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Studies Toward the Total Synthesis of Antascomicin B

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STUDIES TOWARD THE TOTAL SYNTHESIS OF ANTASCOMICIN B

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of the requirements for the degree of
Doctor of Philosophy in Chemistry

By

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ABSTRACT:

The following dissertation describes synthetic efforts toward the synthesis of the C21-C34 fragment of antascomicin B. Our initial enzymatic approach is detailed as well as an asymmetric transfer hydrogenation (ATH) strategy that will be used in the eventual total synthesis of the molecule. Several investigations into anomalies observed during (ATH) reactions are also discussed.

This dissertation is approved for recommendation to the Graduate Council.

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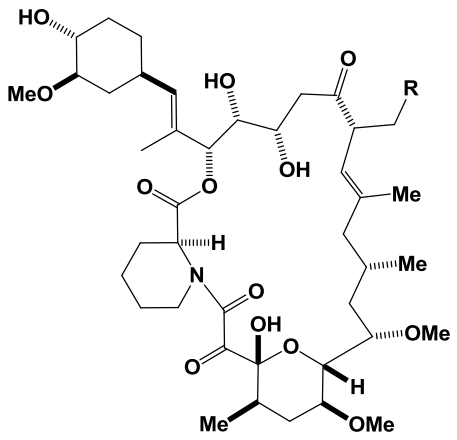
1.1 Introduction

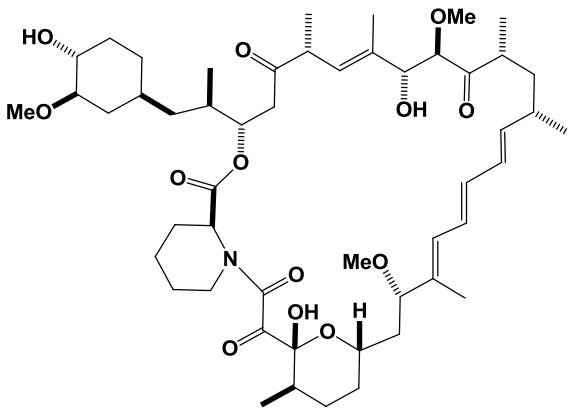
1.1.1 Antascomicin B

FK-520 (Ascomycin, Immunomycin), rapamycin (Rapamune®, sirolimus), and FK-506 (Prograf®, tacrolimus, fujimycin) have powerful immunosuppressive properties (Figure 1).[1, 2, 3] These molecules are not directly immunosuppressive, but rather they form a complex with the intracellular binding protein FKBP12 (FK-506 binding protein, macrophilin), and it is this complex that is responsible for the immunosuppressive effects. Both FK-506/FK-520 and rapamycin bind to FKBP12 in a similar fashion, but they differ in non-FKBP12 binding (effector) domains which results in different modes of immunosuppressive action. The open effector domain of both the FK-506/FKBP12 and FK-520/FKBP12 complexes binds calcineurin,[1, 4-6] forming a ternary complex that prevents the transcription of genes responsible for coding interleukin-2 (IL-2) and its receptor. The target of the effector domain of the rapamycin/FKBP12 complex is mTOR, a protein responsible for controlling cell growth and proliferation. This ternary complex blocks entry of lymphocytes into the cell, thus inhibiting cell proliferation.[3, 6, 7]

Figure 1



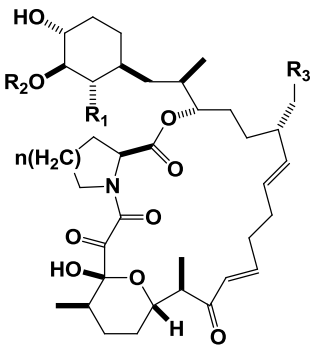
	FKBP12 IC_{50}
FK-506 R = $CHCH_2$	2.0
FK-520 R = CH_3	1.6



	FKBP12 IC_{50}
Rapamycin	2.0

In 1996, a group at Sandoz Pharma conducted a study to identify strains of bacteria that could produce macrophilin-binding metabolites.[8] Of the approximately 12,000 strains that were tested, only one produced compounds that could bind macrophilin. The producing strain was a soil bacterium of the genus *Micromonospora* collected from soil samples from China. The active compounds of interest are known as antascomicin A, B, C, D, and E (Figure 2).

Figure 2



					FKBP12 IC_{50}
Antascomicin A	R_1=H	R_2=H	R_3=H	n=2	2
Antascomicin B	R_1=OH	R_2=H	R_3=H	n=2	0.7
Antascomicin C	R_1=OH	R_2=CH_3	R_3=H	n=2	1
Antascomicin D	R_1=H	R_2=H	R_3=H	n=1	5.2
Antascomicin E	R_1=H	R_2=H	R_3=OH	n=2	0.7

The antascomicins bind FKBP12 to the same degree as rapamycin and FK506, yet show no immunosuppressive activity. They do not inhibit proliferation of T-cells and, moreover, they actually antagonize the inhibitory effects of rapamycin and FK506.[9]

In 1992, Snyder discovered that FKBP12 exists in much higher concentrations in the brain and nervous system than the immune system.[10] This was the first indication that immunophilins such as FKBP12 might play a neural role. Snyder later showed that the FKBP12/rapamycin and FKBP12/FK506 complexes did in fact display neurotrophic activity in mouse models.[11] However, the immunosuppressive characteristics of these complexes limited their usefulness in the treatment of damaged nerves. This encouraged researchers to seek out non-immunosuppressive FKBP12 binding ligands.[12]

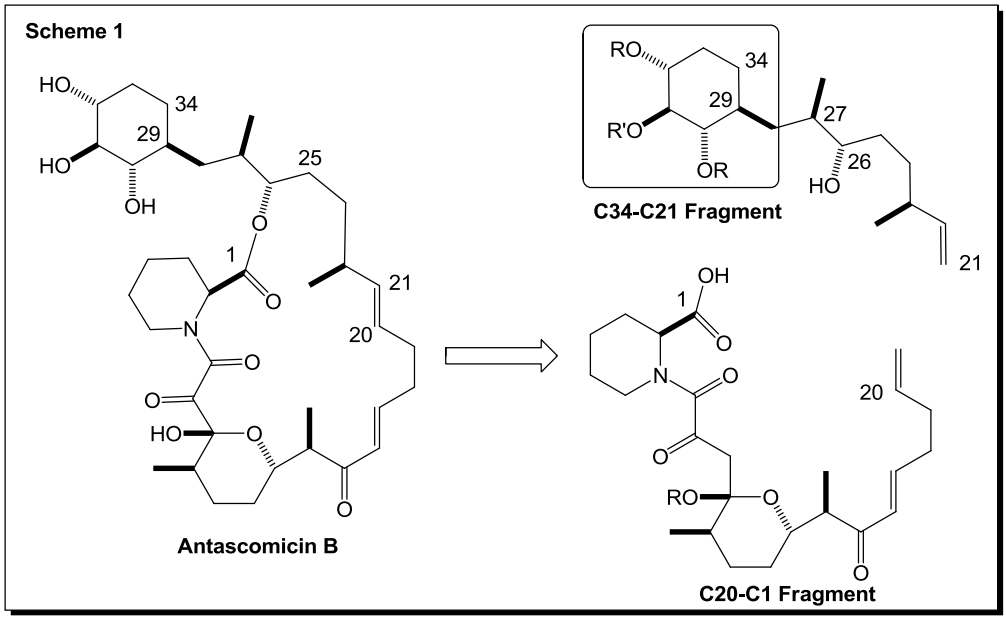
The antascomicins and other small molecules that bind FKBP12, but do not cause immunosuppression, lack the effector domain required for calcineurin or mTOR.[13] FKBP12 binding complexes that lack an effector domain were shown to have potent neuroprotective and neuroregenerative properties in mouse models of Parkinson's disease.[12] The antascomicins are among the few naturally occurring molecules that have been identified that bind FKBP12 but do not show immunosuppressive activities. This leads us to believe that the antascomicins could be potential chemotherapeutics in the treatment of the devastating, neurodegenerative Parkinson's disease.[12, 13]

Biologically, antascomicin B is an interesting target because, of all the antascomicins, it showed the greatest affinity towards binding with FKBP12, is mobile across the blood brain barrier,[10] and does not show any immunosuppressive effects.[12]

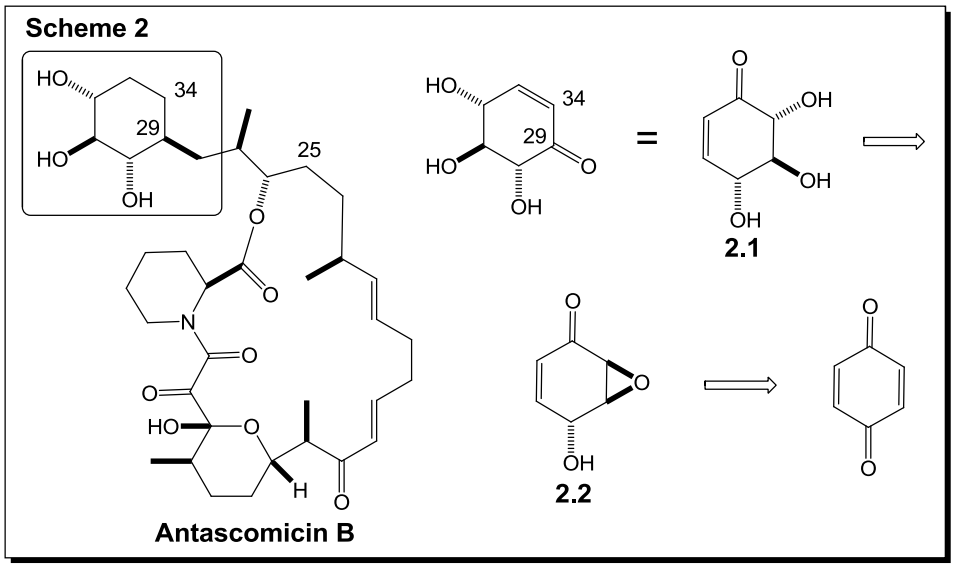
In 2005 the total synthesis of antascomicin B was reported by Stephen Ley's group at Cambridge University.[14] The C18-C34 fragment of antascomicin A has been synthesized by Fuwa *et al*.[15] Chakraborty et al. have published syntheses of the C1-C21 and C22-C34 fragments of antascomicin A.[16, 17]

1.1.2 The C34-C29 Unit of Antascomicin B

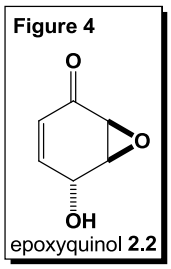
Our group has been engaged in the total synthesis of antascomicin B for several years.[18-20] Retrosynthetically, we envision antascomicin B being the product of late convergence of the C20-C1 fragment and the C34-C21 fragment (Figure 3). In this document, we will report the efforts toward the enantioselective synthesis of the C34-C21 fragment. When looking at the C34-C21 region of antascomicin B, a good starting point presented itself as the terminal trihydroxycyclohexyl C29-C34 moiety.



The C29-C34 cyclitol moiety thus provided us with our first synthetic challenge. In order to complete the eventual total synthesis of antascomicin B, we first had to develop an asymmetric method to produce large quantities of the six carbon fragment. A comparatively efficient, albeitn racemic, five-step synthesis of trihydroxyenone **2.1** has previously been reported,[21] In which epoxyquinol **2.2** was hydrolyzed to *anti-anti*-trihydroxyenone **2.1** (Scheme 2). Therefore, the first challenge was obtaining large quantities of enantiopure epoxyquinol **2.2**.



1.1.3 Epoxyquinols



Epoxyquinol **2.2** (Figure 4) is an important intermediate for a number of reasons. It is in itself a very synthetically useful molecule: all 6 carbons possess unique reactivity. This imbues epoxyquinol **2.2** with potentially broad applications in synthesis. The synthesis of the target has been reported previously,[22] but prior to our work,[20] no efficient asymmetric approach to *trans*-epoxyquinol **2.2** had been reported.

The epoxyquinol moiety is the focus of this chapter and two primary topics are covered: asymmetric synthetic strategies toward *trans*-epoxyquinols and the occurrence of *trans*-epoxyquinols in nature.

The first section details syntheses of the desired enantiomer of the six carbon core of either epoxyquinol **2.2** or trihydroxyenone **2.1**. These are syntheses of either **2.2** or **2.1** or syntheses of

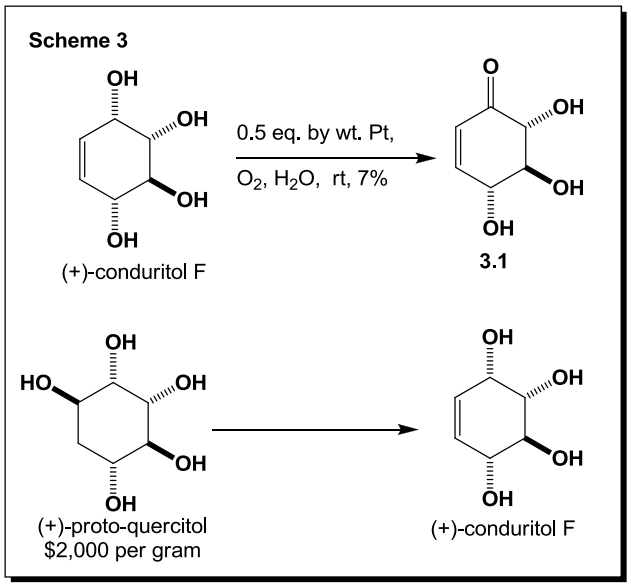
derivatives differentiated only by protecting groups. The following section will cover representative technologies developed toward accessing derivatives or enantiomers of the desired *trans*-epoxyquinol. We will focus attention on elements of the syntheses concerned with how the epoxyquinol was accessed. The final section will cover *trans*-epoxyquinoid natural products. If a relevant asymmetric synthesis has not been covered before the final section, it will be discussed therein.

Several research groups have developed unique methodologies for accessing the epoxyquinol, and there is a general trend for groups to employ their respective technologies toward the syntheses of multiple natural products. That being said, each methodology will be discussed only once using a representative example. If a previously reviewed methodology is applied to the synthesis of a natural product, it will only be mentioned briefly in the text.

1.2 Synthetic Strategies Toward the Epoxyquinol or Trihydroxycyclohexenone Core

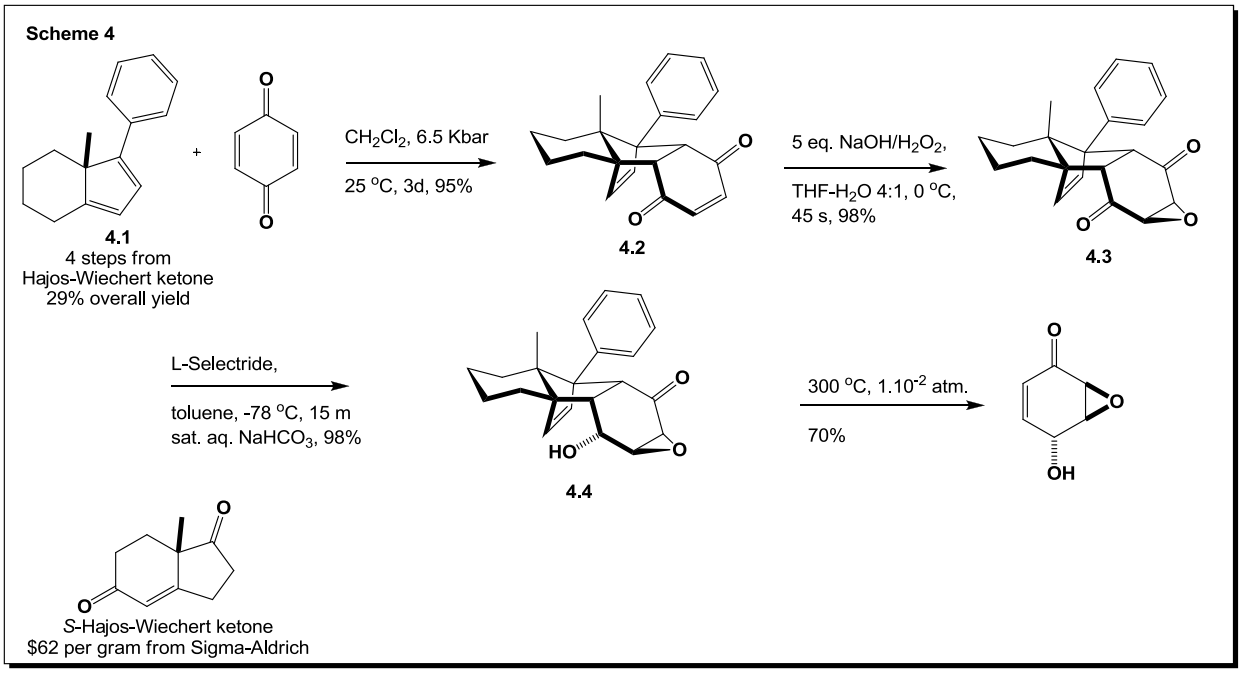
1.2.1 Paulsen

Paulsen reported the platinum catalyzed oxidation of several carbohydrates and cyclitols and found that (+)-conduritol-F would oxidize to trihydroxy cyclohexenone **3.1** (Scheme 3). He reported that only the axial alcohol was oxidized while equatorial alcohols were left intact.[23] (+)-Conduritol F is a naturally occurring substance and was isolated in 1962 from the Oxeye Daisy *Chrysanthemum leucanrhemum*, albeit in small quantities.[24] The synthesis of (+)-conduritol F was reported most recently in five steps from commercially available (+)-proto-quercitol, which is $202 for 100 mg from TCI America (Scheme 2).[25, 26] The high cost of the starting material, combined with the poor yield of the final transformation, make this an impractical approach to the trihydroxycyclohexenone.



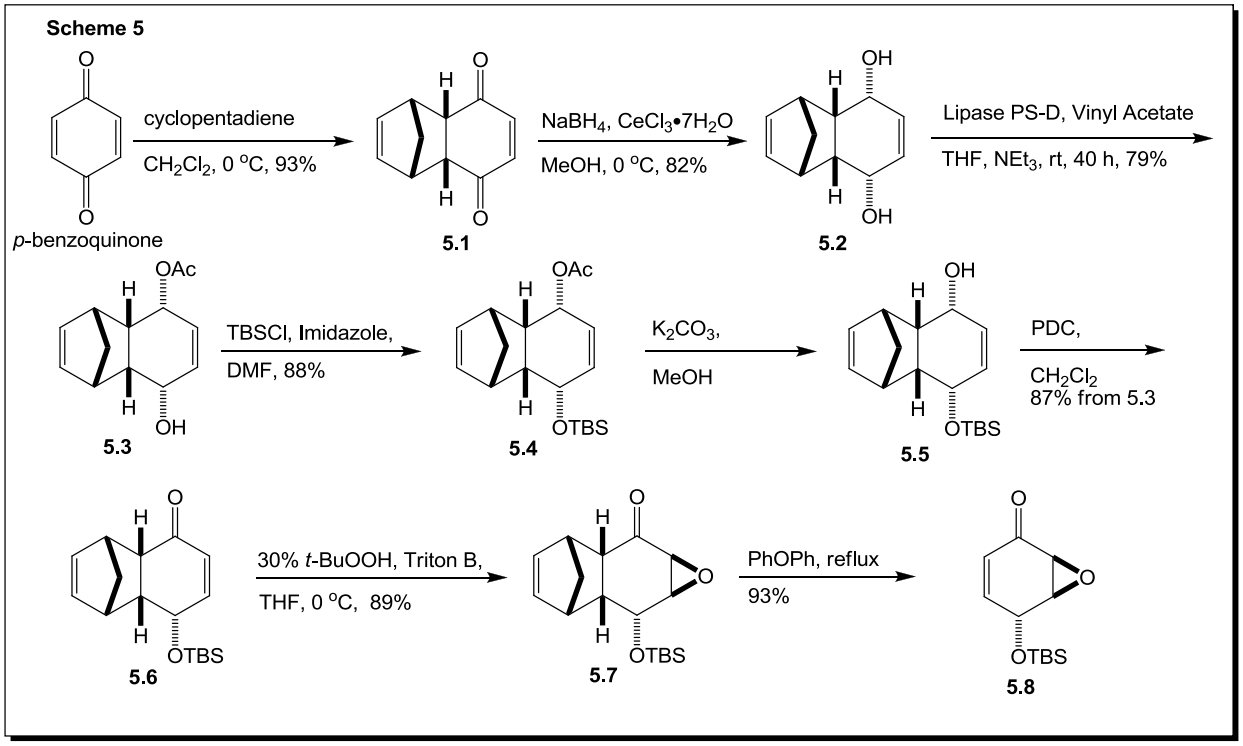
1.2.2 Winterfeldt

In 1993, Winterfeldt *et al.* described the synthesis of the epoxyquinol via Diels-Alder reaction between *p*-benzoquinone and chiral diene **4.1**, followed by epoxidation to **4.3**, which was regio- and diastereoselectively reduced to alcohol **4.4**. Retro Diels-Alder under vacuum furnished the epoxyquinol in high yield (Scheme 4). Diene **4.1** was obtained from Hajos-Wiechert ketone in 4 steps and 29% overall yield. The final retro Diels-Alder was reported on a 162 mg scale and was executed in a kugelrohr apparatus at high temperatures.[27] The major drawback to this strategy is the extra effort required to synthesize chiral diene **4.1**.



1.2.3 Ogasawara

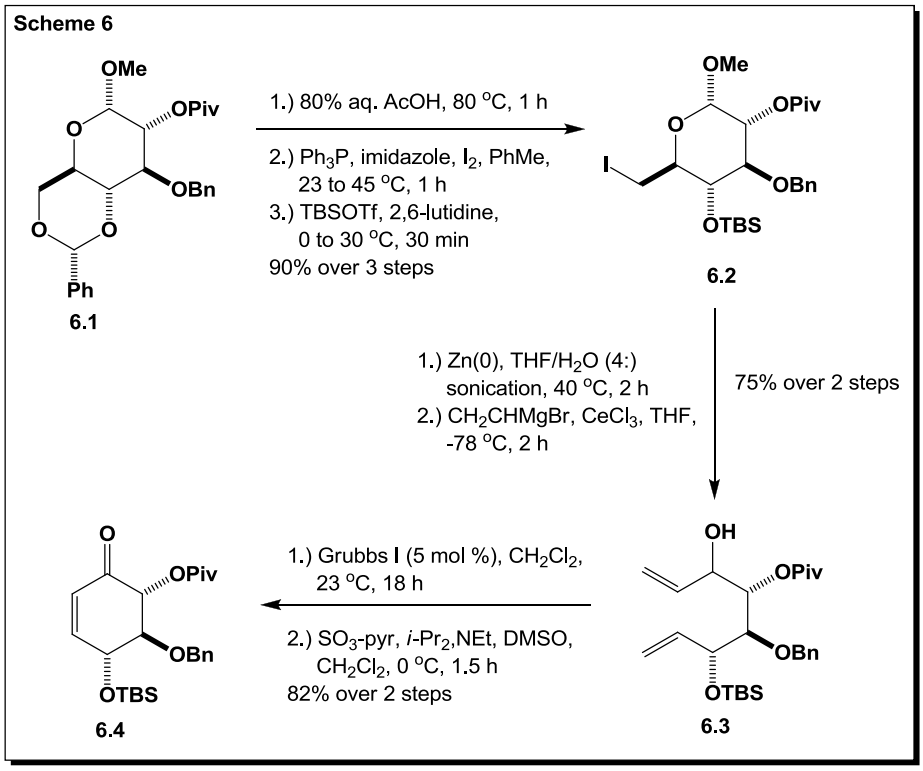
In a report of the total synthesis of the natural product (-)-tricholomenyn A in 1996, Ogasawara and Kamikubo reported the preparation of enantiopure epoxyquinol silylether **5.8** as an intermediate (Scheme 5).[28] This route is one of the most cited in the literature and the enzymatic desymmetrization approach has been used to access myriad chemical targets.[29] Most recently the methodology was applied in the syntheses of several polyoxygenated cyclohexanoids.[30] However, this strategy has several drawbacks. First, even though the Luche reduction has been reported on a 50 gram scale, [31] in our hands, reduction of Diels-Alder adduct **5.1** proved unscalable beyond a 3 gram threshold. Second, the desymmetrization step requires a one equivalent by weight loading of the immobilized enzyme PS-D; the enzyme is quite expensive at around $9 per gram from Sigma-Aldrich. Finally, the synthesis suffers from operational inefficiency in general, involving cumbersome protection-deprotection and redox sequences.



1.2.4 Shair

Most recently, Shair *et al.* developed a ten-step procedure to produce differentially protected trihydroxycyclohexenone **6.4** starting from methyl-α-D-glucopyranoside (Scheme 6).[32] They used a literature procedure to produce benzylidene acetal **6.1** in 4 steps from methyl-α-D-glucopyranoside.[33] Acidic hydrolysis of the acetal followed by conversion of the primary alcohol to an iodide and silylation of the secondary alcohol afforded iodide **6.2** in good yield. Reductive fragmentation of iodide **6.2** by sonication over zinc powder produced an aldehyde, which was converted to allyl alcohol **6.3** after treatment with vinyl Grignard. Ring closing metathesis via first generation Grubbs catalyst formed the six-membered ring which was oxidized to differentially

protected trihydroxycyclohexenone **6.4** via Parikh-Doering oxidation for a total of ten steps and 26% overall yield.



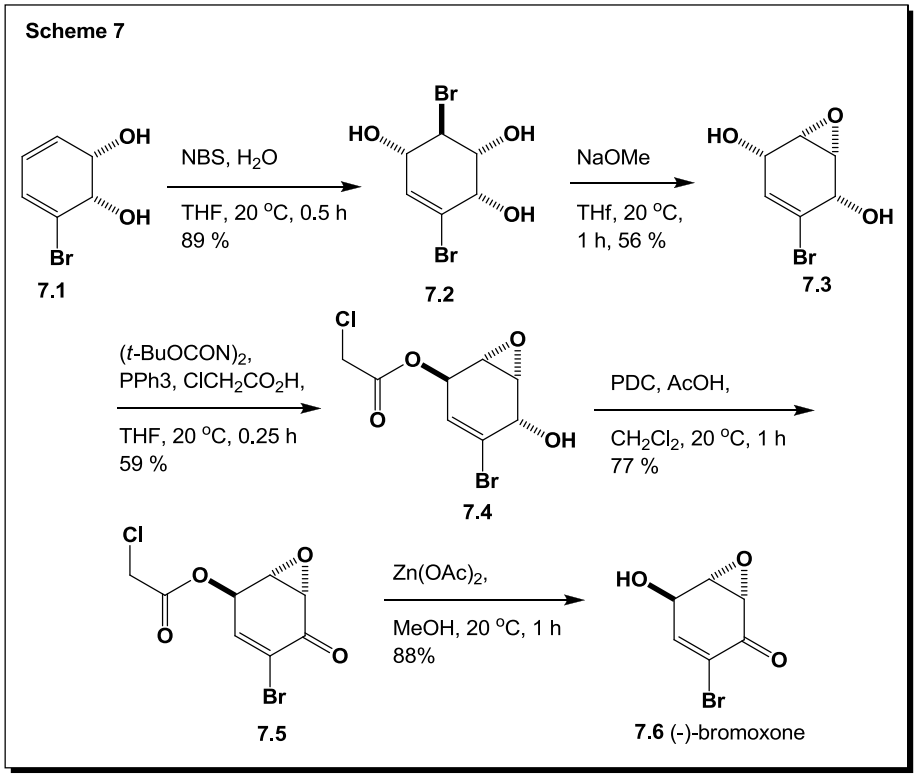
1.3 Syntheses of Epoxyquinol Derivatives

Accessing the core structure of the epoxyquinol has been achieved by several groups by several different methodologies. Those methodologies will be covered in the following section.

1.3.1 Banwell: (-)- Bromoxone

In 2009, Banwell *et al.* published a report wherein (-)-bromoxone (**7.6**) was obtained in enantiopure form from arene *cis*-arenediol halogen **7.1** (Scheme 7).[34] Bromodiol **7.1** is the product of dihydroxylation of bromobenzene mediated by toluene dioxygenase[35] and can be purchased

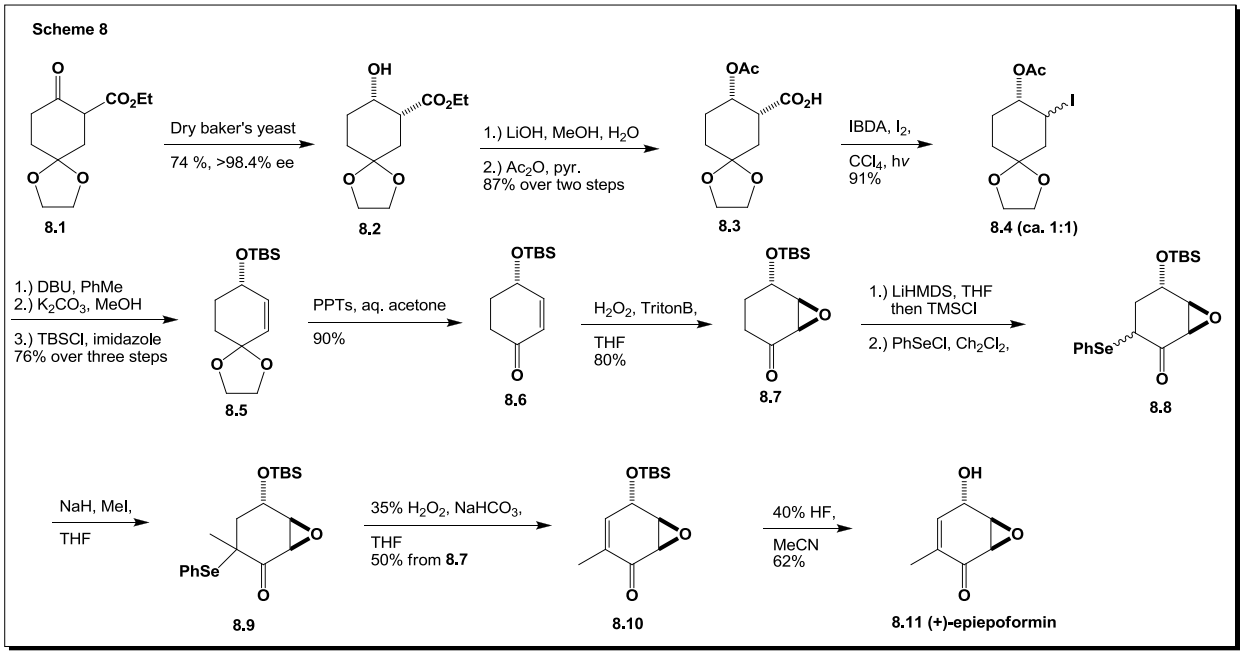
from Sigma-Aldrich for $291 for 5 g. Bromodiol **7.1** was converted to bromohydrin **7.2** which was selectively converted to epoxide **7.3** upon treatment with sodium methoxide. Mitsunobu reaction to the alcohol with chloroacetic acid produced ester **7.4,** thus establishing the *trans*-hydroxy relationship to the epoxide. Oxidation of the remaining alcohol followed by deprotection gave the natural product (-)-bromoxone (**7.6**) in 5 steps and 20% overall yield from bromodiol **7.1.**



1.3.2 Kitahara: (+)- Epiepoformin

Following a procedure developed in 1985,[36] Kitahara's group was able to reduce β-ketoester **8.1** into the corresponding β-hydroxyester **8.2** with high enantioselectivity using baker's yeast (Scheme 8).[37] Hydrolysis of the ester followed by acylation of the secondary alcohol led to acid **8.3**. Oxidative decarboxylation of acid **8.3** delivered a diastereomeric mixture of iodides **8.4**.

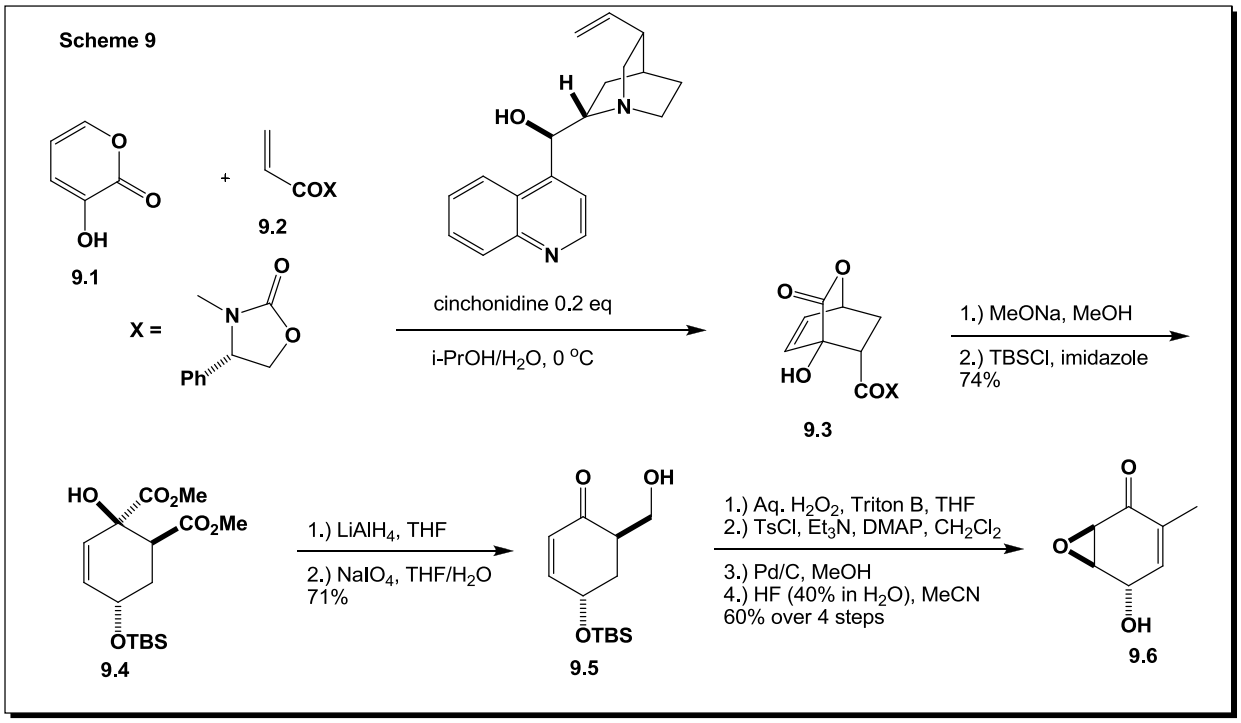
The scrambling of this stereocenter was inconsequential, since subsequent dehydriodination eventually removed it. Hydrolysis of the acetate followed by reprotection as the silylether afforded **8.6**. Deacetalization to enone **8.6** was followed by stereoselective epoxidation to **8.7,** which was then converted to phenylselenide **8.8** in two steps. A methyl group was then introduced via the enolate of **8.8** to give methyl selenide **8.9**. Subsequent oxidative elimination of PhHSe=O and deprotection of *trans*-hydroxy group yielded the natural product (+)-epiepoformin **8.11**.



1.3.3 Okamura: (+)-Epiepoformin

Okamura's group reported the synthesis of (+)-epiepoformin via stoichiometric asymmetric Diels-Alder approach (Scheme 9).[38] Activation of diene **9.1** with the chiral base cinchonidine initiated a Diels-Alder reaction with chiral dienophile **9.2**. The reaction provided Diels-Alder adduct **9.3** as a single diastereomer. Methanolysis followed by silylation of the resultant secondary alcohol gave diester cyclohexene **9.4**. Both esters were reduced to the 1, 2-diol which underwent

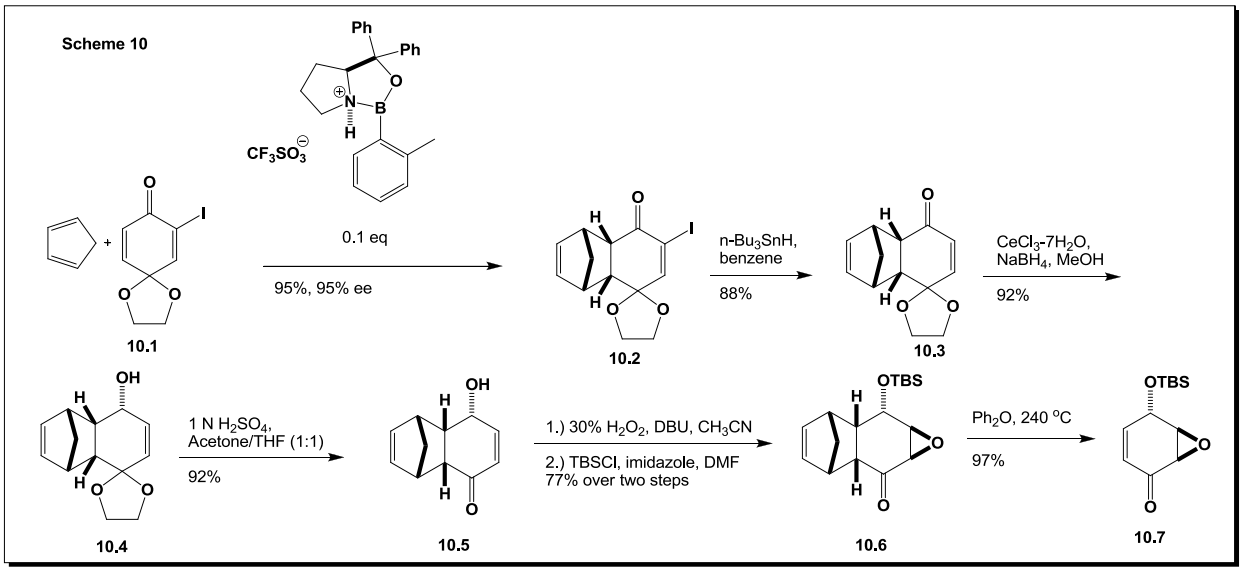
oxidative cleavage to give cyclohexenone **9.5**. The primary alcohol was then converted to the tosylate, which underwent subsequent elimination. The resultant exocyclic double bond was then isomerized to the endocyclic alkene via activated palladium on carbon. Conversion of alcohol **9.5** to the tosylate and hydrogenolysis afforded (+)-epiepoformin (**9.6**) after desilyation.



1.3.4 Ryu: Precursor to (+)-Bromoxone, (+)-Epiepoxydon, and (+)-Epiepoformin

Ryu *et al.* reported syntheses of (+)-bromoxone, (+)-epiepoxydon, and (+)-epiepoformin using a catalytic asymmetric Diels-Alder reaction (Scheme 10).[39] The silyl ether of epoxyquinol **10.7** was an intermediate in the syntheses of all three products. , In the presence of a chiral catalyst, 2-iodo-1,4-quinone monoketal **10.1**, which is obtained in two steps from 2-iodo phenol, underwent an enantioselective Diels-Alder reaction with cyclopentadiene. The iodine was then reduced from the Diels-Alder adduct to give enone **10.3**, which underwent Luche reduction to give

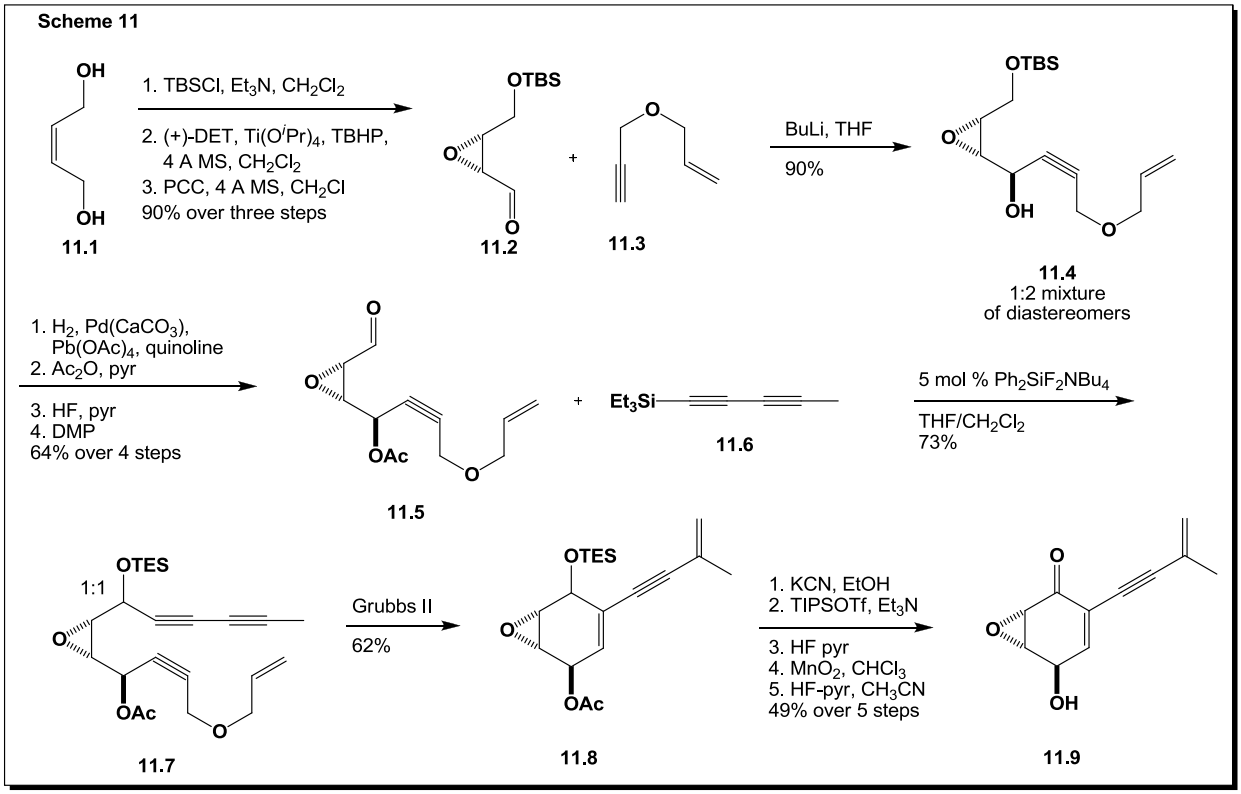
alcohol **10.4**. Deprotection to ketone **10.5** created the opportunity to protect the secondary alcohol as silyl ether **10.6**. Retro Diels-Alder furnished the silyl ether of epoxyquinol **10.7**.



1.3.5. Lee: (-)-Harveynone

Lee *et al*. reported the syntheses of the natural products (-)-harveynone, and (-)-tricholomenyn A using an asymmetric epoxidation and relay metathesis (Scheme 11).[40] Synthesis began with the Sharpless asymmetric epoxidation of diol **11.1**, followed by oxidation to afford epoxy aldehyde **11.2** as a single enantiomer. Addition of acetylide of **11.3** provided a separable 1:2 mixture of diastereomers in favor of the undesired epimer. The desired isomer **11.4** underwent a series of functional group manipulations to yield aldehyde **11.5**, while the undesired ***ent*-11.4** was epimerized to rejoin the synthetic pipeline. Towards the synthesis of harveynone, the aldehyde **11.5** was exposed to triethylsilyl-1, 3-pentadiyne and a catalytic amount of fluoride to provide **11.7**. Upon treatment with second-generation Grubb's catalyst, a relay metathesis occurred to give

dienyne **11.8**. Further functional group manipulation afforded the natural product (-)-harveynone **11.9**.



1.4 Epoxyquinoid Natural Products

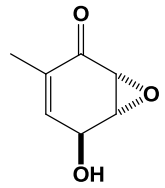
1.4.1 Introduction

The epoxyquinol core appears in a number of natural products, of which the vast majority are fungal metabolites. A rare exception is cetoniacytone A (Figure 13), which is a bacterial metabolite.[41] The current section identifies natural products bearing *trans*-epoxyquinol functionality and discusses biological activity as well as relevant synthetic strategies. Any student interested in epoxyquinols should start their investigation with Marco-Contelles' excellent review.[42] It is a thorough examination of the field up to 2004. It covers natural occurrence, biological

significance, and synthetic efforts toward the epoxyquinoids. That being said, it bears reviewing and updating so as to give the reader of this document a sound background in the subject.

1.4.2 Epiepoformin

Figure 5



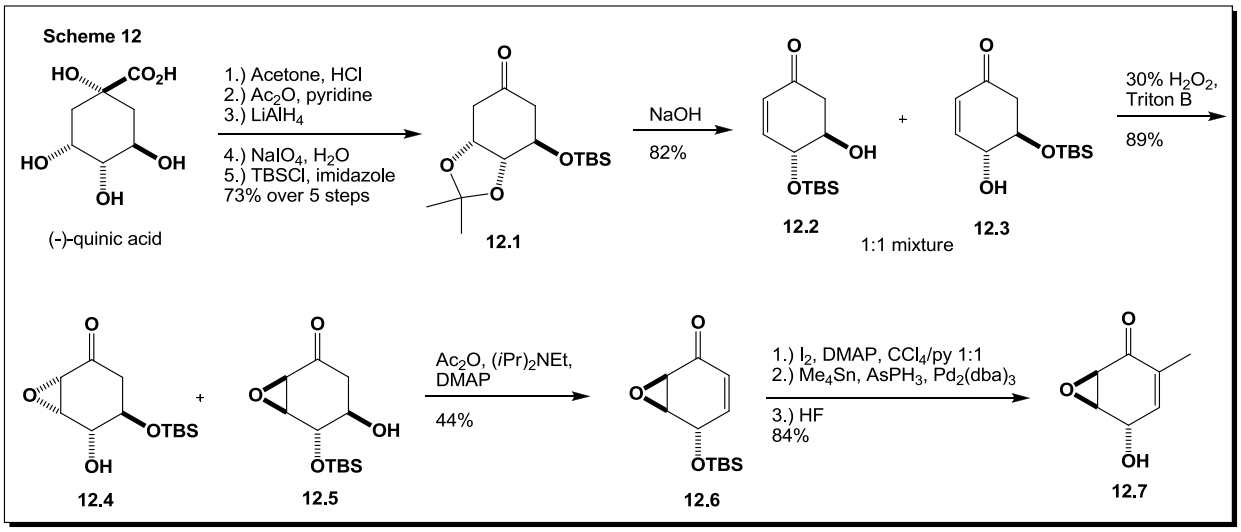
epiepoformin

(+)-Epiepoformin (Figure 5) was first isolated from the culture broth of an unidentified soil fungus taken from the rhizosphere of a potted asparagus plant.[43] The fungus was also found on infected leaves of a crape myrtle tree.[44] (+)-Epiepoformin exhibits strong phytotoxicity and cytotoxicity. Media containing the compound inhibited germination of lettuce seeds significantly. It also provided complete control of redroot pigweed and significant control of white mustard when applied at 4.4 kg/ha.[44]

(±)-Epiepoformin was first synthesized by Ichihara via a retro-Diels Alder approach.[45] The synthesis helped determine the relative configuration of epiepoformin. Ogasawara has accessed both natural (+)-epiepoformin and unnatural (-)-epiepoformin via enzymatic desymmetrization of a *meso*-diol.[46] Okamura accessed (+)-epiepoformin using a stoichiometric asymmetric Diels-Alder approach.[47]

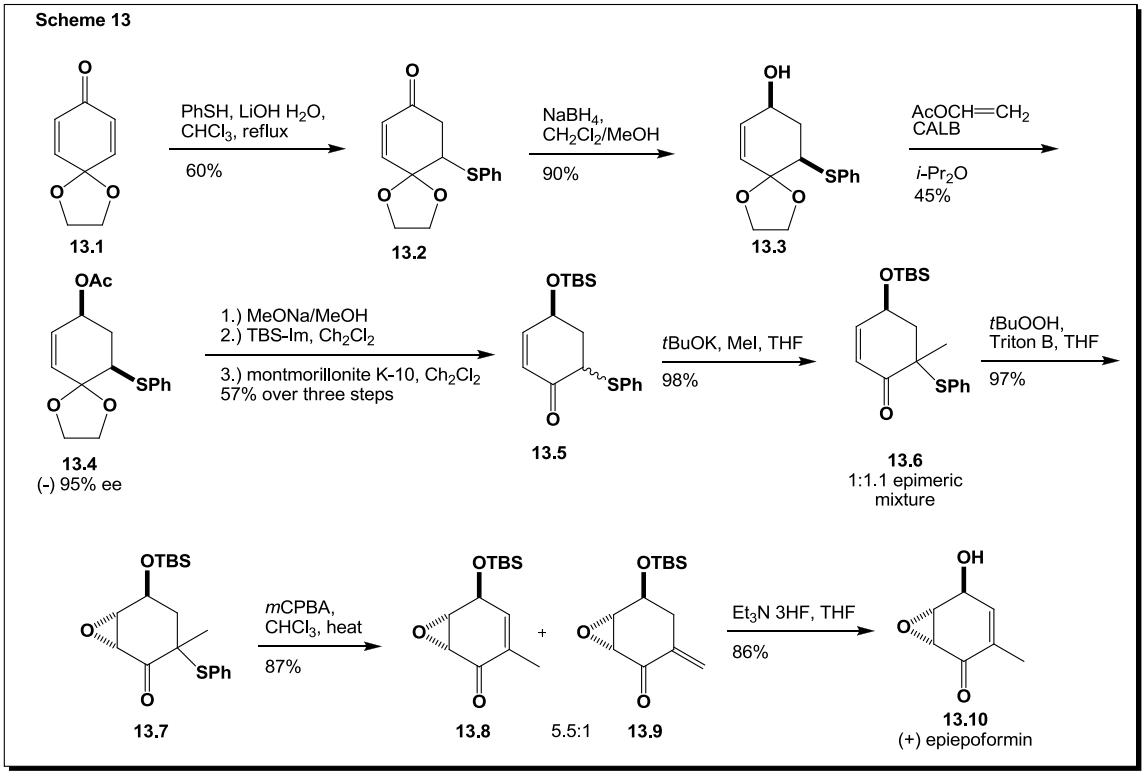
Maycock developed a route to (+)-epiepoformin using quinic acid as starting material (Scheme 12).[48, 49] β-Silylether ketone **12.1** was accessed in 5 steps and 73% overall yield from (-)-quinic acid ($52 for 25 g, Sigma-Aldrich). Base-induced elimination of **12.1** proceeded with an

unintended silyl migration to give a 1:1 mixture of isomeric enones **12.3** and **12.4**, which were epoxidized as a mixture to give epoxides **12.4** and **12.5.** Treatment of epoxides **12.4** and **12.5** with Ac_2O, Hünig's Base, and DMAP gave the desired elimination product **12.6** as well as acylated **12.4** which were separated by column chromatography. Installation of the methyl group followed by deprotection, furnished (+)-epiepoformin in 11 steps with 20% overall yield.

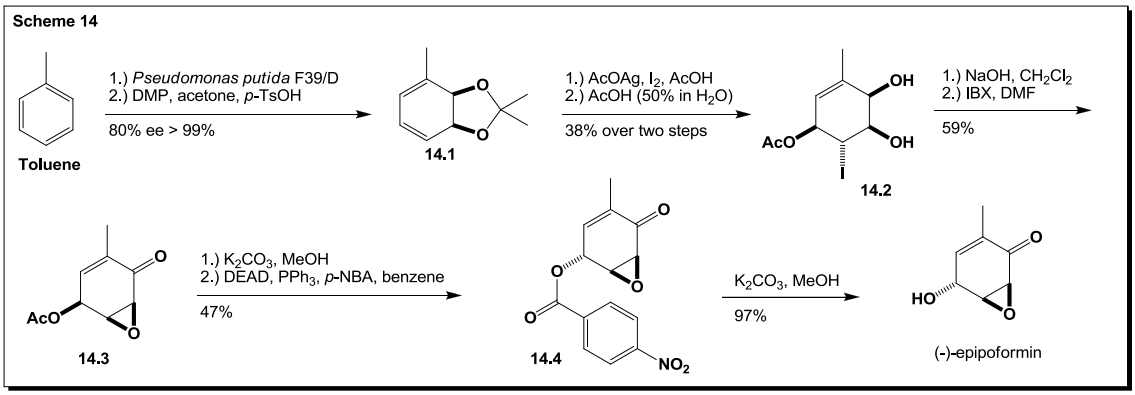


A more recent approach comes from Figuerdo and takes advantage of a thiophenyl directing group and enzymatic resolution to establish the correct stereochemistry (Scheme 13).[50] First, monoacetal protected *p*-benzoquinone **13.1** was treated with thiophenol in the presence of LiOH gave a mixture of products, from which monoaddition product **13.2** was separated. Reduction of enone **13.2** with $NaBH_4$ yielded only *cis*-alcohol, which led to a mixture of enantiomers **13.3** which were separated via enzymatic acylation to yield the desired acetate **13.4**. Deacylation, followed by reprotection as the silylether led to hydrolysis of acetal to form ketone **13.5**. The thiophenyl stereocenter was scrambled during this step but this proved inconsequential. Methylation via the enolate of **13.5** gave a mixture of epimers **13.6**. Employment of a bulky peroxide in the epoxidation step led solely to the *trans*-epoxide **13.7**. Oxidation of the thiophenyl group led to a mixture of both

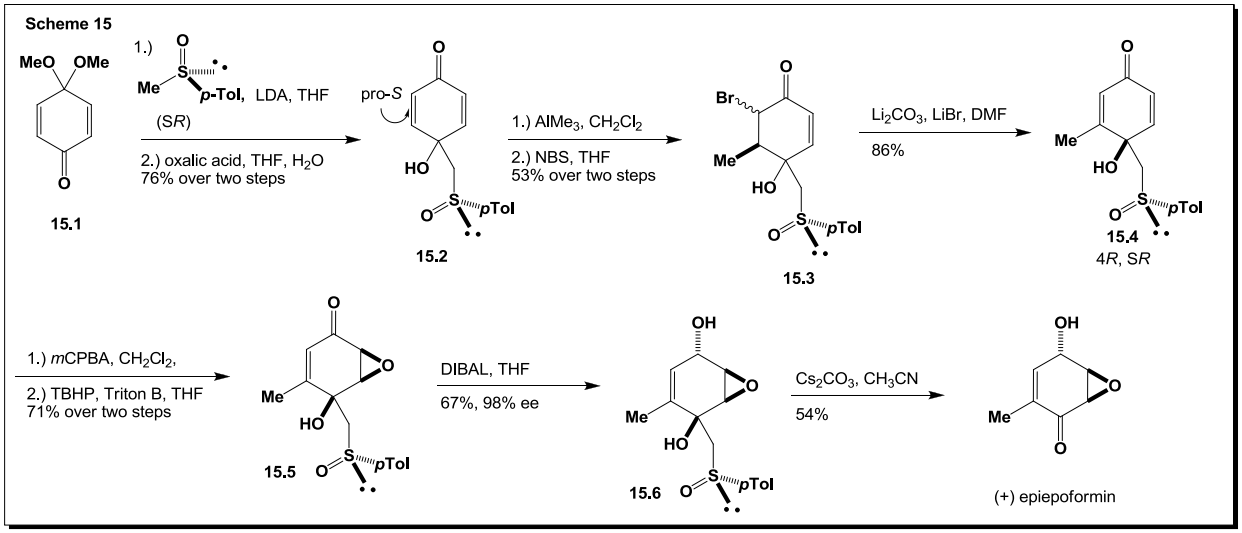
endocyclic and exocyclic alkenes **13.8** and **13.9**. Fortunately, conditions designed to cleave the silylether also isomerized the exocyclic alkene to the natural product (+)-epiepoformin in 10 steps and 10% overall yield from **13.1**.



Schapiro has recently published a synthesis of unnatural (-)-epiepoformin (Scheme 14).[51] The synthesis commenced with whole cell oxidation of toluene to afford a dihydrodiol which was converted to acetonide **14.1**. Selective iodohydroxylation followed by hydrolysis of the acetonide gave iododiol **14.2**. Oxidation and ring closure yielded epoxide **14.3**. Deacylation yielded the natural product (-)-epoformin. Mitsunobu inversion over (-)-epoformin gave *p*-nitrobenzoate **14.4**, which was hydrolyzed to (-)-epiepoformin.

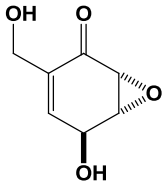


(+)-Epiepoformin was synthesized in Carreno's lab using a chiral sulfoxide auxiliary addition to quinone monoketal **15.1** (Scheme 15).[52] Diastereoselective conjugate addition of a methyl group followed by α-bromination gave **15.3**. Elimination of HBr gave dienone **15.4**. Regioselective epoxidation led to **15.5** which was reduced to epoxy alcohol **15.6**. Base promoted cleavage of sulfoxide **15.6** furnished (+)-epiepoformin for a 9 step synthesis from **15.1** in 9% overall yield.



1.4.3 Epiepoxydon

Figure 6

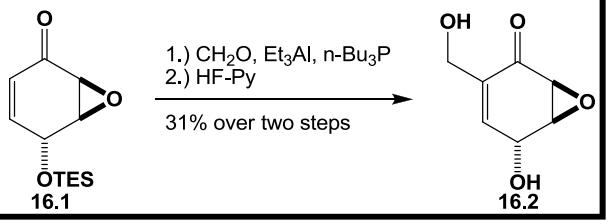


epiepoxydon

Epiepoxydon (Figure 6) was first reported in the literature as a synthetic product.[53] Later, it was isolated from the fermentation broth of a fungus found on diseased crape myrtle leaves.[44] It has also been isolated as an intermediate in the patulin pathway in *Penicillium urticae* and in all instances it has been characterized as a phytotoxin.[54, 55] It was reported to have significant cytotoxic activity in the brine shrimp assay and also towards human cancer cell lines. It exhibited an LC_{50} of 3.6 μg/ml against human breast cancer cells.[56, 57]

Epiepoxydon has been synthesized a number of times: the first effort was from Ichihara's group who reported a racemic synthesis of the target via a retro-Diels Alder strategy.[53, 58, 59] Ogasawara modified the retro-Diels Alder approach to make it asymmetric. [60] Taylor reported a synthesis of (±)-epiepoxydon from epoxyquinol **16.1** using a Baylis-Hillman reaction (Scheme 16).[61]

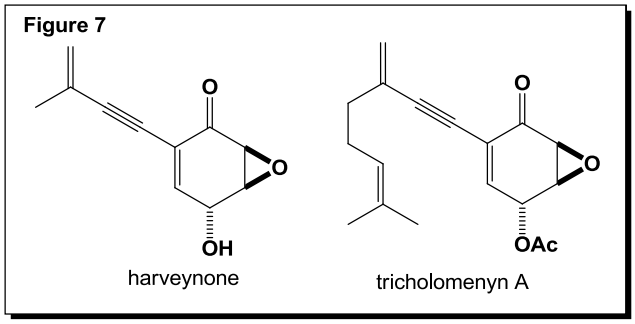
Scheme 16



Mehta has reported the enantioselective synthesis of (+)-epiepoxydon via enzymatic desymmetrization of the corresponding *meso*-diol.[62] Kitahara reported the synthesis of (+)-epiepoxydon using baker's yeast to induce asymmetry.[63] Ryu's group synthesized (+)-epiepoxydon through a catalytic asymmetric Diels-Alder approach.[64] Banwell reported the synthesis of (+)-epiepoxydon where absolute configuration was achieved by dihydroxylation of bromobenzene mediated by toluene dioxygenase.[65]

1.4.4 Harveynone and Tricholomenyn A

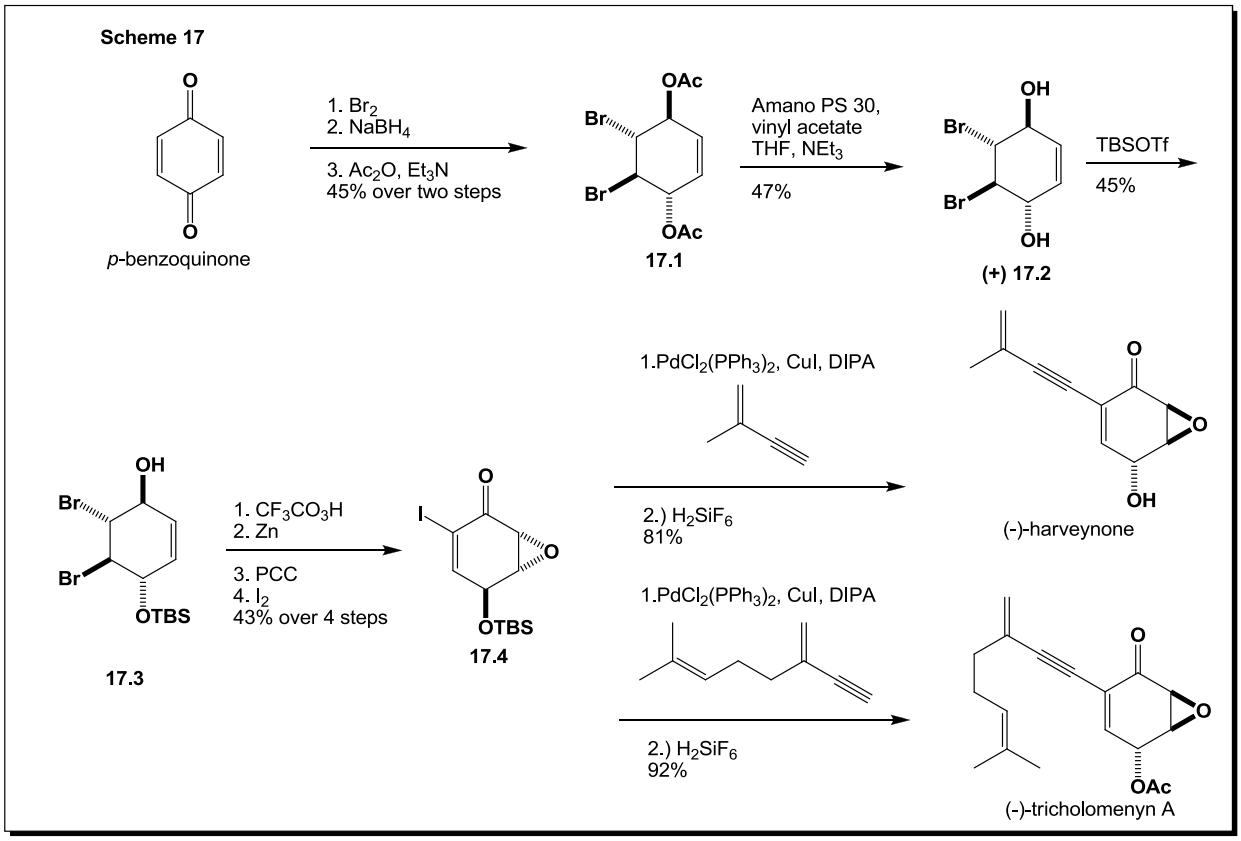
Figure 7



(+)-Harveynone (Figure 7) also know as "PT-toxin" is produced by the tea gray blight fungus *Pestalotiopsis theae* and is a known phytotoxin.[66] (-)-Harveynone was isolated from the fungus *Curvularia harveyi*; it is also phytoxic and has shown anti-tumor activity.[67] Tricholomenyn A was isolated from the fungus *Tricholoma acerbum* and is an antimitotic.[68]

(+)-Harveynone and (-)-tricholomenyn A were both synthesized by Ogasawara using a Stille-coupling reaction betweenan enzymatically derived epoxyquinol and the appropriate acteylenic fragment. Their work determined the absolute configuration of (+)-harveynone.[28, 69] Around the same time, Taylor reported the synthesis of (±)-harveynone and (±)-tricholomenyn A in a fashion similar to Ogasawara's.[70] Maycock reported the synthesis of (+)-harveynone from (-)-quinic acid.[49] Taylor reported a synthesis of the (-) form of both natural products that used

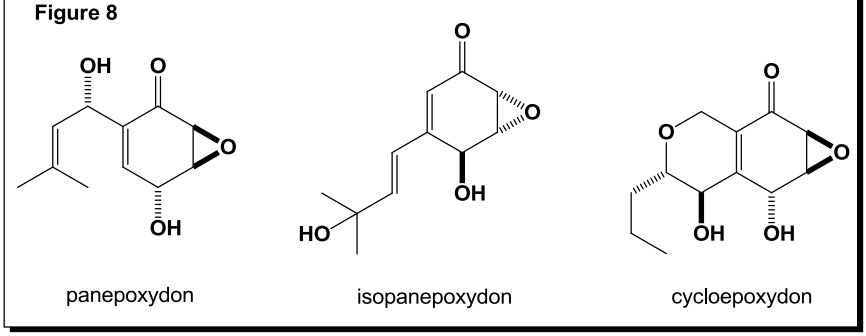
immobilized lipase to effect enzymatic resolution of diacetate **17.1** to enantiopure diol **17.2** (Scheme 17).[70] After functional group manipulation to achieve the epoxyquinol core **17.4**, they were able to furnish both natural products using a Sonogashira coupling with the appropriate alkyne. The syntheses were carried out in 11 total steps with 3% yield for (-)-harveynone and 4% yield for (-)-tricholomenyn A. The epoxyquinol core was built in 9 steps with 4% overall yield.



Negishi reported a similar protocol wherein Pd-catalyzed cross-coupling with the appropriate alkynylzinc precursor afforded racemic harveynone and tricholomenyn A.[71] Total syntheses of (-)-harveynone and (-)-tricoholomenyn A have been reported by Banwell[72, 73] and Lee.[74] Taylor also recently reported the synthesis of (-)-harveynone via halogen-substituted para-benzoquinone monoketal.[75] Carreno reported development of a very late stage intermediate of (+)-harveynone via a chiral sulfoxide auxiliary; unfortunately they were unable to convert it to the natural product.[52]

1.4.5 Panepoxydon, Isopanepoxydon, and Cycloepoxydon

Figure 8

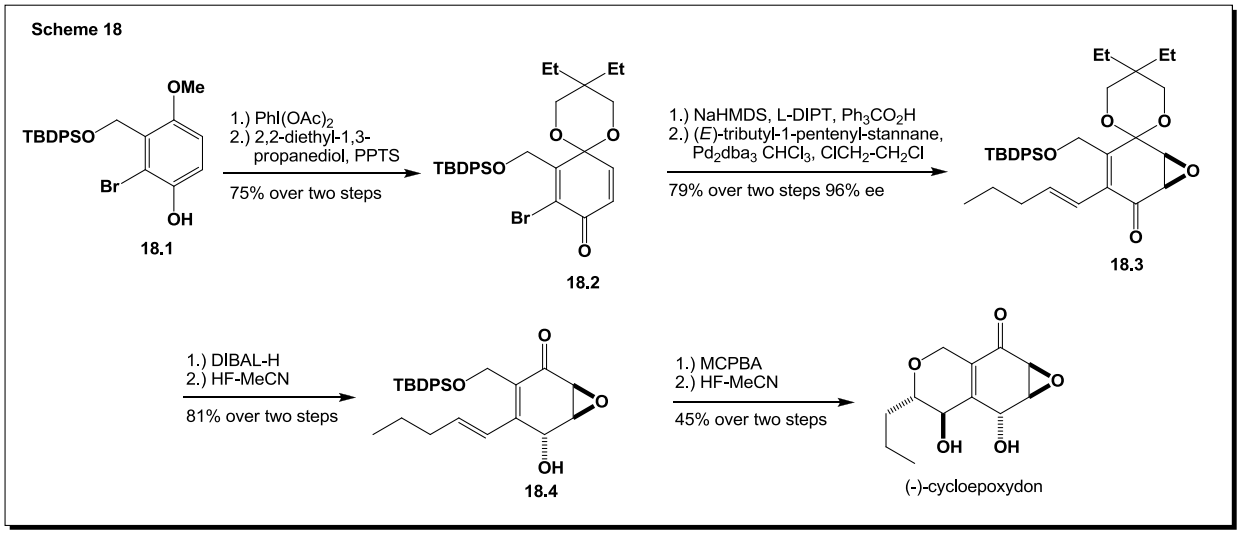


Panepoxydon (Figure 8) was isolated from the culture broth of the fungus *Lentinus crinitus* and the basidiomycete *conchatus*; it was found to inhibit the NF-κB- activated expression of secreted alkaline phosphatase (SEAP) at an IC_{50} value of 5 μg/ml.[76,77] Panepoxydon has been shown to have cytotoxicity values ranging from IC_{50} 0.9-1.9 μg/ml against various cell lines and it showed activity against the malarial parasite *P. falciparum* with an IC_{50} of 3.4 μg/ml.[78] It also showed significant inhibitory activity on trypanthione reductase (TR) in the parasitic protozoa *Trypanosoma* cruzi with IC_{50} of 3.4 μg/ml.[79]

Cycloepoxydon was separated from the culture broth of deuteromycete 45-93.[77] It inhibited the TPA-induced NF-κB- and AP-1- mediated SEAP expression with observed IC_{50} of 1-2 μg/ml and 3-5 μg/ml, respectively.[76, 80]

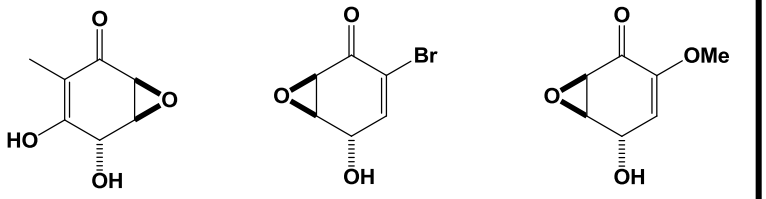
Crews and Woods accomplished the total syntheses of (±)-panepoxydon and (±)-isopanepoxydon.[77] Mehta reported the synthesis of cycloepoxydon via an enzymatic kinetic resolution of a racemic epoxyquinol.[81] Porco reported the total synthesis of (-)-cycloepoxydon via an asymmetric epoxidation mediated by tartrate (Scheme 18).[82] The synthesis began with arene **18.1** which was accessed from commercially available 2, 5-dihydroxybenzaldehyde ($14 per gram

from Sigma-Aldrich) in 5 steps in 59% overall yield. Hypervalent iodine oxidation gave a dimethoxyketal which was transketalized to **18.2**. Tartrate mediated asymmetric nucleophilic epoxidation and subsequent Stille coupling gave epoxide**18.3**, which was then reduced with DIBAL-H followed by acetal hydrolysis to yield epoxyquinol **18.4**. Epoxidation of exocyclic alkene, followed by tandem deprotection and cyclization gave (-)-cycloepoxydon in 13 steps overall with 13% yield. The epoxyquinol core was achieved in 11 steps with 28% yield from 2, 5-dihydroxybenzaldehyde.



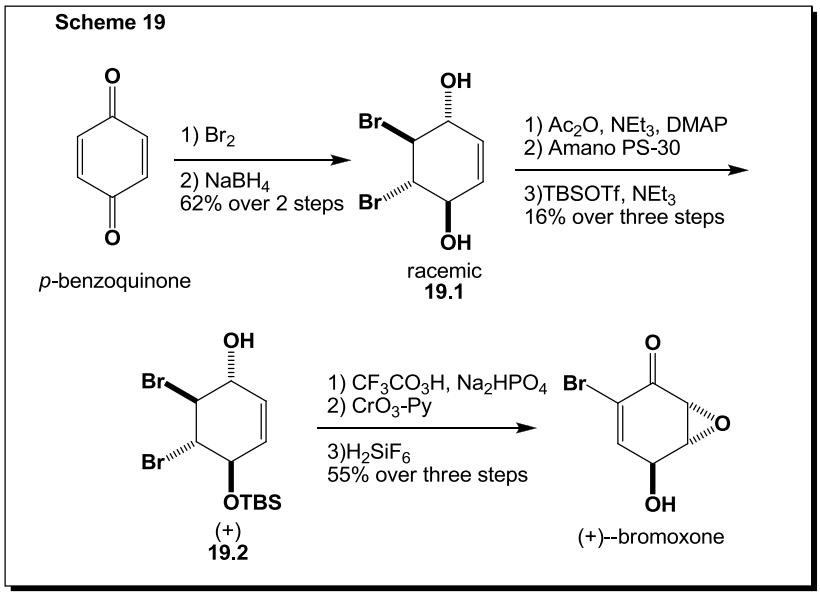
1.4.6 Terremutin, Bromoxone, and Chaloxone

Figure 9



Terremutin was isolated from the fungus *Aspergillus terreus.*[83] Synthesis of terremutin from terreic acid confirmed the absolute configuration.[84] Through a β-carotene-linoleate model assay and an H_2O_2 radical scavenging assay, terremution was shown to have antioxidant activity comparable with ascorbic acid.[85]

Bromoxone was isolated from a marine worm *Phyllum hemichordata*[86] and was shown to have antitumor activity.[87] (±)-Bromoxone was synthesized by Taylor.[88] The first enantioselective synthesis of (+)-bromoxone came from Johnson's group. They added bromine to *p*-benzoquinone and reduced the resulting diketone with sodium borohydride to give dibromodiol **19.1** (Scheme 19). [89] The diol was then subjected to enzymatic resolution followed by silylation to give the desired enantiomer (+)-**19.2**. Epoxidation followed by elimination of HBr and deprotection gave (+)-bromoxone in 8 steps with 5% overall yield.

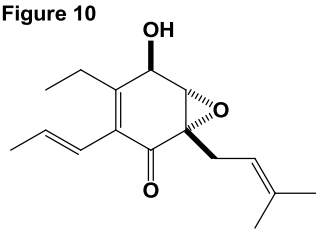


Ryu reported the synthesis of (+)-bromoxone via the Diels-Alder strategy described above (Scheme 10).[39] (+)-Bromoxone was accessed by Schapiro via a route similar to one described above (Scheme 14).[90] Banwell also reported the synthesis of (-)-bromoxone.[91]

Chaloxone is a metabolite of the fungus *Chalara microspora*[92] and is thought to be derived from the shikimic acid pathway. Fex reported the synthesis of chaloxone in racemic form from bromination of *p*-benzoquinone.[93] No other syntheses or biological data have been published on chaloxone.

1.4.7 Jesterone

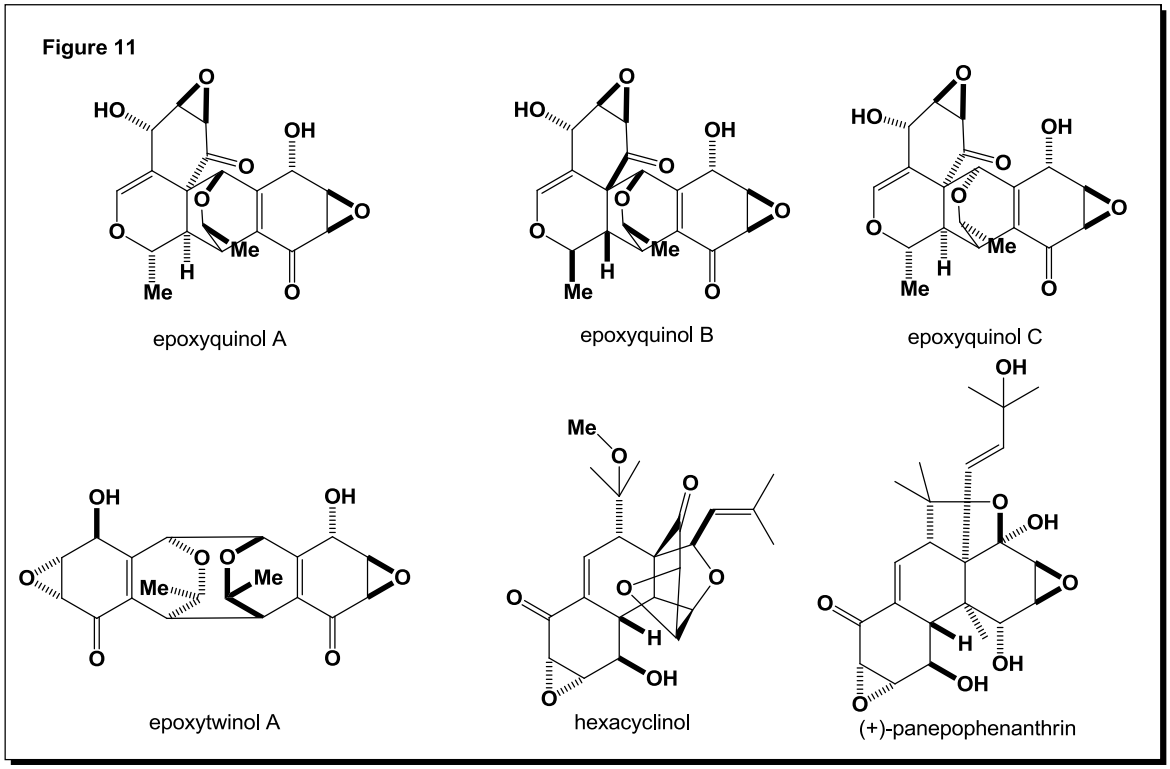
Figure 10



Jesterone

Jesterone was isolated from fermentation broth of the fungus *Pestalotiopsis jesteri*[94] and it displayed an interesting selective antimycotic activity toward the oomycetous fungi, which are amongst some of the most plant pathogenic of all disease causing fungi.[94] (-)-Jesterone has been synthesized by Porco[95] and (±)-jesterone by Mehta.[96] The dimer of jesterone is a potential anti-tumor agent.[97]

1.4.8 Epoxyquinol A, B, C and Epoxytwinol, Hexacyclinol, and Panepophenanthrin



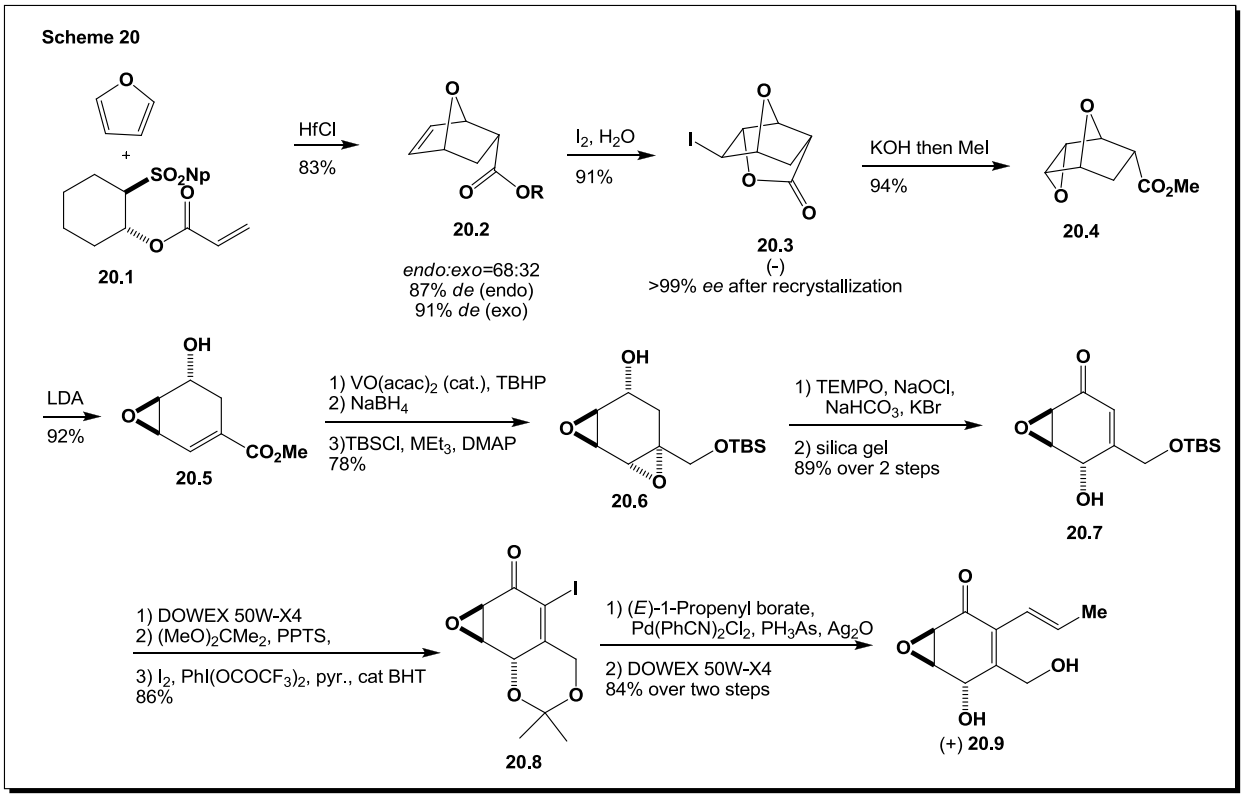
Epoxyquinol A, B, and C and epoxytwinol are fungal metabolites isolated from an unidentified soil fungus and they have demonstrated antitumor and antiangiogenic effects.[98] Epoxyquinol A inhibits activation of the NF-κB transcription factor.[99, 100] Epoxyquinol A,B, and C inhibit angiogenesis by binding cysteine residues of receptor kinases and crosslinking them to other proteins.[101] They inhibit VEGFR2, EGFR, FGFR, and PDGFR.[102, 103]

Hexacyclinol was isolated from cultures of the fungus *Panus rudis.* It showed an IC_{50} of 1.4 μg/mL for L-929 mouse cancer cell line and an IC_{50} of 0.4 μg/mL for K562 leukemia cells. It also demonstrated toxicity against HeLa cell lines with an IC_{50} of 10 μg/mL, meaning that it could potentially be used to treat cancer.[104] Panepophenanthrin was also isolated from *Panus rudis* and it

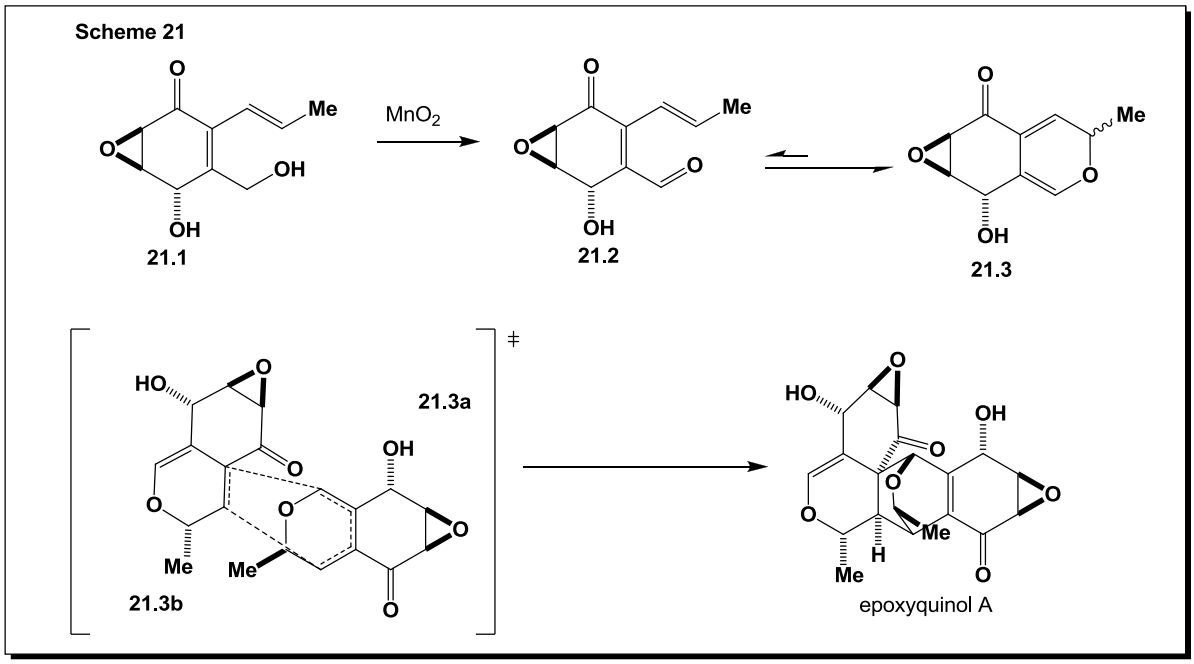
inhibits ubiquitin-activating enzyme.[105] The syntheses of this class of molecules have been reported by several groups and the work will be highlighted below.

Osada and coworkers are credited for first identifying epoxyquinol A, B, and C and epoxytwinol.[99, 100, 103, 106] and they were also the first to report their total syntheses using a Diels-Alder approach.[98, 106-108]

The syntheses commenced with a Diels-Alder reaction between furan and Corey's chiral sulfoxide auxiliary **20.1**, which was produced in three steps from commercially available 2-napthalenethiol, in 84% yield and moderate diastereoselectivity (Scheme 20).[99, 109] Diels-Alder adduct **20.2** was then converted to iodolactone **20.3** which was recrystallized to enantiopurity. Iodolactone **20.3** gave *endo* epoxide **20.4** when treated with potassium hydroxide followed by methyl iodide. β-Elimination driven by LDA gave cyclohexene **20.5**. Epoxidation of alkene **20.5** was followed by reduction of the ester to the alcohol. Silylation gave *bis*-epoxide **20.6**. TEMPO mediated oxidation preceded isomerization with silica gel to give epoxyquinol **20.7**. The epoxyquinol core was accessed in 12 steps and 14% overall yield. Epoxyquinol **20.7** was protected as the less sterically demanding acetonide derivative in order to achieve iodination in good yield to give iodide **20.8**. Suzuki coupling reaction with *E*-propenyl borate gave vinyl epoxyquinol **20.9** in 17 steps and 10% overall yield.



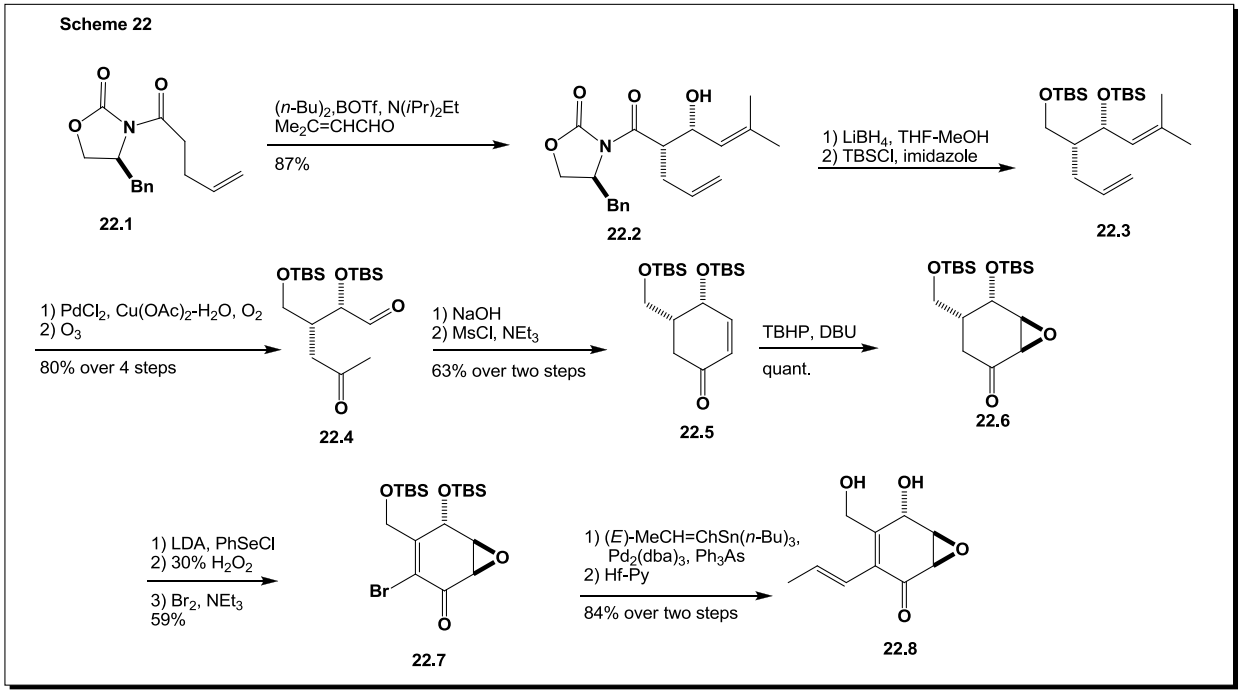
Alcohol **21.1** was then oxidized with MnO_2 to give aldehyde **21.2**, which exhibited an equilibrium cycloisomerization to diene **21.3**. Spontaneous Diels-Alder dimerization of **21.3** gave a mixture of four products: epoxyquinol A was isolated in 24% yield, epoxyquinol B in 33% yield, epoxyquinol C in 1% yield, and epoxytwinol in 8% yield. Epoxyquinol A is the result of an *endo-anti*(epoxide)-*anti*(Me)-hetero Diels-Alder (Scheme 21), epoxyquinol B is from an *exo-anti*(epoxide)-*anti*(Me)-homo Diels-Alder and epoxyquinol C is from an *exo-syn*(epoxide)-*anti*(Me)-homo Diels-Alder. Epoxytwinol A is from a formal [4+4] cycloaddition of diene **21.3a** .[110]



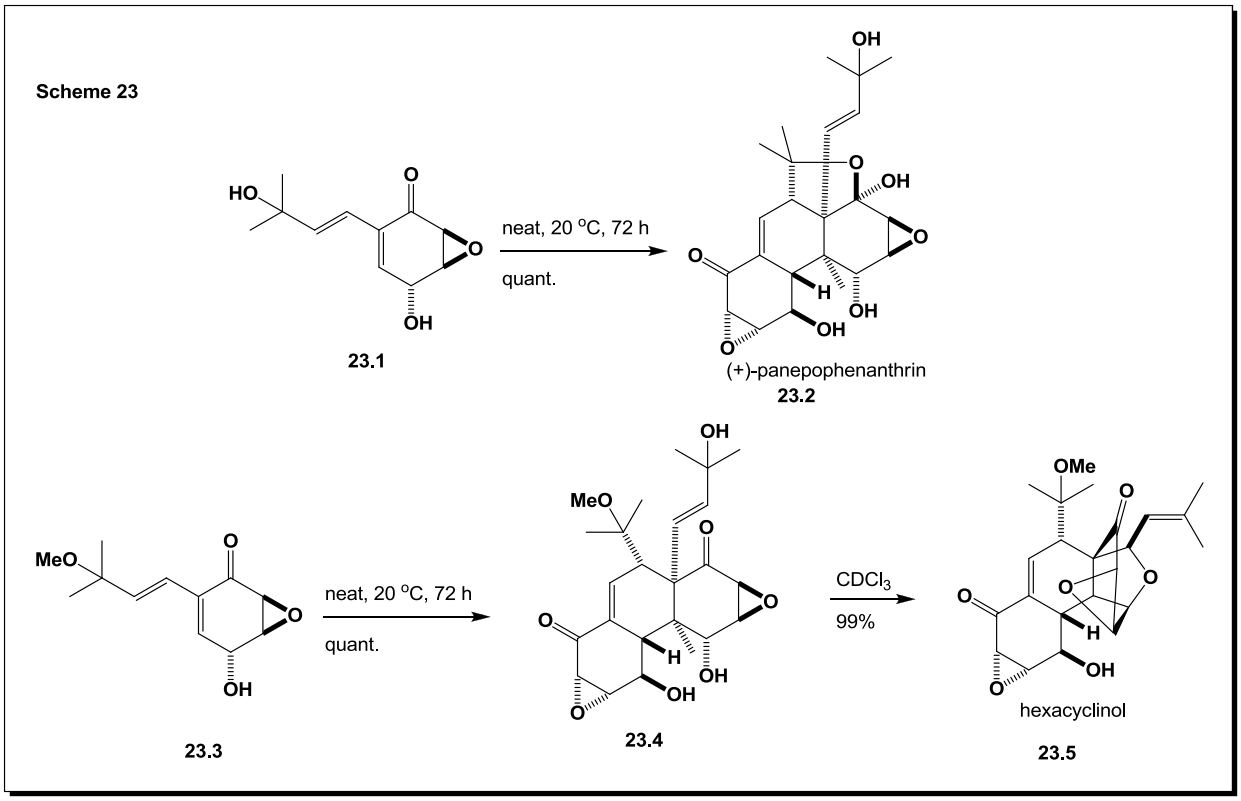
This same Diels-Alder approach has been used by other groups to access the same molecules. Mehta's group employed an enzymatic resolution to access enantiopure **20.9**[111] while Porco utilized a tartrate-mediated epoxidation to access the same compound.[112] Porco also used the tartrate epoxidation and the Diels-Alder strategy to synthesize (+)-hexacyclinol.[113] Ryu reported the synthesis of **20.9** through an asymmetric Diels-Alder approach.[114]

Kuwahara reported the synthesis of the epoxyquinols A-C using an asymmetric aldol and Diels-Alder approach (Scheme 22).[115] The synthesis commenced with an Evans asymmetric aldol reaction between *N*-acyl-2-oxazolidinone **22.1** and senecialdehyde to afford the *syn*-aldol **22.2**. Chiral auxiliary **22.1** can be accessed in one step from commercially available (*S*)-4-benzyl-2-oxazolidinone ($19 per gram from Sigma-Aldrich) in 99% yield.[116] The aldol auxiliary was reductively cleaved to give a diol which was then protected as disilylether **22.3**. A Wacker oxidation of the terminal alkene to a methyl ketone was followed by ozonolysis of the trisubstituted alkene to give aldehyde **22.4**. Ketoaldehyde **22.4** underwent an intramolecular aldol condensation to give enone **22.5**. Epoxidation of the alkene **22.5** gave epoxyquinol **22.6** . The Diels-Alder

precursor **22.8** was completed by α-selenylation, oxidative elimination, bromination, Stille coupling and deprotection to complete the 13 step synthesis in 22% overall yield.



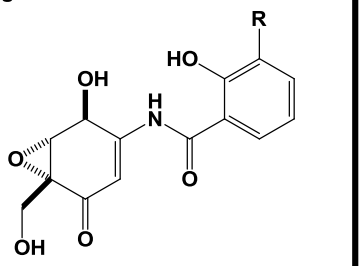
Banwell reported the syntheses of both (+)-hexacyclinol and (+)-panepophenanthrine.[117] The epoxyquinol element of each molecule was achieved via whole cell dihydroxylation of iodobenzene.[118] Epoxyquinol **23.1** is thought to be the biosynthetic precursor to (+)-panepophenanthrin (**23.2)**. Upon standing neat, **23.1** underwent quantitative dimerization to afford (+)-panepophenanthrin (**23.2**). The methoxy epoxyquinol monomer **23.3** also dimerized spontaneously to compound **23.4**, which underwent presumably adventitious rearrangement to (+)-hexacyclinol **23.5**.



Moses reported a similar synthesis of (+)-panepophenanthrin using enzyme mediated desymmetrization to set the absolute configuration of the epoxyquinol monomer.[119] (+)-Panepophenanthrin was synthesized in Lee's lab using a tandem metathesis approach.[120]

1.4.9 Epoxyquinomycin C and D

Figure 12

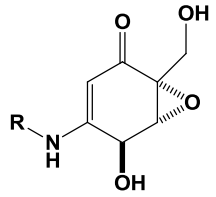


Epoxyquinomycin C (R=H)
Epoxyquinomycin D (R=Cl)

Epoxyquinomycin C and D (Figure 12) were isolated from fermentation of the bacteria *Amycolatopsis sp.*; epoxyquinomycin C was shown to have weak antibacterial properties.[121] There have been no syntheses reported for either molecule.

1.4.10 Cetoniacytone A and B

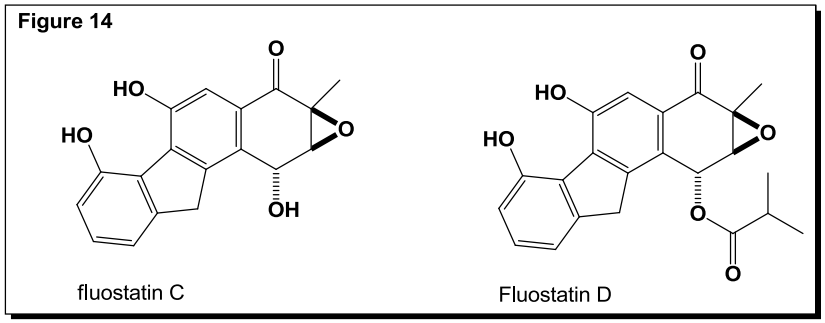
Figure 13



cetoniacytone A R=$COCH_3$
cetoniacytone B R=H

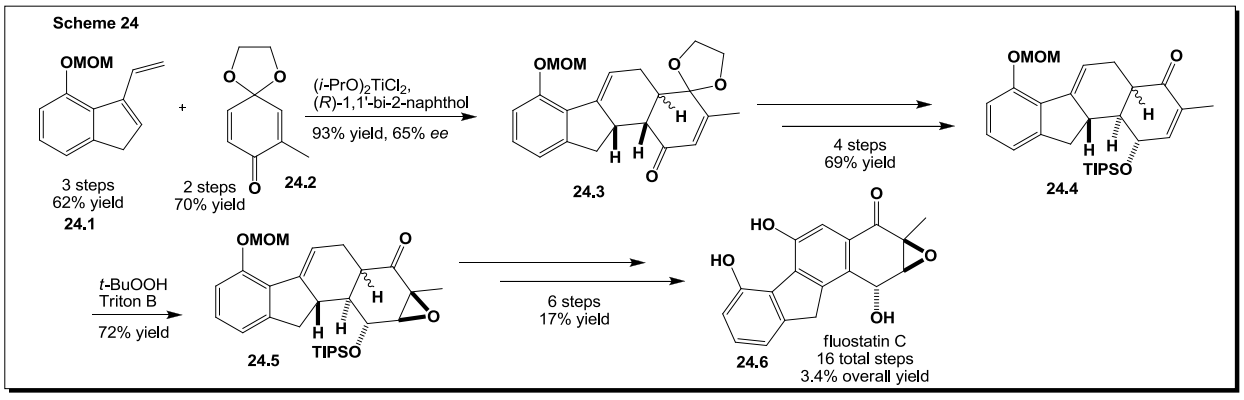
Cetoniacytone A and B are moderately active antitumor agents produced from *Actinomyces* sp. strain Lu9419, an endosymbiotic bacteria isolated from the gut of the rose chafer insect *Cetonia aurata*.[41, 122] There have been no syntheses reported for either molecule

1.4.11 Fluostatin C and D

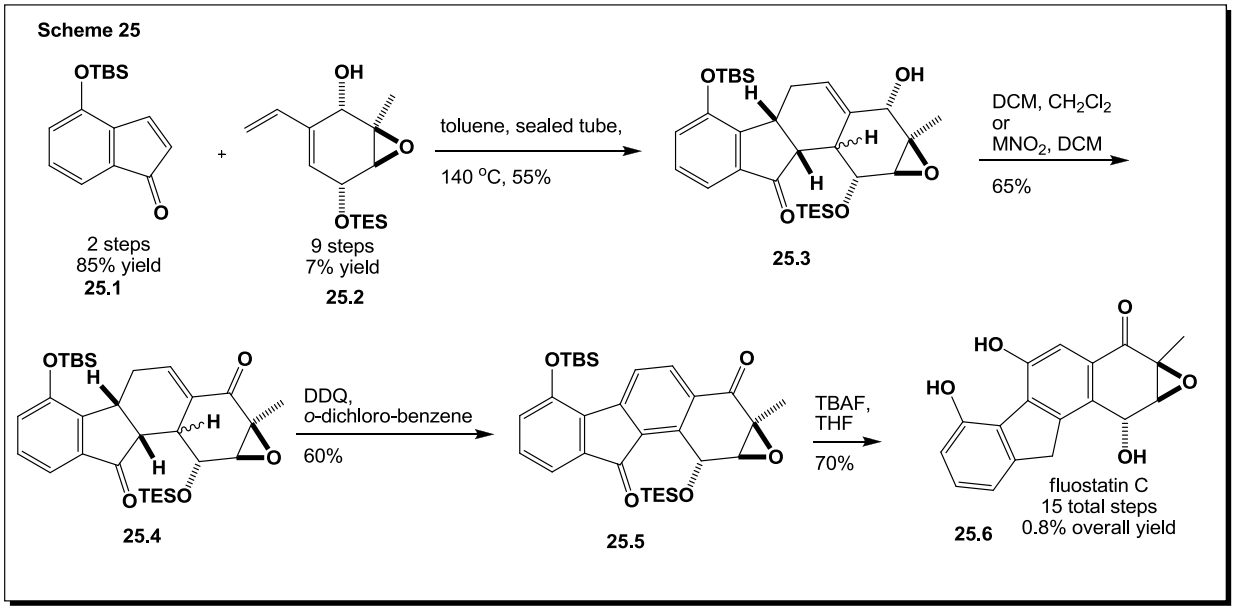


Fluostatin C and D are the only two members of the fluostatin family which bear *trans*-epoxyquinol functionality.[123] They were isolated from the culture broth of *Streptomyces* strain Acta 1383.[123] Fluostatin C showed a mild inhibitory effect on the growth of the human tumor cell lines of HMO2, HepG2, and MCF-7 while fluostatin D showed no activity.[124]

Enantioselective total syntheses of fluostatin C have been reported by Danishefsky[125] and Mehta.[126] Danishefky used a Diels-Alder reaction to establish the core of the molecule (Scheme 24). Ketone **24.3** was reduced with Superhydride and the epoxide was installed with Triton-B and *t*-BuOOH (Scheme 24). Fluostatin B was constructed in 16 total steps (14 longest linear sequence) and 3.4% overall yield.

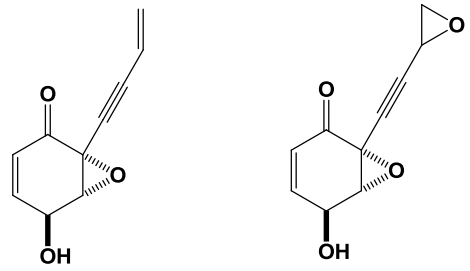


Mehta achieved the synthesis of fluostatin C using an enzymatic desymmetrization to prepare diene **25.2.** Diels-Alder reaction was followed by oxidation and desilylation, completing the synthesis in 15 total steps (13 longest linear sequence) and 0.8% everall yield (Scheme 25).



1.4.12 Speciosin A and B

Figure 15



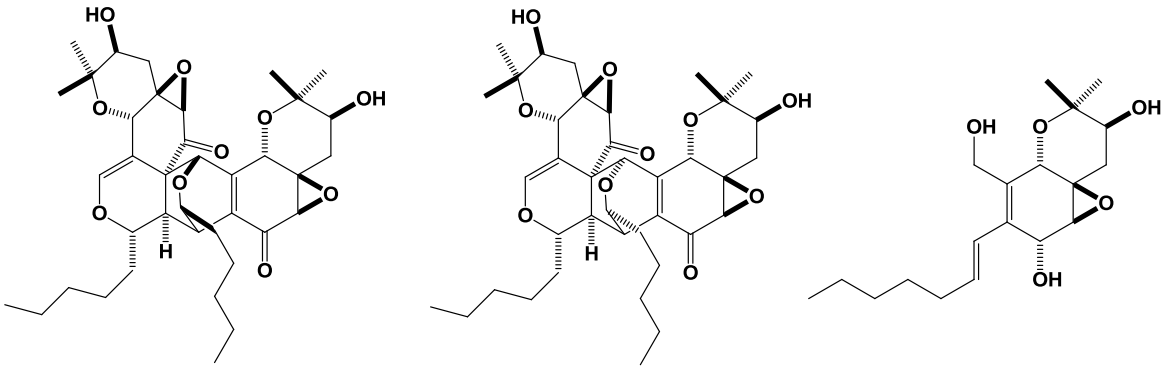
speciosin A speciosin B

Speciosin A and B are the only two compounds from a family of structurally similar molecules that bear *trans*-epoxyquinol functionality. They were isolated from the fungal culture of *Hexagonia speciosa,* which is common to the tropical and subtropical regions of China.[127, 128]

Racemic total syntheses of speciosin A and B were reported by Taylor via Pd-catalyzed cross coupling, Diels-Alder, and diastereoselective epoxidation strategies.[129]

1.4.13 Pestaloquinol A and B

Figure 16



pestaquinol A pestaquinol B cytosporin D

Che and Zou recently reported the isolation and identification of two dimeric epoxyquinols pestaloquinol A and B from the fermentation broth of the fungus *Pestalotiopsis sp.* taken off the branches of the Kusamaki conifer *Podocarpus macrophyllus.*[130] Cytosporin D is believed to be the biosynthetic precursor of these unprecedented nonacyclic pentaketide structures. There have been no syntheses reported for any of these molecules.

Of all the reported syntheses of the epoxyquinol moiety, there has not been a method developed that is satisfactorily efficient. We sought to develop a strategy to access the intermediate in a method similar to that reported for the racemic synthesis,[21] which achieves the molecule in four steps from *p*-benzoquinone

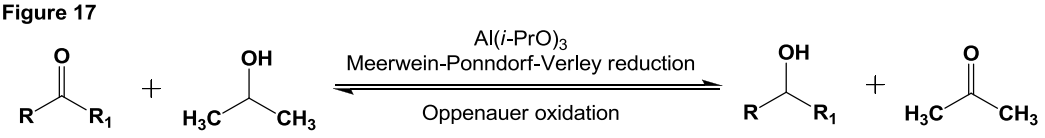
CHAPTER 2. ASYMMETRIC TRANSFER HYDROGENATION

2.1 Introduction

Simply put, a transfer hydrogenation is the transfer of the elements of hydrogen from a donor to an acceptor. Reactions that can be considered transfer hydrogenation are: intramolecular hydrogen migrations, hydrogen disproportionation between identical acceptor and donor, and transfer hydrogenation-dehydrogenation between distinct donor and acceptor units.[131] The latter classification, and more specifically transfer hydrogenation between ketones and alcohols, will be the focus of this review.

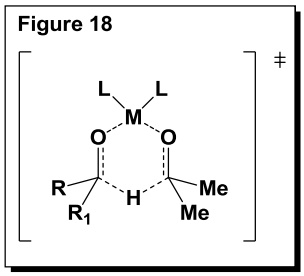
The classic example of the transfer hydrogenation of C=O bonds, the Meerwein-Ponndorf-Verley (MPV) reduction, is the transfer of hydrogen from an alcohol to a ketone catalyzed by an aluminum oxide, usually aluminum isopropoxide (Figure 17).[132] The reverse reaction, oxidation of alcohols to ketones in acetone, is the Oppenauer (O) oxidation.[133]

Figure 17



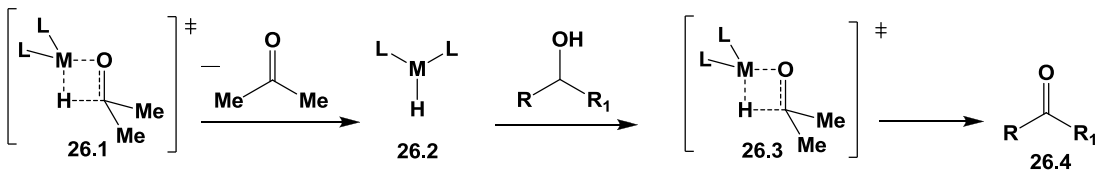
MPV-O reactions proceed through a concerted *direct hydrogen transfer* mechanism, in which both hydrogen acceptor and donor are coordinated to the metal center and hydrogen is transferred directly from donor to acceptor (Figure 18).[134] Direct hydrogen transfer is one of three reaction mechanisms that have been proposed for the transfer hydrogenation of ketones.[135, 136]

Figure 18



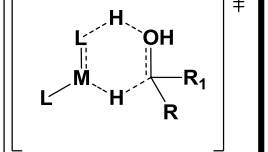
The second transfer hydrogenation mechanism proceeds through a stepwise *hydridic route* (Scheme 26).[135] The first step is the generation of metal hydride **26.2** from reaction with *i*-PrOH, which coordinates an alcohol and transfers the hydride to form a ketone **26.4**. Most transition metal based catalysts for the hydrogenation of ketones with H_2 gas proceed via the hydric mechanism.[137]

Scheme 26



The third and most recently proposed mechanism is *metal-ligand bifunctional catalysis* (Figure 4).[136] Unlike the two other mechanisms, neither the hydrogen donor nor the acceptor coordinates directly to the metal center. Rather, hydrogen transfer occurs in the outer coordination sphere of the metal center, through a six-membered, cyclic transition state (Figure 19).

Figure 19



A significant drawback to traditional aluminum alkoxide MPV reactions is that the metal exchanges ligands too slowly to be used in catalytic amounts.[138] Therefore, stoichiometric amounts of the oxides are generally required. Also, there are very few successful asymmetric reports of traditional MPV reactions. The few examples report low enantioselectivities and rely on the use of chiral alcohols as reductants.[138]

It wasn't until chiral lanthanide and transition metal alkoxides were investigated that significant asymmetric catalytic MPV reductions were reported.[138] In 1993, Evans reported the MPV reduction of acetophenone in *i*-PrOH at 96% *ee* with 5 mol % catalyst generated *in situ* from SmI_3, styrene oxide, and benzylamine.[139] Also in 1993, Genêt reported the reduction of acetophenone in *i*-PrOH using 1 mol % $(CBD)_2Ru(Br)_2$-NaOH with 62% *ee.*[140] In 1994, De Graauw reported the reduction of acetophenone with 33% *ee* using 1 mol % La(O*t*Bu)$_3$ and 1,2:5,6-di-*O*-isopropylidene-D-mannitol as ligand in *i*-PrOH.[141] Although some catalysts showed good conversion and decent enantioselectivity, they suffered from very limited scope. Most MPV methodologies were generally limited by low enantioselectivity and low catalyst activity.[137]

Examples of non-MPV asymmetric transfer hydrogenations (ATH) of ketones are also sparse in the literature prior to the mid 1990's. The few examples suffered from limited scope and poor enantioselectivities. The first report on the subject used $[H_4Ru_4(CO)_8((-)\text{-DIOP})_2]$ to reduce aryl alkyl ketones with low enantioselectivity.[142] Graziani reported the reduction of several aryl alkyl ketones in the presence of dichlorobis(1,4-cyclooctadiene)diiridium- chiral phosphines, isopropanol, and strong base in high yields and good enantioselectivity,[143] and also reported similar reductions employing rhodium based catalysts.[144] Heil demonstrated the enantioselective reduction of several aryl alkyl ketones with rhodium and iridium catalysts bearing 2,4-bis(diphenylphosphinoxy)pentane and either cyclooctane or 1-5 cyclooctadiene ligands in basic isopropanol.[145] Bhatnagar reported similar reductions using chiral phosphine iridium complexes.[146] Alper was able to use $[Ru(C_6H_6)Cl_2]_2$ in the presence of Schiff bases as chiral ligands to effect transfer hydrogenation of aryl alkyl ketones in *i*-PrOH and KOH with moderate enantioselectivity.[147]

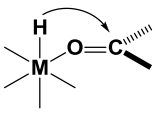
Bäckvall et al. demonstrated that $RuCl_2(PPh_3)_3$-NaOH could catalyze the reduction of ketones in *i*-PrOH. However, this catalyst demonstrated low chemoselectivity, delivering hydrogen

to alkenes as well as to ketones.[148, 149] In 1995, during a screen to identify chiral ligands to complex with $[Rh(C_6H_{10})Cl]_2$, Lemaire observed that the chiral diamine ligand *N*,*N*-dimethyl-diphenylethylenediamine with KOH as basic cocatalyst formed a complex that reduced acetophenone with 67% ee at a catalyst loading of 5 mol %.[150]

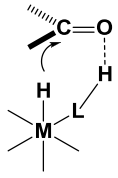
Early development in the field of asymmetric transfer hydrogenation was slow because most of the non-MPV catalysts that were being investigated bore aprotic ligands that tended to drive the catalysts through a hydric mechanism[137] The hydric mechanism requires coordination of the carbonyl oxygen directly to the metal center, which forces the delivery of hydride through a geometrically unfavorable pathway (Figure 20a).[151] Noyori hypothesized that protonation or hydrogen bonding to the carbonyl oxygen atom might facilitate the π-face attack of a nucleophile attached to the metal center.[151] In order for hydrogen bonding to effectively assist in delivery of the hydride, a protic ligand should be employed. The ligand/substrate hydrogen bonding could facilitate hydride delivery and produce the alcohol directly through a more favorable pathway (Figure 20b).[151]

Figure 20

a) geometrically disadvantageous pathway



b) hydrogen bond assisted pathway



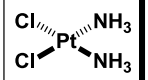
LH = protic neutral ligand

Most transfer hydrogenation catalysts, prior to 1995, contained neutral aprotic ligands. Some examples of these include; tertiary phosphanes, tertiary amines, ethers, phosphites, dienes or

anionic ligands.[151] The use of neutral protic ligands was largely uninvestigated and Noyori was curious as to whether the inherent characteristics of protic ligands could play an active role in the catalytic cycle. Figure 20 illustrates a possible hydrogen-bond-assisted hydride transfer from M to a carbonyl carbon atom utilizing a protic ligand. The LH-OC hydrogen bond facilitates the interaction between the π face of the carbonyl group and the metal hydride.[151] Some of the most popular ligands for transfer hydrogenation are primary or secondary amines. An amine N-H proton is not an inherently good hydrogen bond donor, but when bonded to a metal center their characteristics can change drastically. An interesting example is the origin of the anticancer activity of cisplatin (Figure 21) and its analogs, which use ammonia, primary amines, and secondary amines but never tertiary amines as ligands.[151]

When the nitrogen atom of cisplatin interacts in cells, the acidity of the NH proton is high enough to allow for its interaction with a phosphate moiety in DNA.[151] The double-helix is perturbed which allows the platinum center to complex with a guanidine, thus exhibiting antitumor activity.[151]

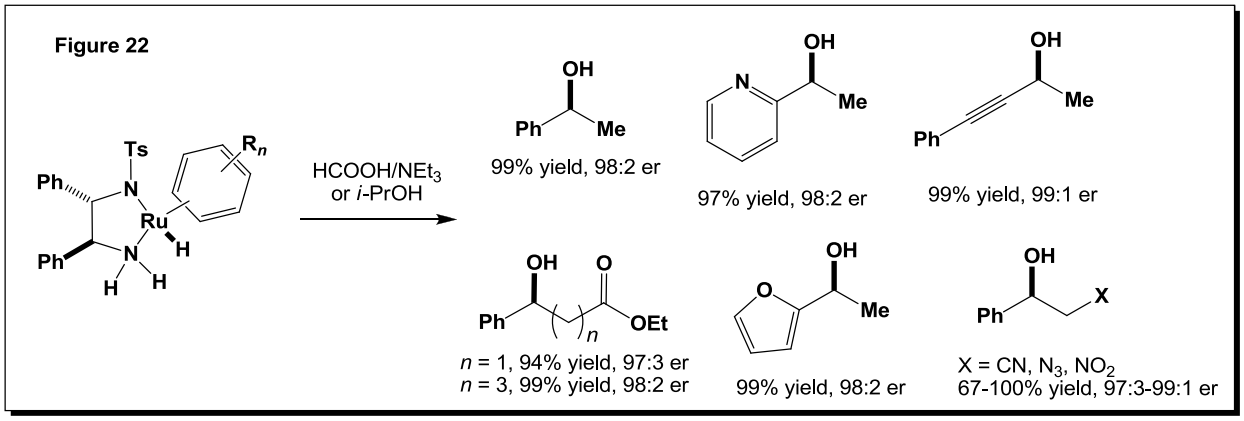
Figure 21



cisplatin

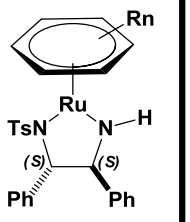
In 1995, Noyori's group reported that a catalyst mixture consisting of [$RuCl_2${(*S*)-BINAP}(DMF)], chiral 1,2-diamine, and KOH was much more selective towards the asymmetric hydrogenation of ketones than typical coordinatively unsaturated BINAP-Ru catalysts.[152, 153] This defined the conceptual turning point for the field of catalytic ATH. Noyori's lab soon developed the novel class of Ru^{II} catalyst that have come to dominate the field. (*S, S*)-Ru-TsDPEN (Figure 22) bearing monotosylated 1,2-diamine and an η^6-arene ligand is currently the gold standard of the

field and effectively mediates the transfer hydrogenation of a broad range of aryl ketones from isopropanol or HCO_2H/NEt_3 mixtures in excellent yields and enantioselectivities often exceeding 99:1 er.[137, 154-157]



The mechanism through which ATH catalysts are thought to proceed is dependent on a protic ligand and is best summarized by a term coined by Noyori: ligand-metal bifunctional catalysis.[136, 153, 158, 159] Noyori and Ikariya's contributions opened the field up to vigorous exploration from many different research groups, and since then, a variety of new catalysts have been reported. Catalysts have been ligated with bidentate ligands including diamines[160], β-amino alcohols[156, 161-165], aminophosphines[166], aminoethanethiols[167, 168] *o*-aminomethylphenyl,[169] tridentate ligands,[170, 171] and tetradentate ligands.[172] The most successful of these ligands are capable of ligand-metal bifunctional cooperation.[159] Another important feature of these protic ligands is that many are available in either enantiomer, meaning that the desired enantiomer of the resultant alcohol can be obtained by simply switching the absolute configuration of ligands. The most efficient types of these chiral ligands have a stereocenter in close proximity to the nitrogen atoms. The 16e ruthenium complex (Figure 23) has a 1, 2 *anti*-relationship between stereocenters on the protic ligand which is optimal for high enantioselectivity of ATH reactions.[173]

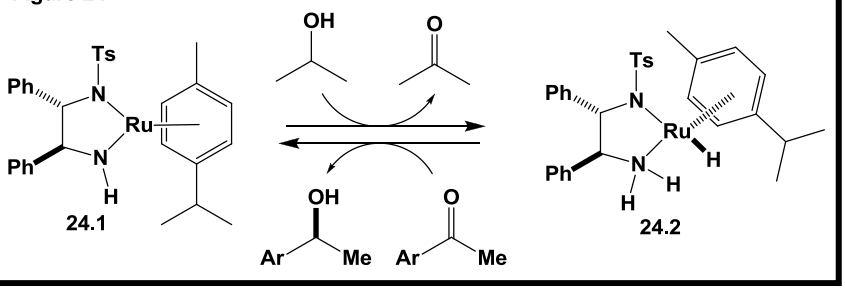
Figure 23



(*S*,*S*)-RuTsDPEN

The catalyst is capable of accepting two hydrogens from a stable source and delivering them in an enantioselective fashion (Figure 24).[174-176] Investigation into ATH has exploded in the last two decades and the volume of work is impressive to say the least. Several reviews of ATH cover the field thoroughly.[135, 137, 153, 159, 175, 177-185] Therefore, this work will be concerned with bringing the reader up to the state of the art of ATH rather than serving as an exhaustive review.

Figure 24

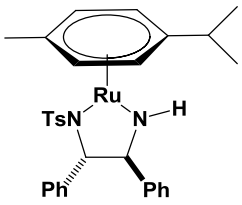


2.2 Ruthenium

Three metals have played a significant role in ATH: ruthenium, rhodium, and iridium. Ruthenium is by far the most popular metal in ATH. Monotosyl diphenylethylenediamine (TsDPEN) is the most widely used protic ligand and *p*-cymene is the η^6-arene ligand with the broadest

application. We will use Ru(*p*-Cy)TsDPEN, (Figure 25) or simpler analogs, as a representative example to explore details regarding mechanism and enantioselectivity.

Figure 25

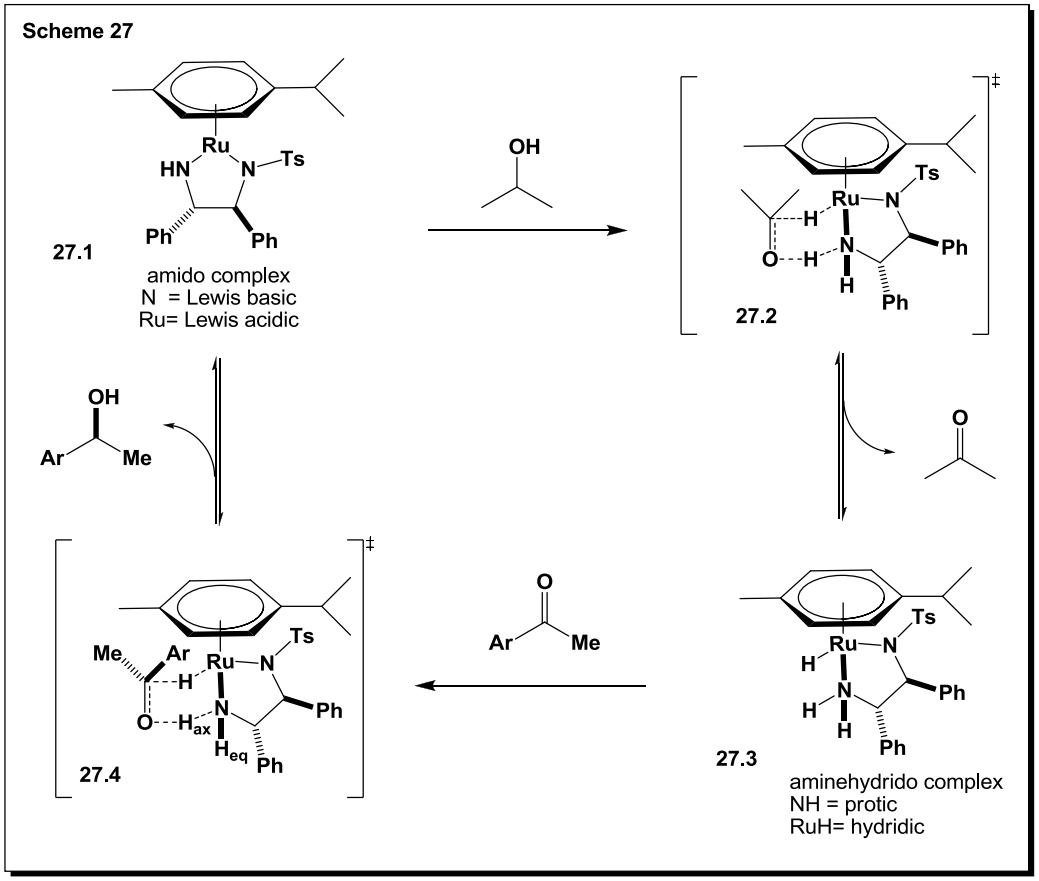


Ru(*p*-Cy)TsDPEN

2.2.1 Mechanism

The mechanism of Ru-catalyzed ATH has been extensively investigated. Computational analysis[161, 186, 187,188] as well as kinetic and isotope labeling studies[157, 189] have established a generally agreed upon mechanism that involves a six-membered pericyclic transition state (Scheme 27).[136, 151, 175, 177, 181, 186, 190, 191] The active oxidizing form of the catalyst is the coordinatively unsaturated 16e square planar amidoruthenium complex **27.1**. The non-tosyl N-Ru bond is equivalent to a double bond with nitrogen's lone pair of electrons contributing to the partial double bond.[158] The N-Ru bond of 16e **27.1** readily dehydrogenates a stable H_2-source such as isopropanol or trialkylammoniumformate through transition state **27.2** and is reduced to saturated 18e aminohydride **27.3**, as a single diastereomer, with a skewed octahedral configuration around ruthenium.[158] The N-H proton on **27.3** then hydrogen bonds with the ketonic oxygen, which initiates the concerted transfer of hydrogen (**27.4**) to a single face of the carbonyl.[136] Since the catalyst can either accept or donate hydrogen, the reaction is reversible[191] and unsaturated amidoruthenium complex **27.1** is regenerated in every catalytic cycle.[153] This mechanism is differentiated from other hydrogenation reactions in that the reaction takes place in the outer

coordination sphere of the metal. Formation of new C-H and O-H bonds occurs via metal-ligand bifunctional catalysis, rather than by the hydridic route.[174, 192-194]



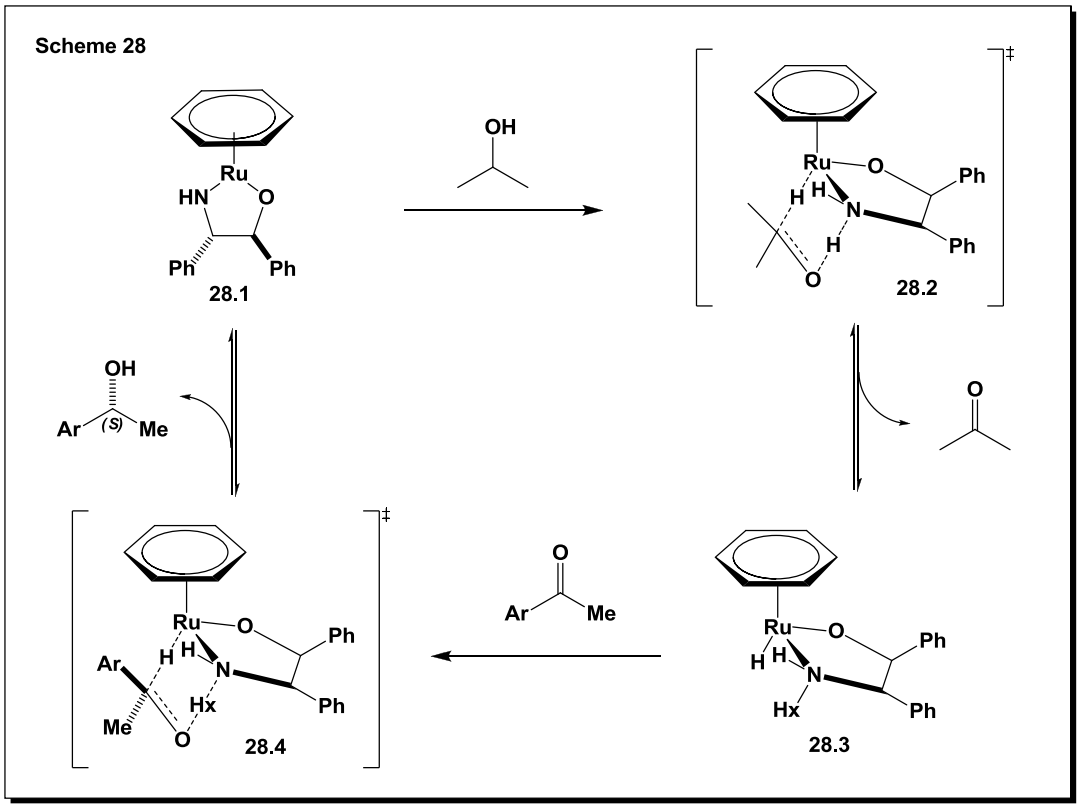
For most applications, *i*-PrOH can serve as a safe and cheap source of hydrogen. However, a serious drawback of *i*-PrOH as hydrogen source is the reversibility of the reaction. Acetone generated from dehydrogenation can continue to participate in the catalytic cycle, which can lead to low conversion and as well as erosion of enantiomeric purity if the reaction mixture is left exposed to the catalyst for extended periods of time.[153] The reversibility can be mitigated by applying mild vacuum to distill off generated acetone and replenishing with fresh *i*-PrOH. However, this reduces the operational simplicity of ATH. Alternatively, triethylammonium formate can serve as an efficient hydrogen source. The byproduct CO_2 can be more easily removed from the reaction mixture, effectively making the reaction irreversible.[190] Another recently reported source of

hydrogen for ATH is $HCOONa/H_2O$ which can be used with water as solvent. Several catalysts have been shown to have high activity and enantioselectivity for the reduction of aryl ketones in aqueous media.[159, 195]

2.2.2 Enantioselectivity

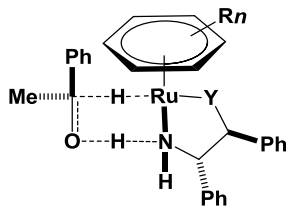
Factors determining the enantioselectivity of ATH are not as universally agreed upon as the mechanism and are the source of some debate. It is worth noting that all rationalizations concerning enantioselectivity were made using acetophenones as ketone. Some hypotheses concerning the source of asymmetric induction include sterics, solvent and electrostatic effects, dispersion forces, and a CH/π interaction between the arene ligand and the aryl ketone.[196]

Besides participating in the transition state, a primary function of the chelating ligand in Noyori ATH catalysts is to establish the absolute configuration of the Ru stereocenter in the 18e aminohydride **28.1**. In the case of (*S,S*)-Ru(diphenylaminoethanol)(Scheme 28), the bulky phenyl rings tend to adopt an equatorial orientation, resulting in ring geometry that confers an *R* configuration at the new Ru stereocenter.[186] The Ru-H aligns with the neighboring axial N-H_x proton and a hydridic-protonic attraction helps to stabilize the alignment between H and H_x (**28.3**).[186] The ketone approaches the catalyst with the bulky substituent pointing away from the phenyl rings of the amino alcohol ligand. Observed transition state energies were significantly lower when the aryl ring of acetophenone was aligned with the η^6-arene ligand of the catalyst, which could be the result of a favorable CH-π interaction.[186] Hydrogen bonding between the ketone and the N-H proton initiates ATH.[186]

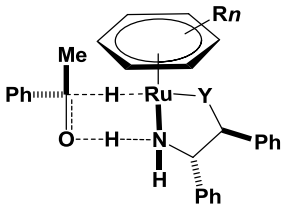


What remains to be answered is why a high level of enantioselectivity is observed for ATH of aryl ketones and ynones, but not for aliphatic ketones. Extensive computational studies indicated that with (*S,S*)-RuTsDPEN, reaction takes place at the *Re* face of acetophenone which, counter intuitively, puts the bulky phenyl group on acetophenone closer to the η^6-arene ligand to give the more sterically congested transition state **26.1** as opposed to the less crowded *Si*-transition state **26.2** which has a methyl group in close proximity with the η^6-arene ligand (Figure 26).[186]

Figure 26



26.1 favored *Re*-TS



26.2 disfavored *Si*-TS

Noyori concluded on the basis of MP2 and B3LYP calculations that the sense of enantioselectivity seen in the transfer hydrogenation of aryl ketones comes from a favorable CH/π interaction between the η^6-arene ligand on Ru and the aryl substituent of the ketonic substrate.[136, 157, 186] The main forces thought to be involved in this interaction are electrostatic and also include a charge-transfer component.[197] Arene ligands with multiple alkyl substituents lead to higher er's, albeit at an expense to reactivity. The benefit comes from stabilization of the transition state which is thought to be due either to the increased ability of π-donation into the favorable C(sp^2)H/π interaction or from a secondary C(sp^3)H/π interaction between alkyl substituents on η^6-arene ligand and the aromatic element of acetophenone (Figure 27).[182] A similar argument, proposing that C-H/π interactions between η^6-arene ligand and alkyne help stabilize the transition state, was made by Cossy to explain the high enantioselectivities observed for Noyori reduction of ynones (Figure 28).[198]

Figure 27

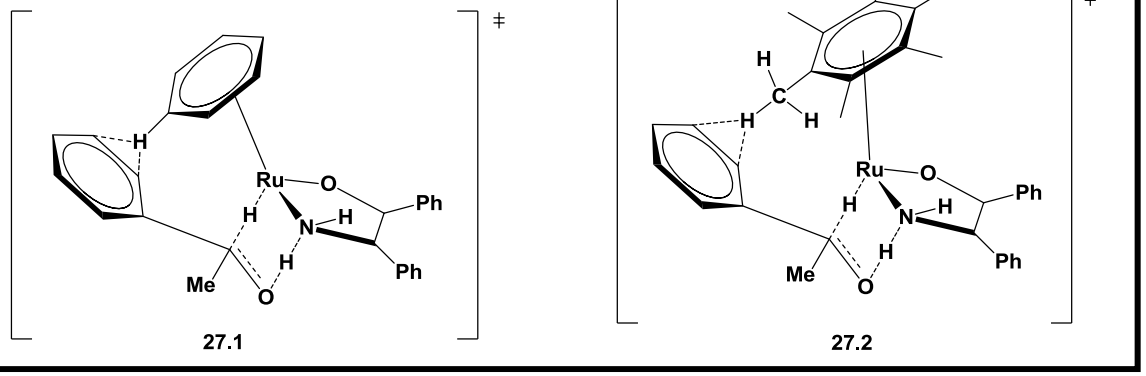
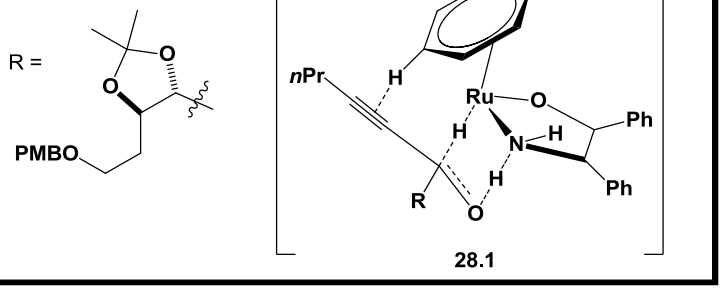


Figure 28

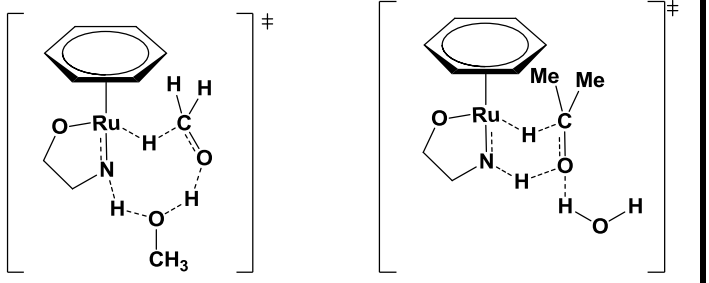


Andersson *et* al. was skeptical that the electrostatic forces behind a CH/π interaction would be strong enough to be the main factor in determining enantioselectivity and so he initiated a study using a combination of B3LYP and LANL2DZ calculations.[197] He argued that the major source of enantioselectivity was actually a delicate balance of dispersion interactions and solvation effects, with sterics and electrostatics also contributing. This balance is affected by both the η^6-arene ligand and by the amine ligand on the catalyst.[197] Unfortunately, these effects only apply to aryl ketones; aliphatic systems generally suffered from poor enantioselectivities. The study did not include ynones.

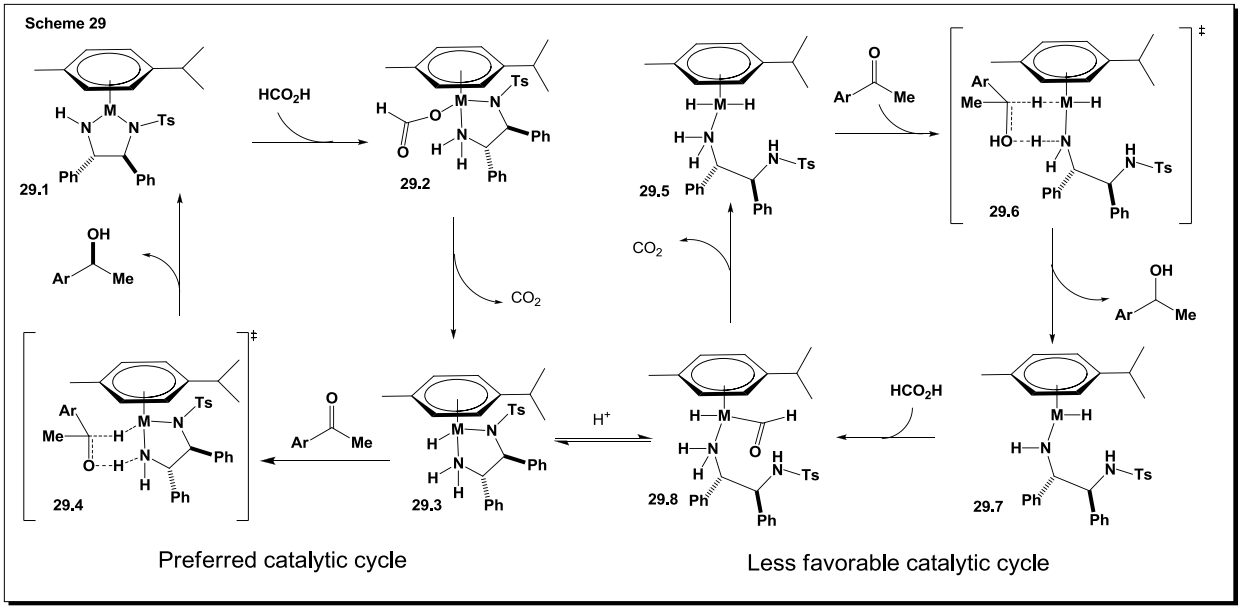
Meijer and Handgraaf conducted calculations using an explicit methanol solvent model (Figure 29, **29.1**).[174] They showed that the solvent may play an active role in the transition state via hydrogen bonding to both the amine and the substrate oxygen, thereby lowering the energy of

the transition state. Involving a solvent molecule directly in the reaction pathway challenged the widely accepted six-membered transition state. They suggested that the mechanism of the reaction in solution might be quite different from that in gas phase and that calculations that do not include an explicit solvent will fail to observe important mechanistic details.

Figure 29

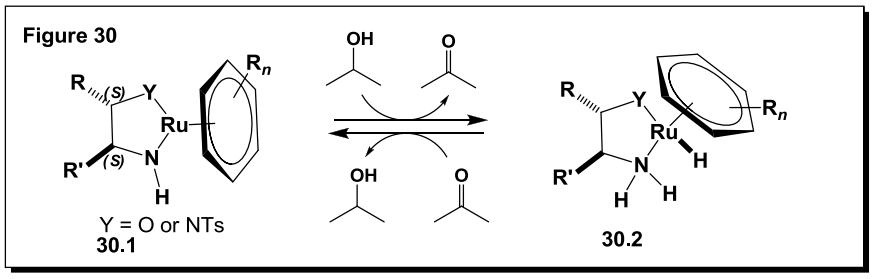


Xiao *et al*. conducted a similar study of the ATH in water (Figure 29).[192] An explicit water molecule was shown to hydrogen bond to the carbonyl oxygen thereby lowering the transition state (**29.2**). They also noted a distinct pH effect on the reaction; the reaction was slow when the pH was both low and high but enantioselectivity suffered only at low pH.[199] They observed that as the concentration of HCO_2H relative to NEt_3 increased, rate and enantioselectivity decreased. When pH was low (HCO_2H:NEt_3 4.6:1), conversion dropped to 39% in 150 h and 80% *ee* for reduction of acetophenone, compared to >99% conv. in 5 h and 97% *ee* for the optimized condtions (0.2:1 HCO_2H:NEt_3). They argued that the cause of the poor catalyst performance can be explained through a mechanism where both the Tosyl N and ruthenium center are protonated in acidic conditions leading to cleavage of the chelate bond. Without the structural stability of the chelate, the catalyst is presumably driven into a less active and less enantioselective catalytic cycle. (Scheme **29**) While this alternative mechanism does justify Xiao's results, there is no direct evidence to support it, and the theory has not yet been adopted by the ATH community.



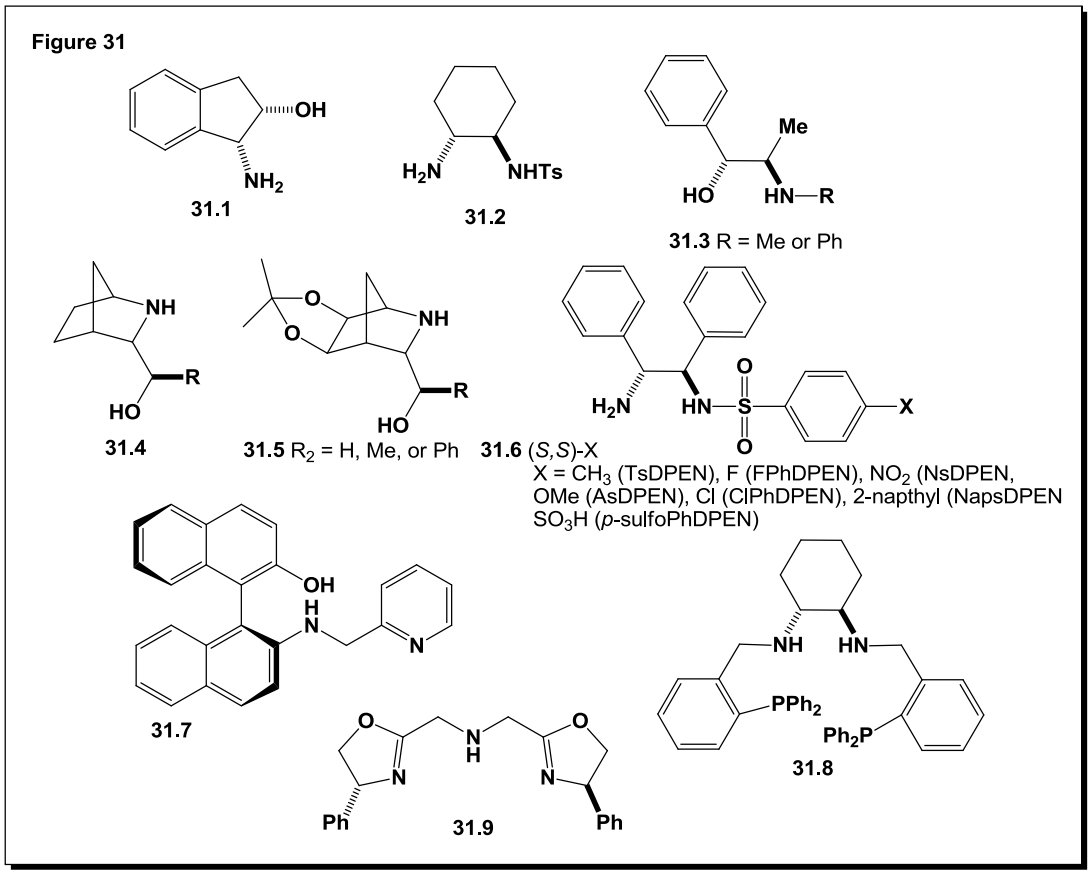
2.2.3 Noyori's Catalyst Scope

One general structure of the Ru^{II} based ATH catalyst (Figure 30) dominates the literature; it exists as the pair of 16e amido complex **30.1** and 18e hydridoamine **30.2**. Very few successful examples depart from this basic structure.[173] Within this generic framework there has been an amazing amount of diversity in ligands.

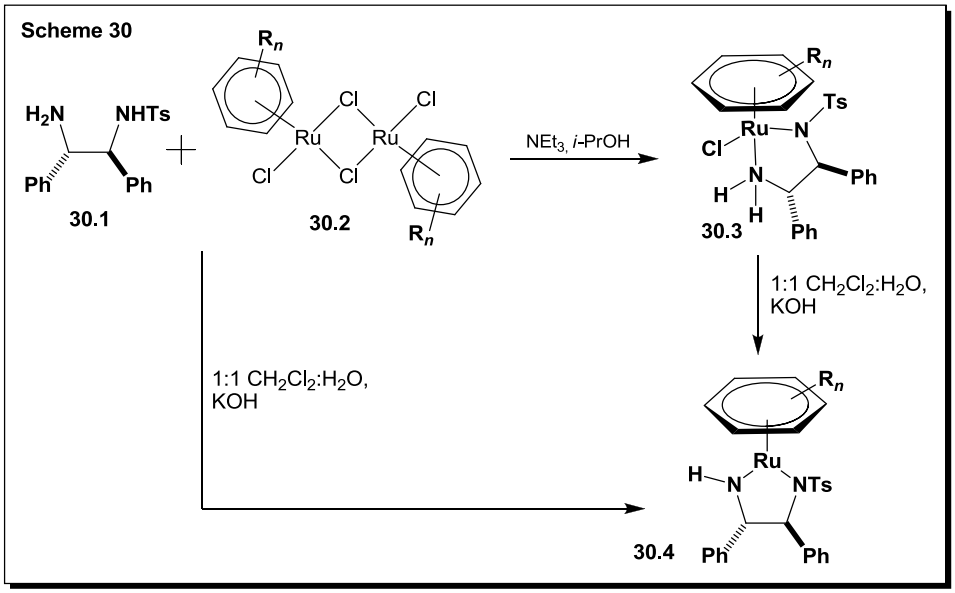


A full review of the various ligands employed in ATH is beyond the scope of this document. However, some of the most successful ligands (er > 90:10 in reduction of acetophenone) are shown below (Figure **31**). Some important points to note are that protic ligands are required for the

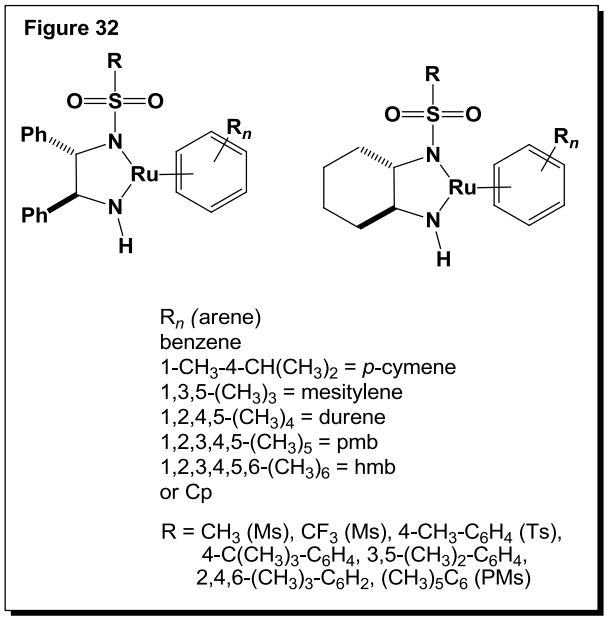
respective catalyst to participate in metal-ligand bifunctional catalysis. Of all ligands, 1,2 amino alcohols such as **31.1, 31.3, 31.4, 31.5,** and **31.7** and *N*-monotosylated diamine ligands such as **31.2** and **31.6** are the best in terms of activity and enantioselectivity toward the reduction of acetophenone in *i*-PrOH. However, when formic acid is the hydrogen source, the 1,2-amino alcohols are completely unreactive while the diamine ligands still show good activity.[182]



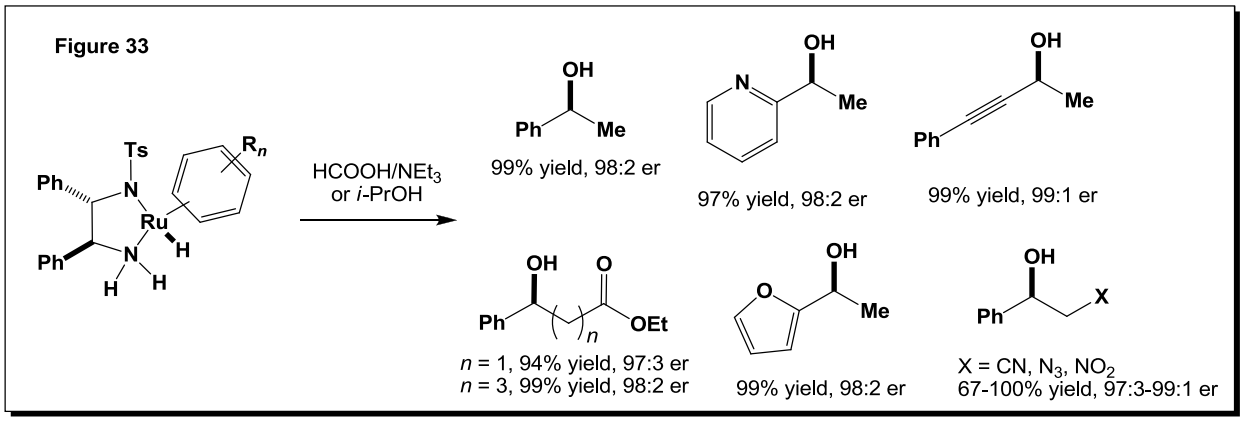
To form the catalyst, protic ligand **30.1** is mixed with η^6-arene Ru dimer **30.2** in the presence of NEt_3 to form 18e chloride **30.3**, which is treated with KOH to form the 16e catalysts **30.4** (Scheme 30)[157] Alternatively, 16e catalyst **30.4** can be formed directly by combining diamine **30.1** with Ru dimer **30.2** in the presence of strong base, which is often done *in situ*.[157, 182]



Different combinations of η^6-arene and diamine ligands have given rise to a considerable amount of diversity in these catalysts (Figure 32), of which Ru(*p*-Cy)TsDPEN has proven to be the most robust in terms of reactivity and enantioselectivity and has also been shown to have the broadest substrate scope.[200]



Ru(*p*-Cy)TsDPEN has been shown to effect the ATH of numerous aryl ketones and ynones in good yield and high enantioselectivity (Figure 33).[158] However, Ru(*p*-Cy)TsDPEN, like most ATH catalysts, suffers from the inability to reliably and efficiently reduce aliphatic ketones asymmetrically. There have been scattered reports of catalyst systems capable of asymmetrically reducing certain dialkyl ketones, but most examples suffer from low conversion, poor enantioselectivity, or narrow substrate scope;[159] relevant examples will be discussed below.

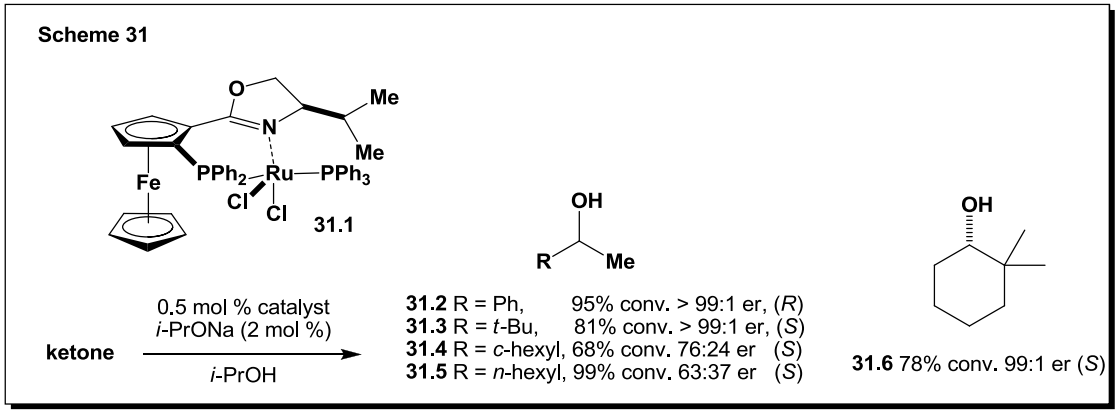


2.2.4 Efforts Toward ATH of Aliphatic Ketones

2.2.4.1 Ru^{II}-Oxazoline

A novel and interesting Ru^{II} catalyst, developed independently by Sammakia[201] and Uemura[202, 203] is $RuCl_2(PPH_3)$(oxazolinylferrocenylphosphine) **31.1** (Scheme 31). It showed enantioselectivity and turn-over rates comparable to Noyori's catalyst for a broad range of aryl alkyl ketones.[159, 204] Catalyst **31.1** was also able to reduce pinacolone to *t*-butylmethylalcohol **31.3.** and 2,2-dimethylcyclohexanone to 2,2-dimethylcyclohexanol **31.6** with unprecedented er's of 99:1, albeit with moderate TON's and TOF's. Interestingly, the sense of enantioinduction observed for dialkyl

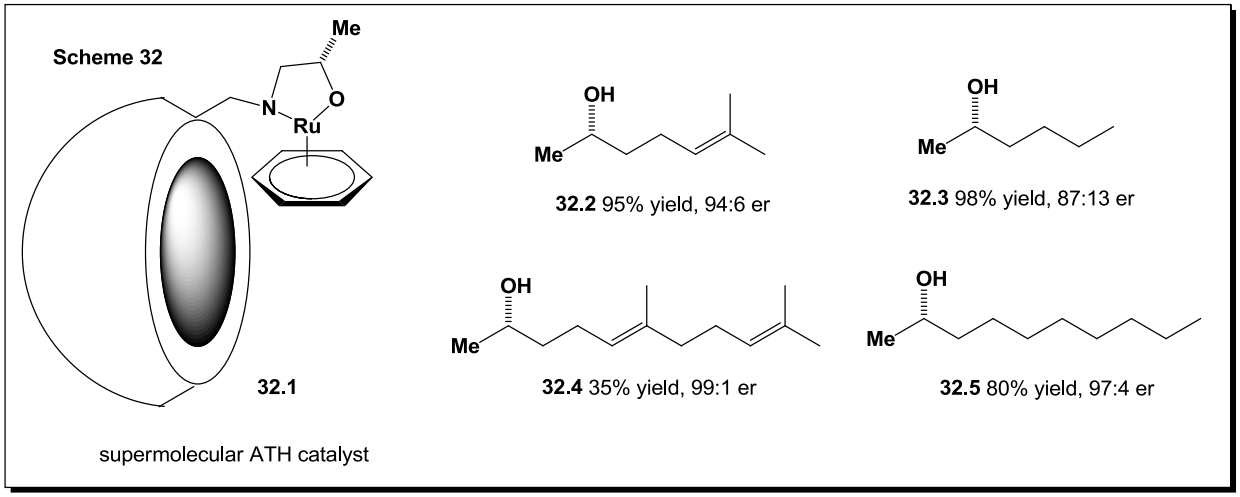
ketones was opposite that for aryl alkyl ketones. Uemura proposed that steric repulsion between the phenyl ring of acetophenone and the phenylphosphine ligands in the transition state were responsible for determining the absolute configuration of the aryl alkyl alcohols. For dialkyl ketones, they observed a trend between the bulkiness of the alkyl group and enantioselectivity (*t*-Bu > c-hexyl > n-hexyl) and suggested that enantioselectivities were also the result of sterics.[182] The author did not comment on the reversal of enantioselectivies. However, given what is known about the mechanism of Noyori's ATH catalyst,[136, 174] one could assume that factors such as: CH-π interactions between aryl groups on the catalyst and the substrate, solvent or electrostatic effects, or dispersion forces might be contributing. Although reviews covering asymmetric ATH of dialkylketones praise catalyst **31** for its ability to reduce certain dialkylketones,[159, 182] low substrate scope and low activity limit its usefulness.



2.2.4.2 Cyclodextrin

A Ru^{II} catalyst complex built from β-cyclodextrin that had been modified to bear amino alcohols **32.1** was able to promote the ATH of aliphatic ketones in water using HCOONa as

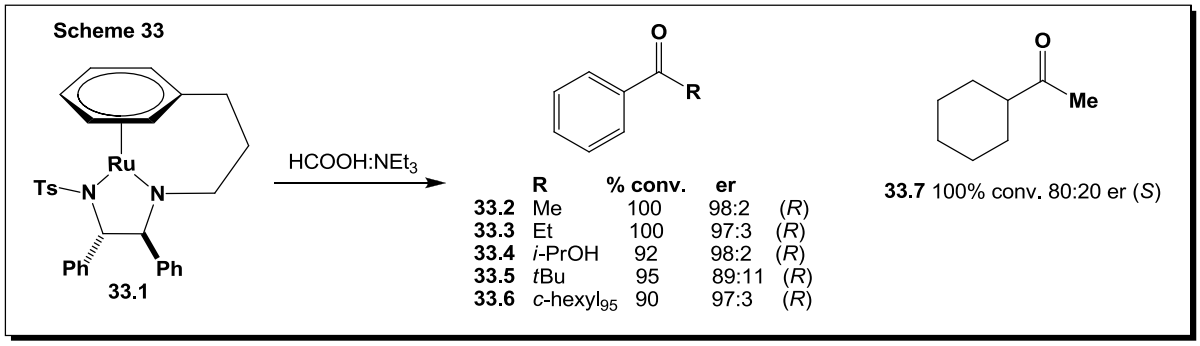
hydrogen source (Scheme 32).[205] The catalyst was proposed to differentiate between the *Re* and *Si* faces of prochiral methyl alkyl ketones through a preordering within the hydrophobic cavity of the β-cyclodextrin.[159] Enantioselectivity was observed to improve as the carbon chain was lengthened (**32.2** vs. **32.4** and **32.3** vs. **32.5**). The catalyst displayed good enantioselectivities and yields for a number of aliphatic ketones but suffered from low S/C ratios. The catalyst also requires that one side of the ketone be significantly more hydrophobic than the other in order for it to distinguish between the prochiral faces. A final drawback of catalyst **32.1** was the synthesis of the *β*-cyclodextrin aminoalcohol, which was nontrivial.



2.2.4.3 Tethers

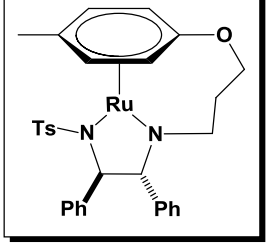
Another strategy to improve the enantioselectivity of aliphatic ketones is the installation of a tether. After several generations of catalysts, Wills demonstrated that a three atom tether linking the arene ligand to non-tosyl nitrogen resulted in a catalyst (**33.1**) with faster reduction rates and higher S/C ratios than untethered Ru(*p*-Cy)TsDPEN (Scheme 33).[206] The bulky alkyl aryl ketones **33.1** through **33.6** were reduced in better yield and higher enantioselectivity with **33.1** than with

the untethered variant. The catalyst also reduced cyclohexyl-methyl ketone **33.7** in 80:20 er which, at the time, was the highest reported er for the reduction of that substrate for any Noyori type ATH catalyst. He reasoned that if the aryl ketones gave the *R* enantiomer because of a favorable CH/π interaction, the switch in enantioselectivity for dialkyl ketone **33.7** was due to steric control in the transition state. Alkyl tethered catalysts offer benefits in terms of activity and enantioselectivity of alkyl ketones but they are more difficult to synthesize.



Wills and Ikariya have both reported a new catalyst (Figure 34) with an ether tether that has similar, if not improved, catalytic activity compared to alkyl tethered **33.1**.[207, 208] The ether tether offers an improvement over the alkyl tether owing to its increased simplicity of synthesis. Namely, a Birch reduction is avoided in the ether synthesis. The exact reason for the increase in enantioselectivity observed with tethered catalysts is not fully understood, but the tethers are thought to give increased structural rigidity to the catalysts which is thought to improve ligand cooperation, therefore improving their activity and enantioselectivity compared to non-tethered catalysts.[159, 207, 208]

Figure 34



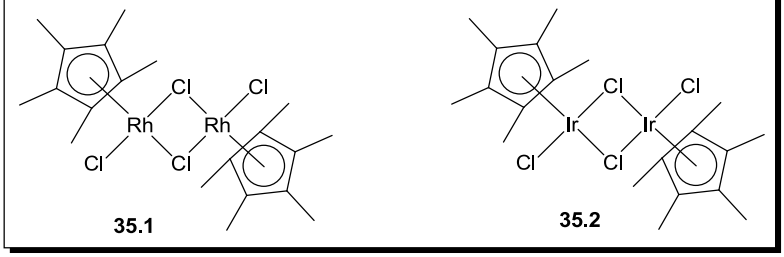
2.2.5 Summary

To date, ruthenium remains the dominant metal used for ATH catalysts. Although, significant strides have been made in improving catalyst design, there is still much work left to be done is terms of developing more advanced catalysts for the asymmetric reduction of dialkyl ketones.

2.3 Rhodium and Iridium

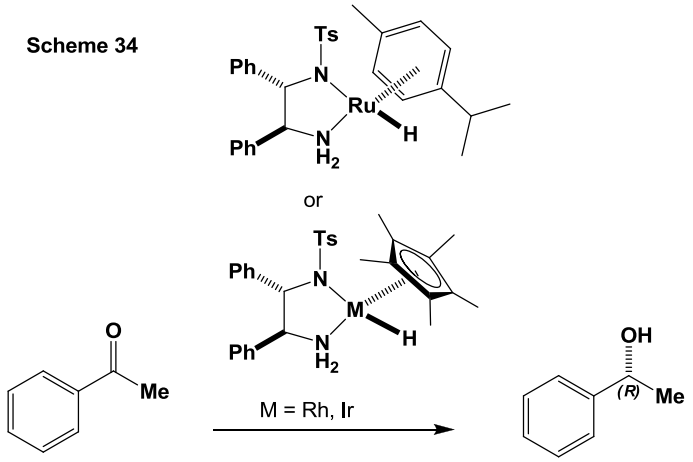
Rhodium and iridium are most commonly encountered in catalysts for the hydrogenation of ketones with H_2. However, several catalysts constructed around rhodium or iridium have demonstrated the ability to mediate ATH reactions and they are worth mentioning. It is convenient to cover these two metals together due to the similarities in the ligands employed. Typical catalysts are constructed from chelation of TsDPEN to Cp* Rh and Ir dimers (figure 35).[209] Rh (**35.1**, $582 per g, Sigma-Aldrich**)** and Ir (**35.2**, $460 per g, Sigma-Aldrich) come at a significant cost disadvantage to the analogous Ru dimer ([{*p*-Cy}$RuCl_2$]$_2$ $35 per g, Sigma-Aldrich). High cost is obviously a significant drawback to Rh and Ir in ATH compared to Ru.

Figure 35



Some of the most common rhodium and iridium catalyst are analogues of Ru-TsDPEN, although they bear Cp* η^5-arene ligand as opposed to η^6 ligands.[153] In 2008 Xiao showed that Cp*Rh-TsDPEN **34.2** had superior activity and enantioselectivity for the reduction of acetophenone in water than Ru-TsDPEN **34.1**, while Ir-TsDPEN **34.3** was slightly lower in enantioselectivity (Scheme 34).[209]

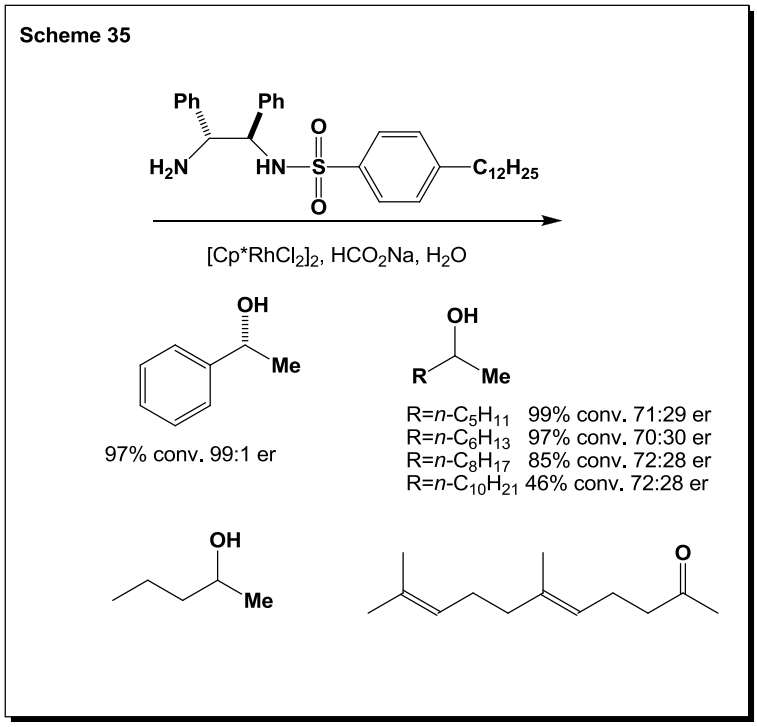
Scheme 34



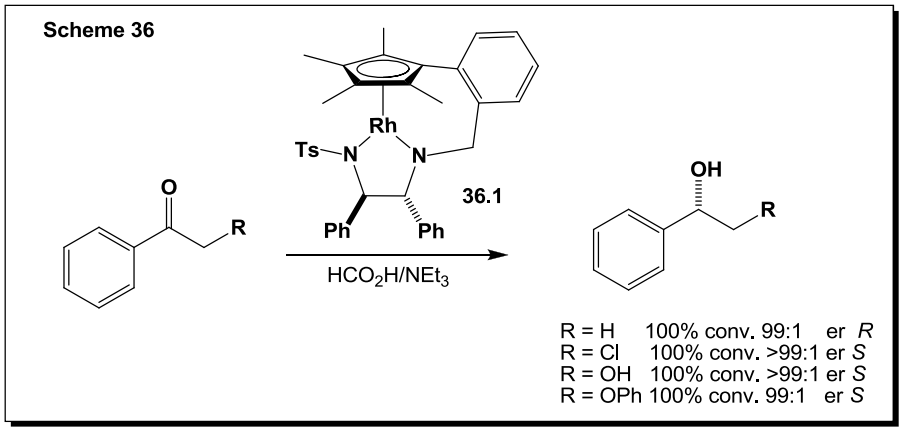
Reductant/Solvent	**34.1** Ru			**34.2** Rh			**34.3** Ir		
	t (h)	% conv.	er	*t* (h)	% conv.	er	*t* (h)	% conv.	er
HCO_2Na/H_2O	1	99	98:2	0.5	99	98:2	3	99	97:3
i-PrOH/KOH	24	81	95:5	24	45	95:5	24	48	94:6
HCO_2H/NEt_3	10	98	99:1	16	18	82:18	16	39	92:8

Adolfsson developed an analog of the TsDPEN ligand which has a long aliphatic chain at the *para* position of the tosyl arene to be used in aqueous media in the presence of sodium dodecylsulfate (SDS)(Scheme 35).[210] They hypothesized that the long hydrophobic chain of the modified catalyst would be forced into micelles formed by SDS in water. The polar metal end of the catalyst would orient toward the hydrophilic surface while the long alkyl tail would align toward the hydrophobic center. They hoped that this alignment would help the catalyst discriminate between the enantiotopic faces of aliphatic ketones within the micelles thereby increasing enantioselectivity. They did in fact observe moderate enantioselectivities for a number of aliphatic ketones. Whether or not the enantioselectivities were the result of interactions between catalyst and surfactant is unknown.

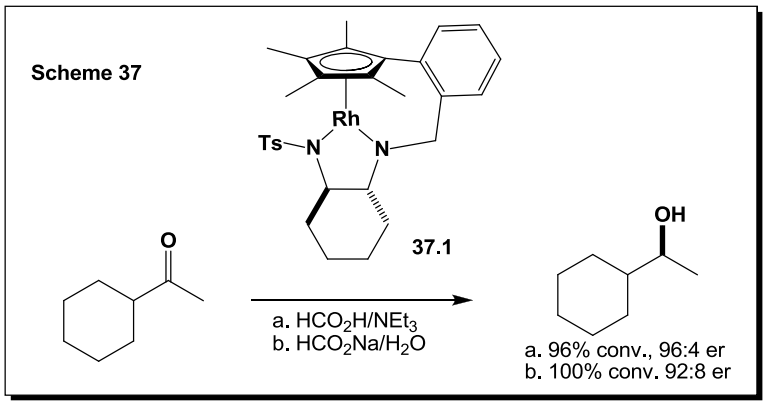
Scheme 35



Wills used a tethered rhodium catalyst for the ATH of several aryl ketones to reduce hydroxymethyl, chloromethyl, and phenoxymethyl aryl ketones with much higher activity and enantioselectivity than both the untethered version of **36.1** or Ru(*p*-Cy)TsDPEN (Scheme 36). [211]



After the positive results that Will's group observed with the tethered Rh-TsDPEN catalyst **36.1**, they identified the Ts-cyclohexyldiamine (TsDAC) ligand as a strong candidate to construct a tethered variant around. Tethered catalyst **37.1** displayed short reaction times, excellent conversions, and high enantioselectivities for a broad range of aryl alkyl ketones and a dialkyl ketone in either organic solvent or water (Scheme 36).[212] The catalyst was also extremely stable and long lived. It was able to convert 100% of 2-acetylfuran to the *R*-alcohol at S/C = 10,000 over 7 days in water without any decrease in enantioselectivity (99:1 er). It was able to reduce methylcyclohexylketone in excellent yields and with the highest enantioselectivity yet observed for an ATH reaction.



Arguably, the most important role that rhodium and iridium will play in the future of ATH is as catalysts for reductions in aqueous media.[159] Rhodium catalysts especially, have displayed some of the highest activities and enantioselectivities for ATH of ketones in water. Additionally, rhodium and iridium ATH catalysts are not O_2 sensitive and do not require the degassing of water prior to the reaction, nor do they require an inert atmosphere.[159]

2.4 Sustainability and the Future

Like all industries, chemistry is being affected by the 'greening' of society. Recent advances in chemistry are often driven by the quest to find environmentally friendly and sustainable reaction conditions. Chemists are exploring reaction conditions and reagents that are safe, efficient, and environmentally benign.[213] Economic and environmental pressures have pushed researchers toward developing catalysts made from non-toxic and abundant metals.[214] A major approach toward this effort in ATH reactions lies in the use of iron based catalysts.[215] Since solvents account for a large amount of chemical waste generated, chemists are always seeking reaction media with lower environmental impacts and some consider water to be such a solvent.

2.4.1 Water

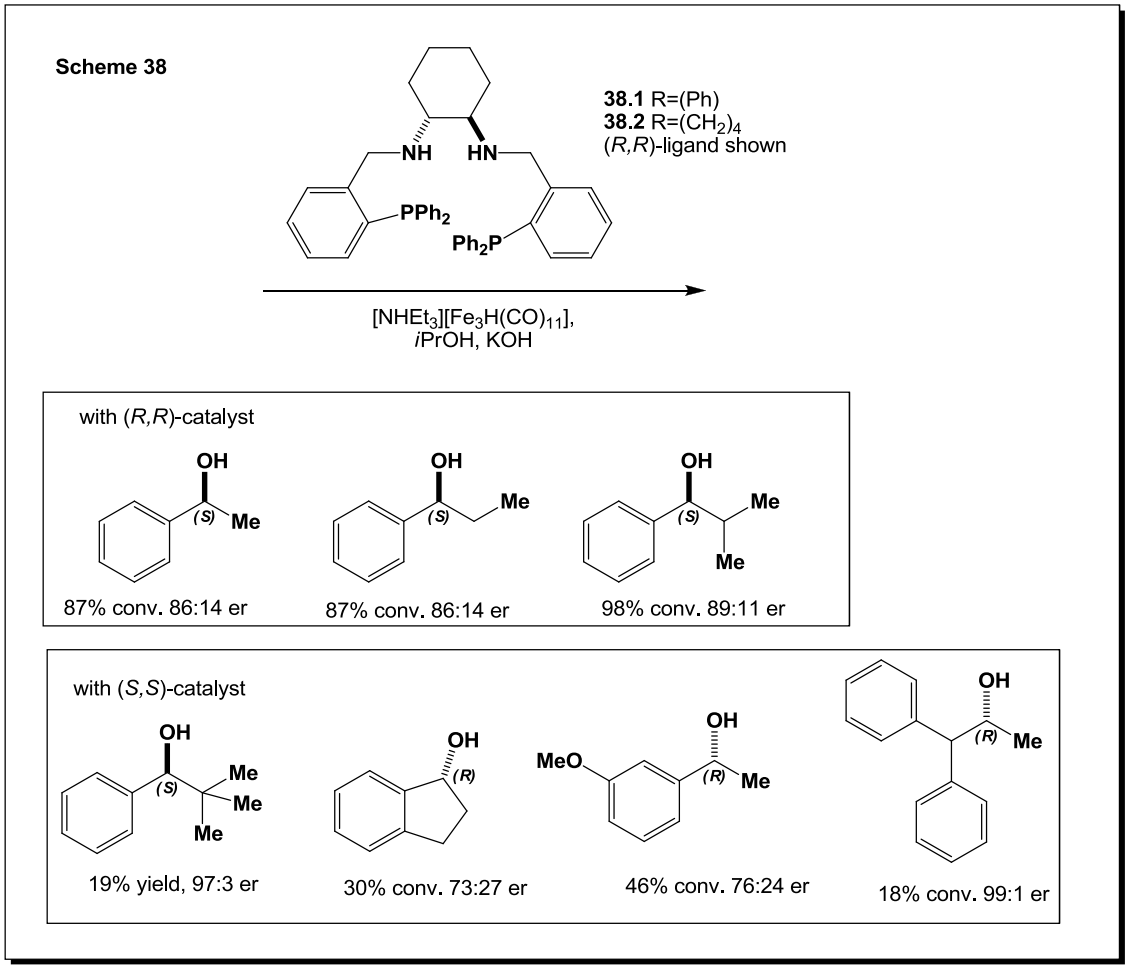
Initial research of ATH in water focused mainly on organic/water biphasic systems; the primary interest of the field was modifying ligands in order to develop water soluble catalysts,[216, 217] which resulted in catalysts with disappointing activities and/or enantioselectivities. In 2004, Xiao discovered that Ru-(*p*-Cy)-TsDPEN, without any modifications, could reduce acetophenone quantitatively in neat water with HCO_2Na in 98:2 er.[218] They soon discovered that $[RuCl_2(p\text{-Cy})]_2$, $[Cp^*IrCl_2]_2$, or $[Cp^*RhCl_2]$ could combine with numerous other traditional ATH ligands, designed for use in organic solvents, to form catalysts that are effective for ATH in water without any further modification.[159]

In general, for the reduction of acetophenone, monotosylated diamine ligands were shown to be efficient and enantioselective for ATH in water while monocamphor-sulfonated diamine ligands gave the best enantioselectivities. Rh catalysts have shown the best performance in terms of rate and enantioselectivity.[159] The best example to date of the successful aqueous ATH of a dialkyl ketone is Will's reduction of cyclohexylmethylketone with 100% conversion and 92:8 er using catalyst **37.1** (Scheme 37).

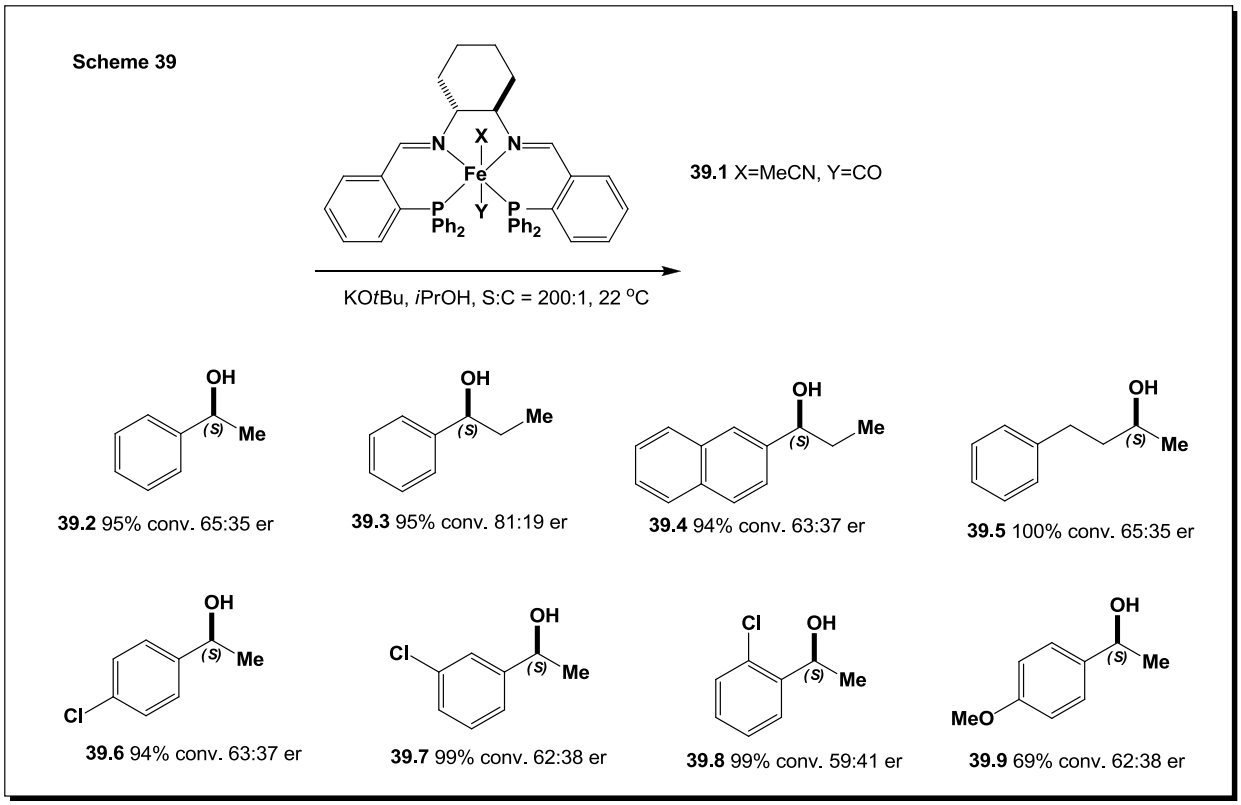
2.4.2 Iron

Since ruthenium has been shown to efficiently effect ATH reactions, it is not unreasonable to hope that iron might also be a suitable metal for ATH catalysts. Iron is significantly cheaper, found in greater abundance, and is much more environmentally benign than ruthenium, rhodium, or many other transition metals, meaning that many benefits would be conferred if stable, active, selective, and efficient catalysts could be designed around iron.[215]

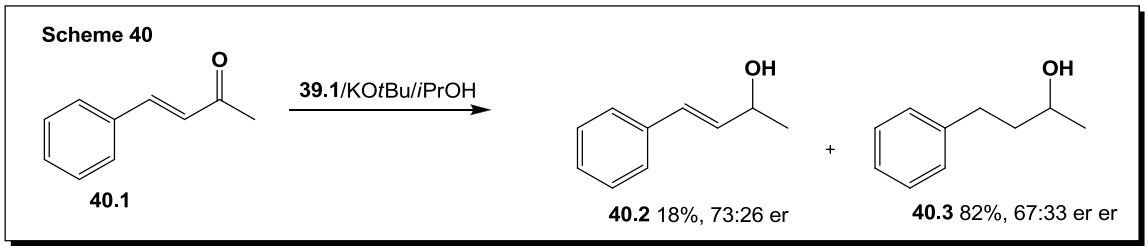
The first report of an iron catalyzed ATH came from Gao *et al*.[219] They showed that clusters of $(NHEt_3)[Fe_3H(CO)_{11}]$ and chiral diaminophosphine ligands could reduce aryl alkyl ketones. The reactions did not proceed to completion, but high enantioselectivities (97:3 er) were sometimes observed, especially when the aryl ketones also bore large alkyl groups. They did not report X-ray data for the catalyst structures (Scheme 38).



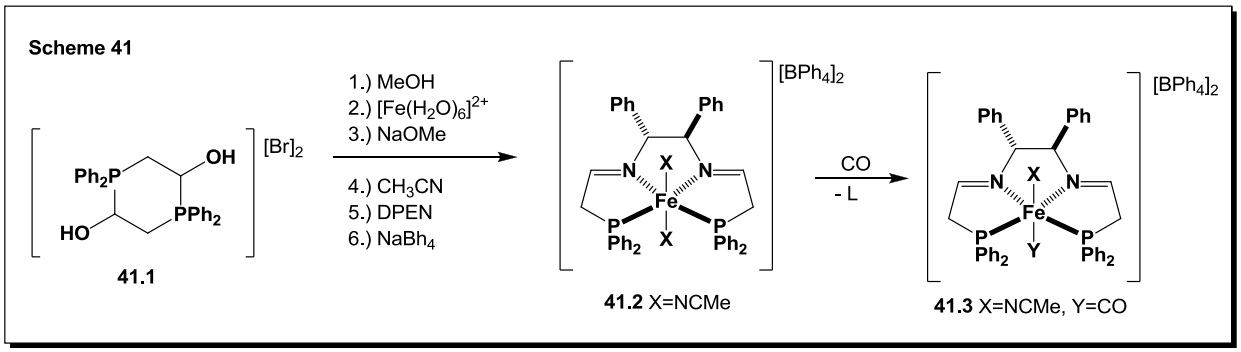
Morris reported the reduction of several aryl ketones with the preformed Fe^{II} tetradentate complex **39.1** (Scheme 39).[220] The reductions proceeded in high conversions and low to moderate enantioselectivity.



The dominant ATH product of α, β-unsaturated ketone **40.1** with catalyst **39.1** was reduction of both C=C and C=O bonds. The er of saturated alcohol **40.3** (67:33 er) is consistent with the reduction product of the saturated ketone, alcohol **39.5** (65:35 er, Scheme 40), which suggests that, in the case where both bonds are reduced, the reduction of alkene precedes the reduction of ketone thus indicating that the catalyst is more selective for alkene reduction. Reduction of minor product unsaturated alcohol **40.2** was moderately more enantioselective.

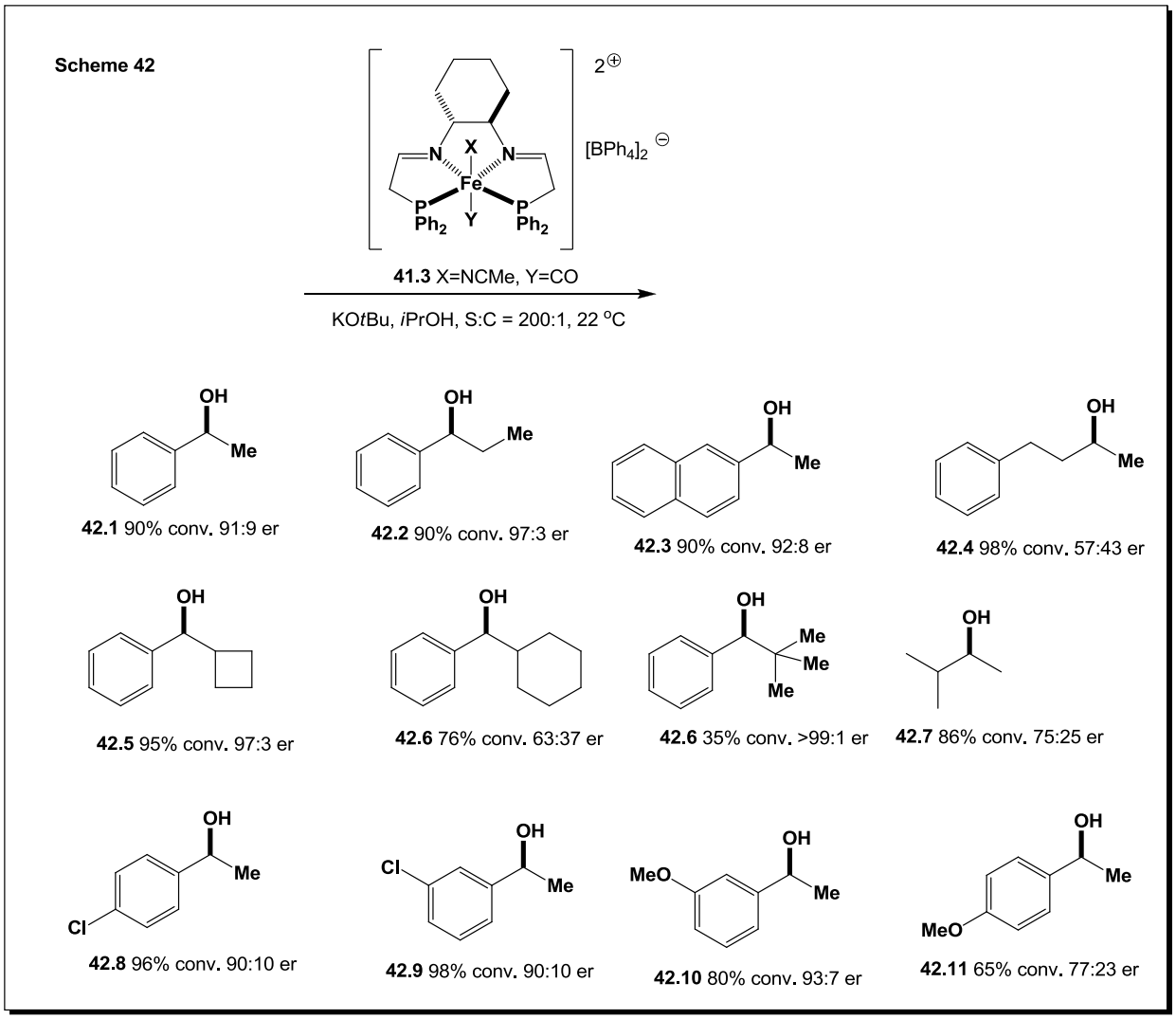


Intrigued by the ATH results seen with catalyst **39.1**, Morris sought to improve the catalyst by modifying the linkers between the nitrogen and phosphorus atoms to make them both shorter and non-aromatic; DPEN was substituted for cyclohexyldiamine as chiral ligand.[220] A major benefit is that the modified catalyst **41.3** can be formed in one-pot (Scheme 41).

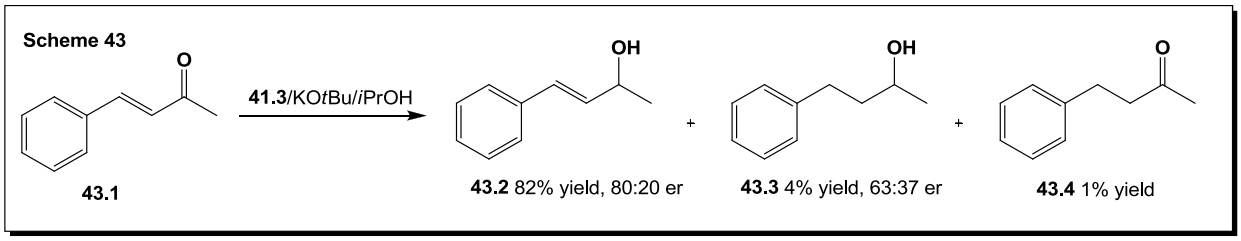


41.1 **41.2** X=NCMe **41.3** X=NCMe, Y=CO

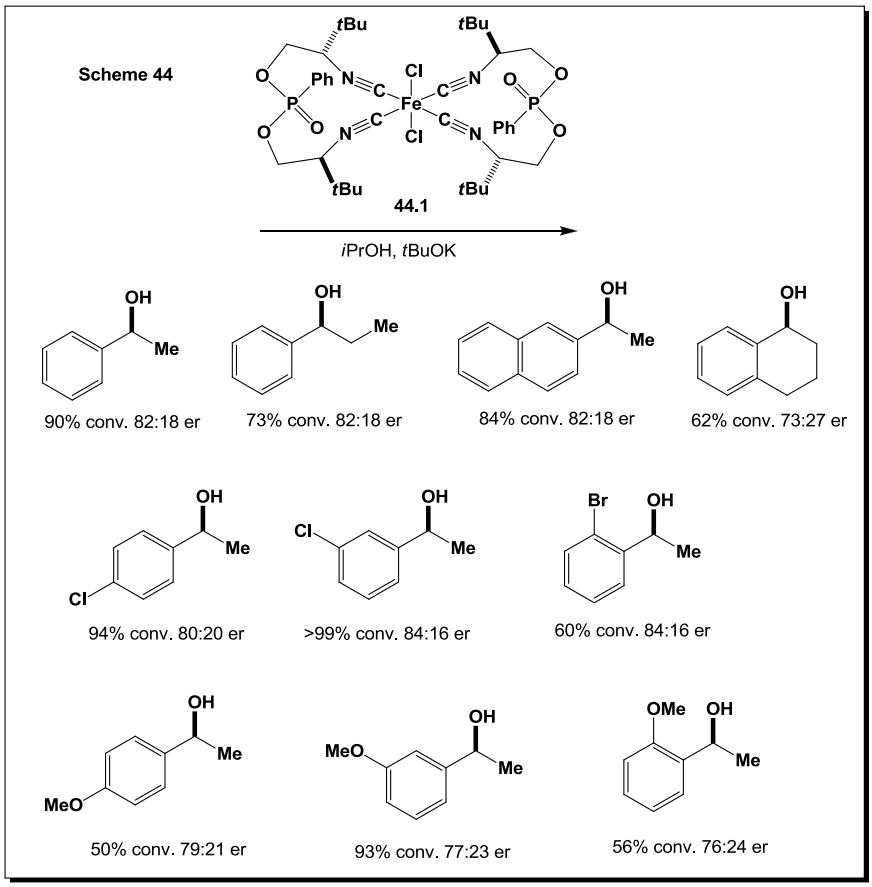
Catalyst **41.3** exhibited good conversion as well as moderate to good enantioselectivity for the ATH of aryl alkyl ketones in *i*-PrOH with bulky alkyl substituents showing the highest enantioselectivities. (Scheme 42).[220] Catalyst **41.3** was able to reduce methyl isopropyl ketone to alcohol **42.7** with an enantiomeric ratio of 75:25 in favor of the (*S*) enantiomer. However, enantioselectivity was significantly lower for 4-phenyl-2-butanol **42.4**.



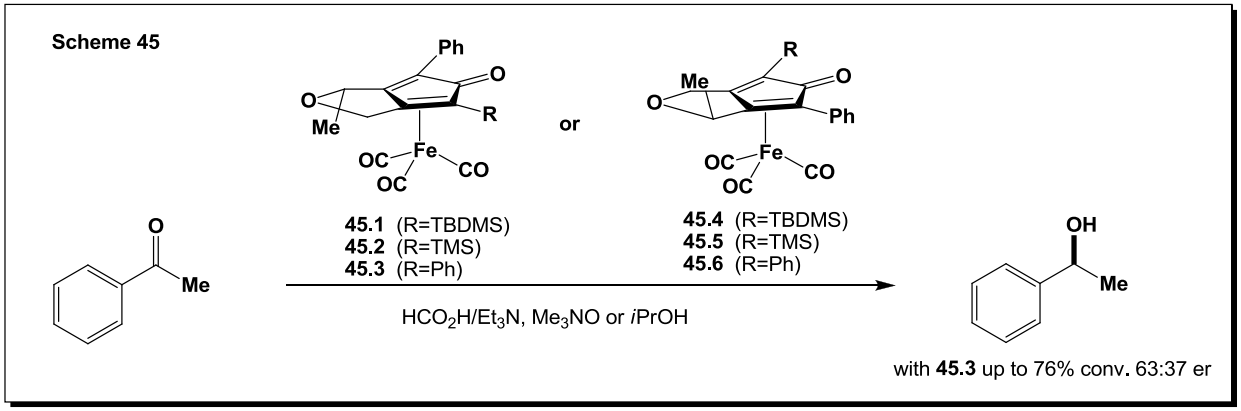
Catalyst **41.3** was also significantly more chemoselective than catalyst **39.1** for reduction of ketones over alkenes (Scheme 43).[220] Enone **43.1** was reduced to allyl alcohol **43.2** in 82% yield with moderate enantioselectivity. Saturated alcohol **43.3** was isolated in only 4% yield with er (63:37) intermediate between allyl alcohol **43.2** (er = 80:20) and reduction product of 4-phenyl-2-butanol, saturated alcohol **42.4** (er = 57:43), suggesting that ketone reduction precedes alkene reduction for at least a portion of the saturated alcohols. The lower enantioselectivity of alcohol **43.3** relative to allyl alcohol **43.2** could be due to the loss of a coordinating effect in cases where the alkene is reduced first.



An interesting class of catalysts was introduced by Reiser's group in 2010 (Scheme 44).[221] Bis-isonitrile ligands derived from chiral oxazolines were utilized to build a family of five catalysts (differing only by substitution on the carbons between nitrogen and oxygen. The most active catalyst **44.1** was tested toward the reduction of a variety of aryl alky ketones. An er of 82:18 was reported for the ATH of acetophenone in *i*PrOH with high conversion, albeit modest enantioselectivities.



Wills continued exploration into ATH using iron cyclone complexes **45.1-45.6**.[222] They made asymmetric variants of cyclone type iron catalysts developed in Casey's lab.[223] The catalysts, most notably **45.3**, reduced acetophenone in good conversion albeit poor enantioselectivity.[223] (Scheme 45)

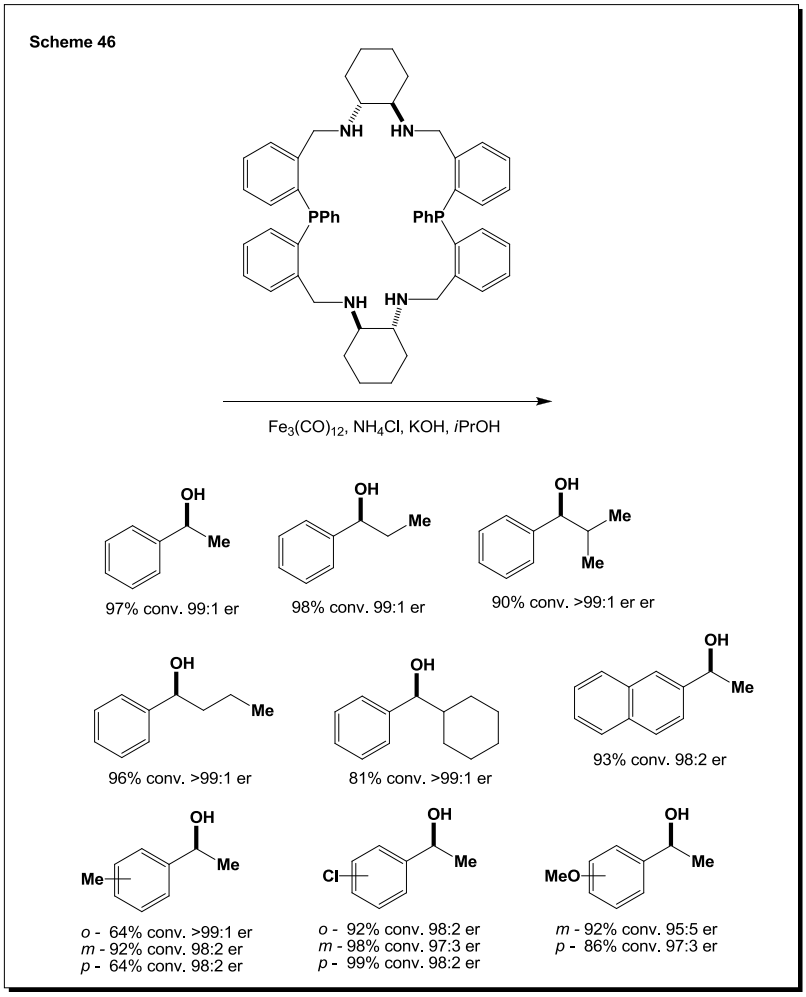


Gao and coworkers recently reported the chiral macrocyclic ligand **46.1** which bears phosphorus and nitrogen donors (Scheme 46).[224, 225]

Ligand **46.1** with tri-iron [$Fe_3(CO)_{12}$] clusters showed high activity and excellent enantioselectivity toward the ATH of a broad range of aromatic ketones. Neither electron withdrawing nor electron donating substituents on the aromatic ring played a significant role in enantioselectivity. However, when substrates had substituents in the *ortho* position, activity was diminished. It was suggested that the added steric bulk around the ketone from the *ortho* substituent led to the decrease in activity.

Although they did not propose a structure for the catalyst, they did suggest that the macrocyclic structure of the ligand might increase the configurational stability of the ligand, increasing the rigidity of the catalyst, thus giving rise to the observed enantioselectivities. Catalyst

46.1 marks the first iron based catalyst that exhibited high enough TOF's, TON's and enantioselectivities to be practically used in academic or industrial settings for the ATH of aryl ketones.[224]



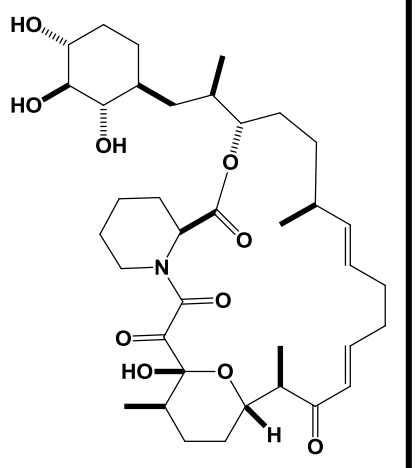
Conclusions:

Some fairly impressive work has been reported in the relatively young field of iron based ATH catalysis, but there is much work to be done towards developing viable iron based catalysts. However, systems based on ligands such as Gao's macrocycle **46.1**, offer hope for the future use of iron in ATH reactions.

CHAPTER 3. STUDIES TOWARD THE SYNTHESIS OF ANTASCOMICIN B

3.1 Introduction

Figure 3



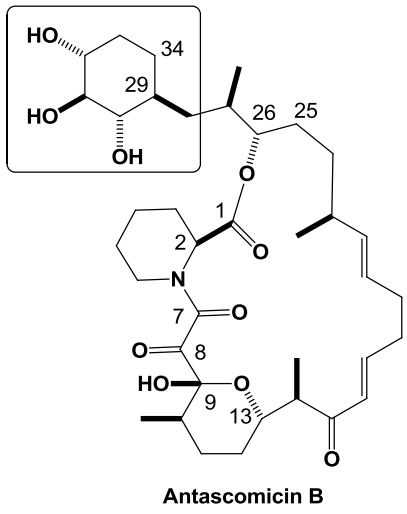
Antascomicin B

Antascomicin B, a metabolite of a strain of the soil bacteria *Micromonospora*, shares structural similarities with ascomycin, FK-506, and rapamycin. It also binds the immunophillin FKBP12 as strongly as these molecules. However, unlike most other FKBP12 binding compounds, antascomicin B does not demonstrate immunosuppressive activity. In fact, it actually antagonizes the immunosuppressive effects of both FK-506 and rapamycin.[226] FKBP12 was found to be present in the brain and spinal cord in concentrations almost fifty times higher than in the immune system, which suggests that immunophilins such as FKBP12 might play a critical role in the regulation of the nervous system.[10] Molecules such as antascomicin B, which strongly bind FKBP12 but do not have immunosuppressive activity, could be potent chemotherapeutics toward neurodegenerative diseases like Parkinson's or Alzheimer's.[12,13]

Antascomicin B, a 37 carbon complex polyketide with 12 stereocenters, is an interesting and challenging synthetic target (Figure 36). It contains a 21 membered macrocycle which includes lactone and lactam linkages, between C1 and C26 and between C2 and C7 respectively, a masked

1,2,3-tricarbonyl on C7, C8, and C9, and a lactol bridge between C9 and C13. Antascomicin B also bears an *anti-anti*-1,2,3-trihydroxycyclohexyl moiety on C34-C29, which is of primary interest to the present work.

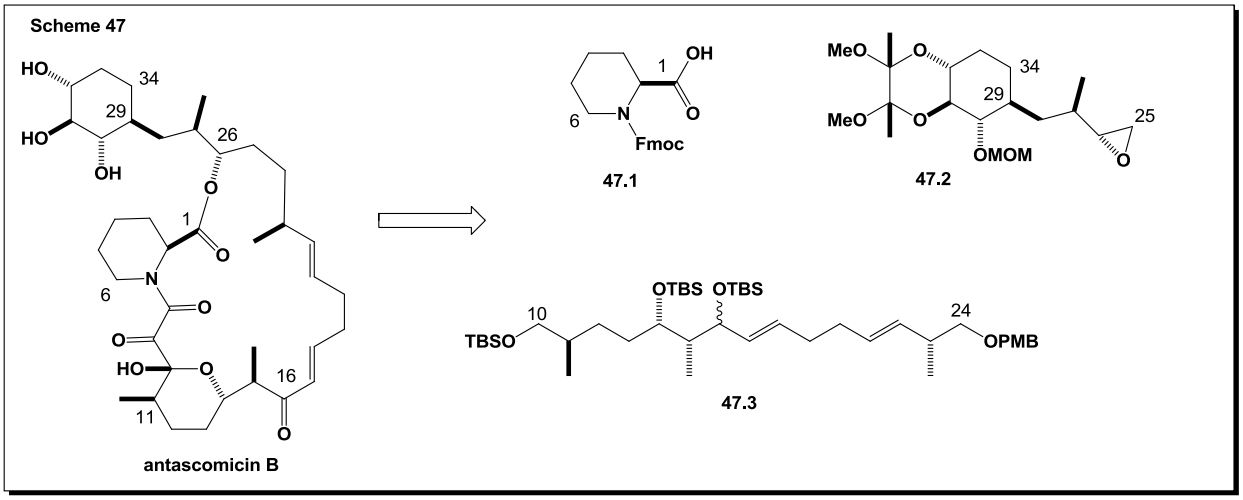
Figure 36



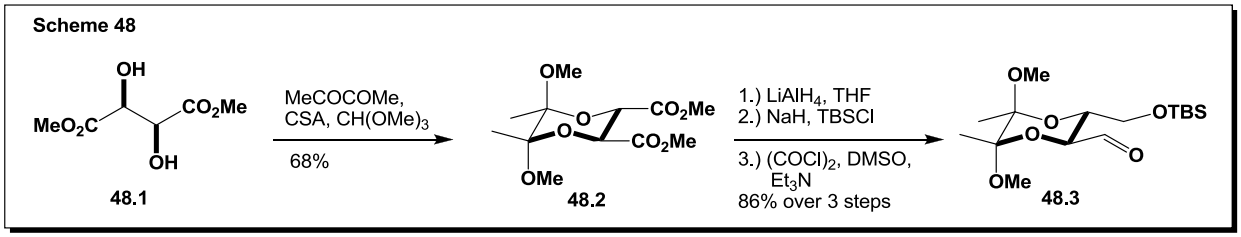
Antascomicin B

3.2 Ley's Synthesis of the C25-C34 Fragment of Antascomicin B

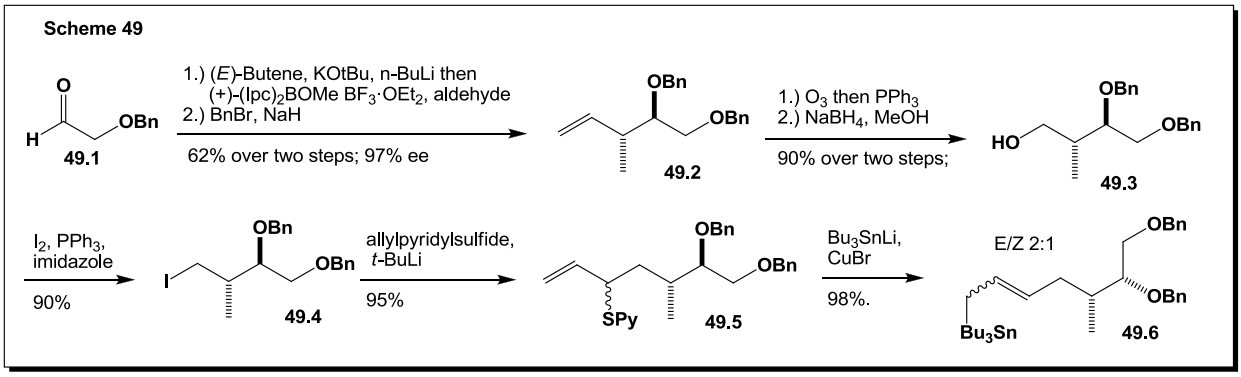
The total synthesis of antascomicin B was reported by the Ley group in 2005 (Scheme 47).[14] Their synthesis design consisted of the convergence of three fragments. The C25 epoxide on fragment **47.2** was coupled with the C24 anion of fragment **47.3** to form the C10-C34 carbon skeleton. The C10-C24 fragment was then joined to pipecolic acid fragment **47.1** via esterification. Carbon-heteroatom bond macrocyclization formed the complete carbon skeleton which was the oxidized and deprotected to give the natural product antascomicin B.



The synthesis of C25-C34 fragment **47.2** is of particular interest to this work; especially the establishment of the trihydroxycyclohexyl moiety. Synthesis of fragment **47.2** commenced with protection of dimethyl (D)-tartrate **48.1** as diacetal **48.2** to set the *anti*-1, 2-diol configuration that will eventually be on C31 and C32. Diacetal **48.2** was then converted to protected aldehyde **48.3**.

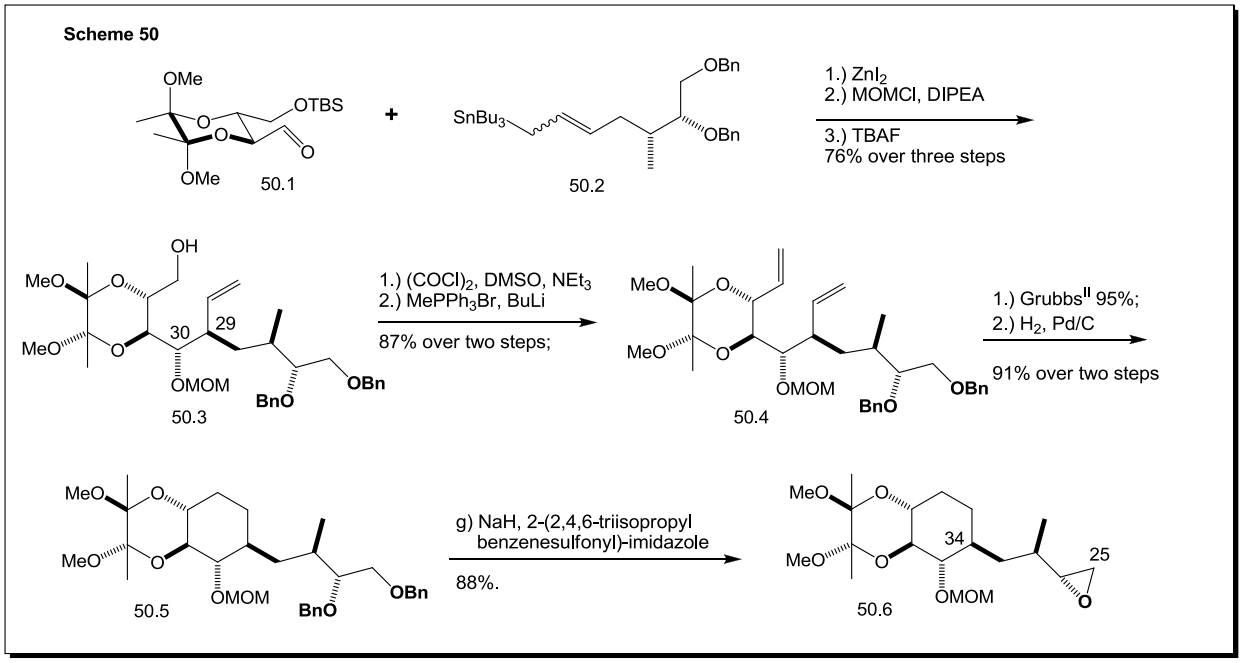


Asymmetric crotylation of commercially available benzyloxyacetaldehyde **49.1** gave the secondary alcohol with high enantioselectivity (Scheme 49), which was benzylated to alkene **49.2**. Reductive ozonolysis of alkene **49.2** gave an ozonide which was resistant to reduction by sodium borohydride. Triphenylphosphine was added to convert the ozonide to the aldehyde, which was reduced to primary alcohol **49.3**. The primary alcohol was converted to iodide **49.4** which was displaced by allylpyridylsulfide to give allylsulfide **49.5** and was subsequently converted to allylstannane **49.6** through an anionic cuprate reaction.



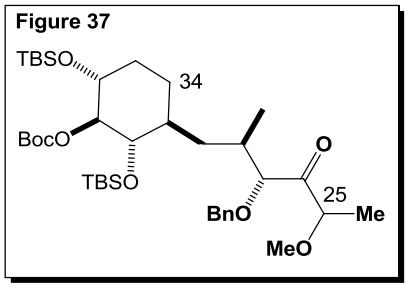
Addition of stannane **50.2** to aldehyde **50.1**, mediated by zinc iodide, followed by protection of the newly formed secondary alcohol and deprotection of primary alcohol afforded **50.3** (Scheme 50). The aldehyde/stannane addition proceeded to establish the third *anti*-hydroxyl group at C30 on the six membered ring, and gave a 7:1 diastereomeric ratio at C29 favoring the desired isomer. Primary alcohol **50.3** then underwent Swern oxidation to aldehyde followed by a Wittig reaction to produce alkene **50.4**. Ring closing metathesis catalyzed by GrubbsII was followed by reduction of the resultant endocyclic C=C double bond and simultaneous removal of both benzyl groups to give the diol **50.5**. The diol was subsequently epoxidized to C25-C34 fragment **50.6**.

Ley's convergent synthesis of the C25-C34 fragment required 19 overall steps with 24.7% yield and a longest linear sequence of 15 steps. Two of the stereocenters on the trihydroxycyclohexyl group were purchased as methyl tartrate and the synthesis required the use of tin, ruthenium, and palladium.



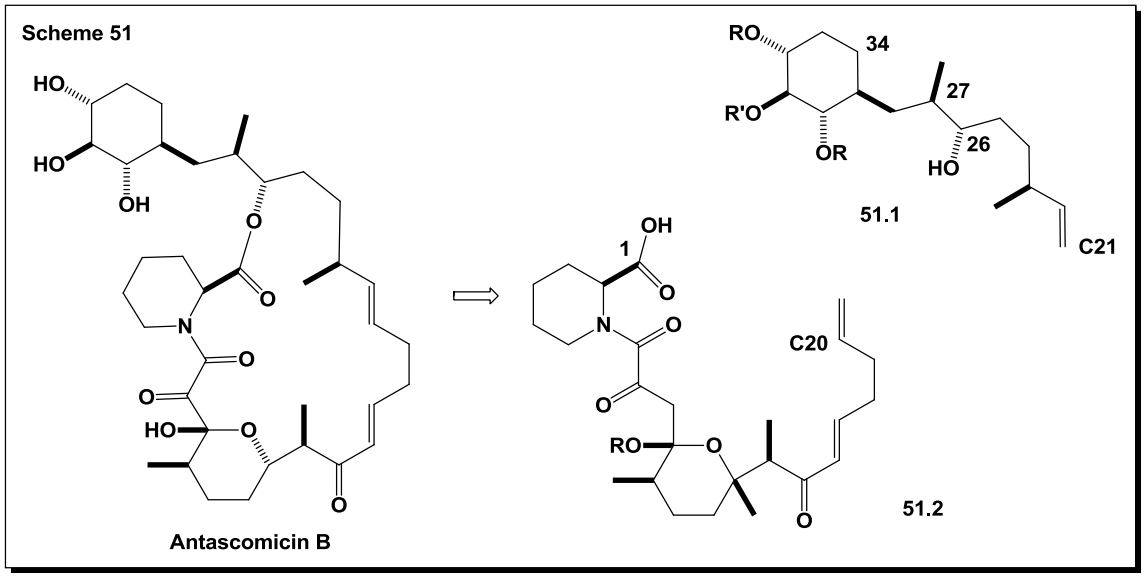
3.3 The McIntosh Group's Synthetic Efforts Toward Antascomicin B

Our group has been engaged in the total synthesis of antascomicin B for a number of years. The present work will highlight our efforts toward the synthesis of antascomicin B including: the synthesis of an advanced model of the C34-C22 fragment, the racemic synthesis of the C34-C21 fragment, and the enantioselective synthesis of the C34-C25 fragment (Figure 37). We also describe plans for the completion of the natural product.

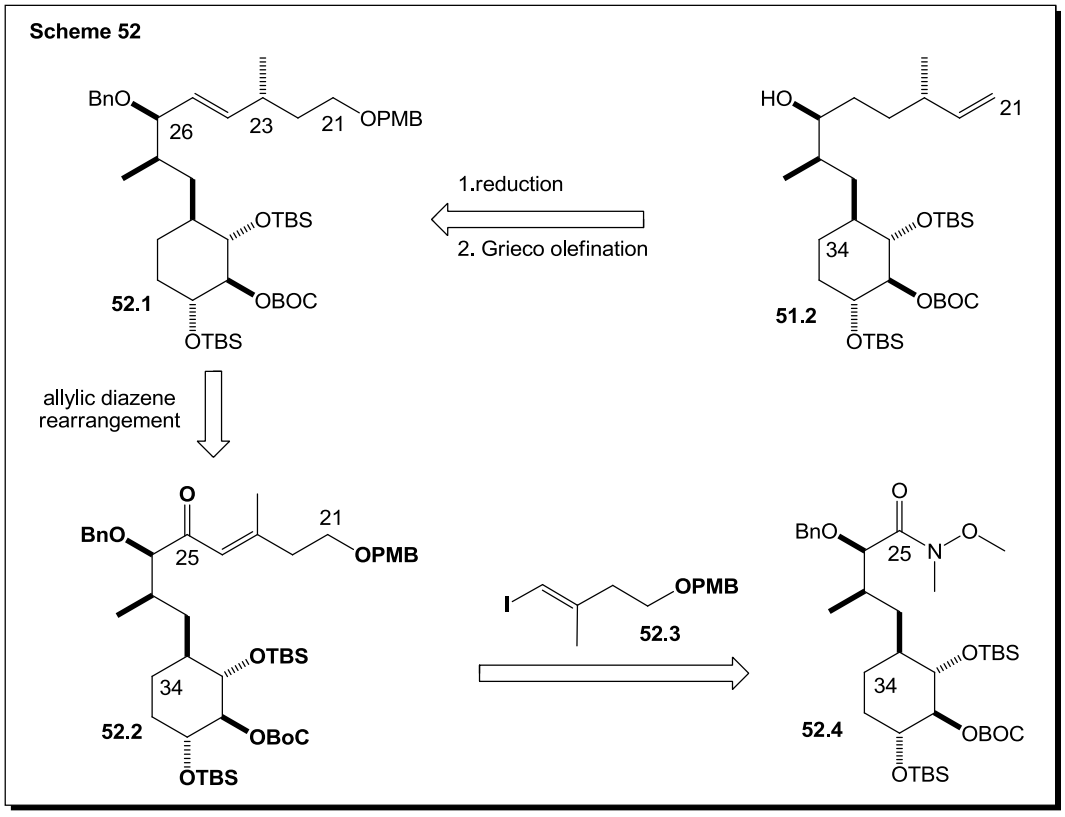


3.3.1. Retrosynthesis

Our current retrosynthetic analysis of antascomicin B involves the convergence of two late stage intermediates: C34-C21 fragment **51.2** and C20-C1 fragment **51.2** (Scheme 51). We envision bringing the two fragments together using Grubb's metathesis and Yamaguchi lactonization. The C20-C1 fragment **51.2** will be prepared from pipecolinic acid. Its synthetic route will include a Suzuki coupling and an amino-Claisen rearrangement.



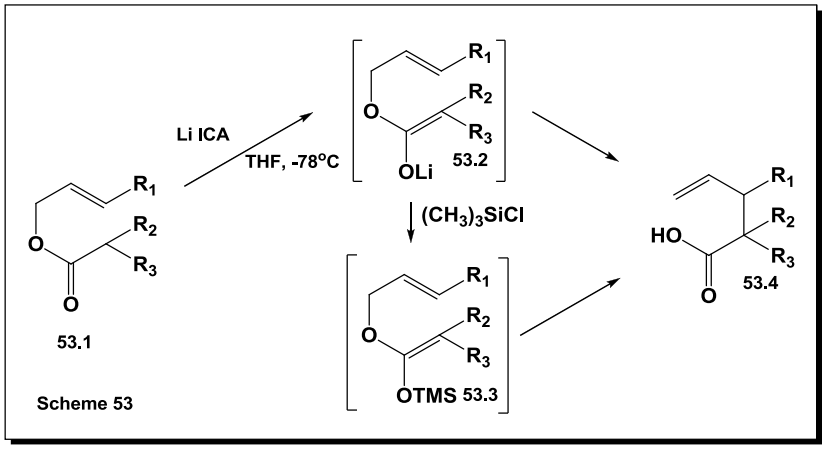
The C34-C21 fragment **51.1** will be accessed from reduction of alkene and partial deprotection followed by Grieco olefination of the primary alcohol of **52.1** (Scheme 52). The final C23 stereocenter in intermediate **52.1** will be set by allylic diazene rearrangement from enone **52.2**, which is generated from homologation of vinyl iodide **52.3** to the enantiopure C34-C25 fragment **52.4**.



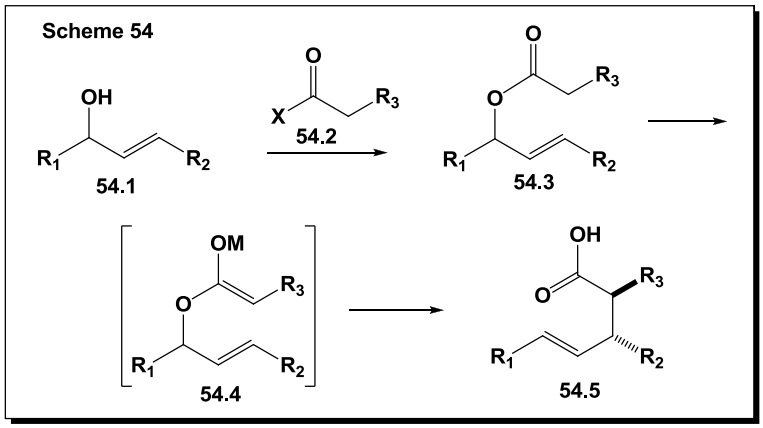
Key reactions in the synthesis of the C34-C25 fragment are an Ireland-Claisen rearrangement, an allylic diazene rearrangement, a directed hydrogenation, and an asymmetric transfer hydrogenation. A brief overview of the Ireland-Claisen and allylic diazene rearrangement and how they apply to our strategies is included below in order to familiarize the reader with the material.

3.3.2 The Ireland-Claisen Rearrangement

A major contribution to the Claisen rearrangement came in 1972 when Robert Ireland discovered that, under relatively mild conditions, Li-enolate anions or more commonly, the corresponding silyl ketene acetals of allyl esters could undergo a Claisen-like sigmatropic rearrangement (Scheme 53).[227]



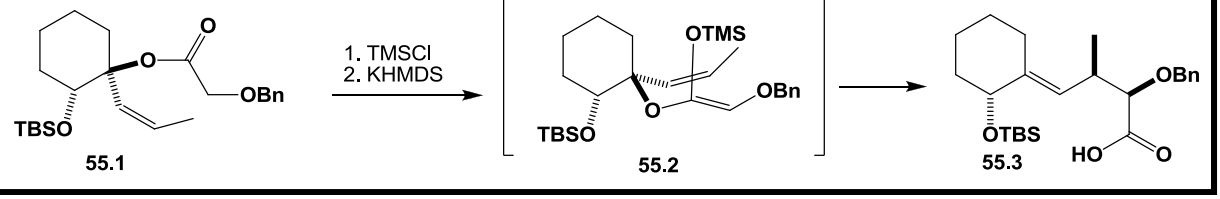
This rearrangement has high value in synthesis for a number of reasons. First, the allyl ester reactants are readily accessible from reaction of the respective allyl alcohol with an activated carboxylic acid.[228] Second, it is usually possible to control the E/Z geometry of the ester enolate. This allows for predictable determination of the stereochemistry in resulting C-C bonds in the rearranged product (Scheme 54).[229]



Our lab has developed a novel variant of the Ireland-Claisen rearrangement of *bis*-allylic esters derived from cycloalkenones (Scheme 55).[228, 230-232] In our variant, the carbinol center of the

allylic ester is contained within a cyclohexyl ring. The silyl ketene acetal intermediate **55.2** rearranges to give alkylidene cycloalkene **55.3**.

Scheme 55

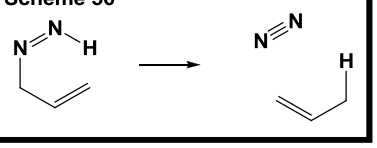


3.3.3 The Allylic Diazene Rearrangement (ADR)

3.3.3.1 Background

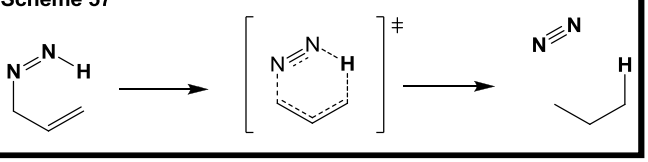
In its simplest form, the allylic diazene rearrangement (ADR) is the retro-ene reaction of *cis*-1-diazo-2-propene to produce propene and molecular nitrogen (Scheme 56).[233]

Scheme 56



Density functional theory studies have determined that the ADR occurs through an early, concerted, six-member, cyclic transition state (Scheme 57).[234]

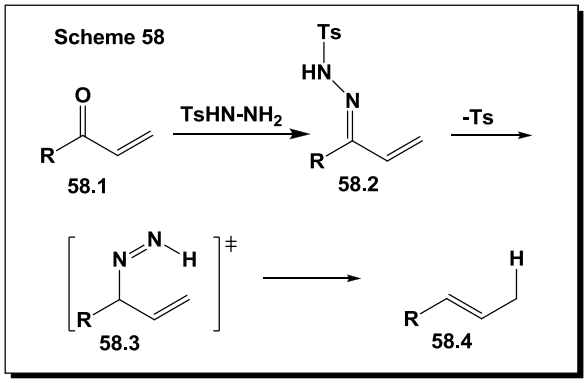
Scheme 57



In 1964 Bumgardener and Freeman reported the reductive deamination of allylic amines by treatment with difluoroamine to afford the alkene and two equivalents of the allylic amine hydrofluoride salt. This report was the first to propose the now-accepted ADR reaction

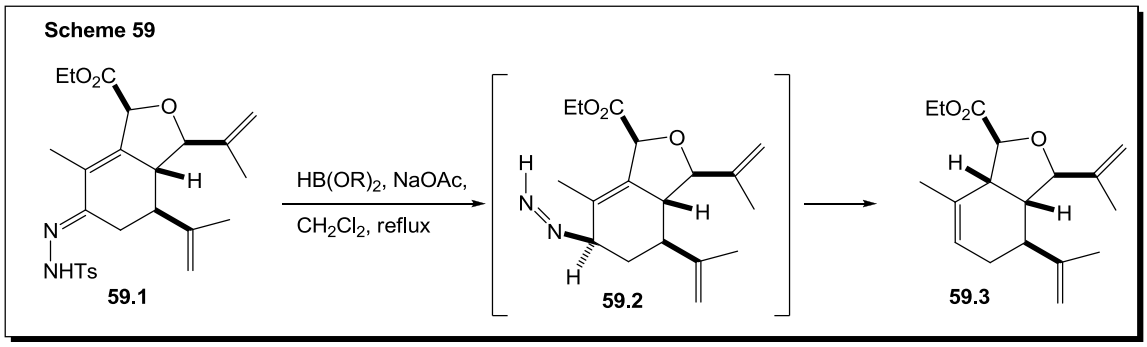
mechanism.[235] The ADR is a pericyclic, 1,5-sigmatropic rearrangement that involves the suprafacial transfer of the terminal diazene hydrogen to the terminal carbon of the alkene.

A common application of the ADR is as the final step in the reduction of an α, β-unsaturated ketone or aldehyde to the reduced alkene (Scheme 58).[236] Enone **58.1** was converted to sulfonyl hydrazone **58.2** which was then reduced to hydrazine **58.3** with catecholborane, $NaBH_4$ or $NaCNBH_3$ in an acidic medium. Upon formation of the allylic diazene, the ADR occurred spontaneously to give the 1, 3-transposition product **58.4**.[236]



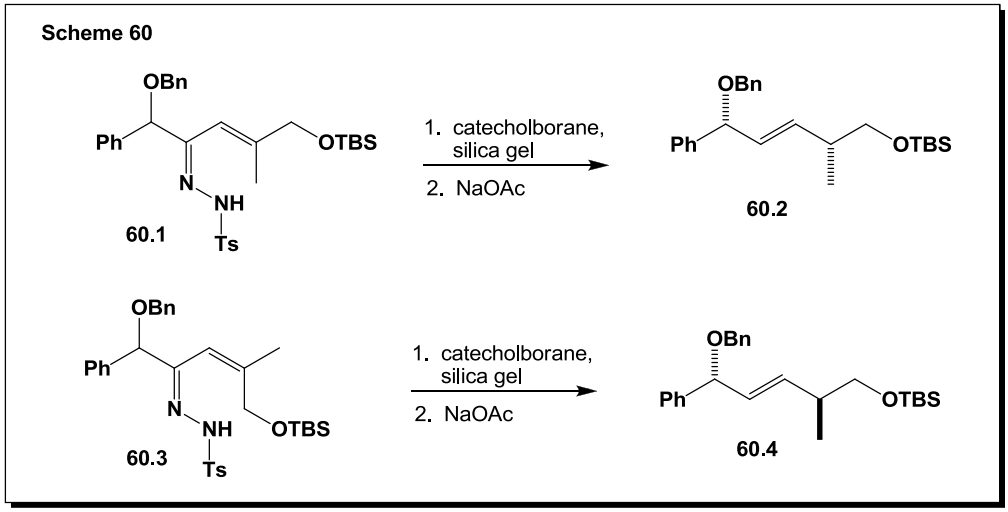
3.3.3.2 The ADR and Cyclic Stereocontrol

The ADR has found great synthetic utility in relaying stereochemistry in cyclic systems,[237] commonly through the reduction of α,β-unsaturated tosylhydrazones.[238] Preparation of tosylhydrazones generally occurs readily when ketones are treated with sulfonyl hydrazides in refluxing ethanol of THF. One example from our lab is the synthesis of a cis-fused hydroisobenzofuran bicycle **59.3** (Scheme 59)[239]

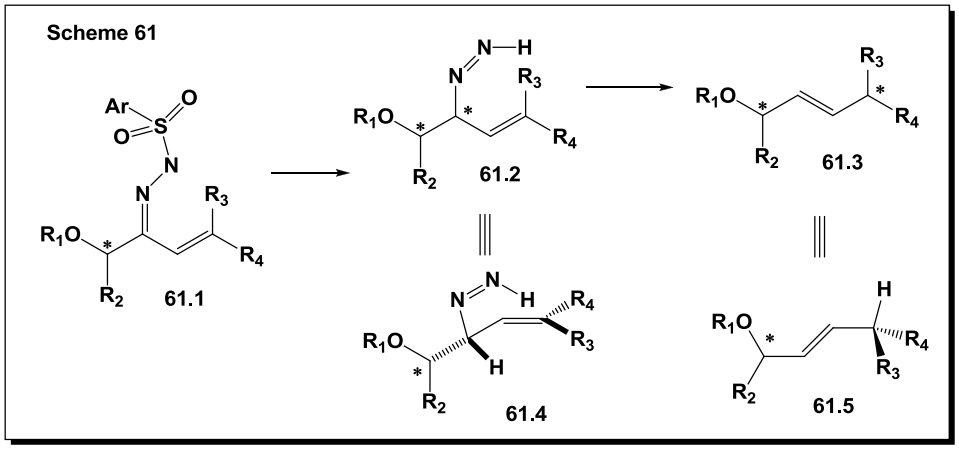


3.3.3.3 The ADR and Acyclic Stereocontrol

Although there have been numerous examples of use of the ADR to install stereocenters in cyclic systems,[237, 240, 241, 242] achieving the same in an acyclic system presents different problems. Prior our work, installation of an sp^3 stereocenter in an acyclic system had not been reported. Our lab demonstrated a method to establish either 1,4-*syn* or 1,4-*anti* stereorelationships using the ADR.[243] The 1,4-*syn* diastereomer of the ADR product was formed when *E*-alkene **60.1** was used while *Z*-alkene **60.3** led to 1,4-*anti* isomer **60.4**. Both isomers showed >20:1 dr (Scheme 60).

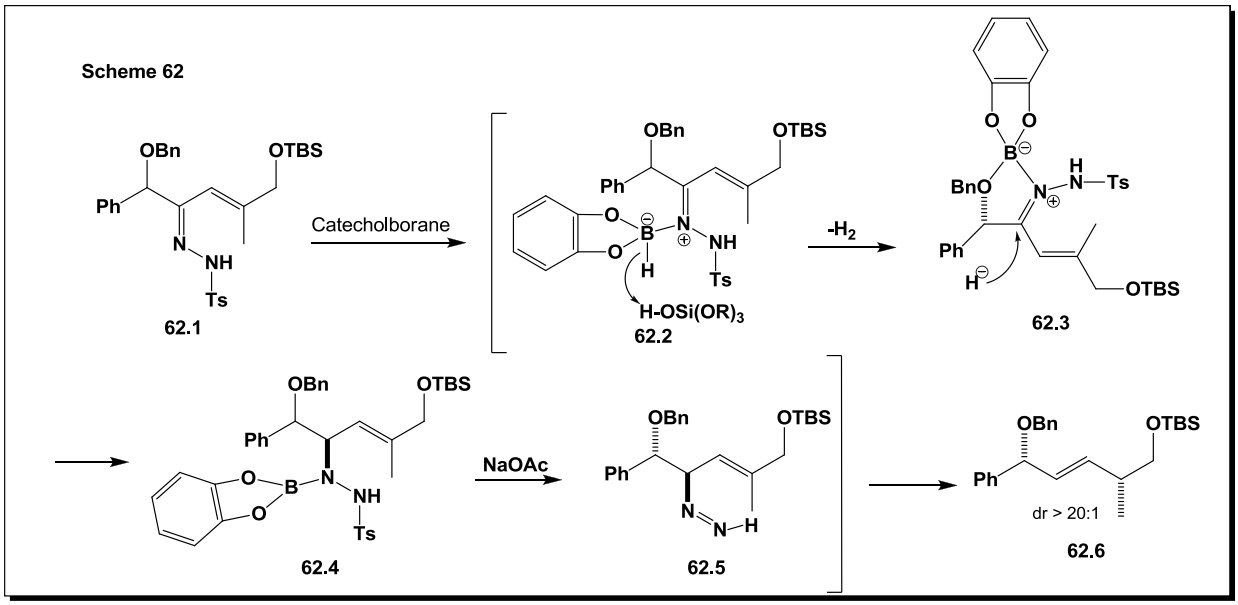


We hypothesized that diastereoselective reduction of acyclic α,β-unsaturated hydrazone **61.1** proceeds through a Cram chelation controlled pathway to afford allylic diazene **61.2**. If the terminal carbon of the allyl group **61.1** is prochiral, the stereochemistry of the diazene will be transferred to the terminal carbon via the ADR. In acyclic systems, allylic strain in intermediate **61.4** controls delivery of the hydrogen (Scheme 61).

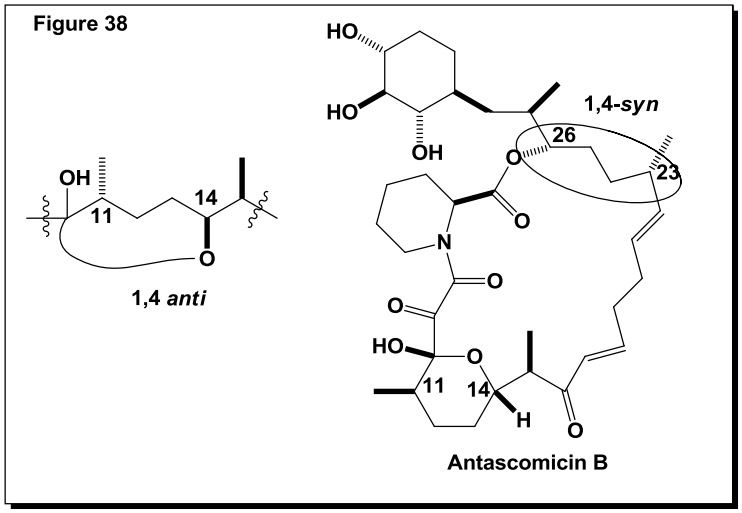


Rosini found that when tosylhydrazones bearing α-alkoxy functionality were treated with sodium cyanoborohydride, they gave exclusively *anti*-hydrazides while tosylhydrazones lacking α-alkoxy functionality gave a mixture of *anti* and *syn*-hydrazides.[244]

Our group expanded on Rosini's observation and applied a similar methodology to acyclic α'-alkoxy-α,β-unsaturated tosylhydrazone **62.1** (Scheme 62). Treatment of hydrazone **62.1** with catecholborane in the presence of silica gel gave the rearranged product with diastereoselectivity in excess of 20:1. Reduction from the less hindered face afforded the 1, 2-*anti* hydrazine **62.4**. Allylic strain dictated hydrogen transfer of the ADR and created the new sp^3 stereocenter in the 1, 4-*syn* alkene **62.6**.



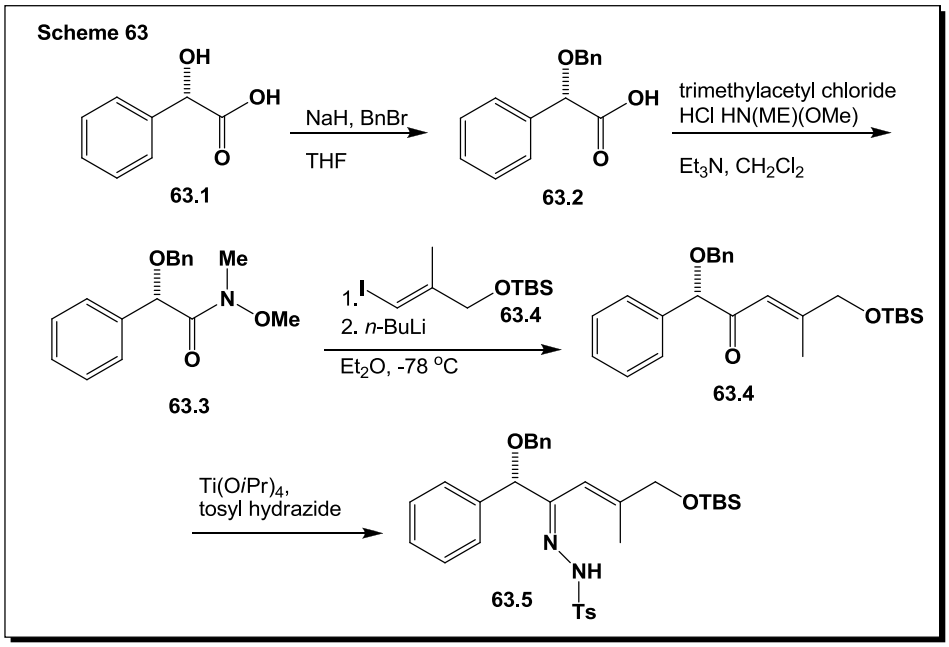
Both the 1,4-*syn* and 1,4-*anti* stereorelationships are found in a variety of marine natural products, such as redispongiolide A and B, and amphidinolide J.[245, 246] Antascomicin B possesses both 1, 4-*syn* (C23-C26) and 1, 4-*anti* (C11-C14) motifs (Figure 38).[226]



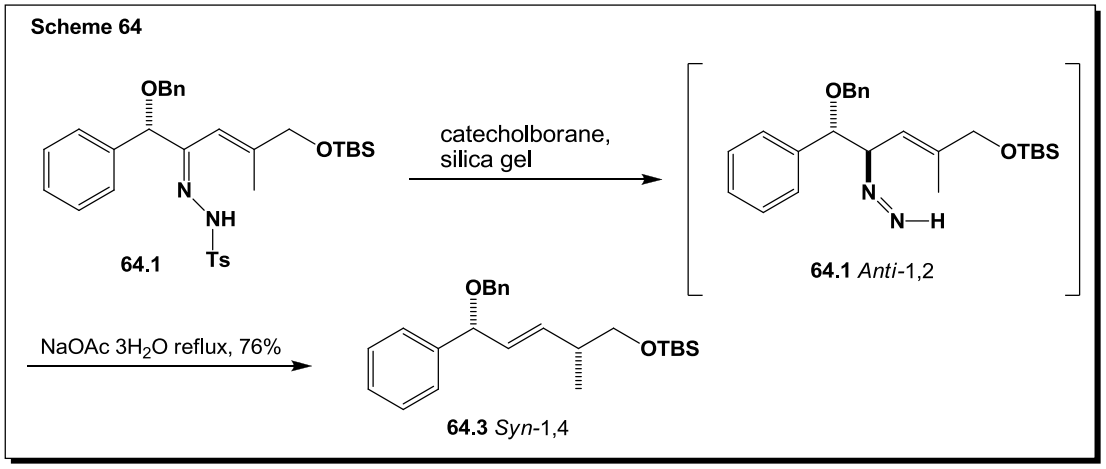
3.3.3.4 Model Studies of the ADR.

Our retrosynthetic strategy toward antascomicin B relies on the ADR to establish the configuration at C23. Therefore, an appropriate model study was necessary to test the feasibility of this transformation.

The synthesis of both *E* and *Z*-α, β-unsaturated enones began with the benzylation of commercially available (*S*)-(+)-mandelic acid **63.1** (Scheme 63). The *o*-benzyl-acid **63.2** was converted, via the mixed anhydride, to Weinreb amide **63.3**. Lithio anion derived from vinyl iodide **63.4** was then added to amide **63.3** to give the α, β-unsaturated ketone **63.4**, which was subsequently converted to tosylhydrazone **63.5**.

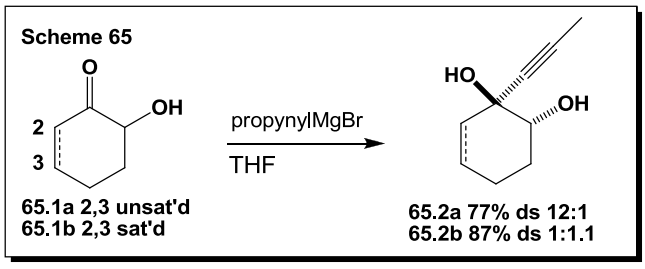


Using modified Kabalka conditions (catecholborane, silica gel, NaOAc-3H_2O, reflux), the reduction of α, β-unsaturated-*E*-hydrazone proceeded with high diastereoselectivity. Reduction from the less hindered face produced 1, 2-*anti*-hydrazine **64.2** followed by ADR to afford 1, 4-*syn*-alkene **64.3** (Scheme 64).



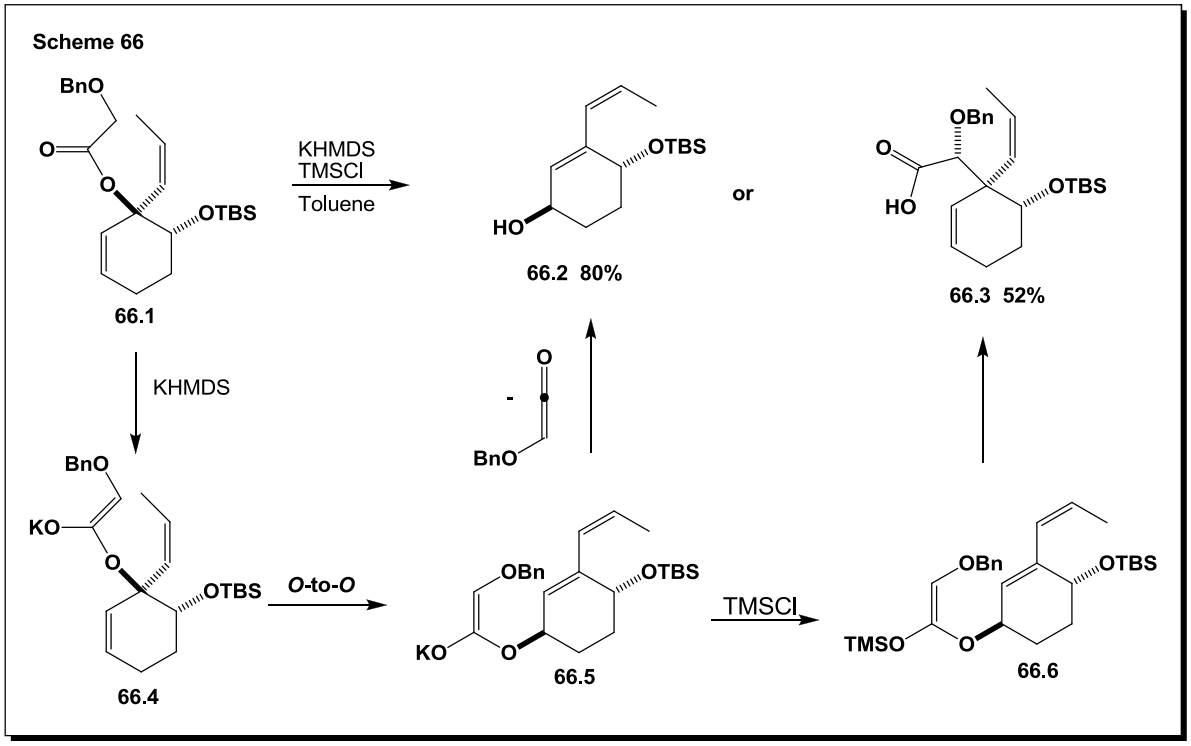
3.3.4 Model Study of the C22-C34 Fragment

An advanced model of the C22-C34 fragment of antascomicin B was prepared by former graduate student Wei Qi in order to test the feasibility of the Ireland-Claisen and allylic diazene rearrangements.[18] The first attempt at the model system proceeded from 6-hydroxy-cyclohexenone **65.1a** (Scheme 65). The unsaturated ring showed much higher diastereoselectivity in the addition of propynylMgBr than did the saturated compound (**16.2b**).



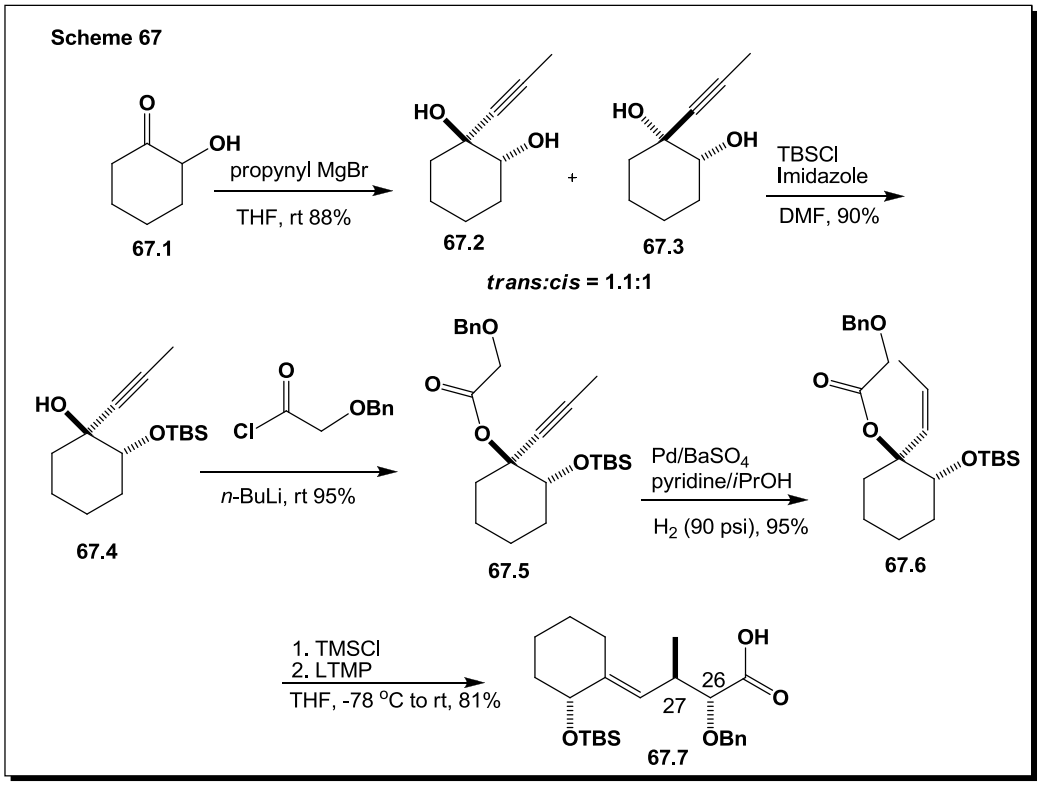
However, endocyclic alkene **65.2** proved unsuitable for the synthesis due to problems encountered during the Ireland-Claisen rearrangement (Scheme 66). Ireland-Claisen precursor

66.1 gave a mixture of products. When glycolate **66.1** was treated with KHMDS and then TMSCl, 1,4-diol **66.2** was major product. When base was added to allyl ester **66.1** in the presence of TMSCl, acid **66.3** was the major product. We speculate that upon formation of enolate **66.4**, a rapid suprafacial [3, 3] *O*-to-*O* rearrangement occurred to produce enolate **66.5** which, in the presence of TMSCl, underwent Ireland-Claisen rearrangement to give **66.3**. In the absence of TMSCl, enolate 66.**5** underwent ketene elimination to give 1, 4-diol **66.2**.

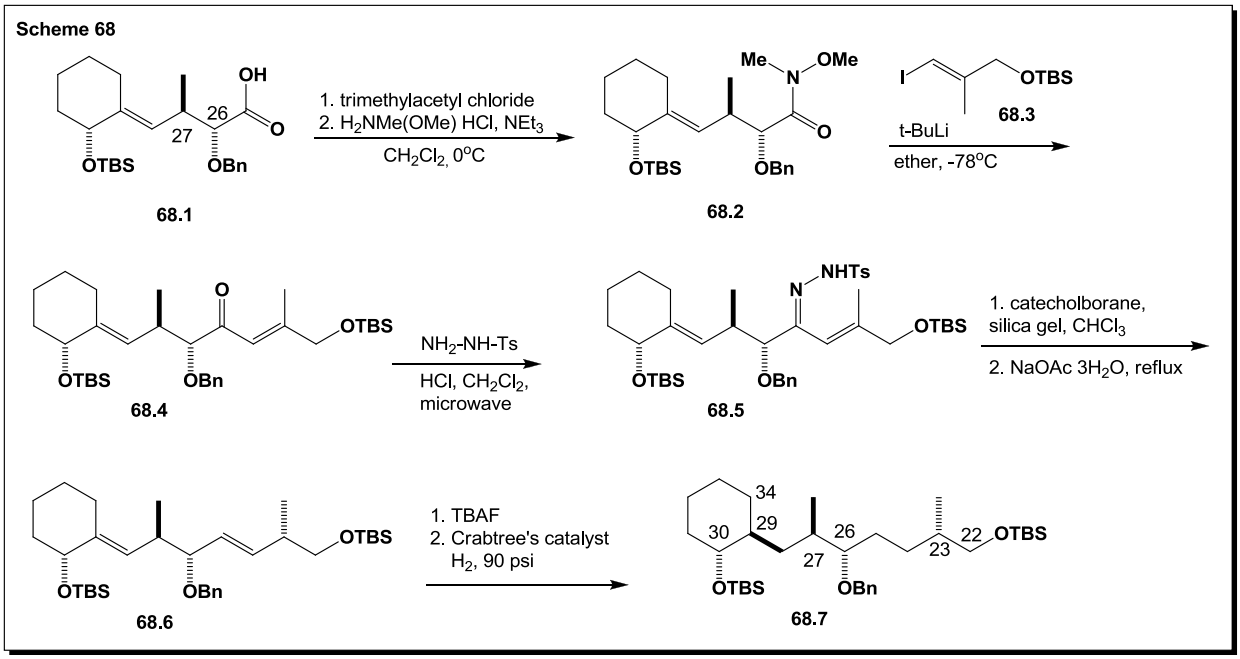


To circumvent the undesired Ireland-Claisen rearrangement products, the synthesis of a saturated analogue was pursued (Scheme 67). Addition of propynylMgBr to commercially available 2-hydroxy-cyclohexanone afforded *anti*-diol **67.2,** albeit in an unselective fashion. The secondary alcohol was silylated to **67.4** followed by acylation of the tertiary alcohol, to afford glycolate **67.5**. The next step in the synthesis was the partial-hydrogention of alkyne to *Z*-alkene to give Ireland-Claisen precursor **67.6**. Ireland-Claisen rearrangement was initiated by addition of LTMP to a

solution of **67.6** and TMSCl in THF to afford pentenoic acid **67.7** with *anti*-configuration at C26 and C27.

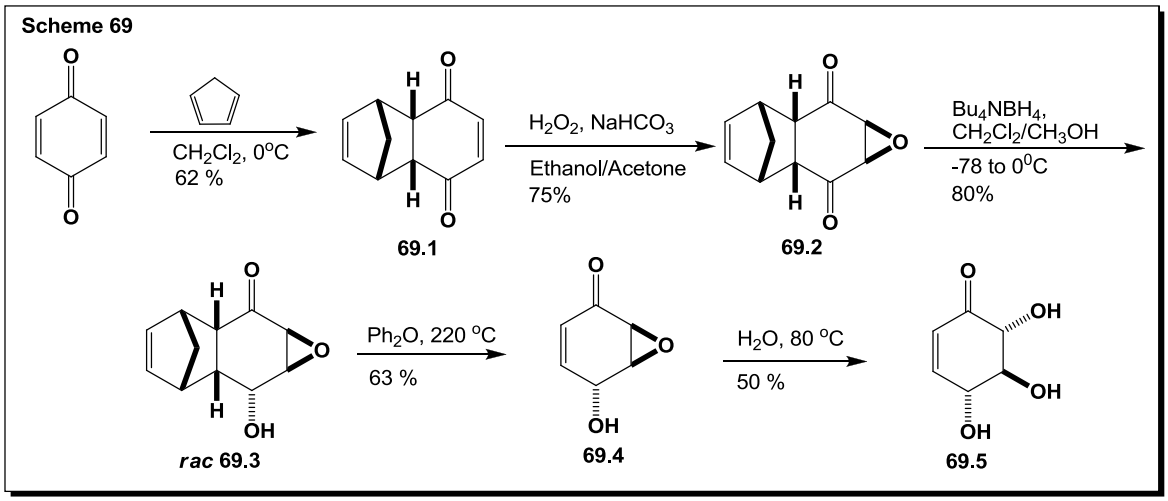


Acid **68.1** was converted to Weinreb amide **68.2** (Scheme 68), which underwent homologation to the lithio anion of vinyl iodide **68.3** to yield α, β-unsaturated ketone **68.4**. Ketone **68.4** was converted into hydrazone **68.5** followed by ADR to give alkene **68.6**. Directed hydrogenation via Crabtree's catalyst set the C29 stereocenter and completed the synthesis of the C34-C22 model compound **68.7**. The model synthesis showed that the Ireland-Claisen and allylic diazene rearrangements were indeed feasible transformations for the synthesis of the C34-C21 fragment of the natural product.

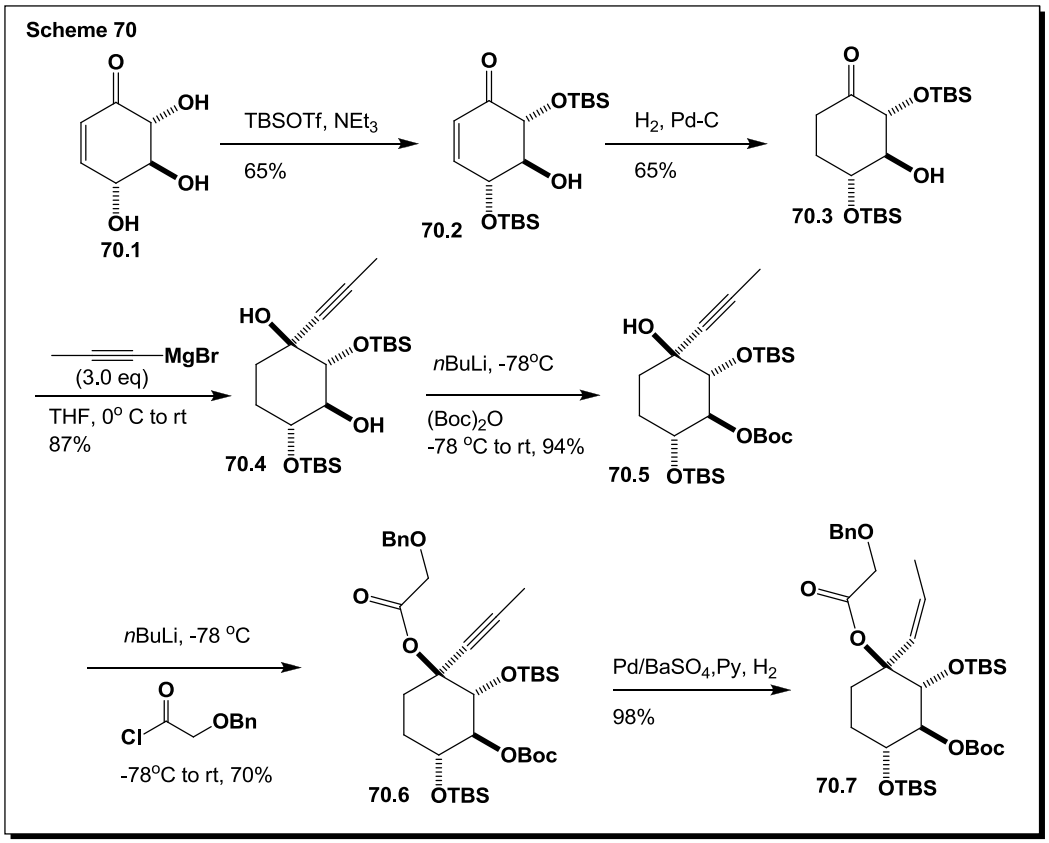


3.3.5 Racemic Synthesis of the C34-C21 Fragment

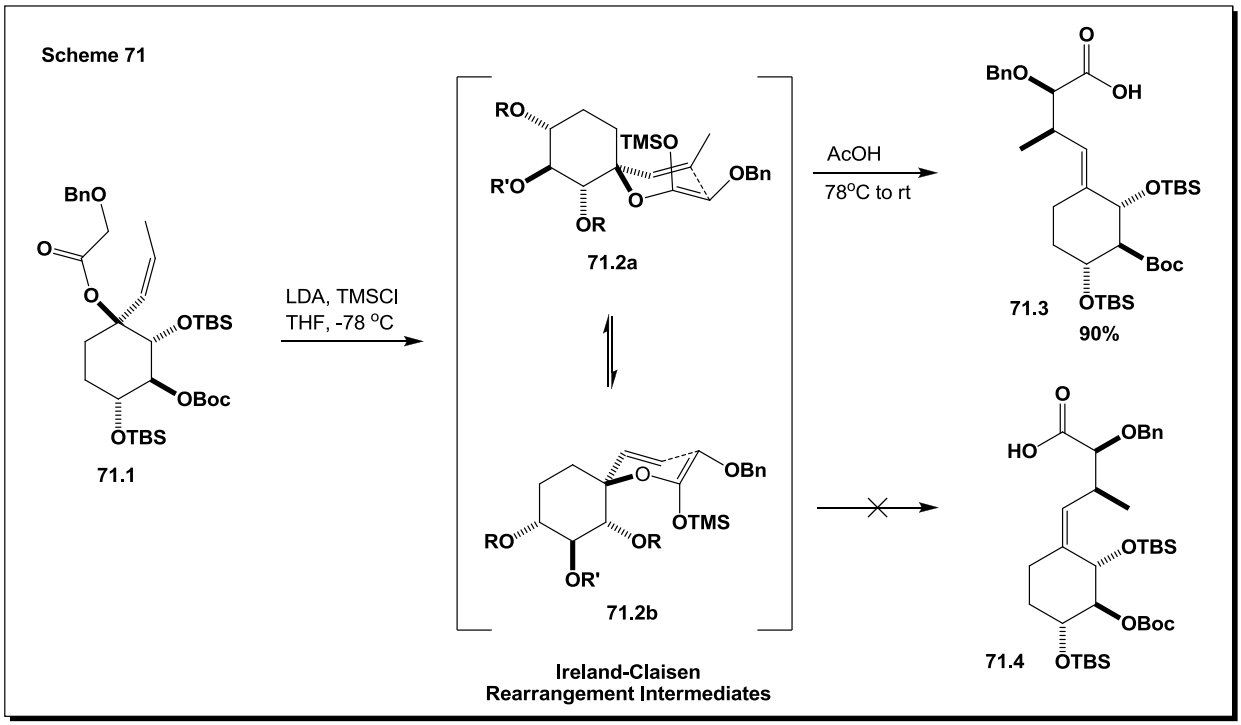
The racemic synthesis of the C34- C21 fragment has recently been completed in our lab, led by post-doc John Hutchison (Scheme 69). The synthesis began with Diels-Alder reaction between *p*-benzoquinone and freshly cracked cyclopentadiene to afford Diels-Alder adduct **69.1**, which was then epoxidized to **69.2**. Epoxide diketone **69.2** was then reduced racemically to give monoreduced epoxide **69.3**. Retro Diels-Alder reaction extruded cyclopentadiene to give epoxyquinol **69.4**, which underwent hydrolysis of epoxide ring to afford *anti-anti* cyclitol **69.5**.



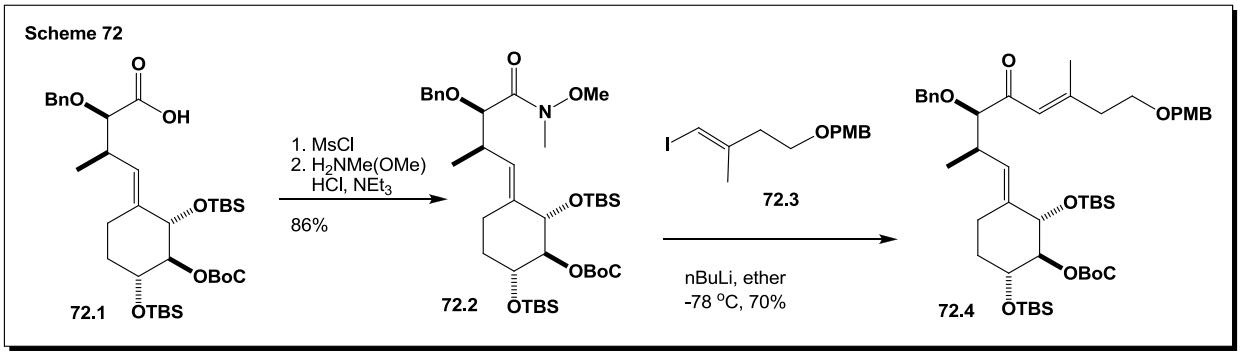
Bis-silylation of cyclitol **70.1** gave bis-silyl alkene **70.2**, which underwent alkene reduction to give cyclohexanone **70.3** (Scheme 70). Propynylation to alkyne **70.4** was followed by Boc protection of the secondary alcohol to form mono alcohol **70.5**. Acylation gave propargyl ester **70.6** which was then semi reduced to *Z*- alkene **70.7**.



When treated to standard Ireland-Claisen rearrangement conditions, the rearrangement of allylic ester **71.1** could proceed through two possible transition states (Scheme 71). Transition state **71.2b** has a carbon bearing a protected hydroxyl functionality in the axial position, which creates an unfavorable 1,3-diaxial interaction between the cyclohexyl silylether and the exocyclic silylenolate. This steric strain is avoided in transition state **71.2a**, which has the bulky silyl group in the equatorial position. The reaction proceeded entirely through transition state **71.2a** resulting in rearranged pentenoic acid **71.3** in high yield.

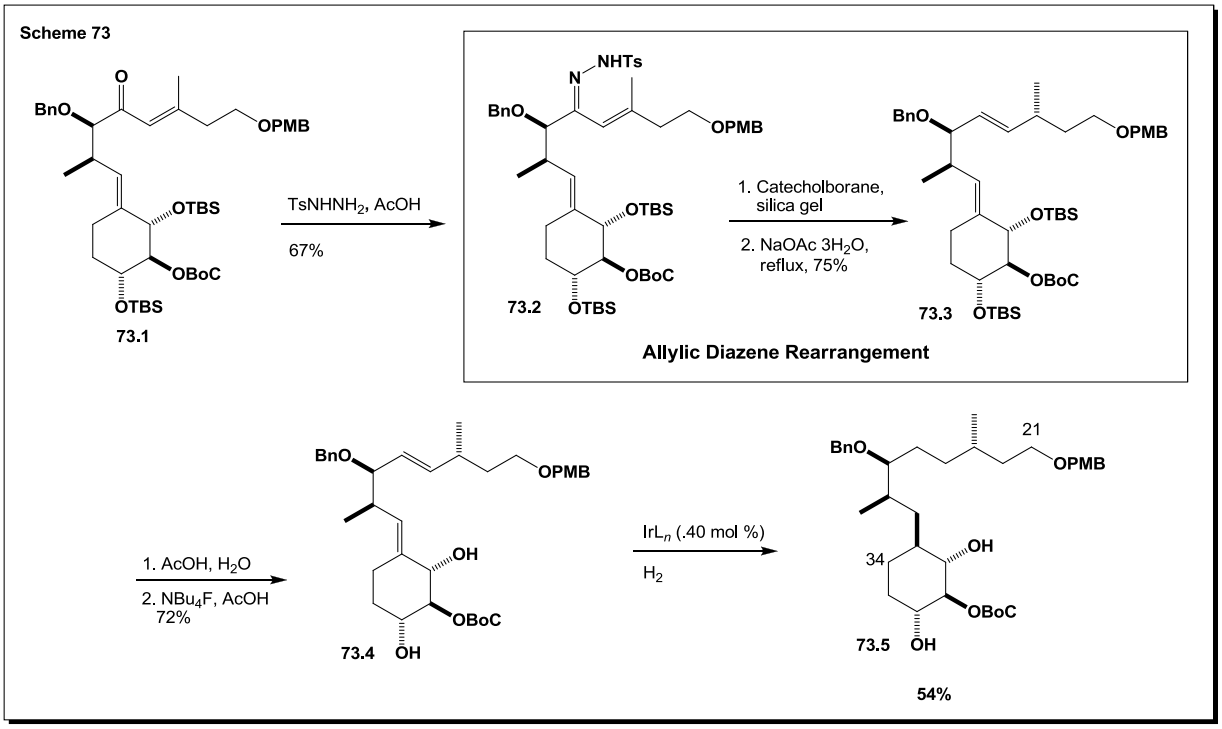


Pentenoic acid **72.1** was converted to Weinreb amide **72.2**, which was in turn treated with lithio ion derived from iodide **72.3** to form enone **72.4** (Scheme 72)**.**



Enone **73.1** was then treated with tosylhydrazide to afford *E*-hydrazone **73.2**, which underwent ADR to give the 1,4-*syn*-alkene **73.3** (Scheme 73). Bis-silylether **73.3** was deprotected to diol **73.4**. We propose that the alcohol α to C29-C28 alkene directed Crabtree's catalyst to effect

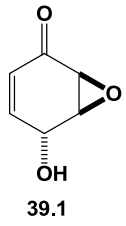
diastereoselective reduction of alkene to set the C29 stereocenter. Concurrent reduction of the C25-C24 alkene occurred to give the saturated C34-C21 fragment of antascomicin B **73.5**. The final Crabtree's reduction proved quite problematic. It required functional group manipulation and very high catalyst loading and it produced the desired product in low yield along with an inseparable byproduct.



3.3.6 Enantioselective Synthesis of the C34-C25 Fragment

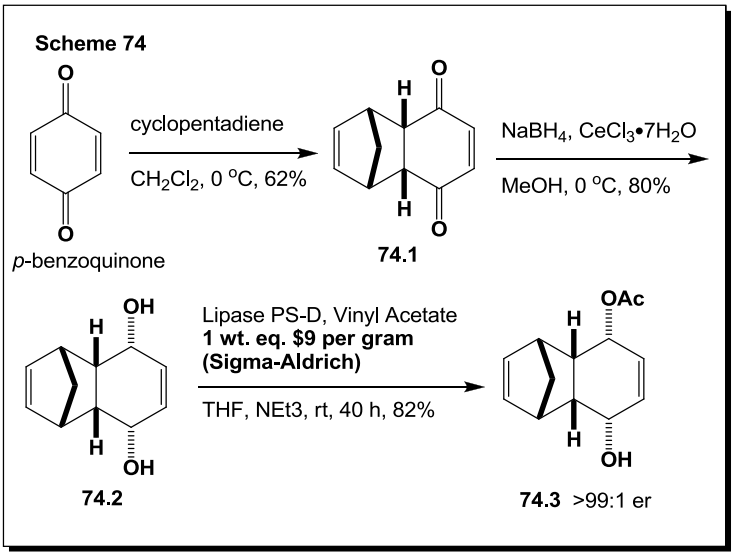
3.3.6.1 Enzymatic Approach

Figure 39



39.1

We envisioned approaching the enantioselective synthesis of the C25-C34 fragment through a route similar to the racemic synthesis. Therefore, we needed to develop a method to readily prepare multi-gram quantities of epoxyquinol **39.1** (Figure 39). Our original route to epoxyquinol **39.1** followed a literature procedure reported by Ogasawara.[247] The synthesis commenced with a Diels-Alder reaction between *p*-benzoquinone and freshly cracked cyclopentadiene to give adduct **74.1** in moderate yield (Scheme 74). Diels-Alder was followed by diastereoselective Luche reduction to afford *meso*-diol **74.2**. Although the reduction has been reported on large scale,[248] we experienced difficulty scaling up the reaction beyond approximately three grams. Desymmetrization occurred during the next reaction which was an enzymatic monoacylation to monoacetate **74.3**.

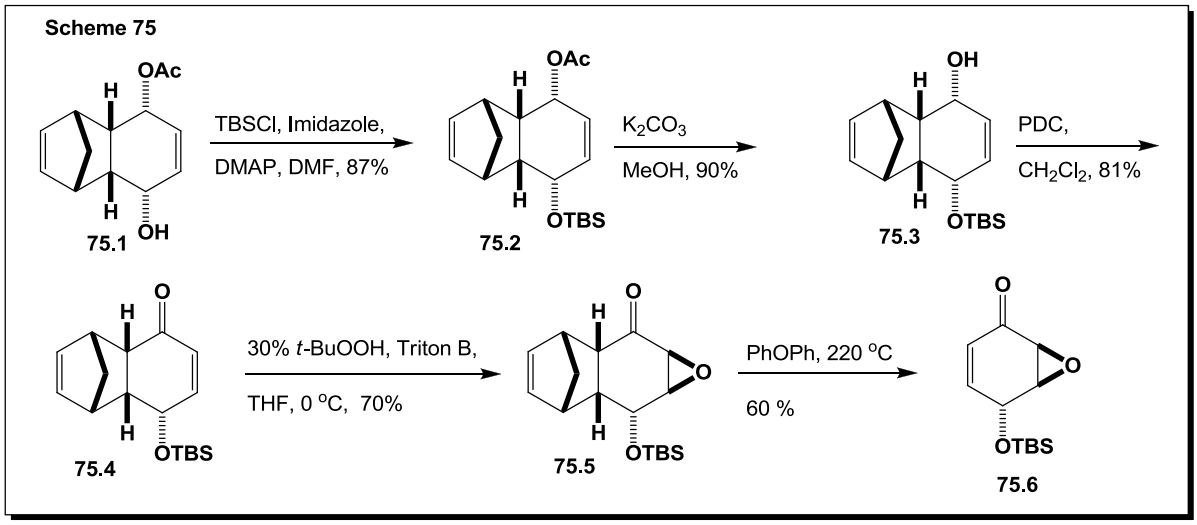


Our initial attempts to replicate the enzymatic acylation gave poor yields (< 5%) and complex reaction mixtures that were difficult to purify (Table 2). Eventually, through direct contact with the corresponding author, it was determined that immobilized Amano lipase PS-D was required for good conversion. Using one equivalent by weight of Amano lipase PS-D in a 10:1 THF:NEt_3 solvent mixture, monoacetate **74.3** was obtained in 82% yield and greater than 99:1 enantioselectivity.

Table 2

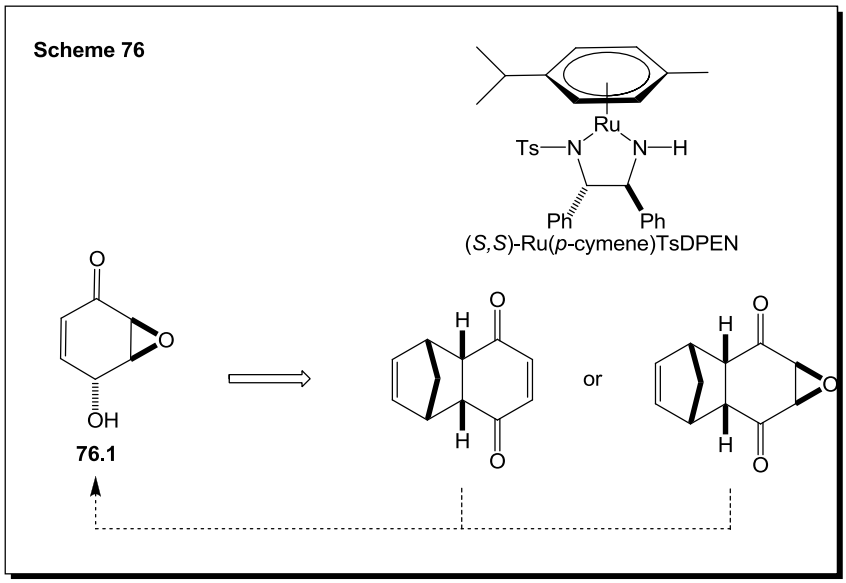
Enzyme	Solvent	Time	Temp. °C	Yield
lipase PS	MeCN	16 d	rt	nr
lipase PS	MeCN	16 d	28	nr
lipase PS	MeCN	16 d	40	nr
lipase PS	MeCN:H_2O 10:1	16 d	rt	nr
lipase PS	MeCN:H_2O 10:1	16 d	28	nr
lipase PS	THF:NEt_3 10:1	16 d	rt	4%
lipase PS-D	THF:NEt_3 10:1	4 d	rt	82%

Secondary alcohol **75.1** was silylated to **75.2** (Scheme 75). Deacylation to alcohol **75.3** followed by oxidation gave enone **75.4** which was epoxidized to **75.5.** Removal of cyclopentadiene via retro Diels-Alder reaction gave silylepoxyquinol **75.6** in eight steps and 11% overall yield.

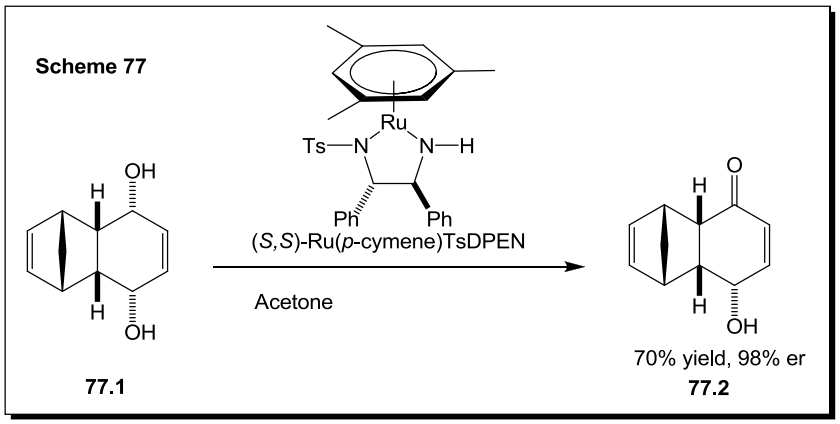


The enzymatic approach to epoxy quinol **75.8** suffers from tedious and inefficient protection/deprotection and redox sequences, use of expensive or hard to obtain reagents, and lack of scalability Therefore, we sought a more efficient approach comparable to the racemic synthesis.

A literature survey indicated that asymmetric transfer hydrogenation using Noyori's RuTsDPEN could offer a mild, scalable approach to enantiopure epoxyquinol **76.1** (Scheme 76).[151]



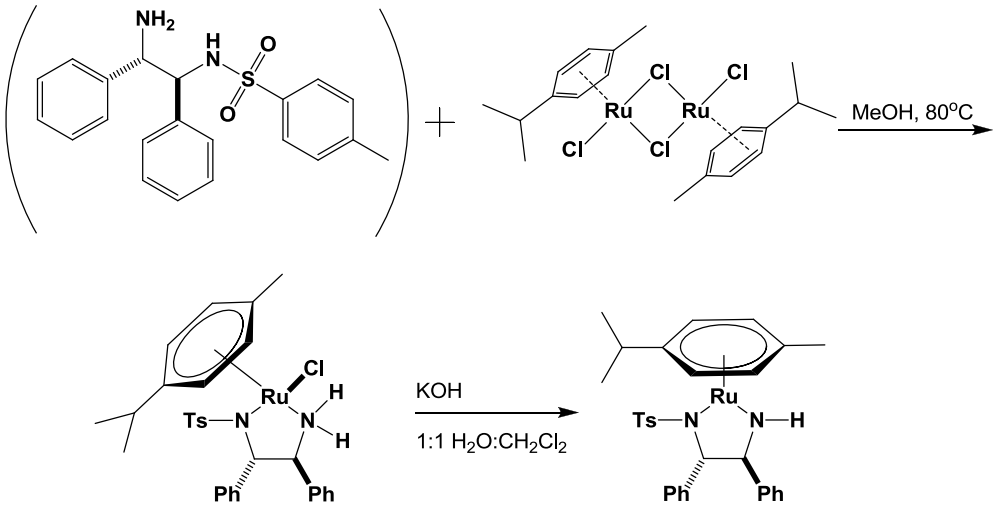
In 1997, shortly after Noyori first introduced his catalyst, he reported the kinetic resolution of several racemic secondary alcohols with RuTsDPEN in acetone.[249] The majority of secondary alcohols screened were aryl, however, they did report the enantioselective oxidation of Luche diol **77.1** using (*S,S*)-Ru(mesitylene)TsDPEN in good yield and high enantioselectivity (Scheme 77). Noyori's example encouraged us to explore catalytic asymmetric transfer hydrogenation as a way to access enantiopure hydroxy enone **77.2**.



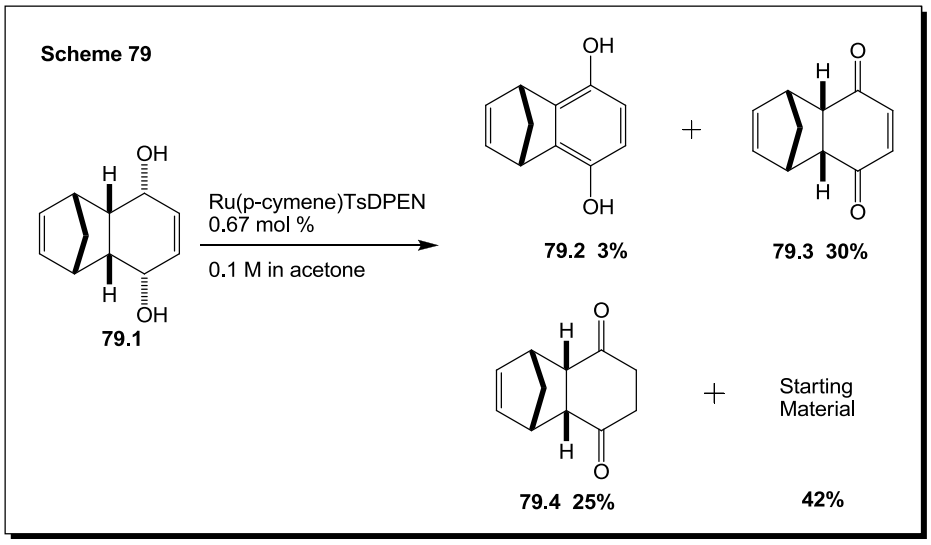
3.3.6.2 Asymmetric Transfer Hydrogenation

We were curious to see if we could reproduce Noyori's result and so we proceeded by constructing the catalyst precursor which we subsequently treated with KOH to form the active catalyst (Scheme 78). The *p*-cymene-Ru dimer was chosen because it is significantly less expensive than the alternative mesitylene dimer.[157]

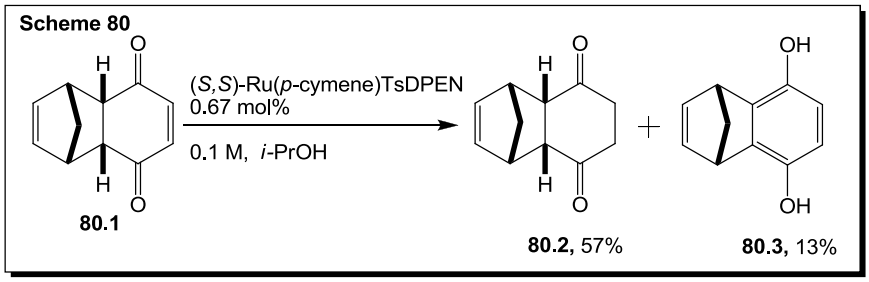
Scheme 78



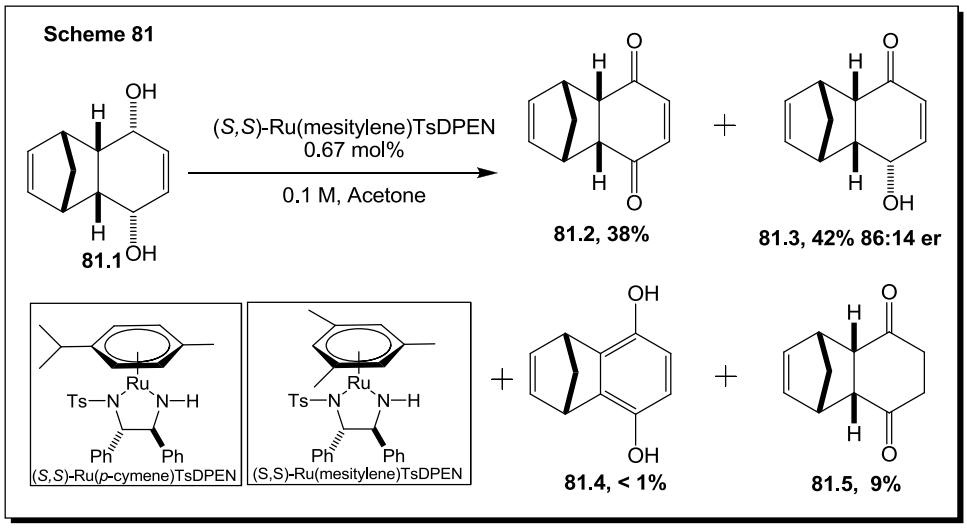
Noyori's experimental details were incomplete and he did not respond to direct communication, so we replicated his conditions as closely possible. We exposed diol **79.1** to (*S,S*)-Ru(*p*-Cy)(TsDPEN) in acetone (0.1 M) at a catalyst loading of 0.67 mol %. However, instead of observing a kinetic resolution, we observed a mixture of unreacted starting material **79.1,** *para*-hydroxy phenol **79.2**, diketone **79.3** resulting from over oxidation, and semi-saturated diketone **79.4** (Scheme 79). The two obvious mechanisms to explain the formation of semisaturated diketone **79.3** are ketone reduction followed by isomerization[250] or direct alkene reduction.



These results were discouraging so we decided to examine the reverse reaction, therefore we applied RuTsDPEN to the mono-reduction of diketone **80.1** (Scheme 80). We kept all reaction condition the same as for oxidation of enediol **79.1** except for the solvent, which we switched to isopropanol. The reaction resulted in diketone **80.2** as major product and hydroquinone **80.3** as minor product.



Given these anomalous results, we decided to repeat Noyori's example exactly by using (*S,S*)-Ru(mesitylene)(TsDPEN) (scheme 81). Interestingly, the mesitylene based catalyst did indeed produce hydroxyl enone **81.3**, although in low yield and moderate enantioselectivity. The reduction also produced all other byproducts observed in reduction from the *p*-cymene based catalyst.



3.3.6.3 No-D NMR

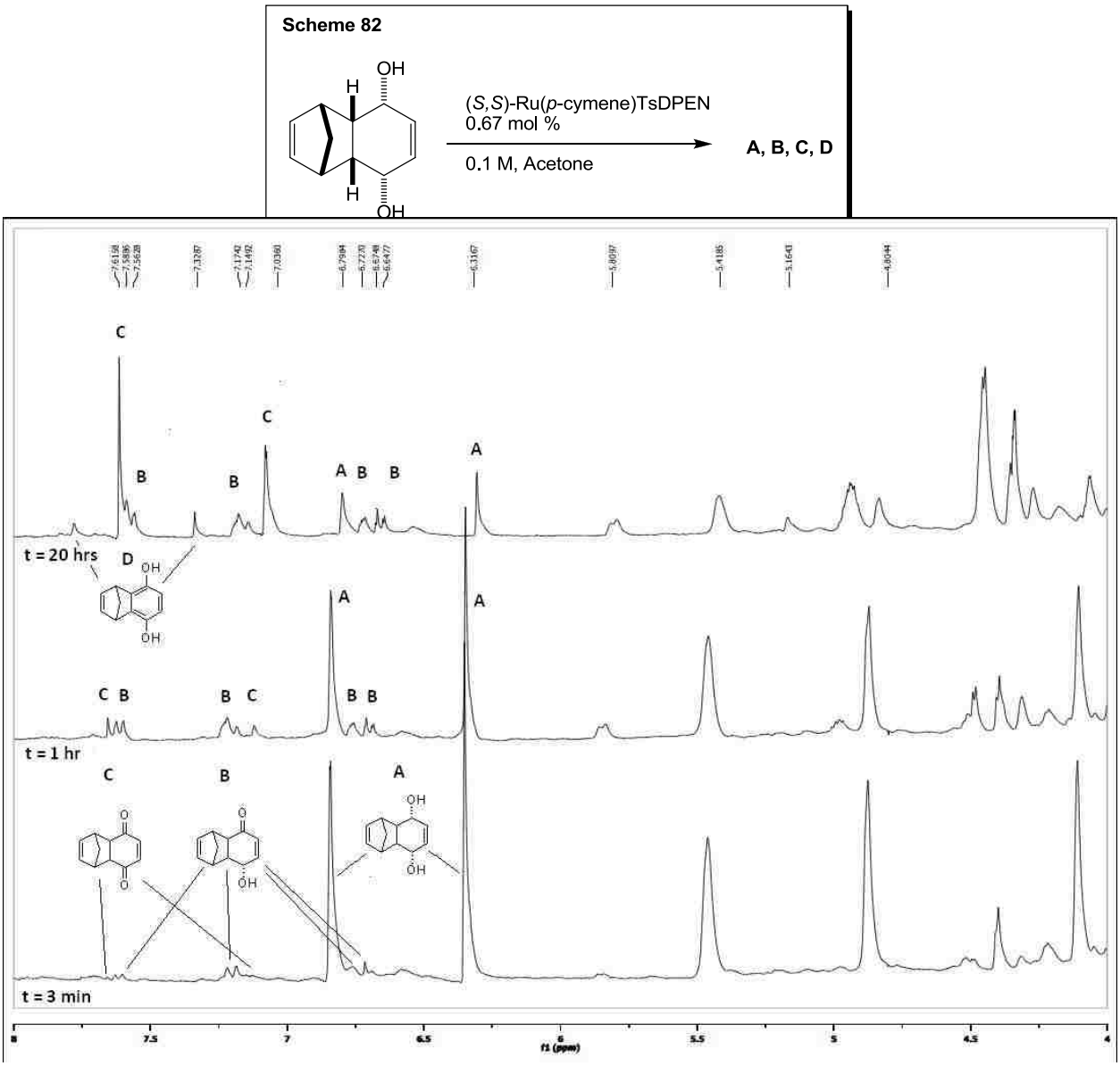
The fact that the mesitylene catalyst could effect monoreduction while the *p*-cymene catalyst did not piqued our curiosity. We also wanted to understand more about the relative rate of product formation. We initiated a series of No-D NMR experiments to probe the reactions further.[251] The experiments were conducted by setting up the reactions as usual, and then transferring a small amount of the reaction mixture to an NMR tube. The reactions proceeded in the NMR tube and scans were taken periodically to observe reaction progress.

In general, analyses were made by observing peaks in the 6-8 ppm region. This region of the spectra contained peaks indicative of all observed products and was far enough removed from solvent peaks so as to ensure reliable and reproducible identification of all species present.

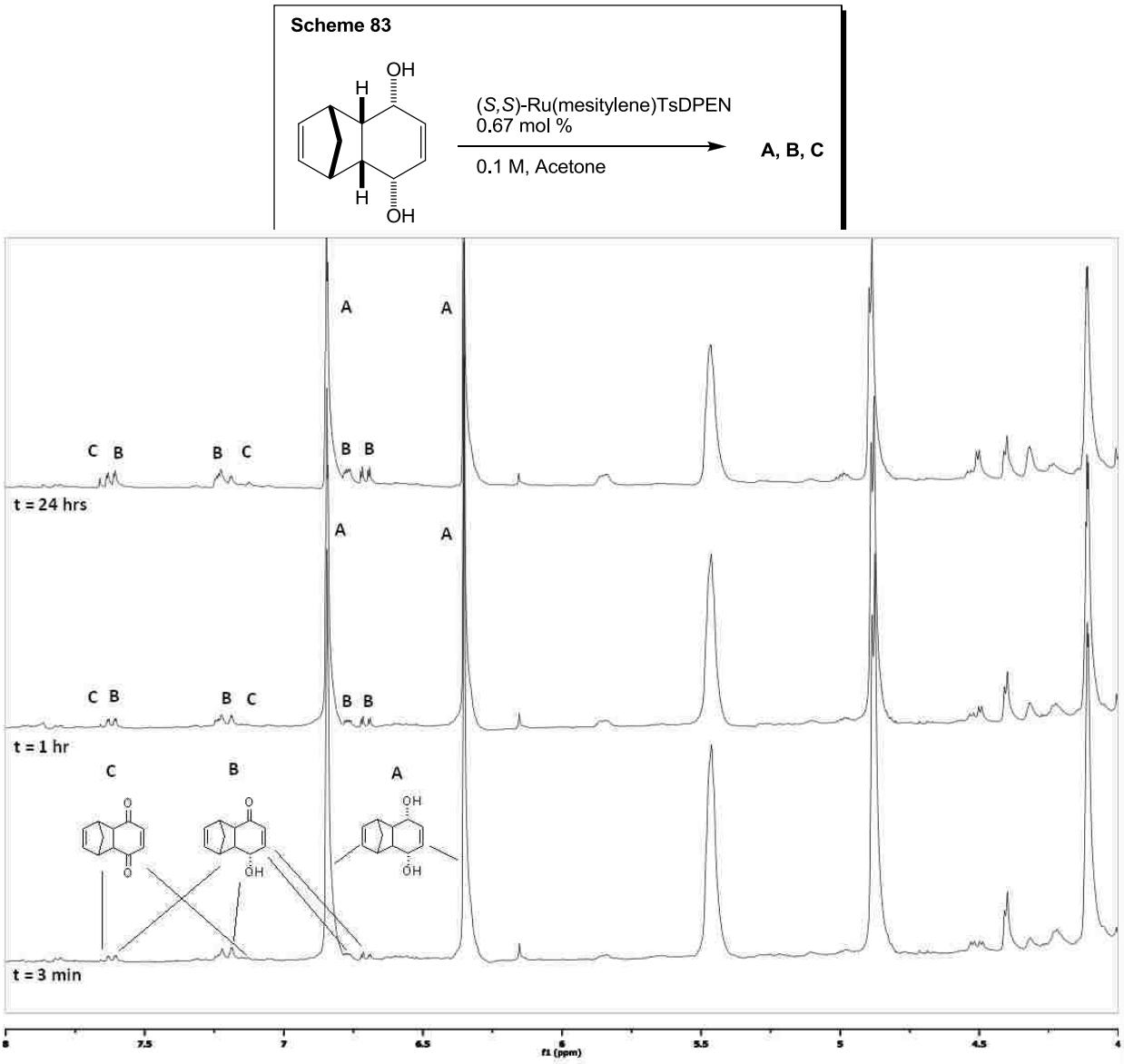
Our first No-D experiment was the oxidation of *meso*-diol **82** using *p*-cymene catalyst. The two large peaks on the t = 3 min spectra below labeled **A** correspond to the starting material; we observed disappearance of the starting material as the reaction progressed. Interestingly, the first product observed was hydroxyl enone **B**, but after one hour, enedione **C** was present in roughly equal amounts. After 20 h, the reaction had proceeded to approximately 75% conversion with the

predominant product being enedione **C** with hydroquinone **D** and hydroxyenone **B** in minor amounts. Another interesting observation is that we never observed the semi-saturated diketone **81.5** in any of these No-D experiments.

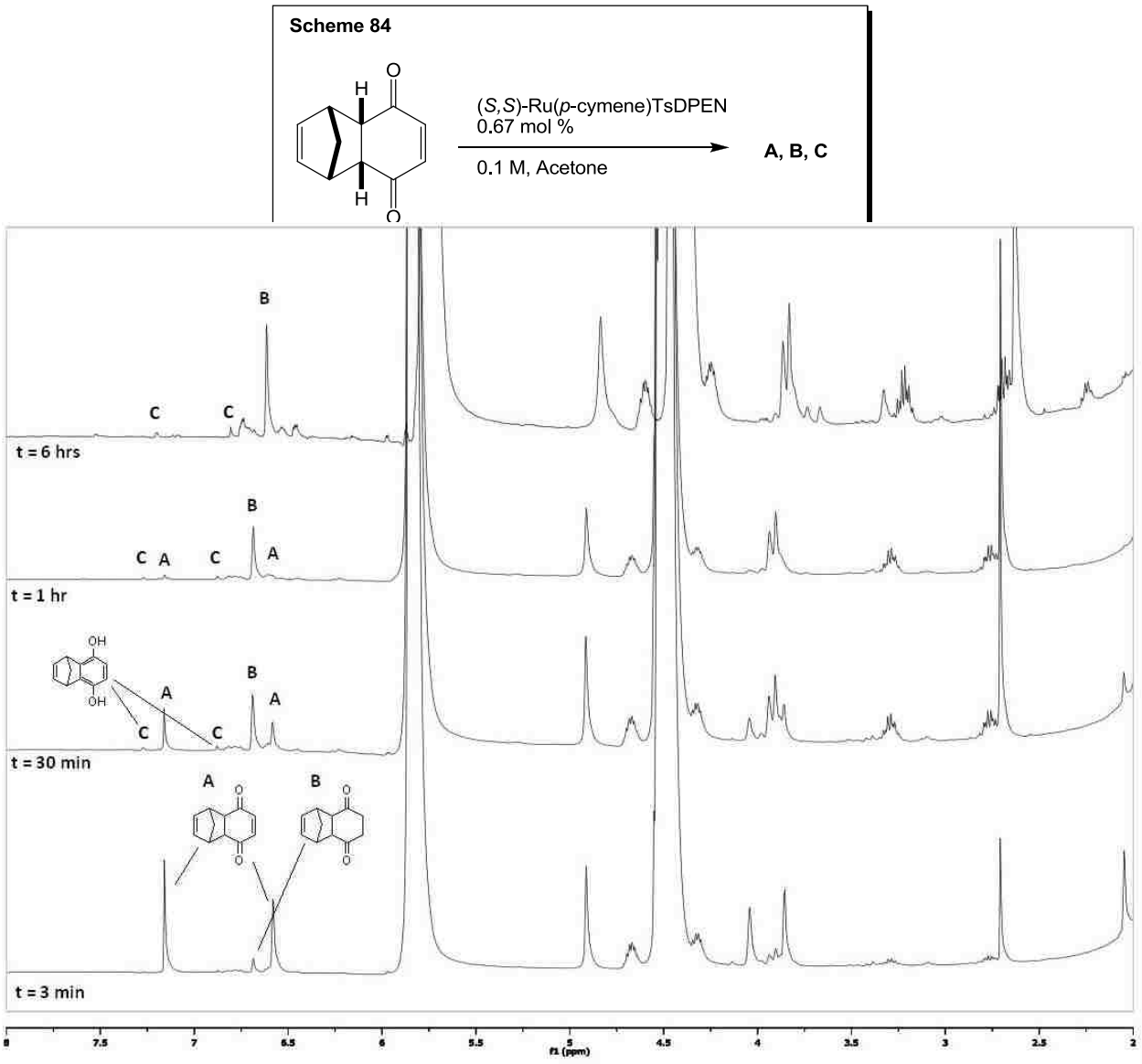
Work up of these reactions involved removing solvent under rotary evaporation followed by column chromatography. When No-D experiments using *p*-cymene catalysts were worked up fully, we observed disappearance of monoreduced product **B** and appearance of semi-saturated diketone **81.5**. This observation suggests that monoreduced product **C** could potentially be isomerizing to semisaturated diketone **81.5** when exposed to *p*-cymene catalyst during heating while undergoing rotary evaporation.



The mesitylene catalyst seemed to be more selective for formation of hydroxy enone **B** (Scheme 83). However, after a day the reaction had only proceeded to roughly 20% conversion. Neither diketone **81.5** nor hydroquinone **81.4** was formed in No-D experiments using mesitylene catalyst. When the reaction mixture was concentrated and heated during rotary evaporation, hydroxyl enone **B** survived and neither byproduct developed significantly.



When enedione **A** (Scheme 84) was reduced with Ru(*p*-Cy)TsDPEN in isopropanol, diketone **B** was present after only three minutes. After six hours, the starting material was exhausted and the principle product was diketone **B**. No ketone reduction product was observed over the course of the reaction. These results imply that either isomerization of keto alcohol to diketone is extremely rapid, or that the alkene was reduced directly. Alkene reduction of certain enones as well as activated alkenes lacking ketone functionality has been reported using the Noyori catalyst.[252]



3.4.2 ATH of Epoxy Diketone

During our studies on the ATH of α-β unsaturated *meso*-diketone and meso-diol, it became evident that we would need to find another synthetic approach. We decided to explore ATH for the desymmetrization of *meso*-diketone **85.1.** *Meso* diketones have been desymmetrized by asymmetric hydride reductions,[253, 254] whole cell reductions,[255-263] and asymmetric deprotonations.[264] Although Noyori reduction of an achiral diketone has been reported,[265] to the

best of our knowledge, it has not been employed to desymmetrize *meso*-diketones until our efforts.[20]

We started exploring the use of ATH to desymmetrize meso-diketone **85.1** using inexpensive *i*-PrOH as reductant and solvent. We were delighted to observe that monoreduction did in fact occur and the Noyori reduction gave a single diastereomer, unlike the racemic reduction, which gave approximately 6:1 dr.[21] Initial attempts using a catalyst loading of 0.04% in *i*-PrOH afforded the monoreduced epoxide in the modest enantiomeric ratio of 70:30 (Table 3). We were eventually able to improve er to 85:15 by increasing the catalyst loading to 0.16 mol %. We later found out (by comparison with de-silylated enzymatic product **75.6**) that monoreduced alcohol **85.2** was in fact the incorrect enantiomer for our synthesis.

Scheme 85

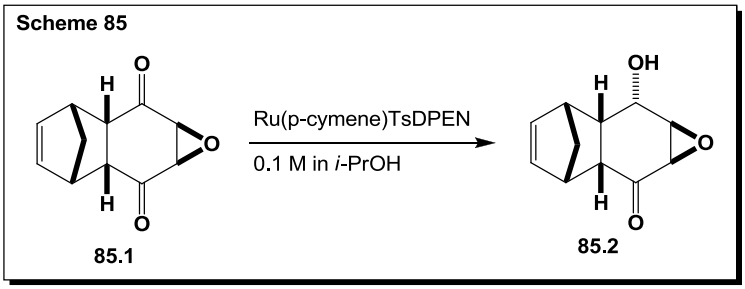


Table 3

Entry	Cat. Load (mol %)	Temp (°C)	Solvent	Time (h)	er[a]
1	0.04	23	i-PrOH	1	70:30
2	0.04	0	"	12	80:20
3	0.08	0	"	7	80:20
4	0.08	-60	"	24	no rxn
5	0.16	0	"	5	80:20
6	0.08	23	"	2	80:20[b]
7	0.16	23	"	2	85:15[b]

[a] er was determined by chiral GC. [b]substrate was added over 10 min as a solution in CH_2Cl_2.

Since ATH in *i*-PrOH is reversible,[190] optical purity can deteriorate if reactions are allowed to proceed over extended periods of time. In order to eliminate reversibility in hopes of improving the enantioselectivity of the reduction, we investigated the use of formic acid and trialkylamine base as reductant. [136, 190, 266-268] In ATH reactions, formic acid is oxidized to carbon dioxide and is more easily removed from solution than acetone, essentially making the reaction irreversible.

Using formic acid and trialkylamine as the stoichiometric reductant and DMF as cosolvent, we investigated the effect of catalyst loading, identity of the amine, acid:amine ratio and acid:ketone ratio on the enantioselectivity of reduction of epoxide diketone **86.1**.[20] Reaction conditions produced the keto alcohol in 83:17 to 90:10 er (table 4). The catalyst loading, identity of the amine, acid:amine and acid:ketone ratio had relatively modest effects on er.

Scheme 86

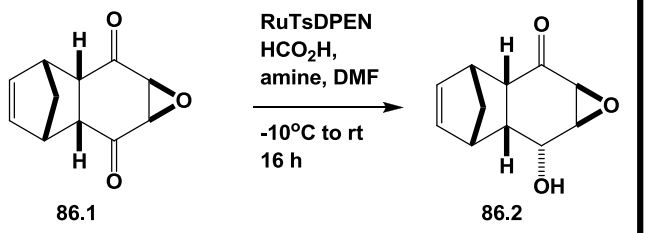


Table 4

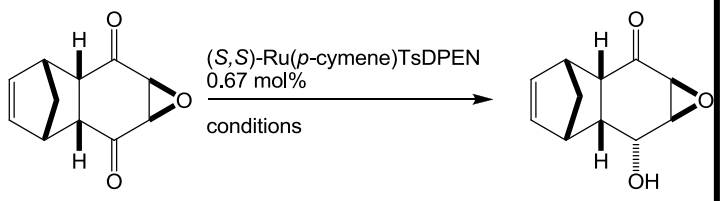
Entry	Catalyst Loading	Acid:amine Ratio	Amine	er	Acid:ketone ratio
1	0.04	7:1	$NEt(iPr)_2$	17:83	5:1
2	0.08	"	"	10:90	5:1
3	0.1	"	"	10:90	5:1
4	0.16	"	"	10:90	5:1
5	0.1	"	NEt_3	10:90	5:1
6	0.12	"	"	10:90	5:1
7	0.2	"	"	10:90	5:1
8	0.1	"	"	17:83	10:1
9	0.02	5:2	$NEt(iPr)_2$	14:86	3.2:1
10	0.04	"	"	14:86	3.2:1
11	0.1	"	"	14:86	3.2:1
12	0.1	"	"	20:80	2.5:1
13	0.1	"	NEt_3	13:87	3.2:1
14	0.1	"	"	15:85	2.5:1

Interestingly, the major enantiomer observed from the reduction with formic acid was opposite that observed when the reduction occurred in *i*-PrOH. The absolute configuration of monoreduced epoxide **86.2** was confirmed to be the desired enantiomer by comparison to the product obtained from Ogasawara's enzymatic route.

3.4.3 Investigating the Reversal of Enantioselectivity.

As stated above, we observed er of 19:81 for *i*-PrOH mediated reaction and the opposite enantiomer with er of 82:18 for triethylammonium formate (0.2 M) in acetonitrile (Scheme 87).[196] Although solvents have been shown to affect the enantioselectivity of ATH reactions,[269] to our knowledge, a reversal of enantioselectivity due to solvent has not been reported.

Scheme 87



Conditions:	er
iPrOH, rt	19:81
0.2 M HCO_2H/NEt_3 in MeCN -10 °C to rt	82:18

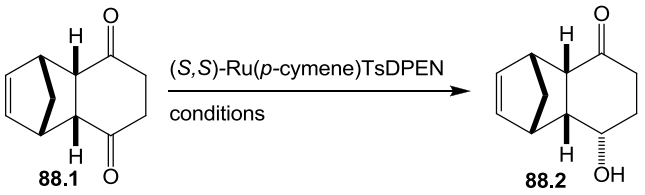
The generally accepted Noyori ATH mechanism, transfer of hydrogen occurs in the outer-coordination sphere of the metal and is reliant of hydrogen bonding for initiation.[161, 181, 186, 190, 197, 267, 270] As discussed previously, the origin of enantioselectivity is the subject of some dispute. Factors include: sterics, solvent effects, electrostatic effects, and dispersion forces.[174, 187] For aryl ketones and ynones, a CH-π interaction between catalyst and substrate has been identified as a major contributing factor to asymmetric induction.[270] However, there have been no models explicitly proposed for enones or dialkyl ketones. Usually when an ATH catalyst reduces acetophenone enantioselectively, it will reduce cyclohexylmethylketone with the opposite sense of enantioinduction, albeit in more modest optical purity.[159] The general explanation is that a favorable CH/π interaction stabilizes the transition state of the reduction of aryl ketones, while the

reduction of dialkyl ketones is controlled solely by sterics.[158] Since the mechanism of ATH of dialkyl ketones has not been investigated in any great detail, and judging from what is known about the ATH mechanism of aryl ketones, it is not unreasonable to believe that there might be more factors at play in the transition state than just sterics.

It has been shown computationally that hydrogen bonding of the ketone oxygen to an explicit solvent molecule, water[192] or methanol,[174] lowers the energy of the transistion state relative to unsolvated transition states.

We hypothesize that the reversal of the sense of enantioselectivity is probably a result of either solvent polarity or hydrogen bonding. The dielectric constants (19.9 for isopropanol and 37.5 for acetonitrile) and the concentration of hydrogen bond donors (13.3 M for neat isopropanol and 0.2 M for formic acid/triethylamine in acetonitrile), could significantly differentiate the respective transition states. The epoxide oxygen could also act as a hydrogen bond acceptor, which could also play a role in differentiating the transition states. The last proposal is supported by the observation that ATH of *meso*-diketone **88.1** provided the known keto alcohol **88.2** with the same sense of enantioinduction for both sets of conditions (Scheme 88).

Scheme 88



Conditions:	er
iPrOH, rt	67:33
0.2 M HCO_2H/NEt_3 in MeCN -10 ^oC to rt	81:19

We wanted to probe the solvent effects on the ATH of *meso*-diketone **89.1** further, so we screened the reaction against a variety of protic and aprotic solvents across a range of dielectric

constants (Scheme 89, Table 5). Our suspicions that solvent was playing a critical role were confirmed by entries 1 and 2 which showed the same sense of enantioinduction for reduction with *i*-PrOH and formate when acetonitrile is used as cosolvent (Entries 1 and 2). This was further supported by the unsurprising entry 12, which showed the same sense of enantioinduction for reduction in *i*-PrOH even when formate was present. No clear trend between dielectric constant and sense of enantioinduction emerged and this suggests that hydrogen bonding, probably involving the epoxide oxygen, is most likely the central factor in the enantioinductive switch. A general trend (with the exception of formamide [entry 3]) showed that higher concentrations of hydrogen bond donors tended to favor the *R*-enantiomer (entries 7-9,12). Another interesting finding was that the aromatic solvents benzene and toluene (entries 10 and 11) were also selective for reduction to the *R*-enantiomer.

Scheme 89

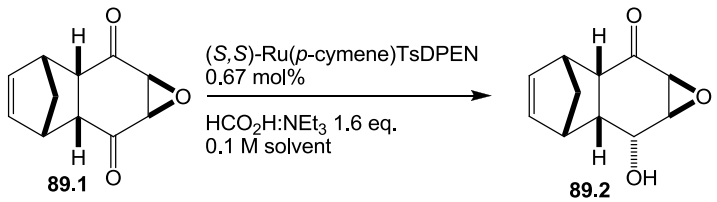


Table 5

entry	solvent	% conv.	er	dielectric constant	H bond donor concentration
1	Acetonitrile	4	18.0:82:0	37.5	0.2 M
2	Acetonitrile[a]	0.2	28.3:71.7	37.5	0.16 M
3	Formamide	3.1	30.9:69.1	111	25 M
4	NEt3	7.9	33.3:66.7	2.42	0.2 M
5	DMSO:H_2O 1:1	0.8	44.6:55.4	46.0:80.1	35 M
6	MeOH	3.9	57.3:42.7	32.7	25 M
7	EtOH	4.8	68.2:31.8	24.5	17 M
8	Benzene	3.9	77.0:23.0	2.27	0.2 M
9	Toluene	1.4	78.4:21.6	2.38	0.2 M
10	i-PrOH	5.1	86.3:13.7	19.9	13 M

[a]*i*-PrOH (1.6 eq.) was used as reductant.

3.3.6.6 Scaling Up

We scaled up our optimized conditions for the reduction of *meso*-diketone **90.1** with formate to 10 mmol in order to conduct a solvent screen, which identified acetonitrile as the optimal cosolvent for the reduction (Scheme 90, Table 6)(entries 1-5). We also discovered that changing the formic acid:ketone ratio from 3:1 to 1:1 led to significant increase in er (entries 3 and 6). Upon increasing the scale beyond 10 mmol, a steady deterioration in enantioselectivity was observed (entries 6-9). We also noticed failure of the reduction to proceed to completion when the reaction was scaled up to 120 mmol (entry 9).

Scheme 90

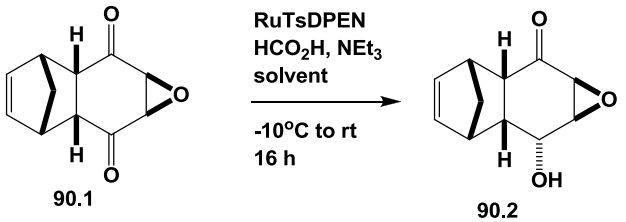


Table 6

entry	solvent	acid:ketone[a]	Scale (mmol)	conc (M)	er
1	None	3:1	10	"	80:20
2	DMF	"	"	0.5	80:20
3	MeCN	"	"	"	82:18
4	THF	"	"	"	70:30
5	CH_2Cl_2	"	"	"	70:30
6	MeCN	1:1	"	0.15	90:10
7	"	"	30	"	82:18
8	"	"	60	"	79:21
9	"	"	120[b]	"	77:23

[a]Molar ratio. [b]Reaction did not proceed to completion.

In the interest of pushing larger scale reductions to completion, we investigated increasing the ratio of formate relative to ketone (Table 7). When formate was increased to 1.2 equivalents

relative to epoxide **91.1**, not only did the reaction proceed to completion, there was also a significant increase in enantioselectivity from 77:23 er to 84:16 er. Once we determined that a scaled down version of the reduction would behave analogously (entry 2), we screened various ratios of reductant to ketone to see if we could improve the enanatioselectivity of the reduction. Eventually, we were able to achieve 93:7 er using 1.7 equivalents of formate (entry 7).

Scheme 91

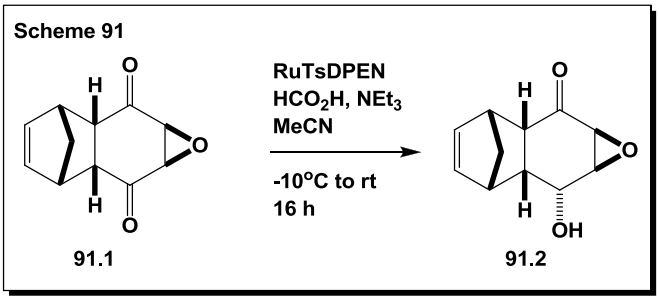


Table 7

entry	scale (mmol)	ketone:acid ratio	er
1	120[b]	1:1	77:23
2	120	1:1.2	84:16
3	60	1:1.2	84:16
4	60	1:1.4	89:11
5	60	1:1.5	91:9
6	60	1:1.6	92:8
7	60	1:1.7	93:7
8	60	1:1.8	87:13
9	60	1:2.0	87:13

[a]reaction did not proceed to completion.

Chiral stationary phase (CSP) gas chromatography (GC) determined that the intrinsic enantioselectivity of the reduction under optimized conditions, analyzed by chiral GC at 4% conversion, proved to be relatively modest (82:18 er). However, this is comparable to other dialkyl ketone transfer hydrogenations.[151, 265]

The fact that the initial er of 82:18 improved to 93:7 by the time that the reaction is worked up, suggested that kinetic resolution was occurring. As expected, extending the reaction time of the reduction resulted in material with significantly improved er (99.6:0.4 at 48 h) (Table 6) as a

consequence of kinetic resolution of the minor enantiomer. The major drawback is that isolated yield dropped to 44%.

Scheme 92

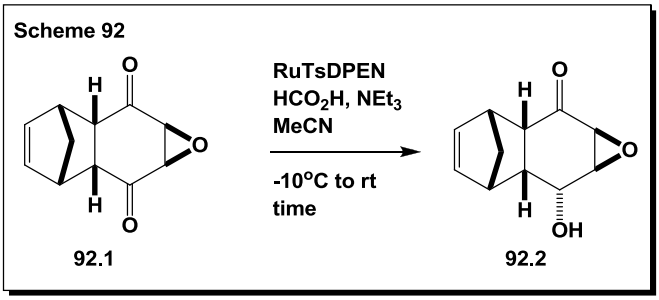
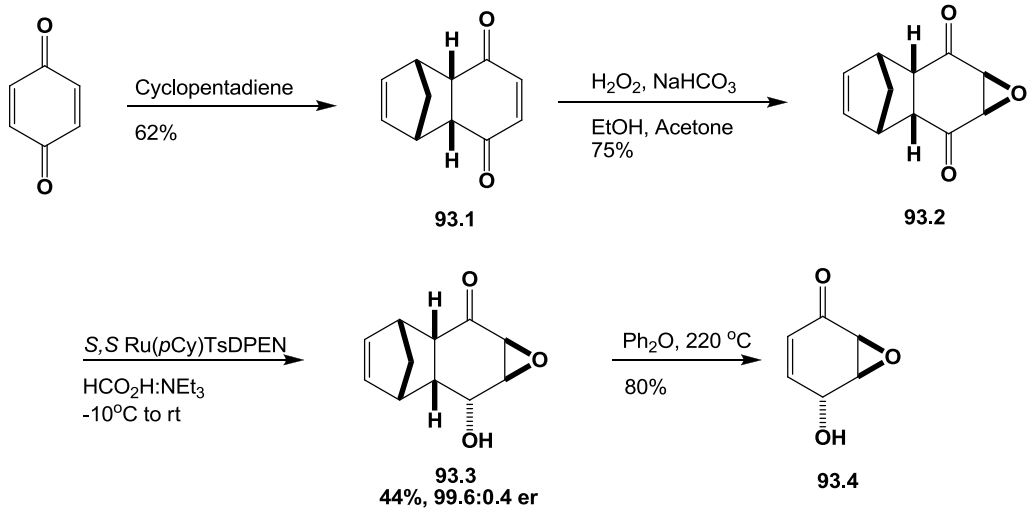


Table 6

entry	acid:ketone ratio	3 h	22 h	26 h	48 h	72 h
1	1.3	81.2:18.8	87.9:12.1	89.9:10.1	93.1:6.9	94.4:5.6
2	1.5	79.2:21.8	87.9:12.1	90.0:10.0	93.4:6.6	95.0:5.0
3	1.6	82.0:18.0	89.9:10.1	92.7:7.3	99.6:0.4	99.6:0.4
4	1.7	82.0:18.0	84.7:15.3	86.8:13.2	97.5:2.5	99.4:0.6
5	1.9	91.1:18.9	87.1:12.9	89.3:10.7	92.8:7.2	94.4:5.6

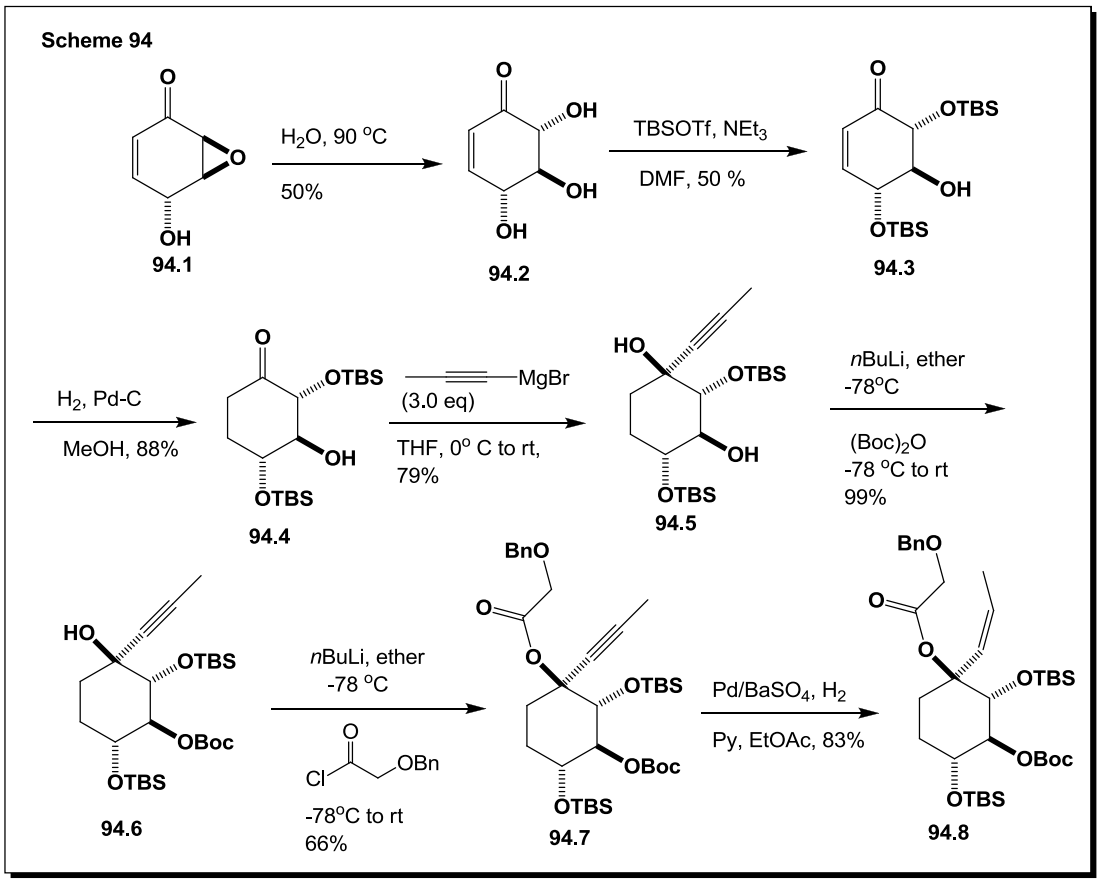
After much effort, we were eventually able to develop an ATH approach that mimics the racemic route and delivers enantiopure epoxyquinol **93.4** in four steps and 16% yield from *p*-benzoquinone (Scheme 93)

Scheme 93

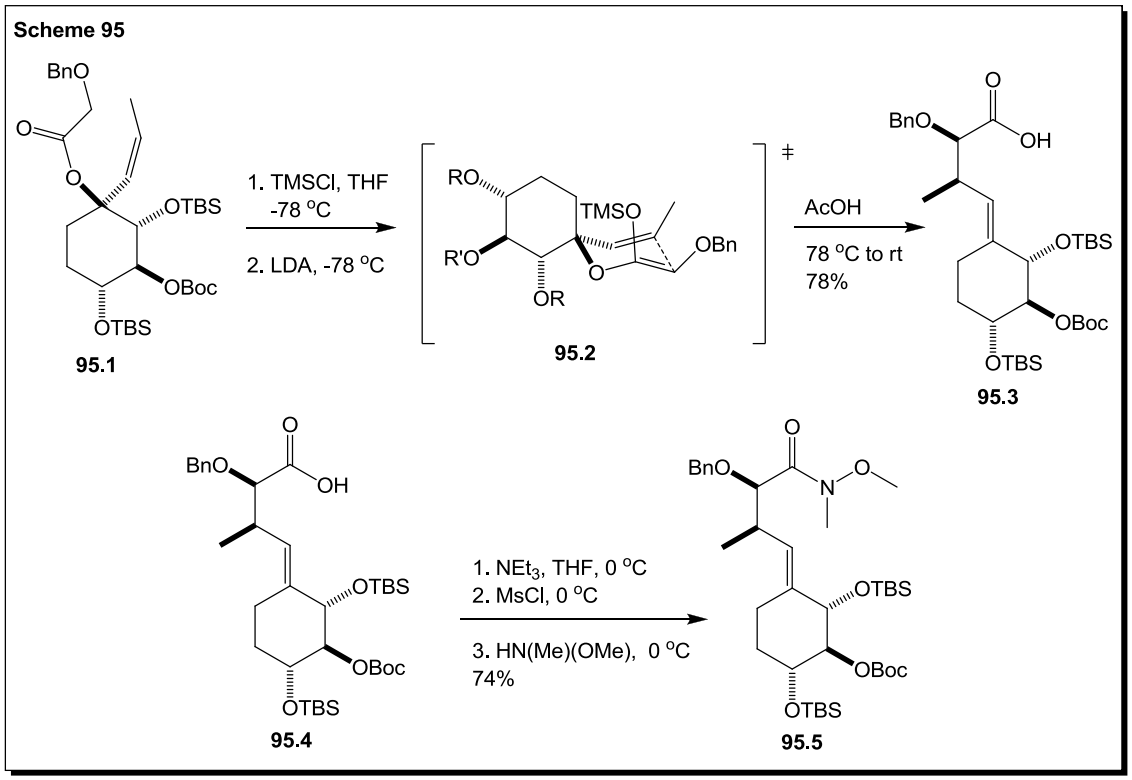


3.3.6.7 Synthesis of the Enantiopure C34-C25 Fragment

With a scalable synthesis of enantiopure epoxyquinol **94.1** in hand, we proceeded to advance the synthesis of the fragment. The next step was hydrolysis of epoxyquinol **94.1** to *anti-anti*-trihydroxycyclohexenone **94.2**, which was protected as bis-silyl ether **94.3** (Scheme 94). Alkene reduction gave cyclohexanone **94.4** which was propynylated to give diol **94.5** as one diastereomer. The secondary alcohol was protected as the carbonate to give propargyl alcohol **94.6** which was subsequently converted to O-benzylglycolic ester **94.7**. Partial reduction of the alkyne to a *Z*-alkene furnished Ireland-Claisen rearrangement precursor **94.8**.

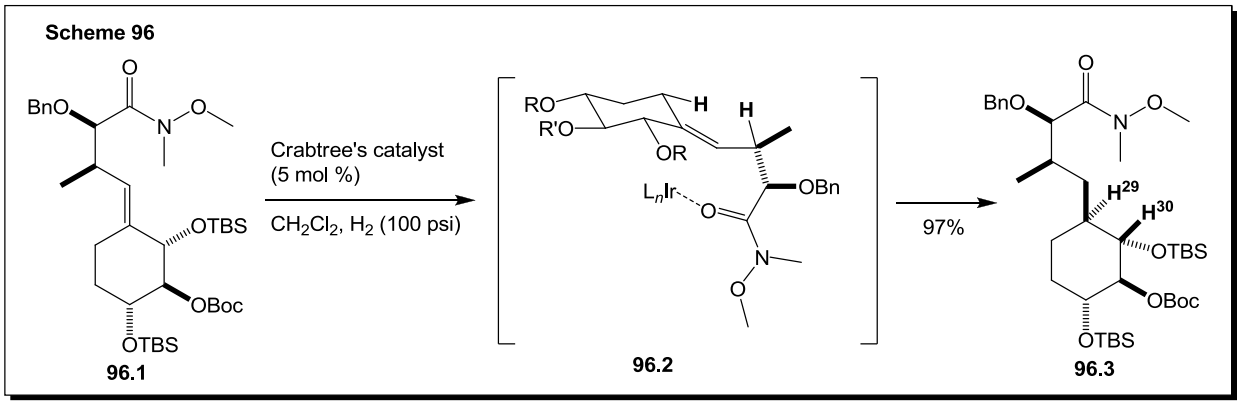


Treatment of allylic ester **95.1** with LDA in the presence of TMSCl, followed by addition of acetic acid gave Ireland-Claisen rearrangement product **95.3** in good yield. Acid **95.4** was then converted to Weinreb amide **95.5**.



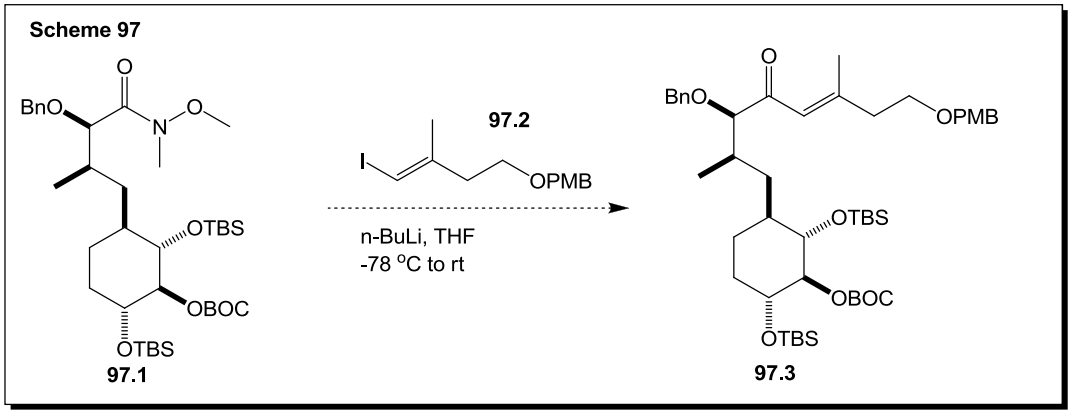
Since it is known that amides can serve as good directing groups for homogenous hydrogenation,[271-274] we wanted to see if we could exploit the amide functionality of **96.1** to set the C-29 stereocenter (Scheme 96). We believed that the existing stereocenters on the pentenoic chain would orient the amide to the desired face of the hydrogenation in the transition state **96.2**. With a 5 mol% loading of Crabtree's catalyst in methylene chloride under 100 psi of H_2, the reaction gave a single product in excellent yield. The presence of *trans*-diaxial coupling between H-29 and H-34 supported our hypothesis and confirmed the configuration at C29. Reducing the C28-C29 bond at this point solves several problems encountered during the racemic synthesis which featured

reduction with Crabtree's catalyst as the final step. It avoids the formation of a byproduct that was impossible to separate without further functional group transformations, it avoids unnecessary deprotection/reprotection sequences, and it solves the problems of low yield and high catalyst loadings.[19] Also, the remaining alkene after ADR can be retained to make rigidified analogs.

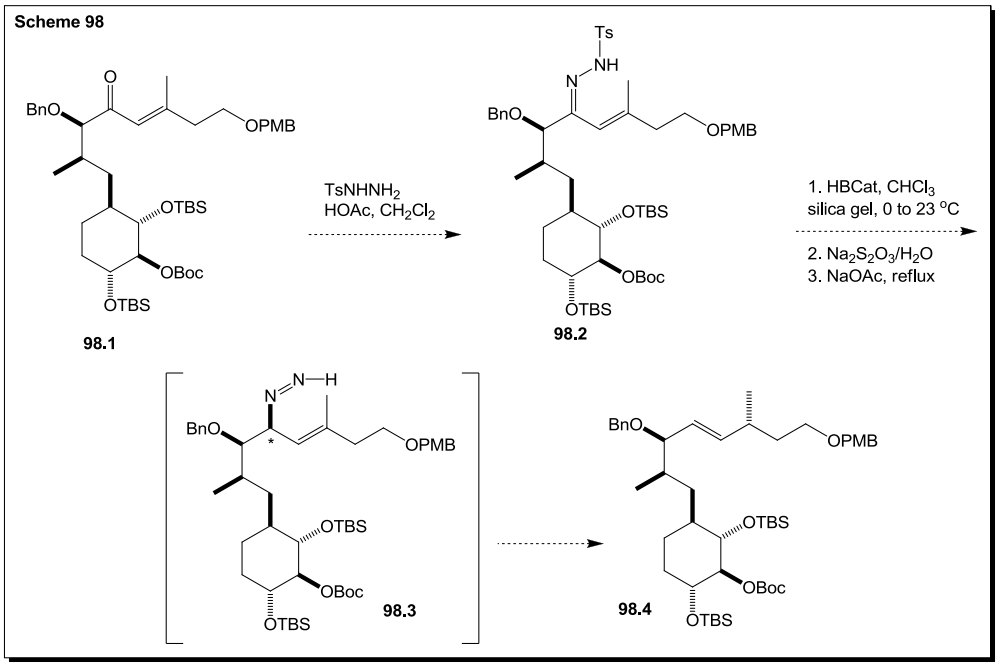


3.4.6 Towards the Completion of Antascomicin B

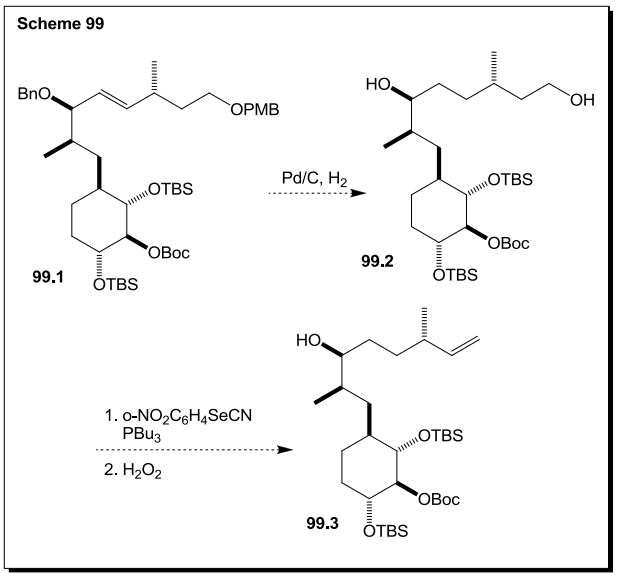
A synthetic strategy has been developed by our lab to complete the synthesis of the C21-C34 fragment and to complete antascomicin B. The next step will be homologation of the lithio anion of iodide **97.2** to Weinreb amide **97.1** to give **97.3** (Scheme 97).



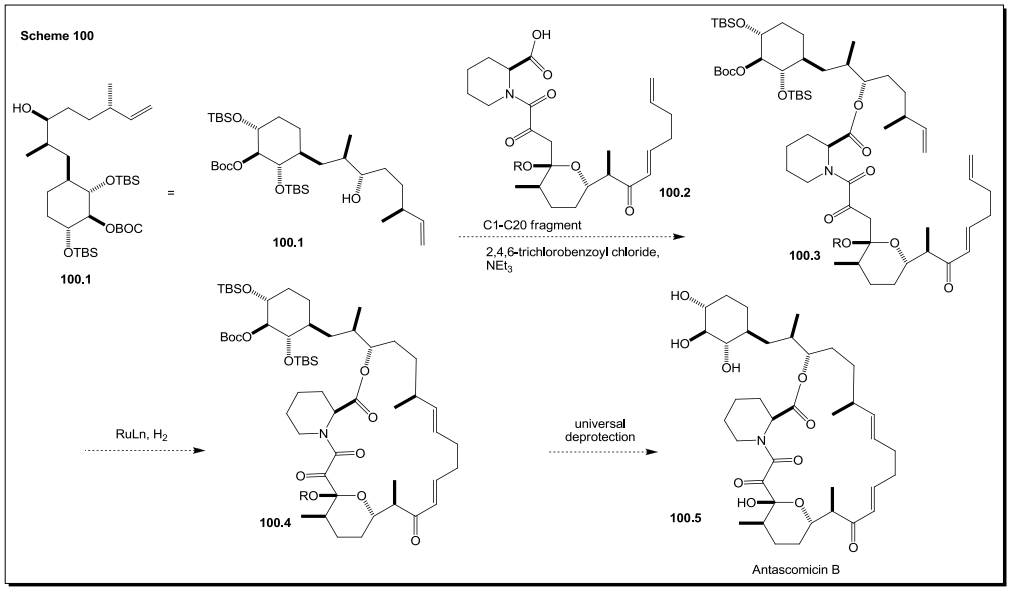
Next, enone **98.1** will be converted to *E*-hydrazone **98.2**. When treated with modified Kabalka conditions, reduction of α,β-unsaturated-*E*-hydrazone **98.2** should occur from the less hindered face to produce 1,2-*anti*-hydrazine **98.3** followed by ADR to afford 1,4-*syn*-alkene **98.4** as in the racemic synthesis (Scheme 98).[18, 19, 243]



Next, treatment with palladium on carbon should reduce the alkene and cleave the benzyl and *para*-methoxybenzyl protecting groups, furnishing primary alcohol **99.2** (Scheme 99).[275] Selective Grieco-Sharpless olefination of primary alcohol **99.2** will install the terminal alkene which will complete the synthesis of the C21-C34 fragment of antascomicin B **99.3**.

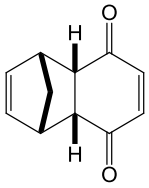


The C34-C21 fragment **100.1** and the C20-C1 fragment **100.2** of antascomicin B will be brought together by Yamaguchi lactonization to form triene **100.3** (Scheme 100).[276] Ring closing metathesis[277] will close the macrocycle leaving universal deprotection as the last steps in the total synthesis of the natural product antascomicin B.



Experimental Section:

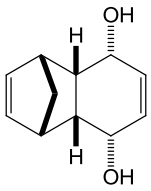
General: Standard extractive workup: the reaction mixture is poured into DI water and extracted 3 times with solvent.



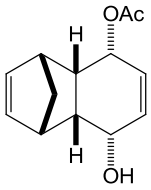
Diketone 74.1. A 1000 mL round bottom, two or three necked flask, equipped with a thermometer was charged with CH_2Cl_2 (400 mL) and *p*-benzoquinone (100 g, 0.93 mol) and cooled to -10 °C in a MeOH/ice bath. Freshly cracked cyclopentadiene (*Note 1)* (30.5 g, 0.46 mol) was added over a period of 30 min. A second 30.5 g 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 allowed to warm to rt over 30 min. The solvent was removed in vacuo and the crude 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 **74.1** as pale-yellow crystals (100.4 g, .577 mol, 62%). Data matched that previously reported.[278]

Note 1: To prepare cyclopentadiene, dicyclopentadiene was placed in a single necked RBF 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.

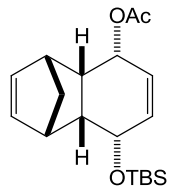
Note 2: The cyclopentadiene was added in two portions to mitigate the dimerization that occurs upon warming to rt.



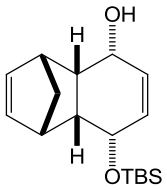
Diol 74.2. A suspension of diketone **74.1** (3 g, 17.2 mmol) and $CeCl_3$-$7H_2O$ (9.61 g, 25.8 mmol) in methanol (100 mL) was cooled to -10 ^oC in MeOH/ice bath. $NaBH_4$ (0.65g, 17.2 mmol) was then added at such a rate that the reaction mixture did not rise significantly above 0 ^oC. Crude product was extracted with CH_2Cl_2, dried with $MgSO_4$, dried in vacuo, and recrystallized from acetone to give diol **74.2** as white crystals (2.45 g, 13.76 mmol, 80%) data matched that previously reported.[29]



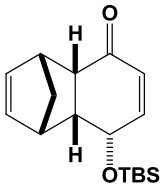
Monoacetate 74.3. A suspension of diol **74.2** (18.3 g, 102.7 mmol), vinyl acetate (56.78 mL, 616.1 mmol), and Amano lipase PS-D (18.3 g) in THF (400 mL) and NEt_3 (40 mL) was stirred at rt for four days. The reaction mixture was filtered through a Celite pad with Et_2O and solvent was removed in vacuo. The crude material was purified by column chromatography over silica gel with 20/80 ethyl acetate/hexane to give monoacetate **74.3** as colorless crystals (18.54 g, 84.2 mmol, 82%). Data matched that previously reported. [29]



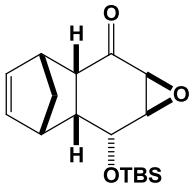
Silylacetate 75.2. Monoacetate **75.1** (16.0 g, 72.7 mmol) was added to a solution of imidazole (13.30 g, 195.5 mmol), TBSCl (14.30 g, 94.8 mmol), and DMAP (0.87 g, 6.3 mmol) in DMF (500 mL). The reaction mixture was allowed to stir at rt for 4.5 h then quenched with water, extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude material was purified by column chromatography over silica gel with 10/90 ethyl acetate/hexane to give silylacetate **75.2** as colorless oil (21.1 g, 63.2 mmol, 87%). Data matched that previously reported.[29]



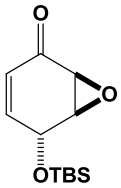
Silyl Alcohol 75.3. Silylacetate **75.2** (20.5 g, 61.3 mmol) was added to a solution of K_2CO_3 (16.95 g, 122.6 mmol) in MeOH (300 mL) and H_2O (60 mL). The reaction mixture was allowed to stir at rt for 6 h. The crude product was extracted in Et_2O, dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography over silica gel with 10/90 ethyl acetate/hexane to give silyl alcohol **75.3** as colorless oil (16.14 g, 55.17 mmol, 90%). Data matched that previously reported.[29]



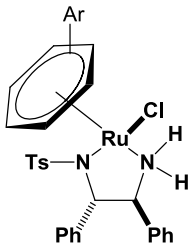
Silyl Ketone 75.4. Silyl alcohol **75.3** (17.9 g, 61.1 mmol) was added to a solution of PDC (45.97 g, 122.2 mmol) in dichloromethane (100 mL) and allowed to stir at rt for 4 h. Reaction mixture was filtered over Celite with CH_2Cl_2 and concentrated in vacuo. The crude material was purified by column chromatography over silica gel with 20/80 ethyl acetate/hexane to give silyl ether **75.4** as a colorless oil (14.38 g, 49.5 mmol, 81%). Data matched that previously reported.[29]



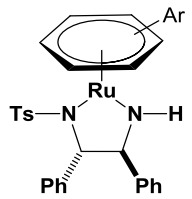
Epoxide 75.5. Silyl ketone **75.4** (14.78 g, 50.5 mmol) was added to a solution of *t*-Bu Hydroperoxide (34.73 mL, 254.2 mmol) and Triton B (35.47 mL, 51.0 mmol) in benzene (200 mL). The solution was heated under reflux for 2h. Reaction mixture was extracted with Et_2O, dried over $MgSO_4$, and concentrated in vacuo. Crude material was purified by column chromatography over silica gel with 10/90 ethyl acetate/hexane to afford epoxide **75.5** as yellow oil (10.9 g, 35.5 mmol, 70%). Data matched that previously reported.[29]



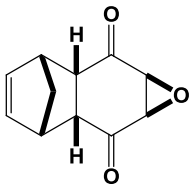
Enone 75.6. Epoxide **75.5** (4.08 g, 13.31 mmol) was dissolved in 100 mL of diphenyl ether. The reaction mixture was heated to 190 °C until completion as monitored by TLC, and then allowed to cool to rt. The solvent was removed from the mixture by column chromatography over silica gel with hexane. The product epoxide enone **75.6** was isolated as a white crystal by column chromatography over silica gel with 10/90 ethyl acetate/hexane (1.92 g, 7.99 mmol). Data matched that previously reported.[29]



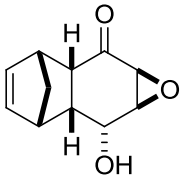
Catalyst Precursor. A mixture of [{$RuCl_2(\eta^6$-*p*-cymene)}$_2$] or [{$RuCl_2(\eta^6$-mesitylene)}$_2$] (306.2 mg, .5 mmol), (*S,S*)-TsDPEN (366.3 mg, 1 mmol), and triethylamine in 2-propanol was added to a round bottom flask and heated under nitrogen to 80° C for 1 h. After completion as monitored by TLC, the reaction mixture was concentrated by rotary evaporation and the resultant solids were collected by filtration and washed with water. The orange crystals were then dried under reduced pressure (509 mg, 0.8 mmol) data matched that previously reported.[157]



Ru-TsDPEN. (180 mg, .276 mmol) of the catalyst precursor was added to a round bottom flask with KOH (.23 g, .41 mmol) and CH_2Cl_2 (4mL) and allowed to stir for five minutes. After five minutes, H_2O (4mL) was added and allowed to stir for 5 minutes. Alternatively Ru-TsDPEN was prepared by dissolving [{$RuCl_2(\eta^6$-*p*-cymene)}$_2$] or [{$RuCl_2(\eta^6$-mesitylene)}$_2$] (306.2 mg, .5 mmol) and (*S,S*)-TsDPEN (366.3 mg, 1 mmol) in CH_2Cl_2 (5 mL) and allowing to stir for 5 minutes. KOH (83 mg,1.5 mmol)and water (5 mL) is then added and the mixture is allowed to stir for an additional 5 minutes. Reaction is complete when the color turns from deep rust orange to dark purple. Reaction was extracted in CH_2Cl_2, dried over CaH_2, and then concentrated in vacuo to give Ru-TsDPEN **31.2** as dark purple crystals (quant. yield). Data matched that previously reported.[157]

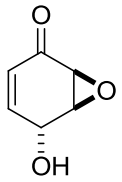


Epoxide 93.2. Diels-Alder adduct **74.1** (36.08g, 207 mmol) was dissolved in THF (450 mL) at rt. 35% H_2O_2 in H_2O (40.22 mL, 414 mmol) was slowly added over 15 min. Following addition of peroxide, saturated aqueos $NaHCO_3$ (45 mL, cat.) was added. Reaction was allowed to proceed for 2h at rt and then extracted with ether, dried over $MgSO_4$, concentrated in vacuo, and purified by recrystallization from EtOH. Product was isolated as white flaky crystals (29.52, 155.3 mmol, 75%) Data matched that reported.

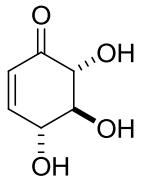


Monoreduced epoxide 93.3. Epoxide diketone **93.2** (190 mg, 1 mmol) was dissolved in a solution of *i*-PrOH and (*S, S*)-RuTsDPEN and allowed to stir until disappearance of starting material by TLC. Rotary evaporation of the crude reaction mixture followed by separation via column chromatography over silica gel and a 20/80 Ethyl Acetate/Hexane mixture afforded the epoxide **3** in variable yields. Alternatively, Ru(p-cymene)(S,S-TsDPEN) (0.25 g, 0.39 mmol, 0.65 mol %) and then epoxydiketone **93.2** (11.4 g, 60 mmol) were added to a solution of formic acid (3.85 mL, 102 mmol), triethylamine (14.3 mL, 102 mmol) and acetonitrile (500 mL) at -10 °C. The reaction mixture was allowed to slowly warm to rt and stirred for ca. 16 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 (10 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) followed by recrystallization in diethyl ether to give monoreduced epoxide **93.3** as colorless crystals (9.8 g, 51 mmol, 85%, er 93:7). For reduction product with higher enantiopurity, repeat the steps for reduction by formic acid and let stir for ca. 48h or until the minor enantiomer is present in insignificant quantities as measured by chiral (β-dex) GC (er 99.6:0.4). The product can be recrystallized to enantiopurity with diethyl ether as colorless crystals (5.10 g, 44%). M.P. 71-73 ^{o}C; $[\alpha]^{23}_{D}$ = -0.71 (*c* 0.56 CH_2Cl_2); IR (film) 3472, 3059, 2989, 1712 cm^{-1}; ^{1}HNMR (400 MHz, CDCl3) δ 1.19 (d, J = 9.54 Hz, 1H), 1.30 (d, J = 8.38 Hz, 1H), 1.45 (dt, J = 8.39 Hz, 1.88 Hz, 1H), 2.97 (ddd, J = 11.20, 5.75, 3.21, 1H), 3.03 (br s, 1H), 3.09 (br s, 1H), 3.17 (dd J = 11.0 Hz, 3.43 Hz, 1H), 3.57 (m, 1H), 3.29 (d, J = 4.36, 1H), 4.65 (ddd, J = 9.35 Hz, 5.73 Hz, 3.39 Hz, 1H), 6.22 (ddd, J = 3.05 Hz, 5.53 Hz, 16.55 Hz, 2H); ^{13}CNMR (400 MHz, $CDCl_3$) δ 42.60, 44.88, 45.06,

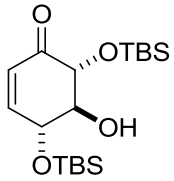
49.58, 51.28, 54.70, 59.54, 67.18, 135.46, 135.67, 208.1. Anal Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.75; H, 6.31.



Epoxyquinol 4. A solution of epoxide **93.4** (10 g, 52.03 mmol) in diphenyl ether (250 mL) was stirred at rt while nitrogen was bubbled through for 30 minutes. The reaction mixture was then heated to 210 ^{o}C (still 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 off solvent. When all solvent was eluted, the reaction mixture was eluted with 20/80 ethyl acetate/hexane. A second silica gel column 1/99 -10/90 MeOH/CH_2Cl_2 1% gradient followed by recrystallization with diethyl ether yielded pure epoxyquinol **93.4** (5.25 g, 41.62 mmol, 80%) as white powdery crystals. M.P. 84-86 ^{o}C; $[\alpha]^{23}_{D}$ = -1.92 (*c* 0.46 CH_2Cl_2); IR (film) 3395, 2993, 1695 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.13 (d, J = 8.71, 1H), 3.50 (ddd, 3.50 Hz, 1.81 Hz, 1.12 Hz, 1H), 3.81 (ddd, J = 3.69 Hz, 2.58 Hz, 1.22 Hz, 1H), 4.72, (dddd, J = 8.37 Hz, 4.61 Hz, 2.26 Hz, 1.11 Hz, 1H), 6.03, (ddd, J = 10.53 Hz, 1.71 Hz, 1.31 Hz, 1H), 6.70 (ddd, J = 10.53 Hz, 4.67 Hz, 2.57 Hz, 1H); ^{13}CNMR (400 MHz, $CDCl_3$) δ 53.31, 57.73, 63.02, 127.12, 144.01, 193.63. Anal Calcd for $C_6H_6O_3$: C, 57.14; H, 4.80. Found: C, 57.07; H, 4.91.

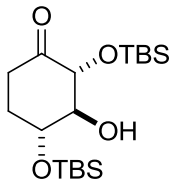


Trihydroxycyclohexenone 94.2. Epoxyquinol **93.4** (10 g, 79.30 mmol) was distributed in 1 gram aliquots to 10 parallel synthesizer tubes and a solution with DI H_2O (20 mL) was made in each tube and they were heated to 90 ^oC for 4 days. H_2O was then co-evaporated with MeCN and the brown residue was adsorbed on silica gel. The silica gel/residue was added to a silica gel column using CH_2Cl_2. Mixture was eluted with 0/99-10/90 MeOH/CH_2Cl_2 at 1% gradient. The second fraction was collected and recrystallized in EtOH to give trihydroxycyclohexanone **94.2** (5.71 g, 39.65 mmol, 50%) as colorless crystals. M.P. 136-138 ^oC; $[\alpha]^{23}_D$ -0.885 (*c* 0.437 1:1 MeOH:CH_2Cl_2); IR (film) 3400, 2835, 1693 ^{1}H NMR (400 MHz, CD_3OD) 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); ^{13}CNMR (400 MHz, CH_3OD) δ 70.12, 75.17, 76.99, 124.57, 150.36, 197.21. Anal Calcd for $C_6H_8O_3$: C, 50.00; H, 5.59. Found: C, 49.89; H, 5.65.

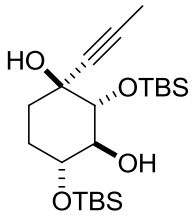


Enone 94.3. A solution of TBSCl (16.67 g, 111 mmol) and imidazole (9.67 g, 142 mmol) in dry DMF (25 mL) was added to trihydroxycyclohexenone **94.2** (4.55 g, 32 mmol) in dry DMF (25 ml). After stirring at room temperature for 4 h, the reaction mixture was quenched with ice water, extracted with ether, 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 enone **94.3** (5.88 g, 16 mmol, 50%) as white crystals. M.P. 101-103^oC; $[\alpha]^{23}_D$ = -0.11 (*c* 0.24 CH_2Cl_2); IR (film) 3394, 1647 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H),

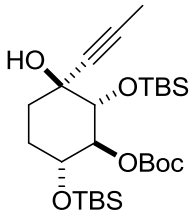
0.19 (s, 6H), 0.24 (s, 3H), 0.94 (s, 9H), 0.96 (s, 9H), 2.56 (d, J = 1.72 Hz, 1H), 3.77 (m, 1H), 4.03 (d, J = 10.55 Hz, 1H), 4.46 (dt, J = 7.96 Hz, 2.16 Hz, 1H), 5.98 (dd, J = 10.36 Hz, 2.41 Hz, 1H), 6.70 (dd, J = 10.36 Hz, 1.91 Hz, 1H); ^{13}CNMR (400 MHz, $CDCl_3$) δ -5.40, -4.91, -4.46, -4.13, 18.15, 18.61, 25.76, 25.94, 72.68, 78.55, 78.70, 126.86, 150.71, 196.78. Anal Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.02; H, 9.74. Found: C, 58.15; H, 9.93.



Hydroxy ketone 94.4. A mixture of enone **94.5** (5.28 g, 14.17 mmol) and 10% Pd/C (0.950 g, 0.90 mmol Pd) in dry methanol (100 ml) was stirred under an H_2 atmosphere (1 atm) for 7 h. Following completion of the reaction by TLC, the reaction 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 **94.4** (4.67 g, 12.47 mmol, 88%) as white crystals. M.P. 76-78 ^{o}C; $[\alpha]^{23}_{D}$ = +0.084 (*c* 0.26 CH_2Cl_2); IR (film) 3414, 1736 cm^{-1}; ^{1}HNMR (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}CNMR (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 $C_{18}H_{38}O_4Si_2$: C, 57.70; H, 10.22. Found: C, 58.39; H, 10.55.

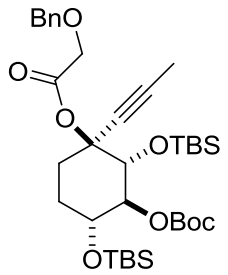


Diol 94.5. Propynyl magnesium bromide (70.7 ml, 0.5 M in THF, 35.32 mmol) was added dropwise to a solution of hydroxyl ketone **94.4** (4.41 g, 11.77 mmol) in THF (200 ml) at -10°C. After warming to room temperature over 5 h, the reaction mixture was quenched with cold NH_4Cl (aq) solution, extracted 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 **94.5** (3.86 g, 9.30 mmol, 79%) as white crystals. M.P. 50-52°C; $[\alpha]^{23}_D$ = +0.031 (*c* 0.26 CH_2Cl_2); IR (film) 3540, 2113 cm^{-1}; ^{1}HNMR (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}CNMR (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.



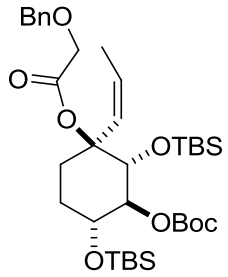
Propargyl alcohol 94.6. *n*-BuLi (2.35 mL, 2.8 M in Hexanes, 6.58 mmol) was added dropwise to a solution of diol **94.5** (2.55 g, 6.15 mmol) in ether (100 ml) at -78°C. After 30 min, Di-*tert*-butyl-dicarbonate (1.75 g, 7.99 mmol) was added dropwise and the reaction mixture was allowed to slowly warm 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 **94.6** (2.55 g, 6.09 mmol, 99%) as white crystals. M.P. 126-128 ^oC; ; $[\alpha]^{23}_D$ = +0.080 (*c* 0.196 CH_2Cl_2); IR (film) 3580, 1752 cm^{-1}; ^{1}HNMR (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 Hz, 1H), 2.40 (s, 1H), 3.40 (d, J = 9.64 Hz, 1H), 3.56 (td, J = 9.80 Hz, 5.85 Hz, 1H), 4.71 (t, J = 9.34 Hz, 1H). ^{13}CNMR (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.

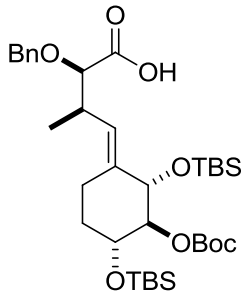


Alkyne 94.7. *n*-BuLi (1.48 ml, 2.8 M in Hexanes, 4.14 mmol) was added dropwise to a solution of propargyl alcohol **94.6** (1.42 g, 2.76 mmol) in ether (35 ml) at -78^{o}C. After 20 min, the acid chloride (1.27 g, 6.90 mmol) was added dropwise and the reaction mixture was allowed to slowly warm to room 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 alkyne **94.7** (1.21 g, 1.82 mmol, 66%, 97% brsm) as a colorless oil. $[\alpha]^{23}_D$ = +0.314 (*c* 1.42, CH_2Cl_2); IR (film) 2266, 1747 cm^{-1}; ^{1}HNMR (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,

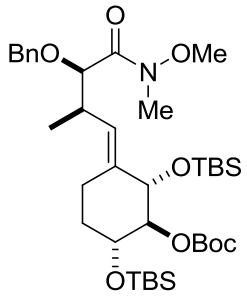
9H), 1.80 (m, 2H), 1.92 (s, 3H), 2.83 (dt, J = 13.08 Hz, 3.55 Hz, 1H) 3.55 (td, J = 9.18 Hz, 7.48 Hz, 1H), 3.64 (d, J = 9.44 Hz, 1H), 4.04 (d, J = 2.45 Hz, 2H), 4.63 (q, J = 11.52 Hz, 11.53 Hz 2H), 4.76 (t, J = 9.33 Hz, 1H), 7.34 (m, 5H); ^{13}CNMR (400 MHz, $CDCl_3$) δ-4.75, -4.56, -4.49, -4.14, 3.90, 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 $C_{35}H_{58}O_8Si_2$: C, 63.40; H, 8.82. Found: C, 61.16; H, 8.66.



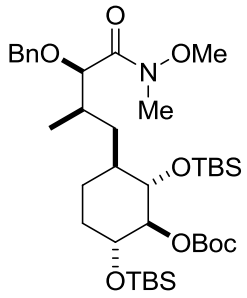
Allylic ester 94.8. A mixture of the alkyne **94.7** (2.1 g, 3.167 mmol), pyridine (0.128 ml, 1.58 mmol), and 5% $Pd/BaSO_4$ (1.35 g, 0.633 mmol) dissolved in ethyl acetate (25 ml) was shaken in a Parr bottle under an H_2 atmosphere (100 psi) for 6 h. The reaction mixture was filtered through celite 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 **94.8** (1.74 g, 2.62 mmol, 83%, 94% brsm) as a colorless oil. $[\alpha]^{23}_D$ = -0.278 (*c* 0.88 CH_2Cl_2); IR (film) 1751 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3), 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}CNMR (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 $C_{35}H_{60}O_8Si_2$: C, 63.64; H, 9.34. Found: C, 63.75; H, 9.18.



Pentenoic acid 95.3. *n*-BuLi (1.07 ml, 2.8 M in Hexanes, 3.01 mmol) was added dropwise to a solution of diisopropylamine (0.423 ml, 3.01 mmol) in THF (20 ml) at -78°C. After 20 min, this solution was cannulated to a solution of allylic ester **94.8** (1.00 g, 1.50 mmol) and TMSCl (0.57 ml, 4.51 mmol) in THF (20 ml) at -78°C. After 10 min AcOH (0.103 ml, 1.80 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 NH_4Cl (aq) solution, extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. The crude product was then dissolved in ether (5 ml), treated with NEt_3 (0.30 ml, 2.15 mmol), and purified by flash chromatography over silica gel eluting with 1% NEt_3 in ether, then 1% HCO_2H in ether. Removal of excess formic acid in vacuo gave pentenoic acid **95.3** (0.78 g, 1.17 mmol, 78%, 99% brsm) as a colorless oil. $[\alpha]^{23}_D$ = +0.424 (*c* 1.32 CH_2Cl_2); IR (film) 3414, 1750, 1651 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) 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). ^{13}CNMR (400 MHz, $CDCl_3$) 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 $C_{35}H_{60}O_8Si_2$: C, 63.21; H, 9.09. Found: C, 61.29; H, 9.52.



Weinreb Amide 96.2. Freshly distilled MsCl (0.090 ml, 1.16 mmol) was added dropwise to a solution of pentenoic acid **96.1** (0.70 g, 1.05 mmol) and triethylamine (0.439 ml, 3.15 mmol) in THF (30 ml) at 0°C. After 30 min, HN(OMe)Me (0.096 ml, 1.58 mmol) was added dropwise and the reaction mixture was allowed to warm to rt over 6 hours. 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 filtration through a silica gel plug with 1% NEt_3 in ether. Starting material was recovered with 1% formic acid in ether. After removal of solvents under vacuum, Weinreb amide **96.2** was isolated (0.55 g, .776 mmol, 73.9%) as clear oil. $[\alpha]^{23}_D$ = +0.234 (*c* 0.74 CH_2Cl_2); IR (film) 1633, 1732 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) 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); ^{13}CNMR (MHz, $CDCl_3$) δ -4.90, -4.85, -4.83, -4.40, 14.10, 17.86, 18.24, 22.65, 23.46, 25.77, 25.94, 28.02, 31.55, 33.61, 35.31, 61.17, 71.93, 72.55, 73.97, 81.02, 83.89, 125.17, 127.66, 127.93, 128.37, 137.21, 137.65, 152.99, 173.19. Anal Calcd for $C_{37}H_{65}NO_8Si_2$: C, 62.76; H, 9.25; N, 1.98. Found: C, 62.08; H, 9.24; N, 1.93.



Reduced amide 97.3. A mixture of Weinreb amide **96.2** (0.40 g, 0.565 mmol) and Crabtree's catalyst (0.023 g, 0.0282 mmol) in CH_2Cl_2 (100 mL) was shaken in a Parr bottle under H_2 (100 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 **97.3** (0.39 g, 0.55 mmol, 97%) as a colorless oil. $[\alpha]^{23}_D$ = +0.076 (*c* 1.32 CH_2Cl_2); IR (film) 1675, 1748 cm^{-1}; ^{1}HNMR (400 MHz, CDCl3) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.72 (q, J = 13.81 Hz, 1H), 0.86 (s, 9H), 0.88 (s, 9H), 0.89 (s, 3H), 1.23 (m, 3H), 1.48 (s, 9H), 1.72 (m, 2H), 1.88 (dd, J = 13.73 Hz, 3.15 Hz, 1H), 2.06 (m, 2H), 3.10 (t, J = 9.5 Hz, 1H), 3.19 (s, 3H), 3.47 (ddd, J = 11.27 Hz, 9.25 Hz, 4.92 Hz, 1H), 3.58 (s, 3H), 4.12 (d, 6.70 Hz, 1H), 4.36 (d, J = 11.22 Hz, 1H), 4.45 (d, J = 9.06 Hz, 1H), 4.54 (d, J = 11.22 Hz, 1H), 7.30 (m, 5H); ^{13}CNMR (MHz, $CDCl_3$) δ -4.60, -4.46, -3.90, -3.56, 17.94, 18.02, 18.10, 25.69, 25.84, 26.14, 28.08, 32.26, 32.98, 33.57, 39.14, 41.8, 61.08, 71.92, 72.93, 76.35, 81.22, 81.40, 83.69, 127.79, 128.19, 128.35, 137.52, 153.21, 173.18; Anal Calcd for $C_{37}H_{67}NO_8Si_2$: C, 62.58; H, 9.51; N, 1.97. Found: C, 62.78; H, 9.60; N, 1.92.

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