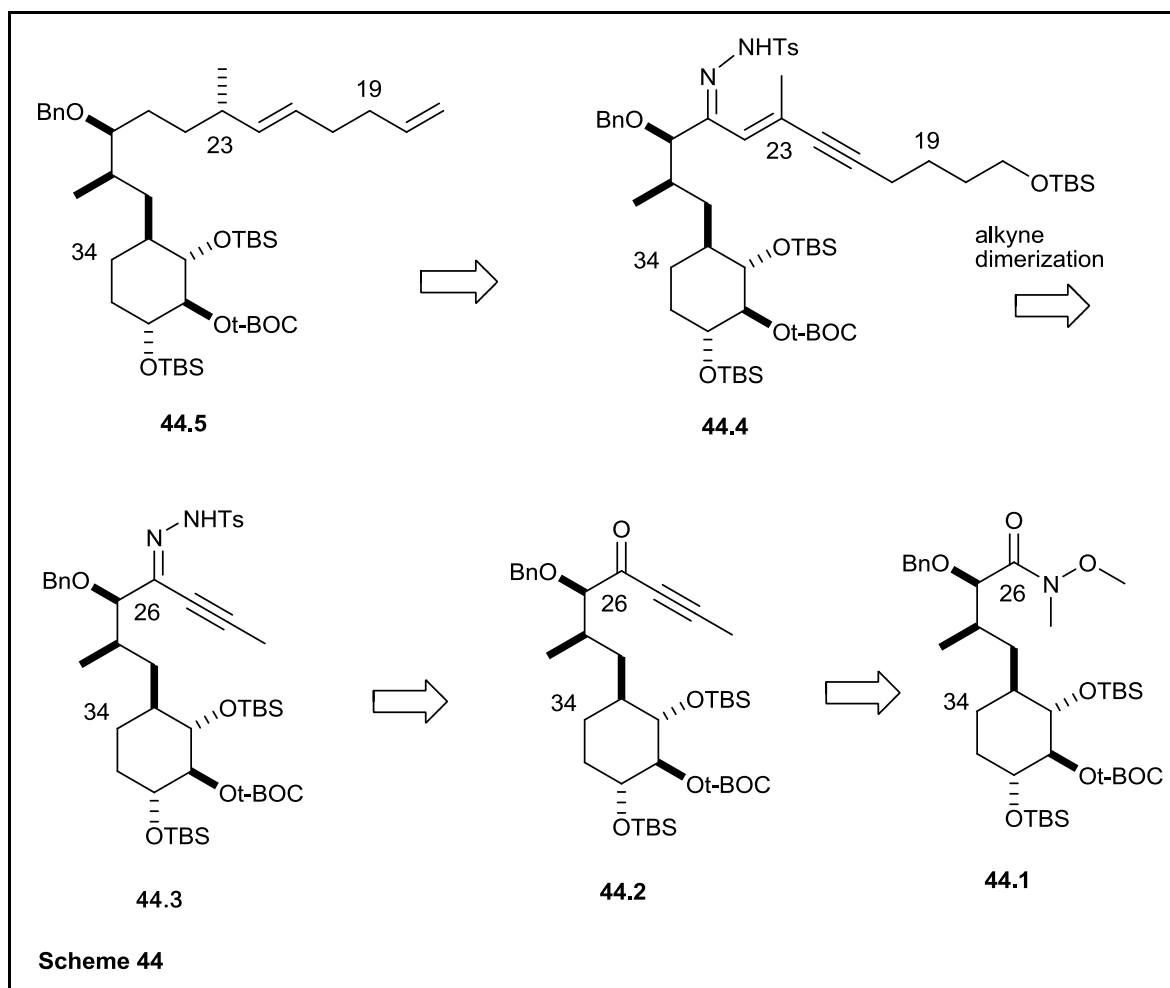
while that of *Z*-hydrazone **43.2** is at ca. 10 ppm due to the hydrogen bonding in the *Z*-hydrazone. However, flash column chromatography produced no measurable amount of the product. The addition of powdered molecular sieves in anhydrous solvent, with or without an acid catalyst also had no effect on the reaction outcome (entries 5-6). An eight-fold excess of tosyl hydrazine for 20 hours also did not form any trace of the desired product. Although the cause for our inability to form the tosyl hydrazone product from the enone was not clear, we were aware the tosyl hydrazone was also inaccessible with the exocyclic double bond reduced (C28-C29) in the model synthesis as well. Although no molecular modeling or calculations were explored, the reason we were unable to form the tosyl hydrazone product when the exocyclic double was reduced is presumably due to an unfavorable conformation. This rationale is due to the fact we were able to form the tosyl hydrazone in good yield for the racemic synthesis, with the exocyclic double in bond intact.¹⁷ The remote distance of the C28 – C29 double bond to the C25 carbonyl carbon does not suggest electronic influence. So, only speculation by the author

could suggest the added degree of rotational freedom of the aliphatic side chain could orient the carbonyl carbon in such a way it is blocked from nucleophilic attack in this instance.

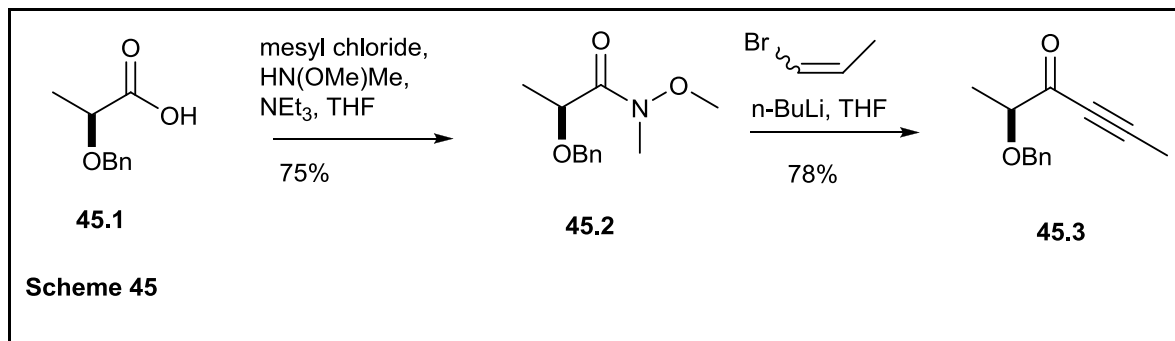
2.5.2 Second generation approach

After unsuccessful attempts at hydrazone formation, we pursued alternative approaches.

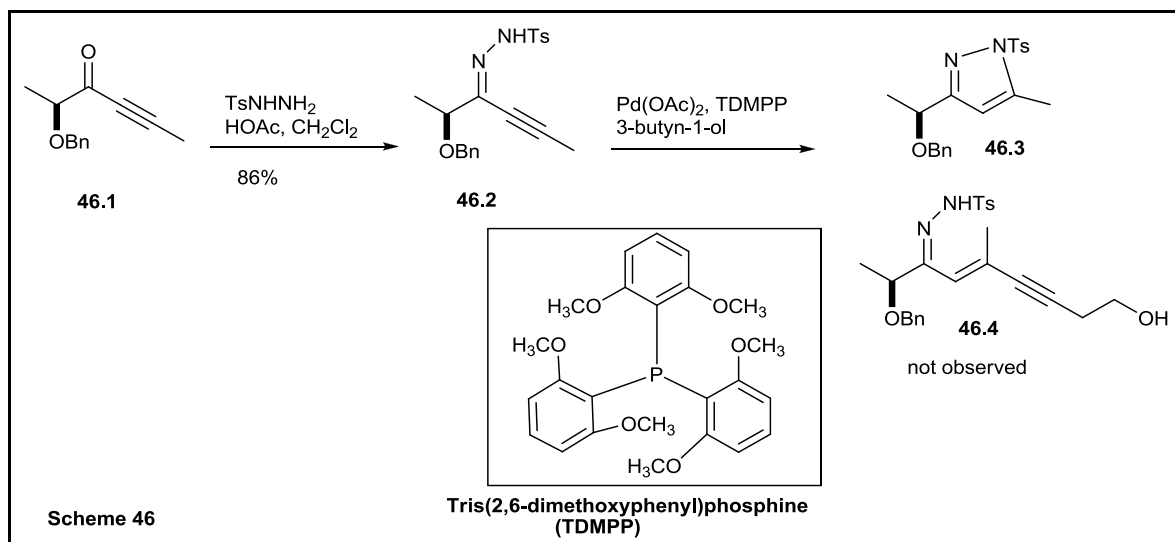
To this end we proposed an alternate route to the northern fragment **44.5** by the allylic diazene rearrangement and partial hydrogenation of **44.4** (Scheme 47). The tosyl hydrazone **44.4** would come from alkyne dimerization of **44.3**.⁸¹ Starting from the reduced Weinreb amide **44.1**, addition of a propynyl Grignard would allow for an alternative plan to progress the synthesis. In route to this new synthetic plan for the allylic diazene rearrangement precursor **44.4**, we chose to test the likelihood of the proposed methodology in a model system using a lactic acid derived substrate.



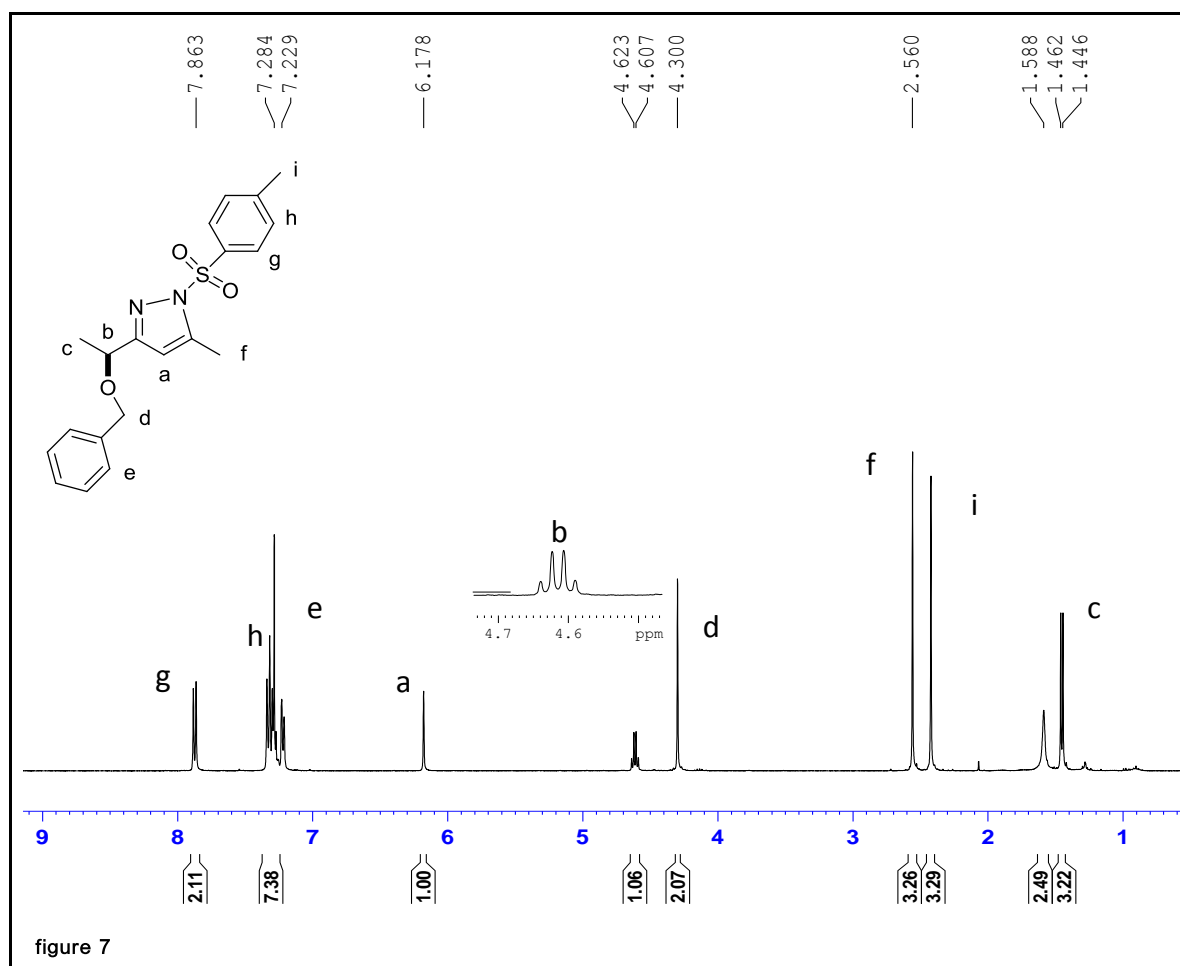
We made an analogous ynone starting from *O*-benzyl-(*S*)-lactic acid **45.1** in two steps by first converting the acid to the Weinreb amide **45.2**. This was followed by addition of the (*E/Z*) 1-bromo-1-propene to give ynone **45.3** (Scheme 45).



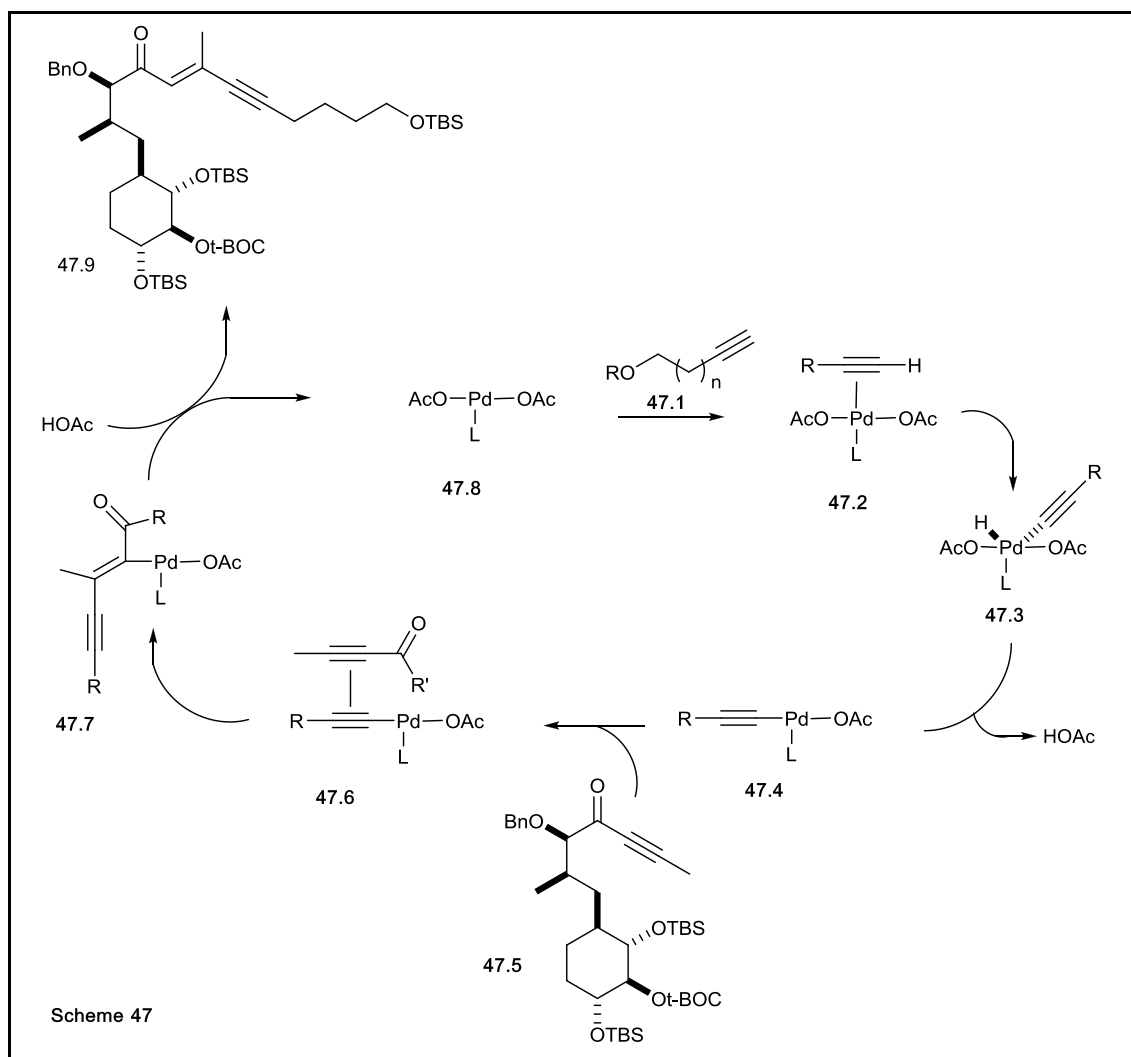
Next, we successfully converted the ynone to the hydrazone **46.2** by the addition of tosyl hydrazide with acetic acid in dichloromethane in 86% yield (Scheme 46). For homologation we followed the general conditions for the cross-coupling reaction by Trost and coworkers, but were unable to avoid the pyrazole cyclization product **46.3** and no dimerization product (**46.4**) was observed.⁸¹



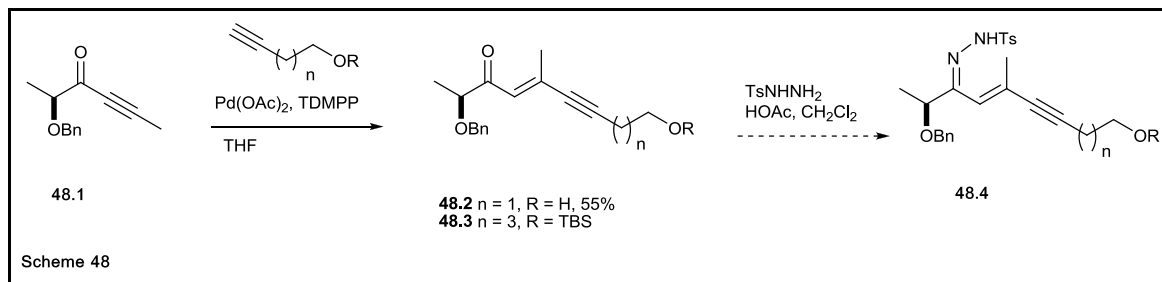
Unfortunately, increased catalyst loading, increased acceptor concentration and changes in the order of addition we were unable to avoid cyclization to form the pyrazole product. The pyrazole product was evident as the only isolated product from the ¹H NMR spectra (Figure 7).



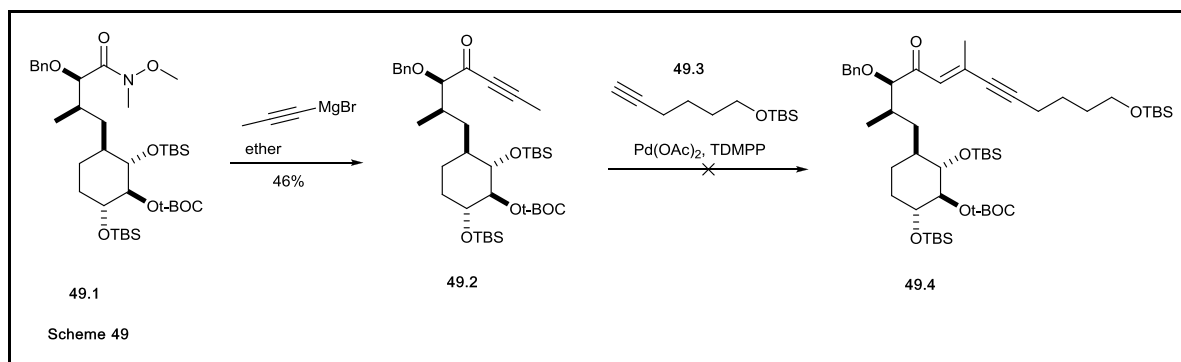
To continue for proof of concept we decided it could still be a viable route if we followed ynone formation with alkyne dimerization and then move on with the hydrazone formation reaction. A working hypothesis for the mechanism proposed by Trost et al. is adapted for this system in Scheme 47.⁸¹ It begins with the coordination of the triple bond with the Pd(2+) species followed by oxidative addition to give **47.3**. Reductive elimination follows with the loss of acetic acid to give the intermediate **47.4**. Coordination of the acceptor alkyne **47.6** followed by migratory insertion gives the intermediate **47.7** which then is protonated to release the product and repeat the cycle.



Coupling to the ynone directly also avoids the chance of pyrazole ring formation encountered in our previous attempt. Fortunately, both 3-butyne-1-ol and O-TBS-hexyne were acceptable alkyne donors for the cross-coupling reaction to the acceptor ynone **48.1** in our model scheme to make compounds **48.2** and **48.3** (Scheme 48).

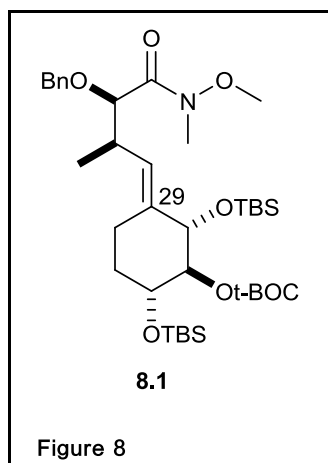


After the success of the tosyl hydrazone precursor formation in the model synthesis, we decided to test likelihood of the actual fragment through this sequence of steps as well. Although the formation of ynone **49.2** was successful in the fully substituted series, the reaction was sluggish and only gave a modest 46% yield (Scheme 49). Unfortunately, the alkyne dimerization to give enone **49.4** was not successful and returned only starting material using our more complex reacting partners, **49.2** and **49.3**. Although several substituted ynones coupled to terminal alkynes were reported by Trost and coworkers, this application would have been one of the more highly congested examples.

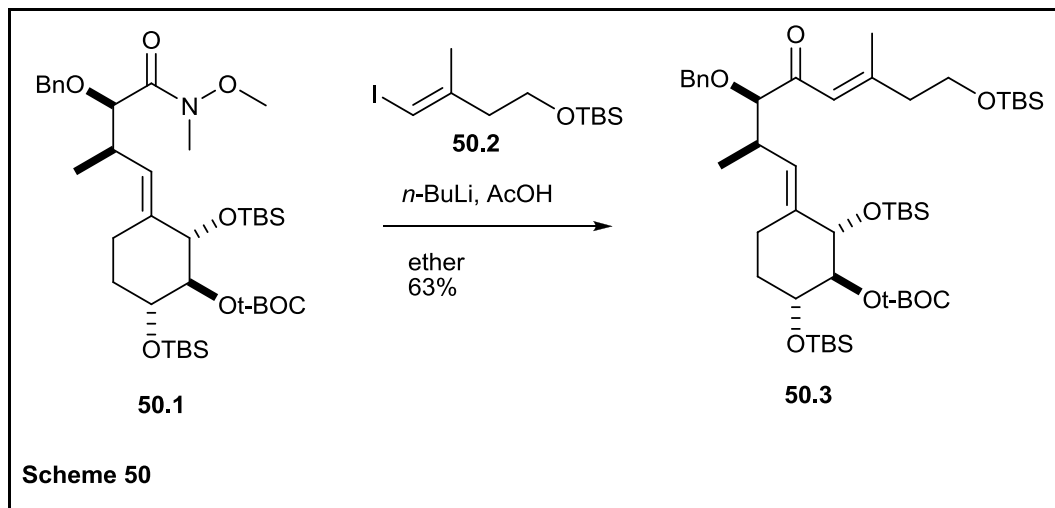


2.5.3 Third generation approach toward allylic diazene rearrangement

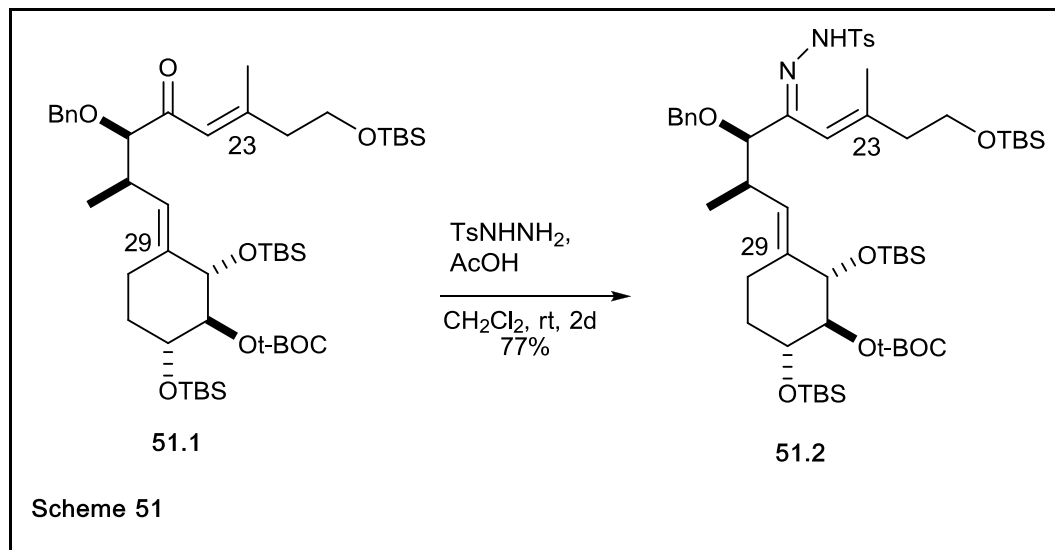
We were unsuccessful in our attempts of completing the new synthetic strategy by reducing the exocyclic double bond at C29 of the Weinreb amide (Figure 8) at an earlier stage in the synthesis. Also, the altogether different synthetic strategy of exploring the alkyne dimerization approach proved ineffective when using the appropriately functionalized material compared to the success with the less functionalized model system.



Our efforts then turned to reproducing the path laid out in our racemic synthesis of the C21-C34 fragment of antascomycin B by homologation of the remaining carbons to the fragment, **50.1**. This was achieved by the addition of the vinyl iodide compound **50.2**, converted to the lithium ion *in situ*, and added to the Weinreb amide to give the dieneone, **50.3** (scheme 50).



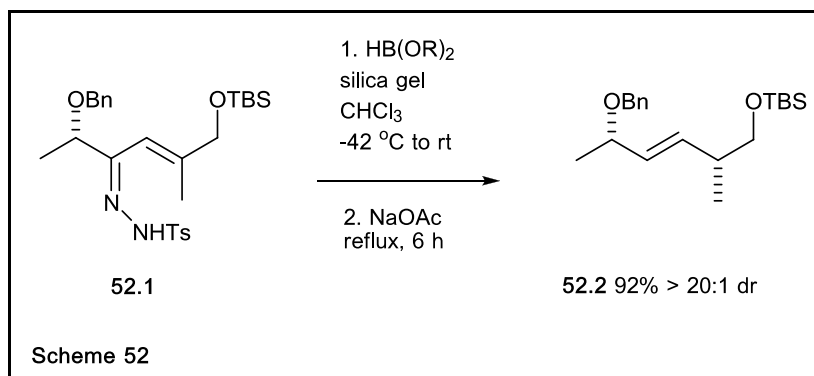
The desired hydrazone formation followed smoothly by reacting the enone **51.1** with tosylhydrazide and 0.7 equivalence of acetic acid in dichloromethane for 2 days to give the (*E*)-tosyl hydrazone **51.2** in 77% yield, determined by ^1H NMR (Scheme 51).



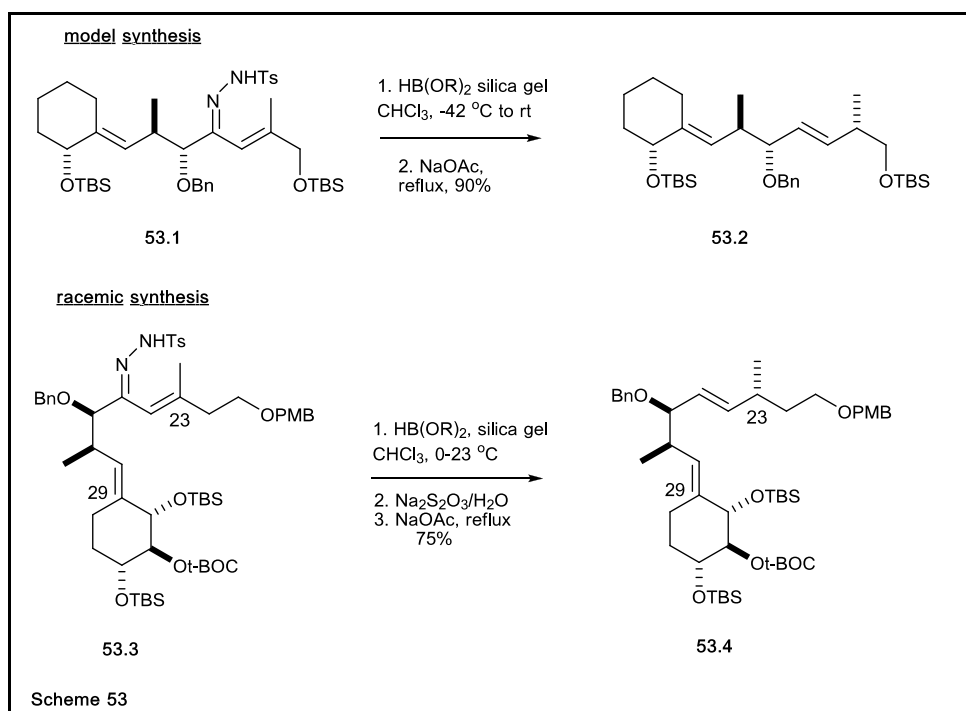
2.6 Application of allylic diazene rearrangement

The earliest example of the allylic diazene rearrangement used to install sp^3 stereocenter in an acyclic system comes from McIntosh's work in 2008.⁶³ In this paper it was found that diastereoselective reduction of α,β -unsaturated tosylhydrazone could be achieved under the influence of an α -alkoxy stereocenter (see scheme 23).

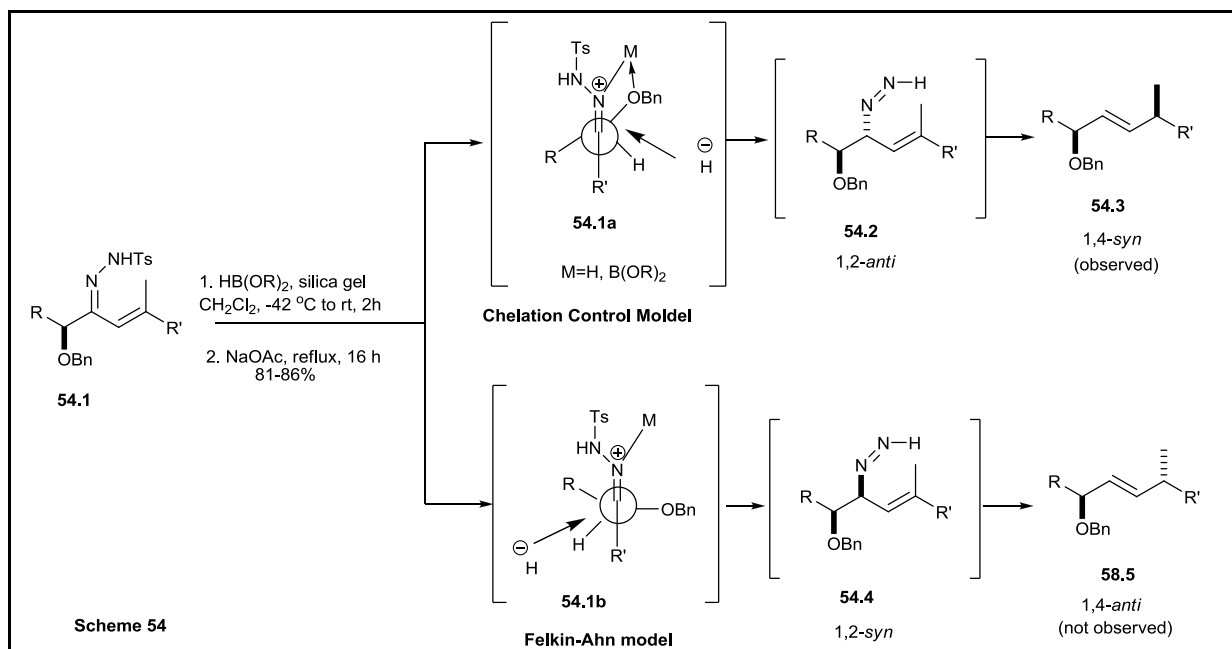
A demonstrative example of this work using a lactic acid derivative is shown is (Scheme 52). The conditions used for the transformation were adapted from earlier work by Kabalka's group with the exception of the additional 2 weight equivalent of silica gel that was found to greatly accelerate the reaction.⁸²



This methodology developed by our group was applied to our model synthesis of the C22-C34 fragment and the racemic C22-C34 fragment of antascomycin B (Scheme 53). Although the role of the silica gel was not fully understood at the time, both examples gave excellent to good yields for the allylic diazene rearrangement (ADR).

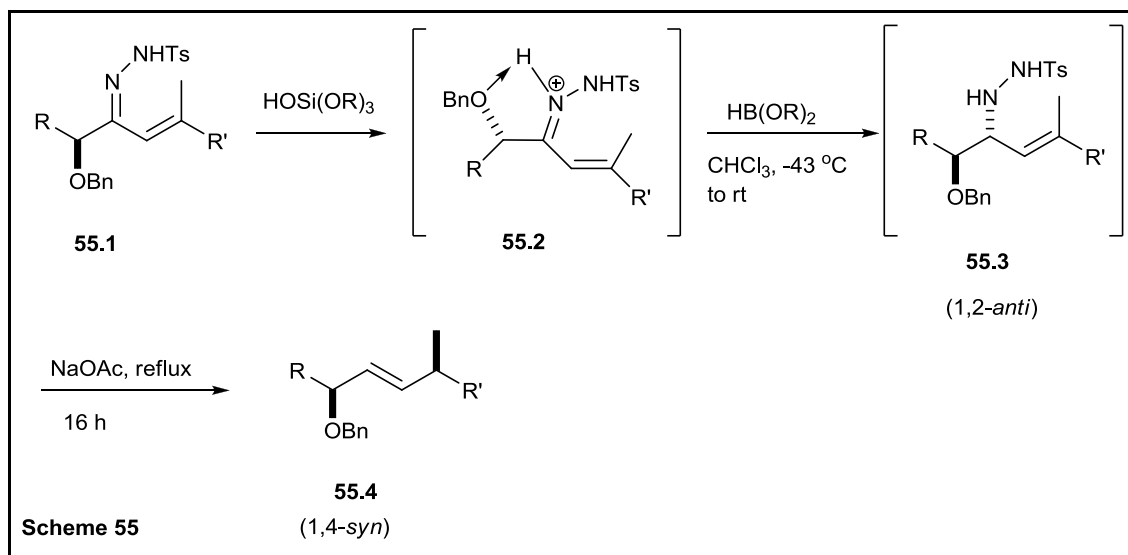


Following the publication of the examples listed above, former group member, Maha Laxmi Shrestha, investigated several aspects related to the allylic diazene rearrangement in her thesis titled, *Further studies on the allylic diazene rearrangement*.⁸³ First, the mechanism was studied and it was hypothesized that the 1,4-*syn* product **54.3** obtained in the ADR would likely go through a 1,2-*anti* isomer **54.2** produced in the hydrazone reduction step (Scheme 54). The chelation controlled model was used to rationalize the 1,2-*anti* product of the reduction. After the hydride attacks from the less hindered side, the subsequent 1,4-*syn* product is formed by suprafacial delivery of the hydrogen atom to the alkene.

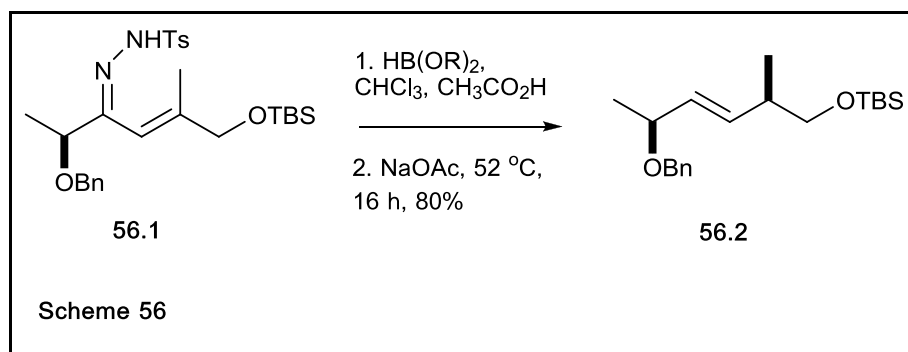


This was shown in contrast to Felkin-Ahn model that would likely result in a 1,2-*syn* intermediate **54.4** and produce a 1,4-*anti* alkene **54.5** that was not observed following the ADR. Evidence was also found by spectroscopic experiments that a chelation model best supports the reduction step of the hydrazone. The coupling constant found by Shrestha⁸³ for **54.2** was (3-5 Hz) for the 1,2-*anti* product. This was in agreement with the 1979 report by Rosini and coworkers using sodium cyanoborohydride and p-toluenesulfonic acid in THF for hydrazone reduction that gave isolated hydrazine products. In this report, Rosini et al. reported coupling constant values for 1,2-*anti* and 1,2-*syn* hydrazine diastereomers as (3-5 Hz) and (8-11 Hz), respectively.⁸⁴

The role of silica gel in the reduction of tosy hydrazones was also investigated. It was hypothesized that the silica gel served as a proton source and would likely facilitate the formation of a 5-membered chelate intermediate **55.2** so the hydride would attack the iminium ion to afford the 1,2 *anti*-product **55.3** by reduction (scheme 55).



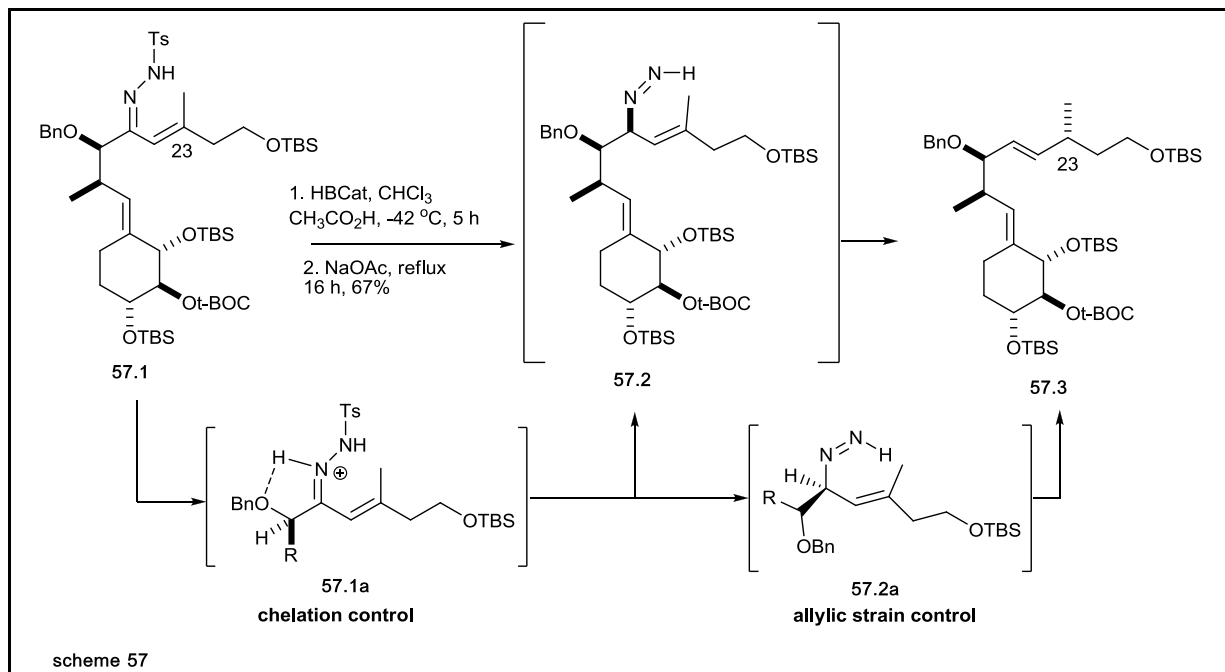
Although the yield and diastereoselectivity when using silica gel in both the model and racemic synthesis gave good to excellent results, replacing silica gel with a protic acid offers some advantages. 1) Replacing the insoluble silica gel with a soluble, well-defined protic acid is preferable. 2) Stoichiometric quantities of silica gel were required to affect the rate of the reaction, making it impractical for large scale application. When the silica gel was replaced with acetic acid (6-10 eq) the trisubstituted alkene (*E*)-hydrazone **56.1** gave good yields for the reduction to give **56.2** (Scheme 56). Additionally, the amount of the costly catecholborane (\$491.06/mol) required for the reaction was reduced by half and the scale of the reaction was doubled when conditions were optimized without any difference in product yield.



The problems encountered from the racemic synthesis were the reduction of the hydrazone required significantly higher loading of catecholborane than was needed in the model and simpler systems. Three charges of 6 equiv each were required to effect the reduction. This excess of catecholborane also demanded an intermediate wash with saturated sodium thiosulfate after the reduction to decompose the

excess borane. After considering some of the drawbacks encountered when executing the reduction/ADR in the racemic synthesis, we decided to use the conditions discussed above for our reduction/ADR in the asymmetric synthesis.¹⁷

Gratifyingly, the hydrazone reduction was successful when the silica gel was replaced with acetic acid and the ADR followed *in-situ* upon the addition of sodium acetate and refluxing (scheme 57). The acetic acid likely served as a proton donor to the 5-membered chelate intermediate **57.1a** so the hydride from catecholborane could attack from the less hindered side to give the 1,2-*anti* product **57.2** (not detected). The 1,4-*syn* product **57.3** is then formed as a result of the allylic strain induced conformation shown in compound **57.2a**.

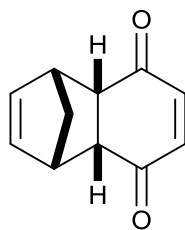


2.7 Conclusion

A 16 step longest linear sequence asymmetric synthesis has been completed for the C21-C34 fragment of the natural product antascomicin B. During the course of the study improvements were made to increase the scale of early intermediates and improve yields of the intermediate steps. The allylic diazene rearrangement (see section 2.6) for the C21-C34 fragment was optimized from the racemic synthesis by replacing the silica gel with acetic acid. The amount of costly catecholborane was reduced and the step needed for a $\text{Na}_2\text{S}_2\text{O}_3$ wash to decompose excess catecholborane was eliminated. A directed hydrogenation reaction using Crabtree's iridium catalyst was successful in the installation of the C29 stereocenter.

Chapter 3

3.1 Experimental

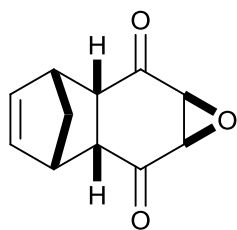


Diketone 25.2. A 2 L round bottom three necked flask, equipped with a mechanical stirrer

and thermometer was charged with CH_2Cl_2 (800 mL) and *p*-Benzoquinone (99.00 g, 0.92 mol). The flask was then cooled to 0 °C with a methanol and ice bath. Freshly cracked cyclopentadiene (*Note 1*) (40 mL, 0.46 mol) was added over a period of 30 min. A second 38 mL portion of cyclopentadiene was added in a similar fashion (*Note 2*). The mixture was then stirred in the ice bath for 1 h and then stirred at rt for 30 min. The solvent was removed in vacuo and the crude red oil material was purified by recrystallization from hexanes. The pale-yellow crystals were washed with cold hexanes, air dried, and then dried completely under high vacuum to give diketone **25.2** as pale-yellow crystals (102.2 g, 59%): spectral data matched those previously reported.⁸⁵

Note 1: To prepare cyclopentadiene, dicyclopentadiene was placed in a single necked round bottom flask with a stirring bar. The flask was then equipped with a vigreux column which was attached to a condenser with recirculating ice water. The flask was then heated to 220 °C. The point of condensation was monitored by thermometer to make sure that the collection did not occur above 42 °C which is the point at which dicyclopentadiene distills. The cracked cyclopentadiene was collected at -78 °C.

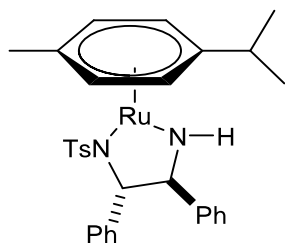
Note 2: The cyclopentadiene was added in two portions to mitigate the dimerization that occurs upon warming to rt.



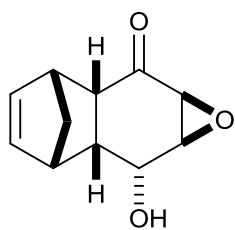
Epoxide-Diketone 25.3. To a 2 L round bottom three necked flask, equipped with a

mechanical stirrer, diketone **25.2** (108.15 g, 0.62 mol) was dissolved in THF (1300 mL) while stirring. H_2O_2 (35%, 120 mL) was added dropwise via addition funnel over approx. 1 h. To the solution, NaHCO_3 (sat., 133 mL) was added dropwise via addition funnel approx. 1 h. The mixture was then stirred for 2 h until no starting material remained by TLC. The solvent was removed in vacuo and the crude material

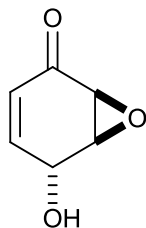
(pale-white solid) was purified by recrystallization (pure-white solid) from ethanol to give **25.3** (83.7 g, 71%). spectral data matched those previously reported.



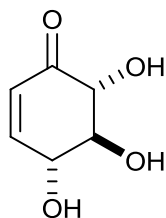
Ru(p-Cy)TsDPEN was prepared by dissolving (1.00 g, 1.63 mmol) and (S,S)-TsDPEN (1.20 g, 3.27 mmol) in CH_2Cl_2 (23 mL) and allowing to stir for 5 minutes. KOH (1.31 g, 2.3 mmol) and water (23 mL) was then added and the mixture was allowed to stir for an additional 5 minutes. Reaction was complete when the color turned from orange to deep purple. Reaction was extracted in CH_2Cl_2 , dried over CaH_2 , and then concentrated in vacuo to give Ru(p-Cy) TsDPEN as dark purple crystals (quant. yield). Data matched that previously reported.⁸⁶



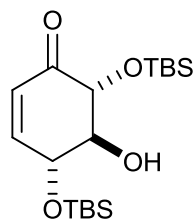
Monoreduced epoxyketo alcohol 26.2. Ru(p-cymene)(S,S-TsDPEN) (0.42 g, 0.68 mmol, 0.65 mol %) and epoxy diketone **25.3** (20.0 g, 0.11 mol) were added to a solution of formic acid (6.75 mL), triethylamine (25.0 mL) and acetonitrile (1000 mL) at $-10\text{ }^\circ\text{C}$. The reaction mixture was allowed to slowly warm to rt and stirred for ca. 48 h. The mixture was concentrated in vacuo and then stirred for ca. 16 h in 30/70 ethyl acetate/hexanes (300 mL) with activated charcoal (1 g). The mixture was filtered through a plug of Celite with 30/70 ethyl acetate/hexanes and concentrated in vacuo. At this point, the residue could be purified by flash chromatography (20/80 ethyl acetate/hexanes) to give keto alcohol **26.2** as colorless crystals (8.10 g, 40%, er 99.6:0.4). Spectral data matched those previously reported.²²



Epoxyquinol 26.3. A solution of monoreduced epoxyketo alcohol **26.2** (20 g, 0.104 mol) in diphenyl ether (200 mL) was dissolved and stirred at rt while degassed with nitrogen for 30 minutes. The reaction mixture was then heated to 180 °C (still gently bubbling through with nitrogen) until decomposition product became a significant spot as monitored by TLC. After cooling to room temperature, the reaction mixture was poured onto a column of silica gel using hexane to elute diphenyl ether solvent. After elution with hexane, the reaction mixture was eluted with 1/99-10/90 MeOH/CH₂Cl₂ 1% gradient followed by recrystallization with diethyl ether to yield pure epoxyquinol **26.3** as white crystals (9.98 g, 76%). Spectral data matched those previously reported.²²

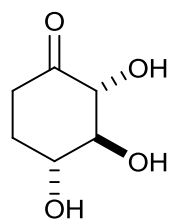


Trihydroxy cyclohexenone 26.4. Epoxyquinol **26.3** (12 g, 79.30 mmol) was distributed in 1 gram aliquots to 12 parallel synthesizer tubes and DI H₂O (12 mL) with stir bar. Each tube was heated to 90 °C for 3.5 days on the heating mantle. H₂O was then co-evaporated with MeCN and the brown residue was adsorbed on silica gel. The silica gel/residue was added to a silica gel column using CH₂Cl₂. Mixture was eluted with 0/99-10/90 MeOH/CH₂Cl₂ at 1% gradient. The second fraction was collected and recrystallized in EtOH to give trihydroxy cyclohexanone **26.4** (6.03 g, 41.84 mmol, 44%) as colorless crystals. M.P. 136-138 °C; $[\alpha]_D^{23}$ -0.885 (c 0.437 1:1 MeOH:CH₂Cl₂); IR (film) 3400, 2835, 1693 ¹H NMR (400 MHz, CD₃OD) δ 3.58 (dd, J = 10.87 Hz, 8.28 Hz, 1H), 4.03 Hz (d, J = 10.88 Hz, 1H), 4.36 (m, 1H), 6.04 (dd, J = 10.33 Hz, 2.56 Hz, 1H), 6.92 (d, J = 10.33 Hz, 1.94 Hz, 1H); ¹³C NMR (400 MHz, CH₃OD) δ 70.12, 75.17, 76.99, 124.57, 150.36, 197.21. Anal Calcd for C₆H₈O₃: C, 50.00; H, 5.59. Found: C, 49.89; H, 5.65.



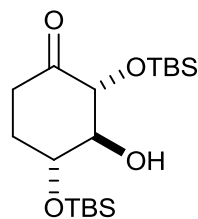
Disilyl ether 27.2. A solution of TBSCl (18.18 g, 120 mmol) and imidazole (10.96 g, 161

mmol) in dry DMF (40 mL) was added to trihydroxy cyclohexenone **26.4** (5.8 g, 40.2 mmol) in dry DMF (25 mL). After stirring at room temperature for 4 h, the reaction mixture was quenched with ice water, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using 5/95 ethyl acetate/hexane, followed by recrystallization with cold hexane to give the disilyl ether **27.2** (8.55 g, 23 mmol, 57%) as white crystals. M.P. 101-103 °C; $[\alpha]_D^{23} = -0.11$ (c 0.24 CH_2Cl_2); IR (film) 3394, 1647 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.11 (s, 3H), 0.19 (s, 6H), 0.24 (s, 3H), 0.94 (s, 9H), 0.96 (s, 9H), 2.56 (d, $J = 1.72$ Hz, 1H), 3.77 (m, 1H), 4.03 (d, $J = 10.55$ Hz, 1H), 4.46 (dt, $J = 7.96$ Hz, 2.16 Hz, 1H), 5.98 (dd, $J = 10.36$ Hz, 2.41 Hz, 1H), 6.70 (dd, $J = 10.36$ Hz, 1.91 Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ -5.40, -4.91, -4.46, -4.13, 18.15, 18.61, 25.76, 25.94, 72.68, 78.55, 78.70, 126.86, 150.71, 196.78. Anal Calcd for $\text{C}_{18}\text{H}_{36}\text{O}_4\text{Si}_2$: C, 58.02; H, 9.74. Found: C, 58.15; H, 9.93.



Trihydroxy ketone 28.2. A mixture of trihydroxy cyclohexenone **27.2** 6.13 g, 42.5 mmol)

and 10% Pd/C (1.2 g, 11.2 mmol Pd) in dry methanol (200 mL) was stirred under an H_2 atmosphere (1 atm) overnight. Following completion of the reaction, the mixture was filtered through celite and concentrated. The crude product was used without further purification.

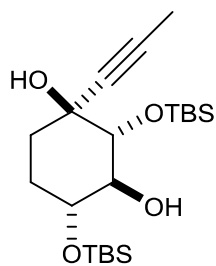


Hydroxy ketone 27.3. A solution of TBSCl (5.82 g, 38.6 mmol) and imidazole (3.50 g,

51.4 mmol) in dry DMF (30 mL) was added to trihydroxy cyclohexanone **28.2** (1.88 g, 12.9 mmol) in dry DMF (10 mL). After stirring at room temperature for 4 h, the reaction mixture was quenched with ice

water, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using 3/97 ethyl acetate/hexane, followed by recrystallization with cold hexane to give ketone **27.3** (3.13 g, 8.34 mmol, 65% over 2 steps).

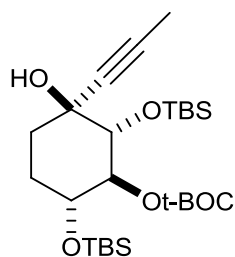
Alternatively, a mixture of disilyl ether **27.2** (1.9 g, 5.1 mmol) and 10% Pd/C (0.20 g, 0.11 mmol Pd) in dry methanol (30 mL) was stirred under an H_2 atmosphere (1 atm) for 7 h. Following completion of the reaction, the mixture was filtered through celite and concentrated. The crude product was purified by flash column chromatography on silica gel using 1/99-3/97 gradient of ethyl acetate/hexane, followed by recrystallization with cold hexane to give hydroxyl ketone **27.3** (4.67 g, 12.47 mmol, 88%) as white crystals. M.P. 76-78 °C; $[\alpha]_D^{23} = +0.084$ (c 0.26 CH_2Cl_2); IR (film) 3414, 1736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.06 (s, 3H), 0.14 (s, 3H), 0.16 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 0.94 (s, 9H), 1.60 (m, 1H), 2.04 (m, 1H), 2.37 (m, 2H), 2.53 (d, $J = 2.53$ Hz, 1H), 3.47 (td $J = 9.96, 1.54$, 1H), 3.87 (ddd, $J = 11.21, 8.67, 4.69$, 1H), 4.07 (d, $J = 9.77$ Hz, 1H); ^{13}C NMR (400 MHz, CDCl_3) δ -5.33, -4.49, -4.44, 18.10, 18.59, 25.78, 25.84, 29.65, 34.67, 35.72, 72.84, 79.71, 205.66. Anal Calcd for $\text{C}_{18}\text{H}_{38}\text{O}_4\text{Si}_2$: C, 57.70; H, 10.22. Found: C, 58.39; H, 10.55.



Diol 29.2. Propynyl magnesium bromide (41.0 mL, 0.5 M in THF, 20.5 mmol) was

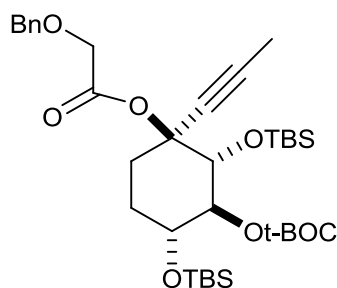
added dropwise to a solution of hydroxyl ketone **27.3** (2.17 g, 5.8 mmol) in THF (80 mL) at -10 °C. After warming to room temperature over 5 h, the reaction mixture was quenched with cold NH_4Cl (aq) solution, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using 3/97-5/95 ethyl acetate/hexane gradient to give diol **29.2** (1.9 g, 4.58 mmol, 79%) as white crystals. M.P. 50-52 °C; $[\alpha]_D^{23} = +0.031$ (c 0.26 CH_2Cl_2); IR (film) 3540, 2113 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.14 (s, 3H), 0.17 (s, 3H), 0.91 (s, 9H), 0.95 (s, 9H), 1.49 (td, $J = 13.48$ Hz, 3.85 Hz, 1H), 1.71 (dddd, $J = 17.06$ Hz, 14.18 Hz, 10.91 Hz, 3.58 Hz, 2H), 1.86 (s, 3H), 1.91 (dt, $J = 12.97$ Hz, 3.38 Hz, 1H), 2.21 (s, 1H), 2.56 (s, 1H), 3.29 (d, $J = 9.25$ Hz, 1H), 3.42 (m, 2H); ^{13}C NMR (400 MHz, CDCl_3) δ -4.70, -4.53, -4.24, -3.83, 3.62, 18.10, 18.43,

25.86, 26.02, 29.38, 33.23, 72.65, 74.50, 77.71, 79.36, 80.27, 82.41; Anal Calcd for $C_{21}H_{42}O_4Si_2$: C, 60.82; H, 10.21. Found: C, 60.81; H, 10.35.



Propargyl alcohol 33.2. *n*-BuLi (3.22 mL, 2.8 M in Hexanes, 9.02 mmol) was added

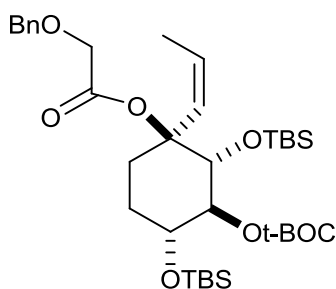
dropwise to a solution of diol **29.2** (3.50 g, 8.44 mmol) in ether (140 mL) at $-78\text{ }^{\circ}\text{C}$. After 30 min, Di-*tert*-butyl-dicarbonate (2.40 g, 11.0 mmol) dissolved in ether (30 mL) was added dropwise and the reaction mixture was allowed to slowly warm to room temperature over 7 h. Following completion of the reaction as monitored by TLC, reaction mixture was quenched with cold NH_4Cl (aq) solution, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by filtration through a silica gel plug using 10/90 ethyl acetate/hexane, followed by recrystallization with cold hexane to give propargyl alcohol **33.2** (4.03 g, 7.82 mmol, 93%) as white crystals. M.P. $126\text{--}128\text{ }^{\circ}\text{C}$; $[\alpha]_D^{23} = +0.080$ (c 0.196 CH_2Cl_2); IR (film) $3580, 1752\text{ cm}^{-1}$; ^1H NMR (400 MHz, CDCl_3) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.49 (s, 9H), 1.78 (m, 2H), 1.88 (s, 3H), 1.92 (t, $J = 3.55\text{ Hz}$, 1H), 2.40 (s, 1H), 3.40 (d, $J = 9.64\text{ Hz}$, 1H), 3.56 (td, $J = 9.80\text{ Hz}, 5.85\text{ Hz}$, 1H), 4.71 (t, $J = 9.34\text{ Hz}$, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ -4.73, -4.48, -4.47, -4.20, 3.68, 17.94, 18.16, 25.80, 25.87, 28.01, 29.76, 33.20, 72.41, 72.96, 78.29, 78.62, 80.99, 81.61, 83.35, 152.98; Anal Calcd for $C_{26}H_{50}O_6Si_2$: C, 60.66; H, 9.79. Found: C, 60.92; H, 10.03.



Glycolate ester 33.4. *n*-BuLi (4.51 mL, 2.8 M in Hexanes, 12.63 mmol) was

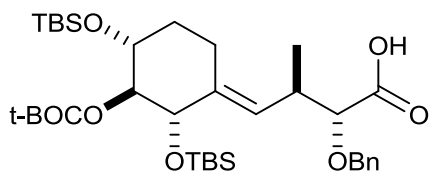
added dropwise to a solution of propargyl alcohol **33.2** (4.33 g, 8.41 mmol) in ether (110 mL) at $-78\text{ }^{\circ}\text{C}$. After 20 min, the acid chloride (3.25 mL, 20.9 mmol) was added dropwise and the reaction mixture was allowed to slowly warm to room temperature over 9 h. When the reaction ceased as observed by TLC,

reaction mixture was quenched with cold NH_4Cl (aq) solution, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using 1/99- 3/97 ethyl acetate/hexane gradient giving glycolate ester **33.4** (3.52 g, 5.30 mmol, 63%, 97% brsm) as a colorless oil. $[\alpha]_D^{23} = +0.314$ (c 1.42, CH_2Cl_2); IR (film) 2266, 1747 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.39 (m, 1H), 1.49 (s, 9H), 1.80 (m, 2H), 1.92 (s, 3H), 2.83 (dt, $J = 13.08$ Hz, 3.55 Hz, 1H) 3.55 (td, $J = 9.18$ Hz, 7.48 Hz, 1H), 3.64 (d, $J = 9.44$ Hz, 1H), 4.04 (d, $J = 2.45$ Hz, 2H), 4.63 (q, $J = 11.52$ Hz, 11.53 Hz 2H), 4.76 (t, $J = 9.33$ Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ -4.75, -4.56, -4.49, -4.14, 3.90, 17.94, 18.17, 25.73, 25.79, 28.01, 29.28, 30.22, 67.36, 71.86, 73.34, 73.99, 76.41, 80.74, 80.97, 81.84, 86.35, 128.02, 128.20, 128.46, 136.97, 152.83, 186.28; Anal Calcd for $\text{C}_{35}\text{H}_{58}\text{O}_8\text{Si}_2$: C, 63.40; H, 8.82. Found: C, 61.16; H, 8.66.



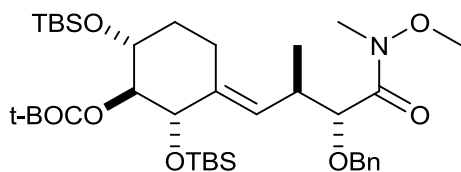
Allylic ester 33.5. A mixture of the alkyne **33.4** (0.84 g, 1.27 mmol),

pyridine (0.05 mL, 0.63 mmol), and 5% Pd/BaSO_4 (0.53 g, 0.25 mmol) dissolved in ethyl acetate (20 mL) was shaken in a Parr bottle under an H_2 atmosphere (90 psi) for 7 h. The reaction mixture was filtered through celite and concentrated. The crude product was purified by flash column chromatography on silica gel using 0/100-5/95 ethyl acetate/hexane gradient to give allylic ester **33.5** (0.74 g, 1.11 mmol, 88%, 94% brsm) as a colorless oil. $[\alpha]_D^{23} = -0.278$ (c 0.88 CH_2Cl_2); IR (film) 1751 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.31 (m, 1H), 1.48 (s, 9H), 1.55 (m, 1H), 1.82 (d, $J = 6.72$ Hz, 3H), 1.91 (m, 1H), 2.75 (dt, $J = 13.16$ Hz, 3.43 Hz, 1H), 3.64 (ddd, $J = 11.05$ Hz, 9.02 Hz, 5.04 Hz, 1H), 4.02 (d, $J = 2.13$ Hz, 2H), 4.08 (d, $J = 9.50$ Hz, 1H), 4.57 (t, $J = 4.56$ Hz, 1H), 4.63 (m, 2H), 5.78 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ -4.66, -4.58, -4.36, -4.21, 15.18, 17.93, 18.15, 25.80, 25.95, 28.01, 28.18, 29.35, 30.95, 67.56, 71.95a, 73.26, 75.66, 77.24, 80.37, 81.81, 86.76, 124.26, 127.96, 128.06, 131.11, 137.14, 153.05, 168.90; Anal calcd for $\text{C}_{35}\text{H}_{60}\text{O}_8\text{Si}_2$: C, 63.64; H, 9.34. Found: C, 63.75; H, 9.18.



Pentenoic acid 34.3. *n*-BuLi (2.25 mL, 1.6 M in Hexanes, 3.6

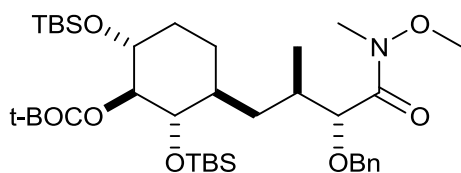
mmol) was added dropwise to a solution of diisopropylamine (0.5 mL, 3.50 mmol) in THF (40 mL) at -78 °C. After 20 min, this solution was cannulated to a solution of allylic ester **33.5** (1.20 g, 1.80 mmol) and TMSCl (0.68 mL, 5.38 mmol) in THF (20 mL) at -78 °C. After 10 min AcOH (0.124 mL, 2.20 mmol) was added and the reaction mixture was allowed to slowly warm to rt. After 3 h, the reaction mixture was quenched with cold saturated NH₄Cl (aq) solution, extracted with ether, dried over MgSO₄, and concentrated in vacuo. The crude product was then dissolved in ether (5 mL), treated with NEt₃ (0.30 mL, 2.15 mmol), and purified by flash chromatography over silica gel eluting with 1% NEt₃ in ether, then 1% HCO₂H in ether. Removal of excess formic acid in vacuo gave pentenoic acid **34.3** (0.973 g, 1.46 mmol, 81%, 99% brsm) as a colorless oil. $[\alpha]_D^{23} = +0.424$ (c 1.32 CH₂Cl₂); IR (film) 3414, 1750, 1651 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ -0.01 (s, 3H), 0.04 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.05 (d, J = 6.81 Hz, 3H), 1.29 (m, 1H), 1.47 (s, 9H), 1.56 (m, 1H), 1.86 (m, 1H), 2.50 (d, J = 13.63 Hz, 1H), 2.98 (m, 1H), 3.65 (ddd, J = 11.28 Hz, 8.89 Hz, 5.14 Hz, 1H), 3.85 (dd, J = 6.41, 3.08, 2H), 4.38 (t, J = 9.16 Hz, 1H), 4.47 (d, J = 11.50 Hz, 1H), 4.73 (d, J = 11.50 Hz, 1H), 5.61 (d, J = 10.49 Hz, 1H), 7.34 (m, 5H). ¹³C NMR (400 MHz, CDCl₃) δ -4.96, -4.90, -4.86, -4.39, 8.50, 17.89, 18.19, 23.31, 25.773, 25.929, 28.01, 33.78, 35.40, 72.54, 72.93, 73.95, 81.16, 83.34, 83.96, 123.74, 127.69, 127.99, 128.33, 136.96, 137.60, 153.12, 175.83. Anal calcd for C₃₅H₆₀O₈Si₂: C, 63.21; H, 9.09. Found: C, 61.29; H, 9.52.



Weinreb amide 35.2. Freshly distilled MsCl (0.12 mL, 1.55

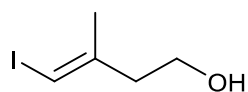
mmol) was added dropwise to a solution of pentenoic acid **34.3** (0.67 g, 1.01 mmol) and NEt₃ (0.42 mL, 3.01 mmol) in THF (30 mL) at 0 °C. After 30 min, HN(OMe)Me (0.15 mL, 2.04 mmol) was added dropwise and the reaction mixture was allowed to warm to rt over 6 hours. The reaction mixture was quenched with saturated NH₄Cl (aq) solution, extracted with ether, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by filtration through a silica gel plug with 1% NEt₃ in ether. Starting material

was recovered with 1% formic acid in ether. After removal of solvents under vacuum, Weinreb amide **35.2** was isolated (0.55 g, .776 mmol, 77%, 97% brsm) as clear oil. $[\alpha]_D^{23} = +0.234$ (c 0.74 CH₂Cl₂); IR (film) 1633, 1732 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ -0.02 (s, 3H), 0.00 (s, 3H), 0.03 (s, 3H), 0.08 (s, 3H), 0.83 (s, 9H), 0.91 (s, 12H), 1.25 (m, 1H), 1.48 (s, 9H), 1.54 (td, J = 14.25 Hz, 13.93 Hz, 2.91 Hz, 1H), 1.76 (m, 1H), 2.62 (d, J = 13.39 Hz, 1H), 2.99 (m, 1H), 3.21 (s, 3H), 3.54 (s, 3H), 3.63 (ddd, J = 11.31, 8.88, 5.13 Hz, 1H), 3.87 (dd, J = 9.41, 1.63 Hz, 1H), 4.13 (d, J = 8.20 Hz, 1H), 4.40 (d, J = 11.80 Hz, 1H), 4.47 (t, J = 9.10 Hz, 1H), 4.59 (d, J = 11.79 Hz, 1H), 5.48 (d, J = 10.22 Hz, 1H), 7.26 (m, 5H); ¹³C NMR (MHz, CDCl₃) δ -4.89, -4.82, -4.83, -4.39, 14.10, 17.87, 18.25, 23.48, 25.77, 25.95, 28.03, 29.71, 33.71, 35.46, 61.17, 71.98, 72.57, 73.98, 79.15, 81.06, 83.98, 125.18, 128.02, 128.23, 128.37, 137.38, 137.65, 153.08, 173.19. Anal Calcd for C₃₇H₆₅NO₈Si₂: C, 62.76; H, 9.25; N, 1.98. Found: C, 62.08; H, 9.24; N, 1.93.



Reduced Weinreb amide 36.2. A mixture of Weinreb amide 7.2

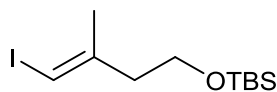
(0.40 g, 0.565 mmol) and Crabtree's catalyst (0.023 g, 0.0282 mmol) in CH₂Cl₂ (100 mL) was shaken in a Parr bottle under H₂ (90 psi) overnight. The reaction mixture was concentrated in vacuo and purified by flash column chromatography on silica gel using 20/80 ethyl acetate/hexane to afford reduced amide **8.2** (0.39 g, 0.55 mmol, 97%) as a colorless oil. $[\alpha]_D^{23} = +0.053$ (c 1.32 CH₂Cl₂); IR (film) 1675, 1748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.05 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.90 (s, 9H), 0.92 (m, 2H), 1.27 (m, 1H), 1.50 (s, 9H), 1.73 (m, 2H), 1.90 (d, J = 13.60 Hz, 1H), 2.07 (m, 2H), 3.12 (t, J = 9.44 Hz, 1H), 3.22 (s, 3H), 3.47 (ddd, J = 11.32 Hz, 9.20 Hz, 4.96 Hz, 1H), 3.60 (s, 3H), 4.14 (dd, 7.14 Hz, 1H), 4.38 (d, J = 11.21 Hz, 1H), 4.48 (t, J = 9.10 Hz, 1H), 4.56 (d, J = 11.24 Hz, 1H), 7.35 (m, 5H); ¹³C NMR (400 MHz, CDCl₃) δ -4.62, -4.47, -3.91, -3.56, 17.92, 18.01, 18.08, 25.61, 25.82, 26.12, 28.06, 29.68, 32.24, 32.97, 33.55, 39.12, 39.12, 41.81, 61.07, 71.91, 72.92, 76.34, 81.20, 81.40, 83.68, 127.79, 128.19, 128.35, 137.51, 153.20, 173.19; Anal Calcd for C₃₇H₆₇NO₈Si₂: C, 62.58; H, 9.51; N, 1.97. Found: C, 62.78; H, 9.60; N, 1.92.



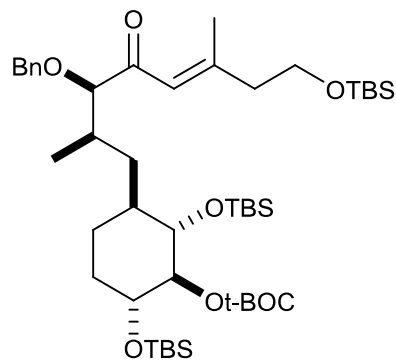
(E)-4-iodo-3-methylbut-3-en-1-ol 37.2. To a stirred solution of zirconocene

dichloride (1.04 g, 3.56 mmol) in anhydrous CH₂Cl₂ (65 mL) at -25 °C was added trimethylaluminum (44.2

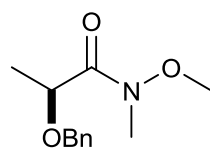
mL, 44.2 mmol) dropwise. After stirring the resulting yellow mixture for 10 min at -25 °C, water (0.39 mL, 21.67 mmol) was cautiously added dropwise (Caution: exothermic reaction!). After an additional 10 min stirring, commercially available 3-butyne-1-ol (1.00 g, 15.4 mmol), pretreated with trimethyl aluminum (4.42 mL, 4.42 mmol) in anhydrous CH₂Cl₂ (20 mL) at 0 °C, was added drop-wise *via* cannula. The reaction mixture was allowed to warm to ambient temperature and the resulting yellow thick slurry was stirred overnight. The reaction mixture was then cooled to -25 °C and a solution of I₂ (5.43 g, 21.4 mmol) in anhydrous Et₂O (35 mL) was added dropwise *via* cannula. The mixture was allowed to warm to ambient temperature and was stirred for an additional 3 h. The reaction mixture was slowly quenched with a saturated aqueous solution of potassium tartrate (20 mL). The aqueous phase was extracted with Et₂O and washed with Na₂S₂O₃ and brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel using 15/85 ethyl acetate/hexane provided the desired vinyl iodide **37.2** (1.42 g, 6.70 mmol, 47%) as a yellow oil. Spectral data matched those previously reported.



Iodide 37.3. A solution of TBSCl (0.70 g, 4.64 mmol) and imidazole (0.64 g, 9.4 mmol) in anhydrous DMF (5 mL) was added to (*E*)-4-iodo-3-methylbut-3-en-1-ol **37.2** (0.8 g, 3.77 mmol) in anhydrous DMF (5 mL). After stirring at room temperature for 2 h, the reaction mixture was quenched with ice water, extracted with ether, dried over MgSO₄, and concentrated in vacuo. . Purification of the residue by flash chromatography on silica gel using 10/90 ethyl acetate/hexane provided the desired vinyl iodide (0.98 g, 3.00 mmol, 80%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 0.06 (s, 6H), 0.91 (s, 9H), 1.88 (s, 3H), 2.44 (t, J = 6.56 Hz, 2H), 3.71 (t, J = 6.62 Hz, 2H), 5.94 (s, 1H); ¹³C NMR (MHz, CDCl₃) δ -5.31, 18.23, 24.28, 25.91, 42.67, 61.34, 76.39, 145.14.

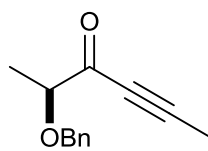


Enone 32.3. *n*-BuLi (0.54 mL, 1.19 mmol) was added dropwise to a solution of iodide **152** (0.39 g, 1.2 mmol) in anhydrous ether (12 mL) at -78 °C and stirred for 30 minutes. The solution was then cannulated dropwise to amide **149** (0.42 g, 0.59 mmol) in ether (12 mL) at -78 °C. The solution was stirred at -78 °C for 4 h until no starting material remained by TLC analysis. The reaction was quenched with AcOH (0.07 mL, 1.22 mmol), washed in saturated NH₄Cl (aq), extracted in ether, dried with MgSO₄ and concentrated in vacuo. The oily residue was purified by flash chromatography on silica gel using 10/90 ethyl acetate/hexane provided the enone **153** (0.26 g, 0.31 mmol, 52%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 0.04 – 0.08 (m, 18H), 0.87 (m, 21H), 0.89 (s, 6H), 1.24 (m, 2H), 1.27 (m, 3H), 1.36 (m, 1H), 1.50 (s, 9H), 1.66 (m, 2H), 1.77 (m, 3H), 1.98 (m, 2H), 2.10 (m, 1H), 2.27 (s, 3H), 2.40 (t, *J* = 6.48 Hz, 2H), 2.52 (m, 1H), 3.12 (t, *J* = 9.52, 1H), 3.46 (d, *J* = 7.20 Hz, 1H), 3.51 (m, 1H), 3.78 (t, 6.48 Hz, 2H), 4.34 (d, *J* = 11.28 Hz, 1H), 4.48 (m, 2H), 4.51 (m, 1H), 6.48 (s, 1H), 7.35 (m, 5H); ¹³C NMR (400 MHz, CDCl₃) δ -4.95, -4.47, -3.87, -3.57, 17.94, 19.98, 25.84, 28.08, 33.08, 33.47, 38.16, 41.95, 44.76, 61.38, 72.39, 72.92, 81.21, 83.63, 90.97, 120.64, 128.14, 128.36, 137.65, 153.15, 158.65, 202.29

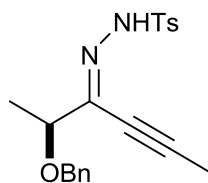


Lactic acid derived Weinreb amide 45.2. Freshly distilled mesyl chloride (1.43 g, 12.5mmol) was added to a solution of *O*-benzyl-(*S*)-lactic acid **45.1** (1.50 g, 8.3 mmol) and Net₃ (2.56 g, 9.8 mmol) in THF (40 mL) at 0 °C. After 30 min, HN(OMe)Me (1.01 g, 1.38 mmol) was added dropwise and the reaction mixture was allowed to warm to rt overnight. The reaction mixture was quenched with saturated NH₄Cl (aq) solution, extracted with ether, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by filtration through a silica gel plug with 1% NEt₃ in ether. Starting material

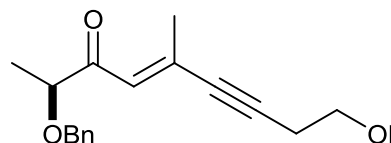
was recovered with 1% formic acid in ether. After removal of solvents under vacuum, Weinreb amide **45.2** was isolated (1.39 g, 75%) as a colorless oil. Spectral data matched those previously reported.⁶³



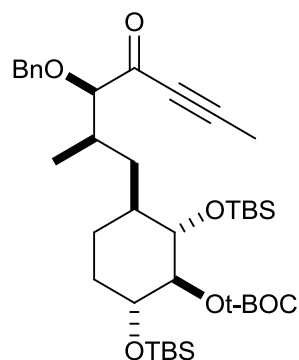
ynone 45.3. To a dry 2 neck round bottom flask was added (E/Z)-bromopropene (42.0 mL, 4.9 mmol) in THF (5 mL). After 20 min. at -78 °C, *n*-butyl lithium (0.35 mL, 0.77 mmol in hexane) was added dropwise over 30 min. The reaction temperature remained at -78 °C for an additional 1 h before amide **45.2** dissolved in THF (2 mL) was added dropwise over 30 minutes and mixed an additional 1 hr. The reaction mixture was quenched with saturated NH₄Cl (aq) solution, extracted with ether, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by Flash chromatography and provided ynone **45.3** (0.27 g, 78%) as clear oil. ¹H NMR (400 MHz, CDCl₃) δ 1.43 (d, J = 6.92 Hz, 3H), 2.07 (s, 3H), 4.02 (q, J = 6.84 Hz, J = 6.88, 1H), 4.47 (d, J = 11.64 Hz, 1H), 4.70 (d, J = 11.63 Hz, 1H), 7.37 (m, 5H); ¹³C NMR (400 MHz, CDCl₃) δ 4.38, 17.82, 72.07, 78.30, 80.77, 93.75, 127.95, 128.48, 137.53, 189.83.



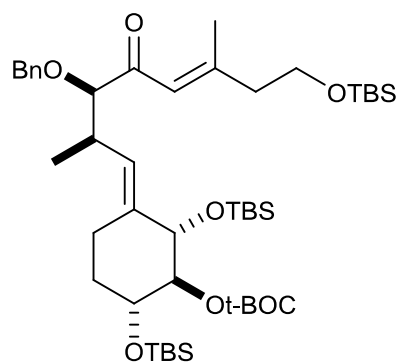
hydrazone 46.2. To a solution of ynone **45.3** (0.33 g, 1.63 mmol) in CH₂Cl₂ was added tosyl hydrazide (0.61 g, 3.27 mmol) and AcOH (0.093 mL, 1.63 mmol) and stirred overnight at rt. The crude reaction mixture was concentrated in vacuo, purified by flash chromatography on silica gel using 20/80 ethyl acetate/hexane to give hydrazone **46.2** (0.52 g, 86%) as a white solid. M.P. 67 – 70 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (d, 6.48 Hz, 3H), 2.16 (s, 3H), 2.39 (s, 3H), 4.06 (q, 6.46 Hz, 1H), 4.13 (d, 11.76 Hz, 1H), 4.21 (d, 11.72 Hz, 1H), 7.16 (m, 2H), 7.31 (m, 5H), 7.84 (d, 8.20 Hz, 2H), 8.36 (s, 1H); ¹³C NMR (400 MHz, CDCl₃) δ 4.95, 19.22, 68.27, 70.42, 103.48, 127.91, 129.67, 135.33, 137.72, 141.02, 144.36.



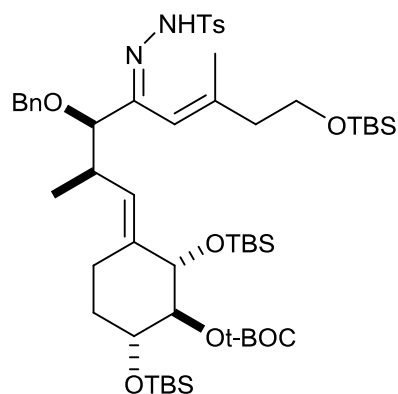
enone 48.2. A mixture of palladium acetate (14 mg, 0.062 mmol) and TDMPP (27 mg, 0.061 mmol) in THF (2 mL) was stirred 15 min at room temperature. A solution of ynone **45.3** (0.250 g, 1.24 mmol) and 3-butyne-1-ol (0.14 mL, 1.85 mmol) was added. After 6 h of stirring at room temperature, the reaction was concentrated in vacuo and the residue was purified by flash chromatography 15/85 ethyl acetate/hexane to give **48.2** (0.18 g, 84% yield). ^1H NMR (400 MHz, CDCl_3) δ 1.35 (d, J = 6.92 Hz, 3H), 2.33 (d, J = 1.40 Hz, 3H), 2.68 (t, J = 6.26 Hz, 2H), 3.81 (t, J = 6.28, 2H), 3.94 (q, J = 6.86 Hz, 1H), 4.44 (d, J = 11.68 Hz, 1H), 4.59 (d, J = 11.64 Hz, 1H), 6.77 (s, 1H), 7.73 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ 17.96, 20.93, 23.99, 60.87, 71.89, 81.14, 92.74, 125.61, 127.89, 137.9, 140.00, 202.12.



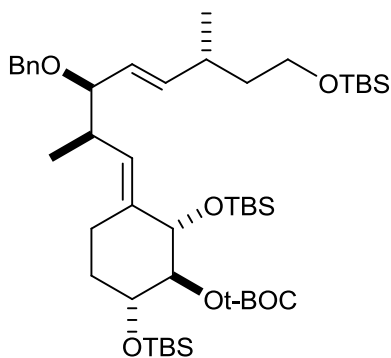
Ynone 49.2. To a dry round bottom flask was stirred Weinreb amide **36.2** (0.14 g, 0.2 mmol) in ether (10 mL) at -78°C . After 20 min., propynyl magnesium bromide (1.92 mL, 0.96 mmol) was added dropwise and the reaction temperature remained at -78°C for an additional 3 h. The reaction mixture was quenched with saturated NH_4Cl (aq) solution, extracted with ether, dried over MgSO_4 , and concentrated in vacuo. The crude product was purified by Flash chromatography on silica gel using 10/90 ethyl acetate/hexane and provided the ynone **49.2** (0.062 g, 46%) as clear oil. ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.06 (s, 6H), 0.08 (s, 3H), 0.88 (d, J = 1.52 Hz, 18H), 0.94 (d, J = 6.56 Hz, 3H), 1.28 (m, 3H), 1.49 (s, 9H), 1.60 (s, 2H), 2.07 (s, 3H), 2.12 (m, 1H), 3.12 (t, J = 9.42 Hz, 1H), 3.49 (m, 1H), 3.62 (d, J = 5.56 Hz, 1H), 4.36 (d, J = 11.36 Hz, 1H), 4.46 (t, J = 9.10 Hz, 1H), 4.66 (d, J = 11.36 Hz, 1H), 7.37 (m, 5H); ^{13}C NMR (400 MHz, CDCl_3) δ -4.60, -4.48, -3.88, -3.63, 4.49, 18.00, 25.83, 26.09, 28.07, 33.08, 33.70, 36.94, 41.82, 72.60, 72.87, 79.39, 81.28, 83.55, 89.04, 93.52, 128.28, 128.38, 137.41, 153.20, 189.88.



Dieneone 50.3. *n*-BuLi (0.80 mL, 0.69 mmol) was added dropwise to a solution of iodide **37.3** (0.40 g, 1.2 mmol) in anhydrous ether (12 mL) at -78 °C and stirred for 30 minutes. The solution was then cannulated dropwise to amide **35.2** (0.43 g, 0.61 mmol) in ether (12 mL) at -78 °C. The solution was stirred at -78 °C for 4 h until no starting material remained by TLC analysis. The reaction was quenched with AcOH (0.07 mL, 1.22 mmol), washed in saturated NH₄Cl (aq), extracted in ether, dried with MgSO₄ and concentrated in vacuo. The oily residue was purified by flash chromatography on silica gel using 10/90 ethyl acetate/hexane provided the dieneone **50.3** in 77% as a clear oil; IR (film) 3441, 1724 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ; -0.01 – 0.08 (m, 18H), 0.86 (m, 18H), 0.90 (d, *J* = 1.41 Hz, 2H), 0.92 (d, *J* = 1.53 Hz, 9H), 0.97 (d, *J* = 6.78 Hz, 3H), 1.27 (s, 1H), 1.30 (d, *J* = 1.65 Hz, 1H), 1.34 (s, 1H), 1.48 (s, 9H), 1.58 (s, 1H), 1.78 (d, *J* = 9.67, 1H), 2.23 (s, 3H), 2.46 (m, 3H), 2.80 (m, 1H), 3.55 (d, *J* = 5.73 Hz, 1H), 3.78 (t, *J* = 6.48 Hz, 2H), 3.80 (d, *J* = 9.42 Hz, 1H), 4.30 (m, 1H), 4.41 (d, *J* = 11.77 Hz, 1H), 4.61 (d, *J* = 11.58 Hz, 1H), 5.63 (d, *J* = 10.56 Hz, 1H), 6.51 (s, 1H), 7.35 (m, 5H); ¹³C NMR (400 MHz, CDCl₃) δ -5.37, -5.30, -4.91, -4.04, 1.02, 17.81, 18.14, 20.19, 23.24, 25.95, 27.52, 28.00, 33.52, 35.59, 37.96, 44.70, 61.43, 62.25, 72.42, 72.50, 72.58, 73.82, 80.92, 83.96, 89.62, 89.80, 120.53, 120.75, 124.02, 127.53, 127.65, 127.73, 128.31, 136.43, 137.89, 152.86, 159.38, 160.64, 203.22. HRMS (*m/z*): [*M*]⁺ calcd. for C₄₆H₈₂O₈Si₃, 846.5317; found, 846.5316.



. **Tosyl hydrazone 51.2.** To a solution of dieneone **50.3** (0.15 g, .177 mmol) in CH_2Cl_2 was added tosyl hydrazide (0.165 g, 0.877 mmol) and AcOH (7.00 μL , 0.184 mmol) and stirred overnight at rt. The crude reaction mixture was concentrated in vacuo, purified by flash chromatography on silica gel using 20/80 ethyl acetate/hexane to give *tosyl hydrazone 51.2* (0.11 g, 63%) as a white solid. IR (film) 3473, 1750 cm^{-1} ^1H NMR (400 MHz, CDCl_3) δ -.03 (m, 6H), 0.03 (s, 3H), 0.08 (s, 9H), 0.12 (m, 2H), 0.70 (t, J = 6.74 Hz, 3H), 0.83 (s, 9H), 0.87 (s, 3H), 0.90 (s, 15H), 0.92 (s, 3H), 1.27 (s, 3H), 1.39 (s, 1H), 1.49 (s, 9H), 1.66 (s, 3H), 1.90 (s, 1H), 2.06 (m, 1H), 2.19 (s, 3H), 2.33 (m, 3H), 2.37 (m, 2H), 2.45 (d, J = 4.41 Hz, 1H), 2.58 (m, 1H), 3.60 (m, 2H), 3.77 (t, J = 5.97 Hz, 2H), 3.85 (m, 2H), 4.01 (d, J = 11.35 Hz, 1H), 4.43 (m, 1H), 5.45 (d, J = 10.02 Hz, 1H), 5.49 (s, 1H), 7.05 (m, 2H), 7.21 (m, 2H), 7.71 (s, 1H), 7.83 (m, 2H); ^{13}C NMR (400 MHz, CDCl_3) δ -5.32, -4.90, -4.85, -4.45, 17.13, 17.32, 17.86, 18.19, 18.35, 18.54, 20.51, 21.48, 21.50, 22.77, 23.37, 25.76, 25.96, 26.00, 26.22, 28.04, 33.53, 35.12, 35.21, 42.46, 60.18, 61.09, 71.17, 72.50, 73.84, 81.05, 83.88, 86.88, 87.29, 114.47, 115.61, 125.49, 125.56, 127.51, 127.91, 128.02, 128.08, 128.29, 129.45, 129.53, 135.47, 135.81, 136.39, 136.50, 137.72, 137.77, 144.07, 146.73, 147.61, 153.03, 154.96. HRMS (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{53}\text{H}_{90}\text{N}_2\text{O}_9\text{Si}_3$, 1014.5675; found, 1014.5675



Diene 57.3. To a mixture of hydrazone **51.2** (0.087 g, 0.085 mmol) and $\text{CH}_3\text{CO}_2\text{H}$ (0.04 mL, 0.69 mmol) in freshly distilled CHCl_3 (2 mL), catecholborane (0.055 mL, 0.513

mmol) was added dropwise at -42 °C. After 2 h, NaOAc·3H₂O was added and the reaction mixture was heated up to 55 °C for 16 h. After completion of the reaction, the mixture was poured into water and extracted with ether. The crude material was purified by flash chromatography over silica gel with 95:5 hexane/EtOAc to obtain pure diene **57.3** as colorless oil (yield 67 %). ¹H NMR (400 MHz, CDCl₃) δ -0.01 – 0.07 (m, 18H), 0.84 – 0.89 (m, 27H), 0.87 (m, 3H) 1.05 (d, J = 6.75 Hz, 3H), 1.26 (m, 2H), 1.48 (s, 9H), 1.57 (dd, J = 1.95 Hz, J = 2.01, 3H), 1.79 (m, 1H), 2.34 (quint, J = 6.9 Hz, 1H), 2.53 (m, 2H), 2.60 (m, 1H), 3.43 (t, J = 7.49 Hz, 1H), 3.63 (m, 1H), 3.87 (d, J = 9.60 Hz, 1H), 4.30 (d, J = 11.97 Hz, 1H), 4.46 (t, J = 9.12, 1H), 4.52 (d, J = 11.97, 1H), 5.29 (dd, J = 15.6 Hz, J = 8.2 Hz, 1H), 5.48 (d, J = 11.70 Hz, 1H), 5.54 (dd, J = 15.40 Hz, J = 7.40 Hz, 1H), 7.32 – 7.33 (m, 5H); ¹³C NMR (400 MHz, CDCl₃) δ -5.24, -4.86, -4.38, 1.03, 17.24, 17.89, 18.20, 18.33, 20.65, 23.37, 25.78, 25.97, 28.03, 33.05, 33.83, 37.00, 39.78, 61.38, 69.21, 72.67, 73.94, 81.05, 83.97, 84.16, 126.04, 126.94, 127.24, 127.84, 128.29, 135.77, 138.85, 140.87, 153.06. HRMS (m/z): [M]⁺ calcd. for C₄₆H₈₄O₇Si₃, 832.5525; found, 832.5519

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