

**ASYMMETRIC SYNTHESIS OF 1,3-AMINO ALCOHOLS AND TROPINONE
DERIVATIVES FROM ENANTIOPURE SULFINIMINES**

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by
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ABSTRACT

Asymmetric Synthesis of 1,3-Amino Alcohols and Tropinone Derivatives from Enantiopure Sulfinimines

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Doctor of Philosophy

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Doctoral Advisory Committee Chair: Prof. Franklin A. Davis

Heterocycles that contain nitrogen, such as piperidine, pyrrolidine and tropane, are widespread as natural product alkaloids and serve as templates for many bioactive drugs and drug candidates. The intent of this research is to develop asymmetric syntheses of piperidine-containing *syn* and *anti* 1,3-amino alcohols as well as tropinone and tropane-containing derivatives using sulfinimines (*N*-sulfinyl imines) as precursors for acid-catalyzed cascade cyclizations.

Chiral *N*-sulfinyl β -amino ketones derived from *N*-sulfinyl β -amino Weinreb amides, serve as novel and direct precursors to *syn* and *anti* *N*-sulfinyl 1,3-amino alcohols

through stereoselective reductions. General reduction conditions have been developed for a variety of substrates. This methodology was applied to a concise formal synthesis of the piperidine-containing natural product, (-)-pinidinol, through an intramolecular cascade-cyclization of a masked-oxo *N*-sulfinyl 1,3-amino alcohol. Special conditions were found for the *syn* reduction of these substrates.

Tropinones and tropanes are structural motifs which encompass many interesting bioactive natural products such as cocaine and scopolamine. The synthesis of these tropinone derivatives, using an asymmetric and intramolecular cascade reaction, allows for facile functionalization of one of the bridgehead carbons. This opens doors to novel derivatives of (-)-cocaine which can be used as potential addiction therapeutics or in new SAR studies of dopamine reuptake transporter blockers. Here a five-membered cyclic imine can be formed through the acid-catalyzed intramolecular cyclization of acyclic ketal-protected *N*-sulfinyl ketones. After reaction with an acylating agent, the tropinone nucleus can be formed through an intramolecular Mannich reaction of an *N*-acyl iminium ion.

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CHAPTER 1

ASYMMETRIC CYCLIZATIONS OF *N*-ACYL IMINIUM IONS

1.1 Introduction

Imines and iminium ions are common reactive intermediates in organic synthesis and the intramolecular cyclization of these intermediates is responsible for a large portion of modern natural product synthesis.^{1,2} Two of the most well-known carbon-carbon-bond forming cyclizations of these intermediates include the Pictet-Spengler and the Mannich reactions (Figure 1.1).^{3,4} The Pictet-Spengler reaction uses a benzene ring or a heteroaromatic ring, such as indole, as the nucleophile to produce 1,2,3,4-tetrahydroisoquinolines or 1,2,3,4-tetrahydro- β -carbolines, respectively.

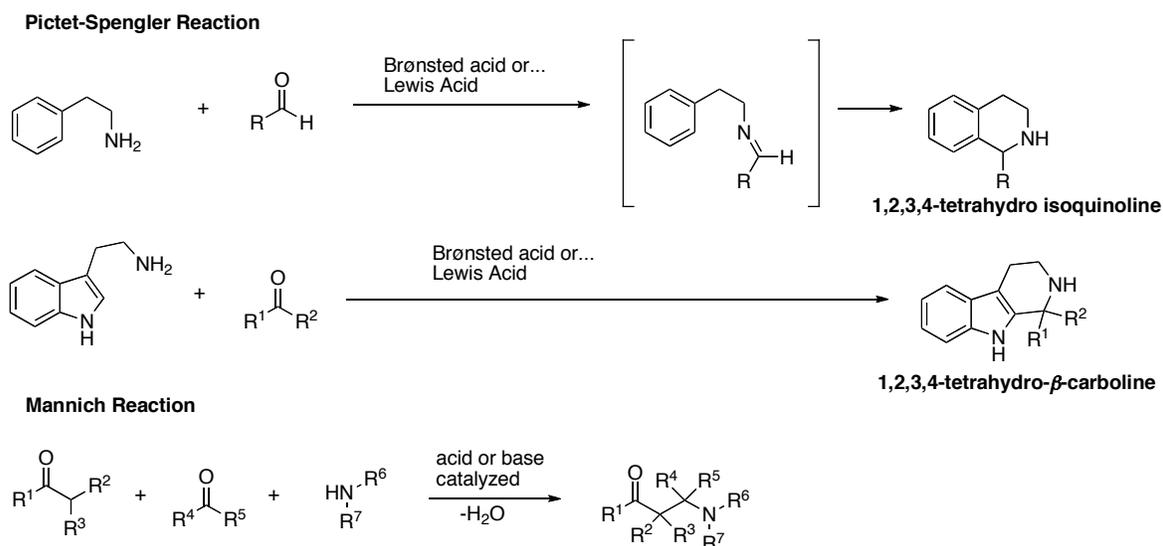


Figure 1.1: General Scheme of the Mannich and Pictet-Spengler Reactions

The Mannich reaction utilizes an enolate or an enol as the nucleophilic component. In fact, the Pictet-Spengler is considered to be a subtype of the Mannich reaction since both of these chemical processes are classified as α -aminoalkylation reactions.¹

Imines and iminium ions are also present in some naturally occurring compounds such as (-)-mersicarpine^{5,8} and the shellfish toxin, (-)-pinnatoxin A (Figure 1.2).^{6,7} Pinnatoxin A, a marine alkaloid whose structure was determined by Kishi and coworkers, is a potent calcium channel blocker. (-)-Mersicarpine belongs to a class of indole-derived alkaloids unique to Malaysian *Kopsia dasyrachis*. Other compounds related to mersicarpine show activities such as reversal of multidrug resistance in cancer chemotherapies.⁸

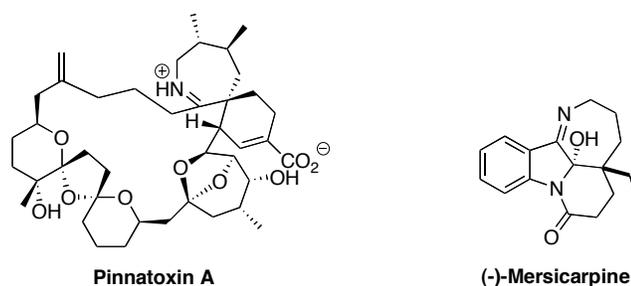


Figure 1.2: Biologically Active Imine and Iminium Containing Natural Products

Iminium ions and more specifically, *N*-acyl iminium ions, are much more reactive than their imine counterparts.^{1,9} This is because the charged *N*-acyl iminium ions owe their increased reactivity to the electron withdrawing carbonyl group. This makes the iminium carbon more electrophilic and therefore more susceptible to nucleophilic attack. Because of this increased reactivity, cyclizations proceed at a faster rate and *N*-acyl iminium ions can accept a wide range of nucleophiles. These characteristics of *N*-acyl iminium ions have

created a large and diverse area of natural product chemistry that includes derivatives of the β -carbolines such as yohimbine (Figure 1.3).¹

This chapter will focus mainly on the properties, preparation and enantioselective cyclizations of cyclic *N*-acyl iminium ions in the current literature. Examples will be shown that demonstrate a brief overview of this diverse field of chemistry.

1.2 Asymmetric Reactions of Cyclic *N*-Acyl Iminium Ions

This section focuses on the reactivity, preparation and asymmetric cyclizations of cyclic *N*-acyl iminium ions. *N*-Acyl iminium ion cyclizations are a broad topic in organic chemistry so examples will mostly be limited to reactions of 5- and 6-membered ring *N*-acyl iminium species. An overview of the reactivity and preparation of cyclic iminium ions will be presented first.

1.2.1. Reactivity of Cyclic *N*-Acyl Iminium Ions

Cyclic *N*-acyl iminium ions are more reactive than their acyclic counterparts. This is because the electrophile is rigidly held and there is less steric blocking of the electrophilic carbon. The order of reactivity is described below for cyclic iminium species with both endocyclic and exocyclic carbonyl groups (Figure 1.3). Five and six-membered cyclic *N*-acyl iminium ions are the most common reactive species with five-membered rings having slightly better reactivities than their six-membered counterparts.⁹ This is most likely due to the increased energy from increased angle strain on the 5-membered *N*-acyl iminium ions. The intrinsic gas-phase reactivity of various cyclic *N*-acyl iminium ions **1** toward the addition of allyltrimethylsilane (**2**) to produce the C-alkylated product **4** were investigated. The carbocation intermediate **3** was analyzed using MS² and MS³ pentaquadrupole mass spectrometric experiments (Scheme 1.1).⁹

It was found that *N*-alkyl iminium ions **A** are inert towards nucleophilic addition and also that *N*-alkyl iminium ions with an endocyclic acyl group **B** are practically inert as well. The

alkyl group is electron donating enough to effectively diminish the carbocation character of the electrophilic carbon and an iminium species with an exocyclic *N*-acyl group such as **C** increases electrophilicity only slightly. This meager increase in electrophilicity has been rationalized though the ease of rotation (~ 10 kcal/mol) of the *N*-COCH₃ bond. Analogous *N*-acyl iminium ions with an exocyclic *N*-CO₂CH₃ bond such as **D** and **E** are very effective electrophiles in forming adducts with allyltrimethylsilane. Reactive intermediates bearing an endocyclic carbonyl group such as **F** and **G** are the most reactive *N*-acyl iminium ions again with the 5-membered ring being more reactive than the 6-membered counterpart. In general, iminium ions such as **C**, **D**, **E**, **F** and **G** are the most widely used in synthesis.¹⁰

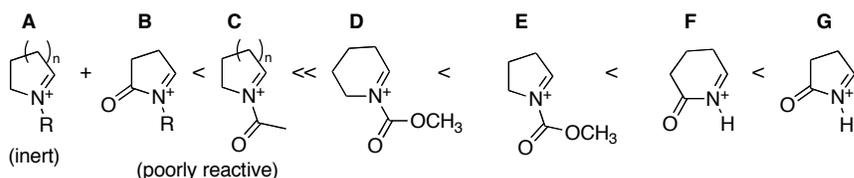
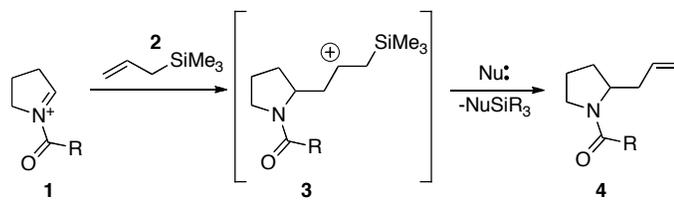
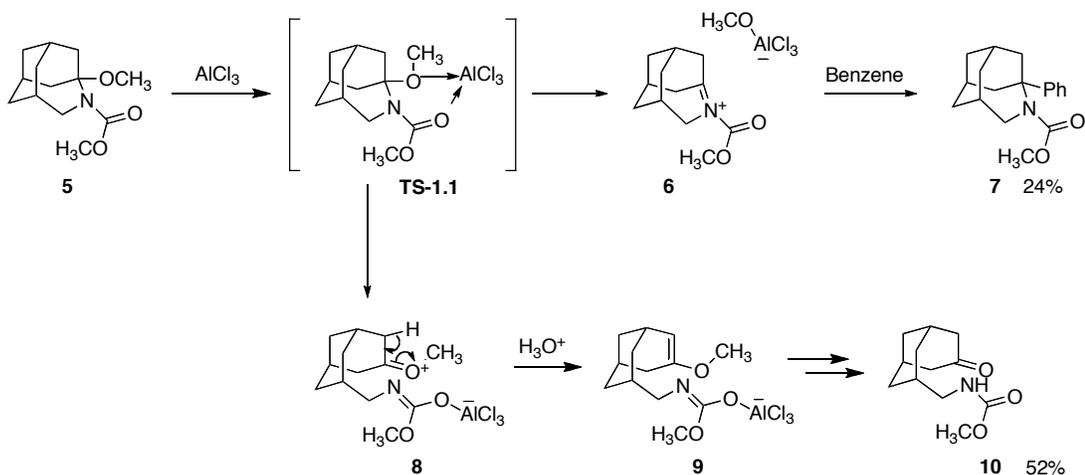


Figure 1.3: Order of Reactivity for Iminium Ions⁹



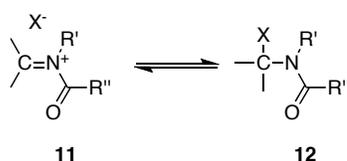
Scheme 1.1

N-Acyl iminium ion reactivity compared with other imine derivatives follows the order of acyliminium ion > alkyliminium ion > imine-BF₃ complex > imine.² Generally speaking, the less available the electron density is on nitrogen for cation stabilization, the more reactive the iminium species. For example, Sasaki and coworkers synthesized an extremely reactive *N*-acyl iminium ion from 3-methoxy-4-azahomoadamantane **5** (Scheme 1.2).¹³ Upon treatment of **5** with aluminum trichloride in benzene as solvent, their group yielded a small amount of the bridgehead substituted product **6** as well as 52% of the ring-opened product **10**. The bridgehead substituted product **7** is believed to occur through the cyclic iminium ion **6** and the other product occurs through aluminum trichloride catalyzed ring opening to give intermediate **8** followed by isomerization to **9** and loss of the *O*-methyl group to give **10**. The high reactivity of this *N*-acyl iminium ion is due to the fact that the carbocation cannot be stabilized as it is prohibited by Bredt's rule and favors relief of ring strain over nucleophilic substitution.

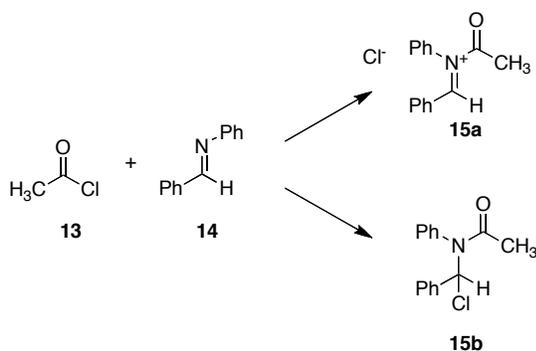


Scheme 1.2

N-Acyl iminium ions **11** also exist as an equilibrium with their covalent adducts **12** (Scheme 1.3). The proportion of these may be significant depending upon the experimental conditions.¹ For example, in trying to elucidate the mechanism of β -lactam formation in the Staudinger synthesis, Bose and coworkers studied ¹H and ¹³C NMR spectra of equimolar quantities of acetyl chloride (**13**) and benzalaniline (**14**) (Scheme 1.4).¹¹ They state that the predominant structure of the product corresponds to **15b** rather than **15a**.



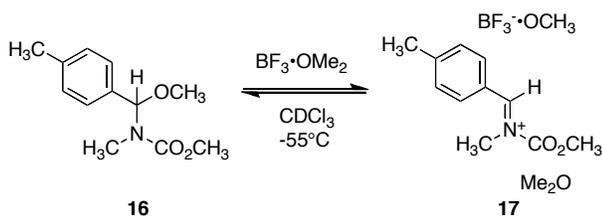
Scheme 1.3



Scheme 1.4

Yamamoto and coworkers also found that an equilibrium does indeed exist for the formation of *N*-acyl iminium ions from α -alkoxycarbamates (Scheme 1.5).¹² It was found that the percentage of the iminium ion **17** increased with each additional equivalent of

$\text{BF}_3 \cdot \text{OME}_2$ that was added to the alkoxycarbamate **16** and the result produced a nice linear graph when the ratio of **16/17** was plotted against equivalents of $\text{BF}_3 \cdot \text{OME}_2$ added.



Scheme 1.5

Cyclization of *N*-acyl iminium ions can be achieved through *exo* and *endo* modes (Figure 1.4). Also, a wide variety of nucleophiles can be used with electrophilic *N*-acyl iminium ions such as arene (Pictet-Spengler), alkene, allyl silane, vinyl silane, alkyne, allene, enol, enolate, and heteroatoms.^{1,2}

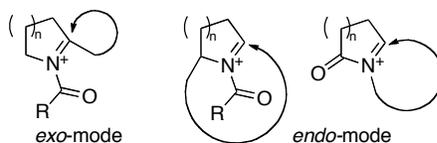


Figure 1.4: Exo and Endo Cyclization Modes

Ring closures of π -nucleophiles tend to be the most complex because the resultant carbocation generation can allow for significant side reactions. Aromatics as nucleophiles

are fairly simple because rearomatization follows cyclization such as with the Pictet-Spengler reaction.

Baldwin's rules, which describe reactions of neutral π -systems, have been unsuccessfully utilized to describe ring closures of iminium ions because they predict *5-endo-trig* cyclizations to be 'unfavored'.² However, an expanded and more accurate description, which takes into effect these cyclizations, has been put forth to describe ring closures of the charged iminium species (Figure 1.5).^{2,32,33} Although alkenes do not usually react in *5-endo-endo-trig* cyclizations, the corresponding enolates can.¹

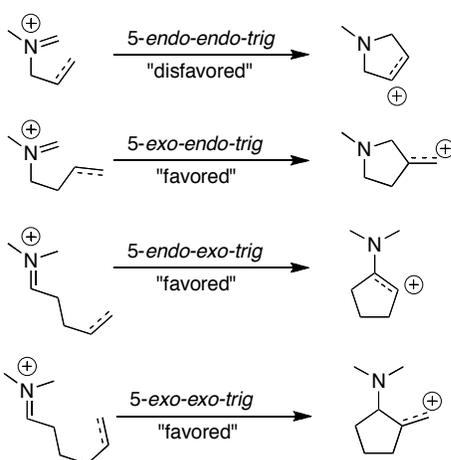


Figure 1.5: Ring Closures of Charged Iminium Species

1.2.2 Preparation of Cyclic *N*-Acyl Iminium Ions

Cyclic *N*-acyl iminium ions can be produced through a variety of ways. Because of their high reactivity, it is usually necessary to generate *N*-acyl iminium ions *in situ*.¹ Differences

in reactivity can be caused by differing solubilities, depending on the substrate. It is generally recommended to use a polar aprotic solvent such as CH₃CN, DMF or CH₂Cl₂ when preparing the reactive *N*-acyl iminium species.¹³

1.2.2.1 Reactions of Aldehydes and Ketones with Amides

Ketones or aldehydes featuring an intramolecular amide moiety such as **18** can undergo cyclization to form α -hydroxy derivatives **19** that upon treatment of acid, can form the *N*-acyl iminium ion **20** (Figure 1.6). This reaction can also form the *N*-acyl enamine (enamide) **21** as a side product.

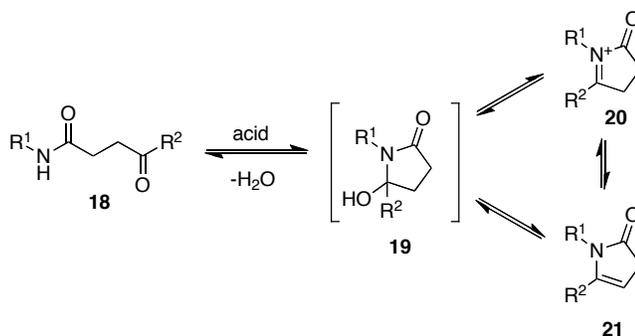
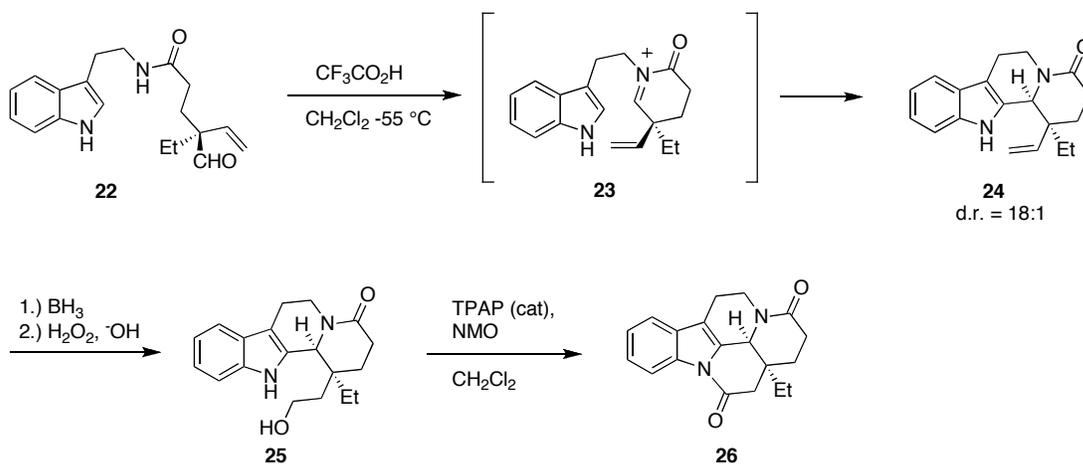


Figure 1.6: Formation of *N*-Acyl Iminium Ions via Condensation of Secondary Amides with Aldehydes or Ketones

In the synthesis of (-)-eburnamonine (**26**), the laboratories of Arthur G. Schultz utilized a surprisingly diastereoselective intramolecular cyclization of a cyclic *N*-acyl iminium ion **23** which was prepared from the corresponding intramolecular cyclization of an aldehyde and a secondary amide **22** (Scheme 1.6).¹⁵ The iminium ion **23** underwent an intramolecular Pictet-Spengler reaction to give **24**. Analogous reactions without the vinyl group produce a diastereomeric distribution of 1:1.¹⁶ Agreeing with similar results from Barton et al, it is theorized that the π -bond of the vinyl substituent directs the selectivity by interacting with the indole ring and iminium ion.¹⁷ Hydroboration to produce the primary alcohol **25** followed by oxidation with tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide gave (-)-eburnamonine (**26**).



Scheme 1.6

1.2.2.2 *N*-Acyl Enamines (Enamides)

Enamides are good precursors to cyclic *N*-acyl iminium ions whose rate of cyclization depends upon protonation with Brønsted acids (Figure 1.7).¹⁸ *N*-Acyl enamines can be synthesized in a number of ways. For example, they can be formed as side products through the condensation of primary amides with ketones. Also, they are formed through the *N*-acylation of enamines or even imines.¹⁹

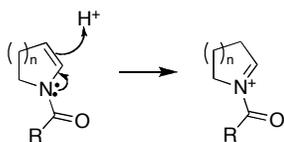
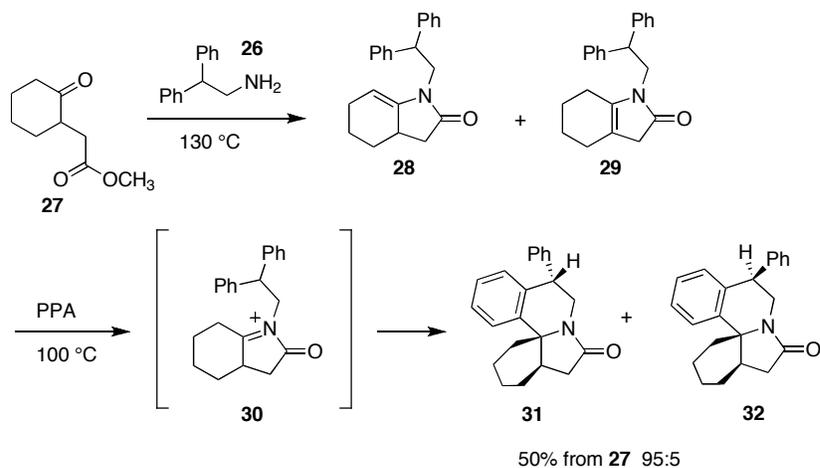


Figure 1.7: Formation of *N*-Acyl Iminium Ions from Enamides

Not only can *N*-acyl iminium ions be activated through C-protonation, but they can also be activated through other electrophilic reagents such as epoxidation with dimethyldioxirane²⁰ or enantioselectively using a Jacobsen's epoxidation.^{10,21}

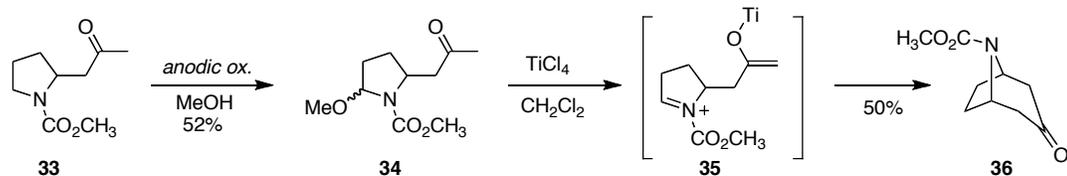
Albeit a racemic synthesis, Maryanoff and coworkers used an enamide as a precursor to a highly diastereoselective cyclization in the synthesis of tetrahydroisoquinoline ring systems (Scheme 1.7).²² They first condensed the ketoester **27** with 2,2-diphenylethanamine (**26**) to yield a mixture of enamines, **28** and **29**. These enamines were protonated to yield the intermediate *N*-acyl iminium ion **30** which underwent cyclization to yield tetrahydroisoquinoline **31** in a 95:5 diastereomeric ratio with its isomer, **32**.



Scheme 1.7

1.2.2.3 Electrochemical Oxidation of Carbons α to Nitrogen

Electrochemical oxidation of carbamates occurs on the carbon α to the nitrogen when 2 Farads/mol of electricity is passed through a methanolic solution at the anode using carbon electrodes. This provides α -methoxy compounds that are good precursors to *N*-acyl iminium ions under acidic conditions (Scheme 1.8).^{23,24} For example, anodic oxidation of methyl 2-(2-oxopropyl)pyrrolidine-1-carboxylate, (**33**) in a solution of methanol using carbon electrodes produces the methoxy derivative **34** which in the presence of titanium tetrachloride, undergoes iminium ion formation to give **35** and a final intramolecular cyclization to give the tropane derivative **36**.



Scheme 1.8

1.2.2.4 Acylation of Imines

Acylation of imines is a direct and powerful way to access *N*-acyl iminium ions (Figure 1.8). However, this product is usually very reactive and may isomerize to the enamine, especially under basic conditions such as with Et₃N. It can also exist in equilibrium with the halogenated intermediate^{1,19}

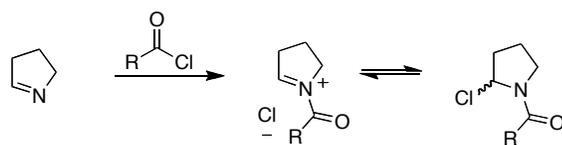
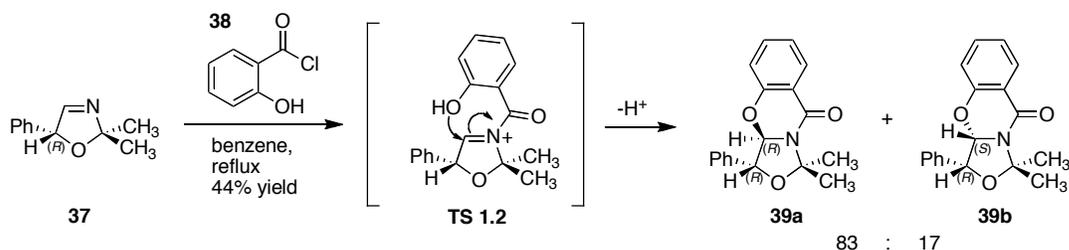


Figure 1.8: Direct Acylation of Imines

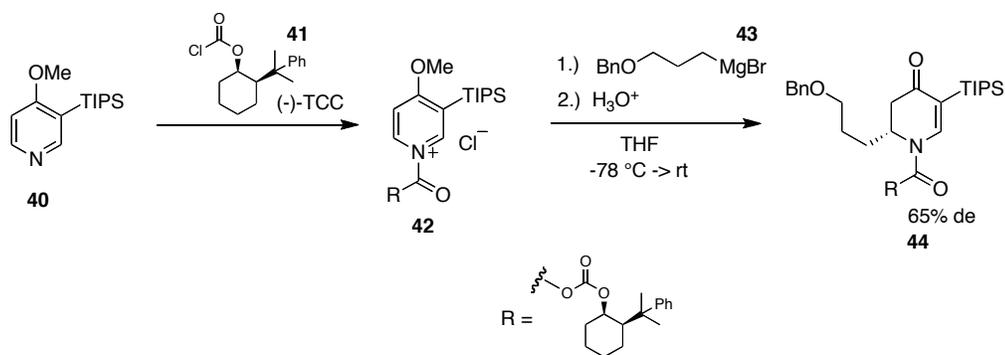
Although this method is seemingly direct, there are not many enantioselective examples in the literature. One recent example by Martens and coworkers utilized a chiral (*R*)-oxazoline (**37**) which reacted with 2-hydroxy benzoyl chloride (**38**) to produce an intermediate *N*-acyl iminium ion (Scheme 1.9).²⁴ This underwent cyclization via **TS 1.2** and

the nucleophilic addition of the oxygen to the iminium carbon yielded oxavalerolactam derivatives **39a** and **39b** in a 83:17 diastereomeric mixture. This result was explained by approach of the nucleophile from the least sterically hindered *si* face.



Scheme 1.9

Addition of acid chlorides to pyridines is especially important in the laboratory synthesis of natural products. The laboratories of Comins and coworkers used a chiral acyl group to direct nucleophilic addition to the pyridinium species (Scheme 1.10).^{25,26} Pyridine derivative **40** is acylated with (-)-*trans*-2-(α -cumyl)cyclohexanol chloroformate (**41**) to give pyridinium species **42**. This was used immediately in the reaction with the Grignard reagent, 3-benzyloxypropyl magnesium bromide (**43**) to yield the enone **44** with modest diastereoselectivity.



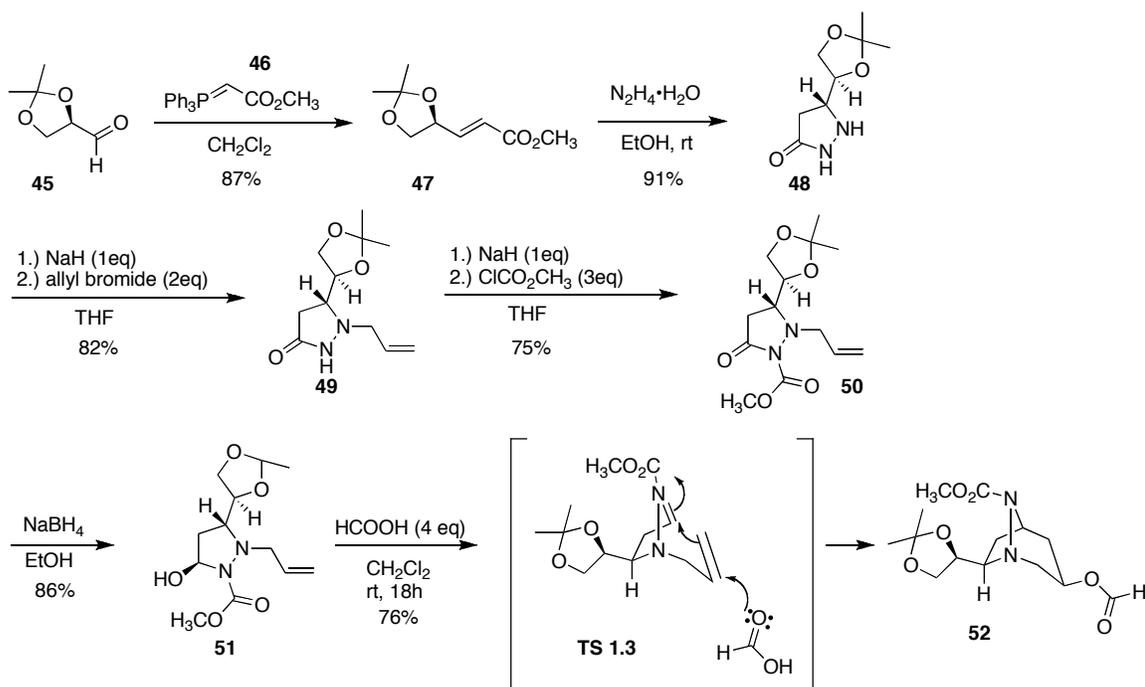
Scheme 1.10

1.2.2.5 Asymmetric Nucleophilic Addition to Imides

Selective reduction of imide carbonyls has allowed iminium chemistry to grow over the last 35 years.¹⁰ In fact, the selective addition of a hydride to a cyclic imide may be one of the most versatile and successful methods for the production of cyclic *N*-acyl iminium ions.

An enantioselective synthesis of azatropanes was accomplished starting from (*R*)-glyceraldehyde (**45**) (Scheme 1.11).²⁷ First, **45** was reacted with the ylide **46** to yield the unsaturated ester **47**. This was subsequently reacted with hydrazine to yield **48** as a 9:1 mixture of diastereomers. The major diastereomer was isolated through repeated recrystallizations. A regioselective allylation produced **44** and reaction with methyl chloroformate gave **50** in decent overall yields. Chemoselective reduction of the ring carbonyl produced **51** as a single diastereomer, even though chirality will be lost in the subsequent cyclization reaction. Using formic acid as Brønsted acid initiator as well as a

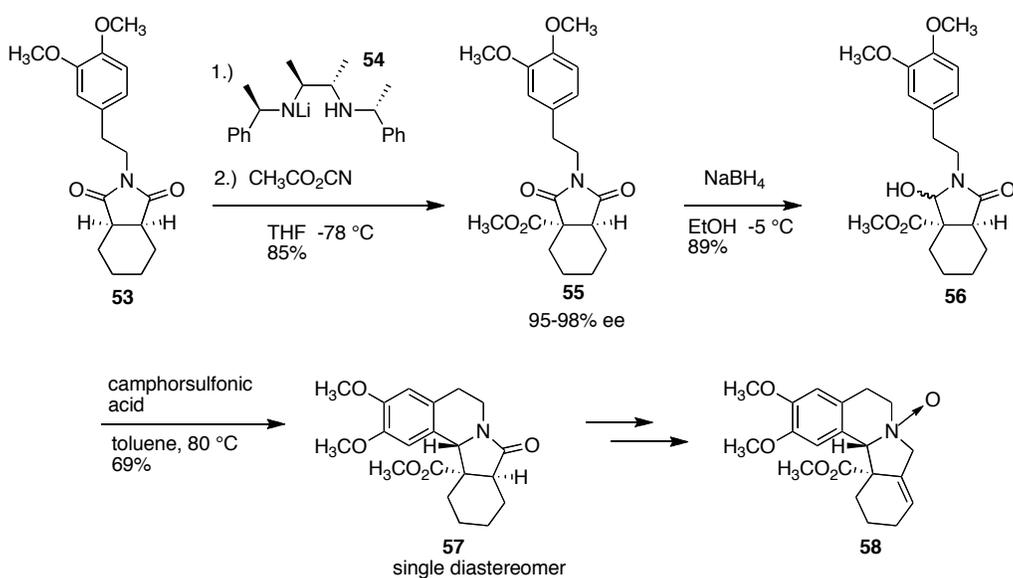
cyclization terminator, **51** goes through iminium ion transition state, **TS-1.3**, to give azatropane derivative **52** in 76% yield as a single diastereomer.



Scheme 1.11

Simpkins and coworkers utilized a desymmetrization of a *meso* cyclic imide **53** to synthesize (+)-jamtine (**58**), which is found in the shrub, *Cocculus hirsutis*: a plant used in traditional Pakistani folk medicine.²⁸ (Scheme 1.12). Through a process of desymmetrization developed in their laboratory,²⁹ they began by stereoselectively deprotonating the *meso* imide **53** with a chiral lithium amide derivative **54** and then adding a carbomethoxy substituent to give **55** in very high ee. Reduction with sodium borohydride in ethanol regioselectively

reduced the *more* hindered carbonyl to give *N*-acyliminium ion precursor, **56**. Iminium ion generation and cyclization to a single diastereomer of tetrahydroisoquinoline **57** was accomplished using camphorsulfonic acid in toluene at 80 °C. This was carried onto what was believed to be the natural product, (+)-jamtine (**58**) and matched data from a previous synthesis by Padwa et al.³⁰ However, spectroscopic data did not match the isolated material and it was concluded that the original proposed structure might be incorrect.

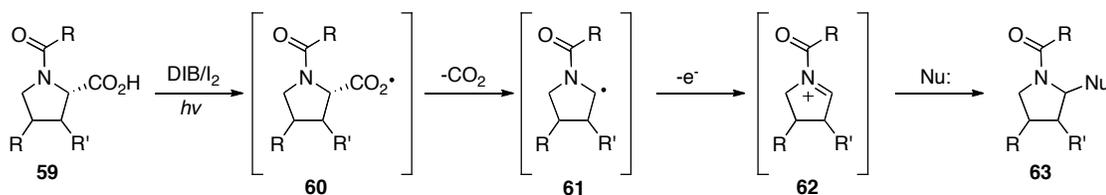


Scheme 1.12

1.2.2.6 Decarboxylation of α -Amido Acids

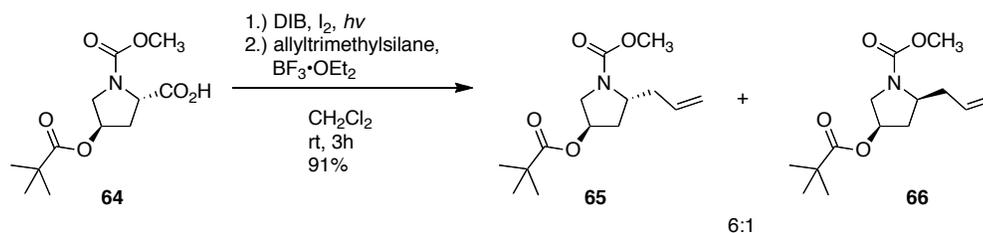
A method related to the electrochemical oxidation of amides α to the nitrogen of amides (*vide supra*) is the oxidative decarboxylation of α -amido acids to yield *N*-acyl iminium ions.^{1,2,10}

A modern oxidative decarboxylation method for the generation of *N*-acyl iminium ions is one which uses a combination of (diacetoxyiodo)benzene and iodine (Scheme 1.13).³¹ Here, a carbon centered radical **61** was prepared from the α -amido acid **59** and is then oxidized further to the cation which exists as the *N*-acyl iminium ion **62**. This can be trapped with a nucleophile to give C-substitution as in **63**.



Scheme 1.13

A stereoselective example of this starts from the pivalate ester of the 4-hydroxy proline derivative **64** (Scheme 1.14). A one-pot decarboxylation to acyl iminium ion intermediate and subsequent trapping with allyl trimethylsilane gave **65** and **66** in a 6:1 diastereomeric ratio.



Scheme 1.14

1.2.3 Cyclizations of *N*-Acyl Iminium Ions

Cyclic *N*-acyl iminium ions can undergo ring-closure with a wide variety of nucleophiles, some of which have been shown previously. These include, benzenoid or heterocyclic nucleophiles, alkenes, alkynes, enols/enolates and hetroatoms. Prediction of ring closure with alkenes follows the modified Baldwin's rules as shown in Figure 1.5. Cyclic iminium ions have significant advantages over their acyclic counterparts since *E/Z* isomerism is prevented.²

Examples of ring closures of varying sizes and nucleophiles will be shown in the following sections. Two excellent reviews that cover this subject exist in the recent literature and the following sections will be brief in comparison.^{1,2}

1.2.3.1 Formation of Four-Membered Rings

The Staudinger reaction is essentially a four-membered cyclization of an *N*-acyliminium ion with an enolate to form β -lactams (Figure 1.9). The Staudinger reaction has gained a lot of attention over the years because of the β -lactam moiety being used in antibiotics and other medicinals.² It was originally theorized that this cyclization occurs through a concerted mechanism but evidence now shows that this reaction can occur through formation of the zwitterionic intermediate followed by conrotatory ring closing to yield the β -lactams.³⁴ The ketene is easily formed *in situ* by reacting the acyl chloride with a tertiary amine such as triethylamine. Some authors have even proposed that an *N*-acyl iminium ion is initially formed via condensation of the acyl chloride with the imine (Figure 1.9).³⁵

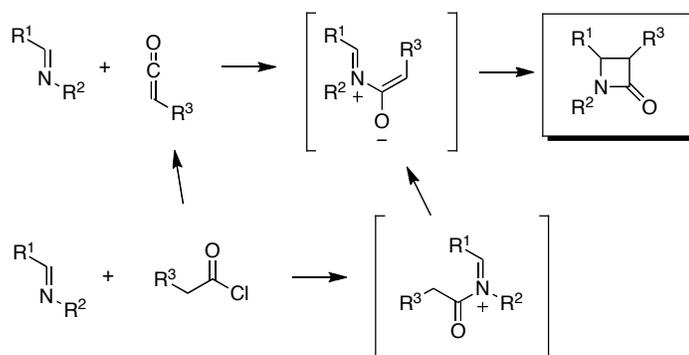
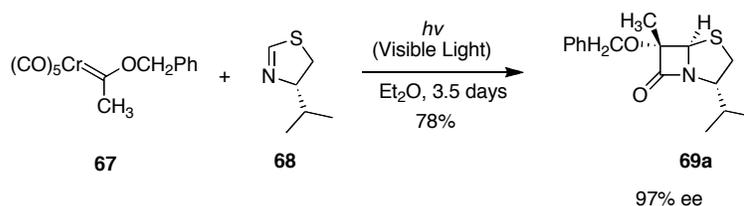


Figure 1.9: Possible Mechanisms of the Staudinger Reaction

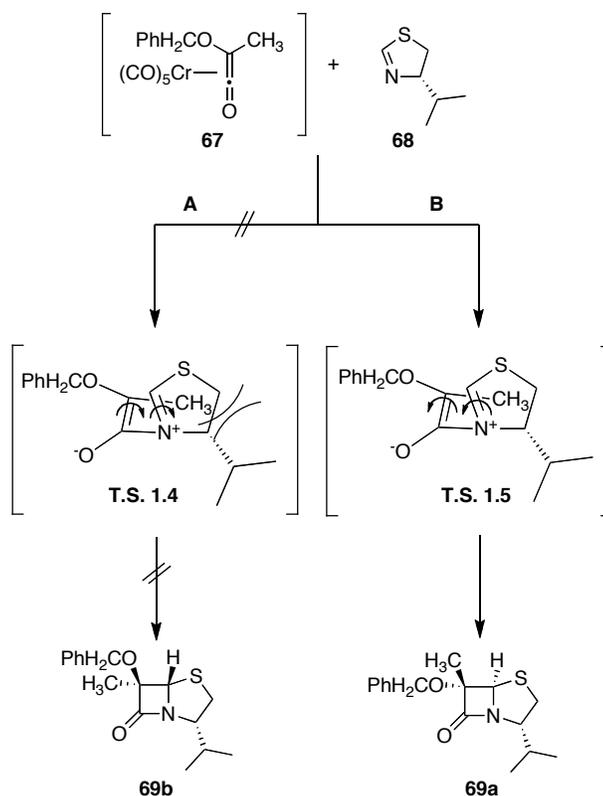
The Staudinger reaction with cyclic *Z* imines gives *trans* β -lactams almost exclusively.⁴ An asymmetric example of the Staudinger reaction with cyclic imines is shown

below (Scheme 1.16).³⁶ During mechanistic investigations of the Staudinger synthesis, Hegedus and coworkers reacted various chiral and cyclic thiazolines such as **68** with ketenes derived from the photolysis of alkoxy chromium carbenes **67**. This procedure gave β -lactams after 3.5 days with good yield and high diastereoselectivity.



Scheme 1.16

This selectivity was rationalized through ‘torquoelectronic effects’ as highlighted in a later paper (Scheme 1.17).³⁷ The imine nitrogen first approaches the carbon LUMO of the ketene from the less hindered side which is bearing the CH_3 group. Two possible modes of conrotatory ring closure to yield two diastereomeric products can then take place as outlined by paths **A** and **B**. However, **69a** is the only product of the reaction and no **69b** was detected. Therefore, conrotatory ring closure via path **A** might be blocked by the steric interactions of the methyl group and the chiral isopropyl group on the imine (**T.S. 1.4**). Only conrotation via path **B** is not hindered and favors the observed product (**T.S. 1.5**).

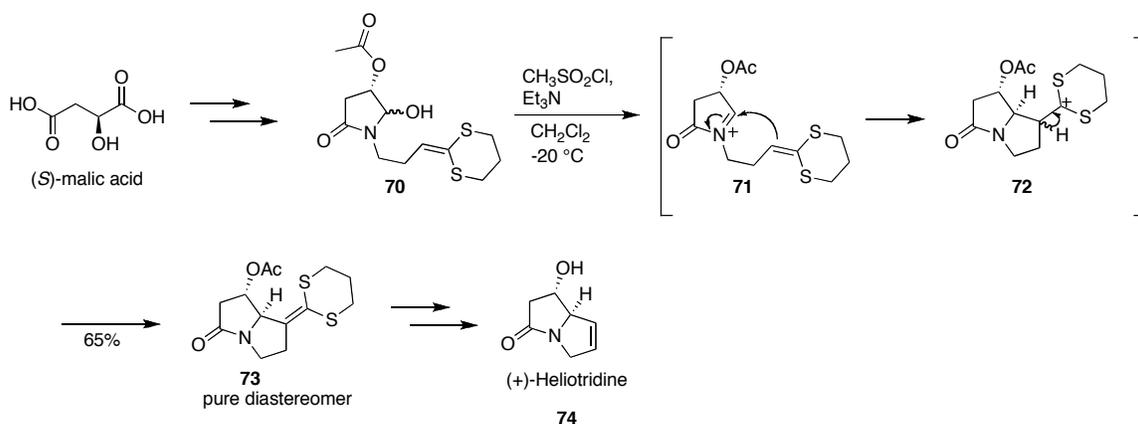


Scheme 1.17

1.2.3.2 Formation of Five-Membered Rings

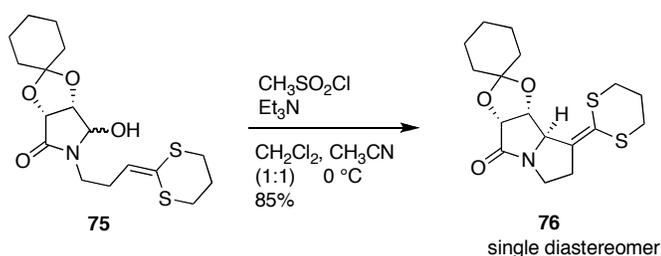
Many examples exist for 5-membered ring cyclizations and many different kinds of nucleophiles can be used. As stated above, *5-endo-endo-trig* cyclizations are prohibited except under photochemical diradical conditions or when an enolate is used.² However, *5-exo-endo-trig* cyclizations can occur and do so quite readily. This process has produced a widespread transformation in the synthesis of natural products.

For example, Chamberlain and coworkers synthesized the natural product, (+)-heliotridine **74**, whose structure has a wide range of biological activities (Scheme 1.18).^{38,39} From (*S*)-malic acid, they synthesized the acetoxy iminium precursor **70** in 3 steps. The affect of the acetoxy group was unknown to this iminium cyclization. They theorized that it would induce diastereofacial selection through neighboring group participation. High diastereoselectivity was, in fact, produced as iminium ion **71** underwent cyclization with the π -nucleophile. The intermediate carbocation **72** is stabilized by the dithiane ring system and undergoes elimination to the pyrrolizidine **73** in good yield and as a pure diastereomer. Further manipulations gave (+)-heliotridine (**74**). In a later paper their group synthesized ketal-protected pyrrolizidine diols **76** from precursor **75** (Scheme 1.19).⁴⁰



Scheme 1.18

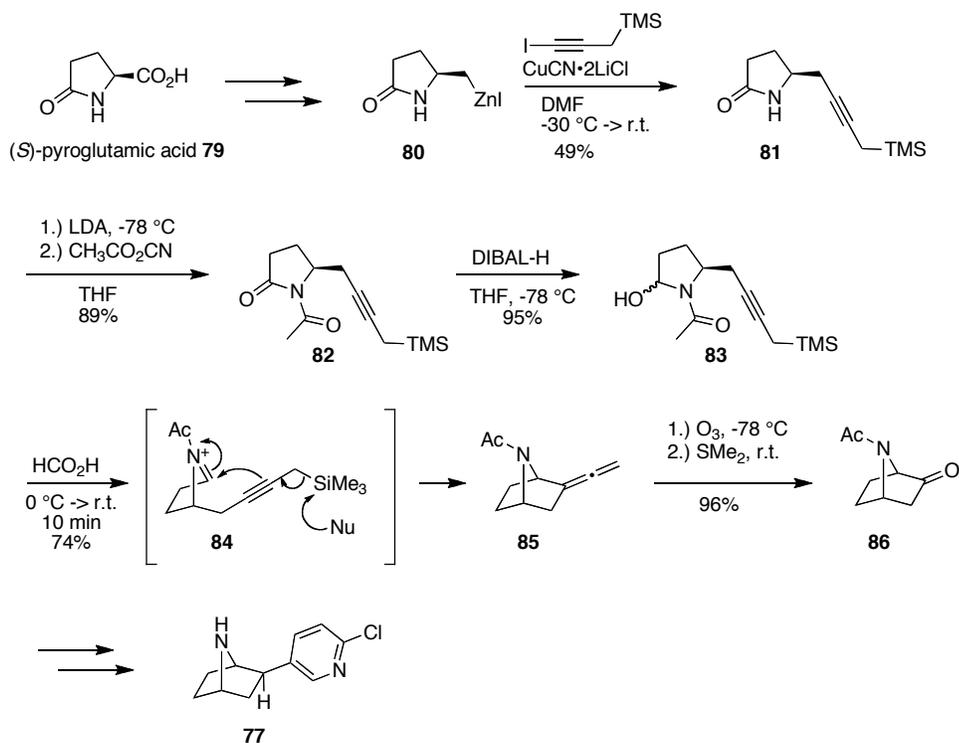
The iminium ion cyclization of **73** was attempted using similar conditions with just CH_2Cl_2 as solvent at $0\text{ }^\circ\text{C}$. However, the reaction time was increased to 2 weeks and it was found that an equal portion of polar solvent reduced the reaction time to 20 hours. After optimization, **74** was produced as a single diastereomer in 85% yield. Here, diastereoselectivity is preserved without the neighboring group participation ability of the acetate.



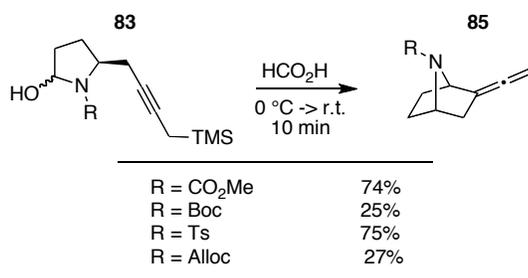
Scheme 1.19

In the first enantioselective synthesis of (-)-epibatidine (**77**), a bicyclic alkaloid which is isolated from an Ecuadorian neotropical frog, a key step was found to be the intramolecular cyclization of a propargyl trimethylsilane with an internal sulfonyl or acetyl iminium ion **84** (Scheme 1.20)(Scheme 1.21).⁴¹ Starting from (*S*)-pyroglutamic acid (**79**), a copper mediated cross coupling of organozinc reagent **80** with trimethylsilyl propargyl iodide was utilized to give **81**. Acetylation followed by reduction produced the iminium ion precursor **82**. It was found that *N*-acylation or *N*-tosylation produced the best yields of **85** as a single diastereomer (Scheme 1.21). Protection with the *t*-butyl and allyl carbamates gave

poor yields of the ketenes, probably due to deprotections and other side reactions. Finally, ozonolysis produced the ketone **86** which represents a completion of the formal synthesis of **77**.



Scheme 1.20



Scheme 1.21

In the laboratories of Hiemstra and Speckamp, an enantioselective route towards the natural product, (+)-gelsemine (**88**), was developed (Figure 1.10).⁴² In this synthesis, they started from iminium ion precursor **89** which is a pure (*E*)-silyl enol ether (Scheme 1.22). The silyl ether was treated with trimethylsilyl triflate (1.6 eq) at -13 °C for 25 min and was followed by a NaHCO₃ workup. Immediate reduction of the aldehyde with NaBH₄ gave a 4:1 mixture of regioisomeric products **90** and **91** in 66% overall yield from **89**.

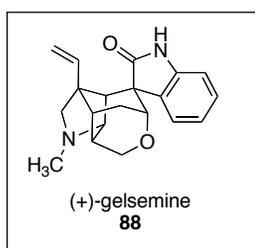
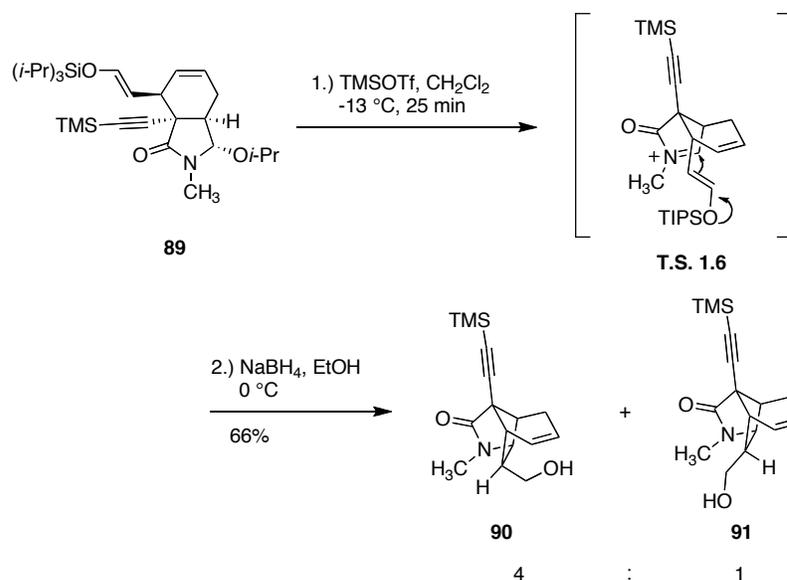


Figure 1.10: Structure of (+)-Gelsemine



Scheme 1.22

An example of a 5-*exo* cyclization can be found in the work towards (+)-meloscine (**92**) as described by Schultz and coworkers (Figure 1.11)(Scheme 1.23).⁴ A series of acid-catalyzed cyclizations were carried out using various *N*-substituted iminium precursors **93**. It was found that the choice of acid as well as *N*-substitution had a substantial effect on the product outcome and also that when the cyclization of **93** was performed with CF₃CO₂H, the reaction produced heterocycle **96** as a mixture of diastereomers. This was explained by the nucleophilic attack of the carbonyl oxygen to the *N*-acyl iminium ion **94** followed by quenching of carbocation **95** with H₂O. When a stronger acid such as trifluoromethane sulfonic acid was used, a mixture of **97** and **98** was produced. This ratio is highly dependent upon the substitution on the nitrogen (Scheme 1.23). The side product **98** was produced as a single diastereomer, although no yields were reported for these reactions.

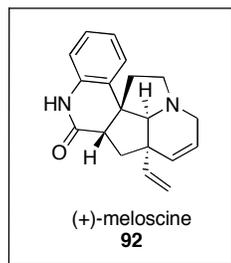
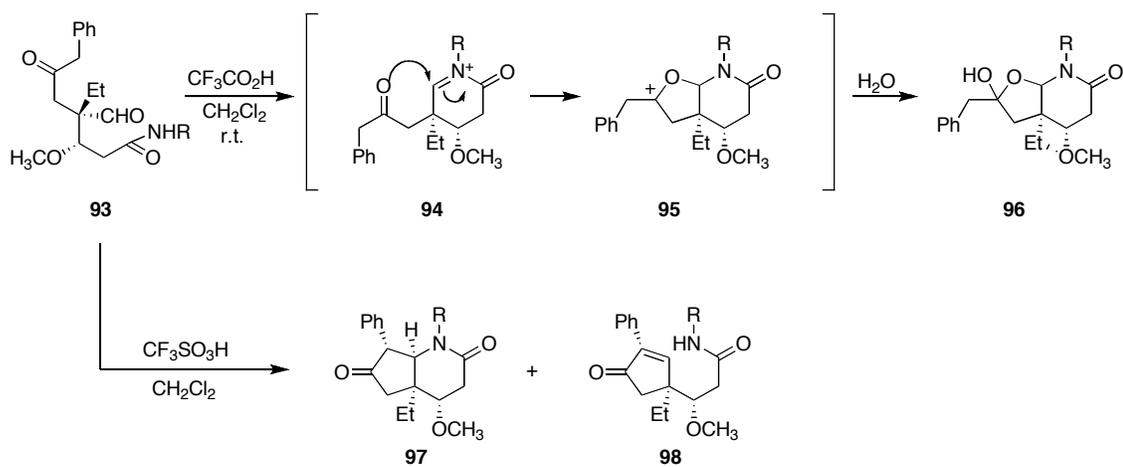


Figure 1.10: Structure of (+)-Meloscine

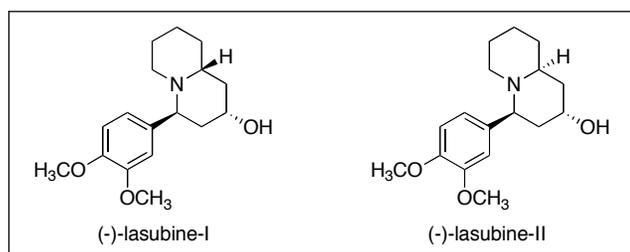
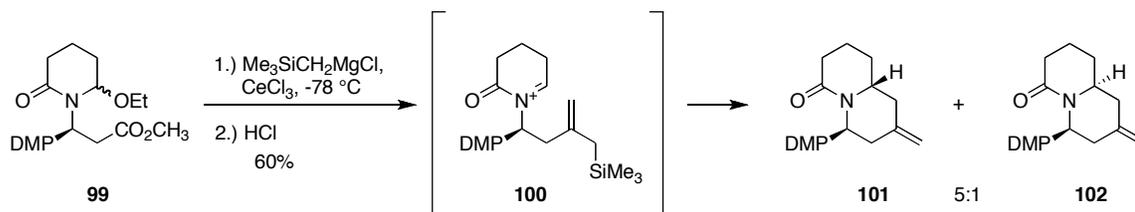


Substrate 93	Ratio of 97 and 98
a. R = <i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	15:1
b. R = C ₆ H ₅ CH ₂	10:1
c. R = CH ₂ =CHCH ₂	3:1
d. R = MeOCH ₂ CH ₂	1:1
e. R = Me	1:10

Scheme 1.23

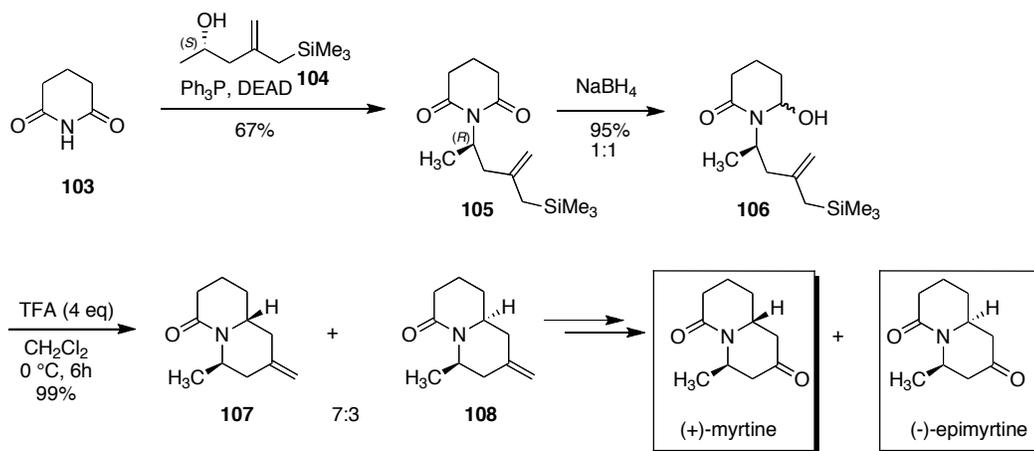
1.2.3.3 Formation of Six-Membered Rings

Formation of 6-membered rings using cyclic *N*-acyl iminium ions is a facile process. This cyclization usually proceeds through a highly ordered transition state to give heterocycles with high diastereoselectivity.² For example, 6-membered ring cyclizations of *N*-acyl iminium ions are important in the synthesis of quinolizidine alkaloids.^{44,45} In the synthesis of (-)-lasubine-I and (-)-lasubine-II, two alkaloids isolated from the leaves of *Lagerstremia subcostata*, it was found that a reaction of ethoxy lactam (**99**) with a cerium-derived reagent produced the bicyclic product in one-pot as a 5:1 mixture of diastereomers **101** and **102** through intermediate *N*-acyl iminium ion **100** (Scheme 1.24).⁴⁵



Scheme 1.24

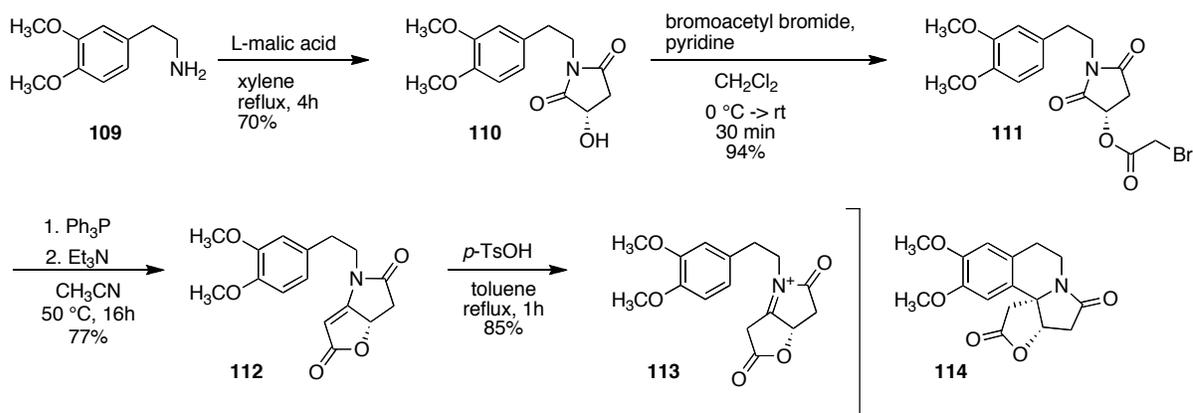
In the same year, the synthesis of (+)-myrtine and (-)-epimyrtine was undertaken (Scheme 1.25).⁴⁴ These alkaloids, obtained from *Vaccinium myrtillus*, were synthesized through an analogous pathway, albeit with a different stereochemical preference. Imide **103** was subjected to Mitsunobu conditions with an alcohol **104** of known stereochemistry to produce **105**. This was reduced with NaBH₄ to produce a 1:1 mixture of the hydroxylactam **106**. Reaction of **106** with 4 equivalents of trifluoroacetic acid in methylene chloride for 6 hours at 0 °C produced a 7:3 diastereomeric mixture of products **107** and **108**. This mixture was separated and carried on to produce the natural products, (+)-myrtine and (-)-epimyrtine. However, no explanation was given for the difference in selectivity.



Scheme 1.25

A highly diastereoselective *N*-acyl iminium ion cyclization was used to synthesize a novel tetracyclic isoquinoline derivative bearing a quaternary carbon **114** (Scheme 1.26).⁴⁶

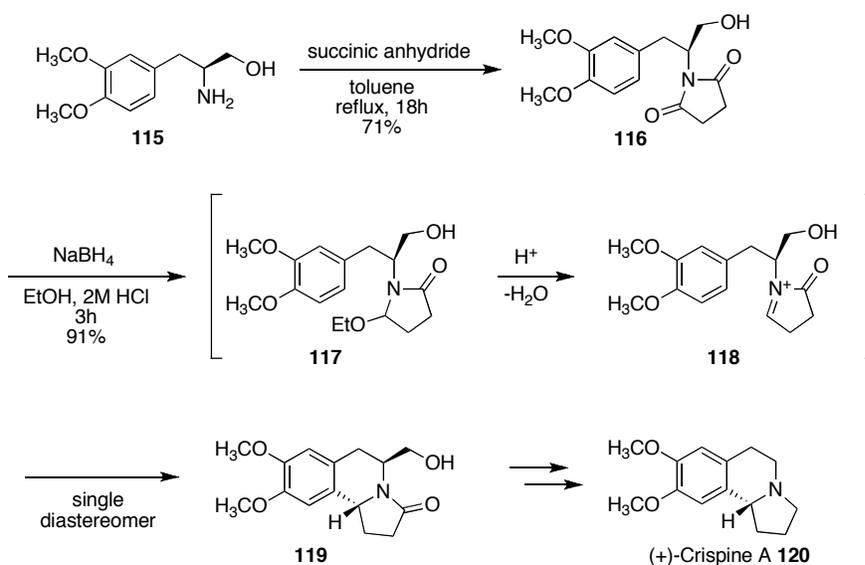
3,4-Dimethoxyphenethylamine (**109**) was condensed with a naturally occurring chiral source, L-malic acid, to produce imide **110**. Acylation with bromoacetyl bromide gave the *O*-acylated product **111** and a subsequent Wittig reaction produced the enamine **112** as the iminium ion precursor. Reaction of this enamine with *p*-toluene sulfonic acid produced the iminium ion **113** *in situ* which underwent a Pictet-Spengler reaction to give **114**. This reaction was completely enantioselective and was finished in one hour. The antipode was synthesized by using L-tartaric acid instead of L-malic acid.



Scheme 1.26

In an analogous reaction, Allen and coworkers utilized a chiral (*S*)-3,4-dimethoxy phenylalanol (**115**) in the synthesis of the anti-tumor alkaloid, (+)-crispine A (**120**) (Scheme 1.27).⁴⁷ Here the amine **115** is used as the source of chirality in a highly diastereoselective cyclization. The amine **115** was condensed with succinic anhydride to yield imide **116**.

Reaction of this imide with NaBH₄ in an ethanolic solution of 2M hydrochloric acid gave the intermediate ethoxy lactam **117** which is most likely in equilibrium with the iminium ion **118**. This intermediate underwent cyclization to **119** as a single diastereomer in very good yields. The proper configuration was determined by X-ray crystallography and the synthetic intermediate was carried onto (+)-crispine (**120**).



Scheme 1.27

The selectivity of the cyclization was explained by invoking a Felkin-Anh transition state (Figure 1.11).^{48,49} Here, it has been postulated that in order for cyclization to occur, either the hydrogen **TS 1.7** or the hydroxy methylene **TS 1.8** can eclipse with the carbonyl. Since hydrogen is the smallest group, **TS 1.8** is thermodynamically favored and therefore gives the desired product.

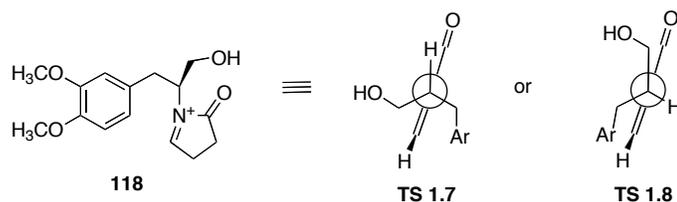


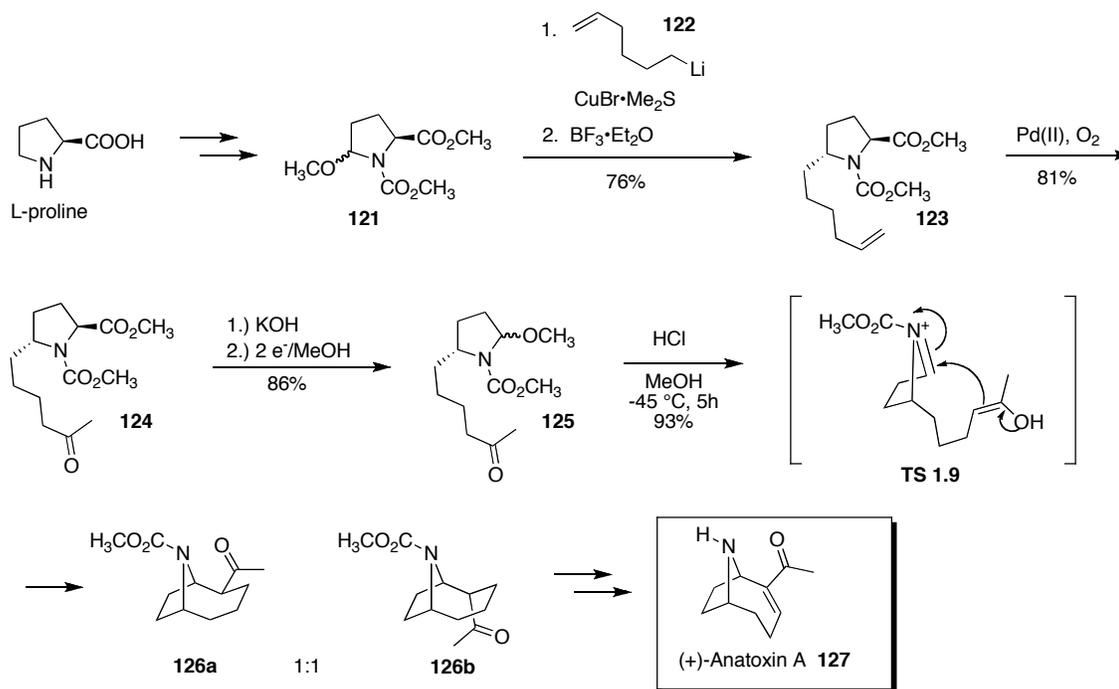
Figure 1.11: Proposed Transition States of Cyclization Towards (+)-Crispine

1.2.2.4 Formation of Seven-Membered Rings

Formation of seven-membered rings can be accomplished in both the *exo* and *endo* modes. However, these cyclizations are less prevalent in the literature because azepines are much less common than piperidines or pyrrolidines as natural product templates.²

In the synthesis of (+)-anatoxin A (**127**), Skrinjar and coworkers used an enol to achieve an intramolecular cyclization leading to a seven-membered ring (Scheme 1.28).⁵⁰ Their group started from naturally occurring L-proline as a chiral source and synthesized iminium ion precursor **121** through anodic oxidation. Using an organocopper reagent **122**, they were able to obtain **123** as the pure *trans* isomer through the intermediate iminium ion. Wacker oxidation produced the ketone **124** in good yield. Saponification followed by another electrochemical oxidation gave iminium ion precursor **125**. Treatment of **125** with various Lewis acids commonly used for *N*-acyl iminium ion cyclizations (TiCl_4 , AlCl_3 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$) failed and gave only unreacted starting material or unidentifiable oligomers. However, treatment of **125** with a methanolic hydrochloric acid solution produced **126a** and

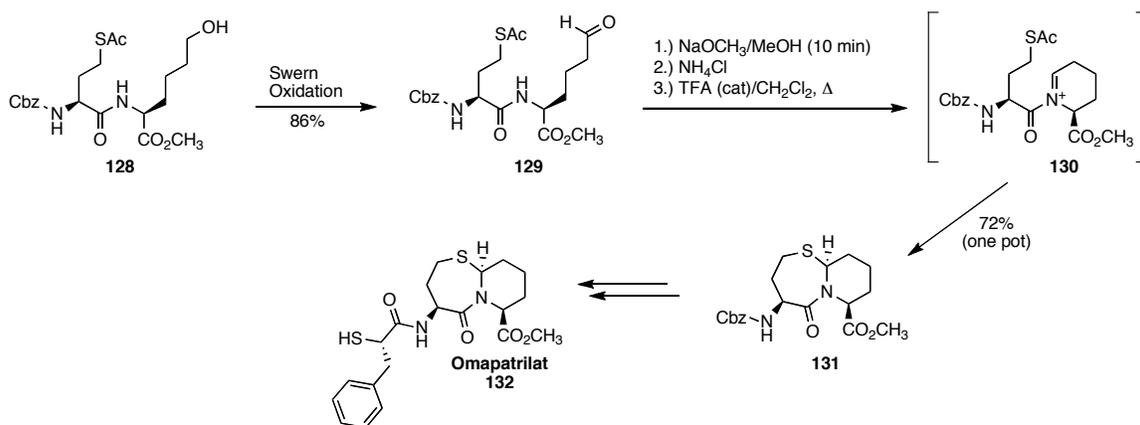
126b as a 1:1 mixture which was taken on to (+)-anatoxin A (**127**). As mentioned before, cyclization occurs via an enol adding to an intramolecular *N*-acyl iminium ion as in **T.S. 1.9**.



Scheme 1.28

The synthesis of OmapatrilatTM (**132**), an ACE inhibitor which was not approved by the FDA due to angiodema concerns, utilizes an *endo* mode cyclization of a sulfur atom to yield a novel dipeptide mimetic (Scheme 1.29).^{51,52} A derivative of the homolog of cysteine (**128**), was oxidized to give the aldehyde **129**. Deprotection of the thiol and subsequent treatment with catalytic TFA gave the intermediate *N*-acyl iminium ion **130** which undergoes nucleophilic addition by sulfur to yield **131** as optically pure and in good yield. It has been

hypothesized that the stereospecificity of the reaction is due to the NH-Cbz group adopting a thermodynamically more stable equatorial conformation in the transition state.⁵³



Scheme 1.29

1.3 Conclusions

Asymmetric *N*-acyl iminium ion cyclizations have been and continue to be important transformations in the synthesis of natural products and novel bioactive compounds. *N*-Acyl iminium ion cyclizations owe their utility to the fact they often possess high diastereoselectivities as well as good to excellent yields. It has been shown that cyclic *N*-acyl iminium ions can be synthesized through a number of different ways and can also be used to produce both carbocyclic and heterocyclic 4, 5, 6, & 7-membered rings. Because of the wide scope of applications, *N*-acyl iminium ion cyclizations continue to be a subject of interest.

CHAPTER 2

ASYMMETRIC SYNTHESIS OF ACYCLIC 1,3-AMINO ALCOHOLS. FORMAL SYNTHESIS OF (-)-PINIDINOL AND (+)-EPIPINIDINOL

2.1 Introduction

Acyclic 1,3-amino alcohols are important structural features of many medicinal compounds. These compounds include HIV protease inhibitors,⁵⁴⁻⁵⁶ μ -opioid receptor agonists,⁵⁷ the potent antibiotic, negamycin^{58,59} and serotonin reuptake inhibitor antidepressants.⁶⁰ This functionality has also been used in the studies of mutagenic deoxyguanosine oligonucleotides (Figure 2.1).⁶¹

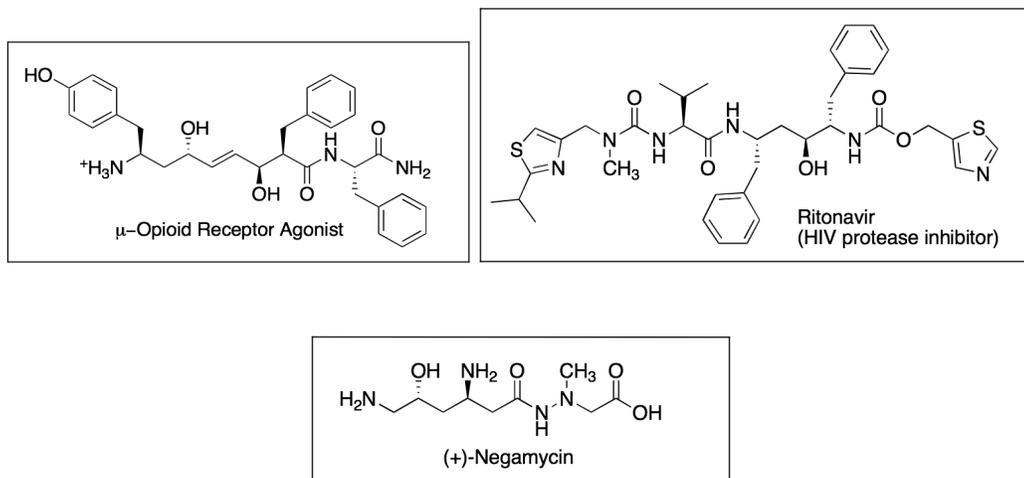
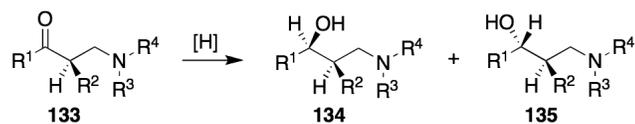


Figure 2.1: Examples of Biologically Active 1,3-Amino Alcohols

In addition to the use of 1,3-amino alcohols in medicinal chemistry, many natural products such as the sedum alkaloids,⁶² paliclavine,⁶³ and marine sponge toxin, dysiherbaine,⁶⁴ contain this moiety. 1,3-Amino alcohols are also useful chiral building blocks in asymmetric synthesis.⁶⁵ Here, the functionality induces chirality through its use as a chiral ligand or chiral auxiliary.

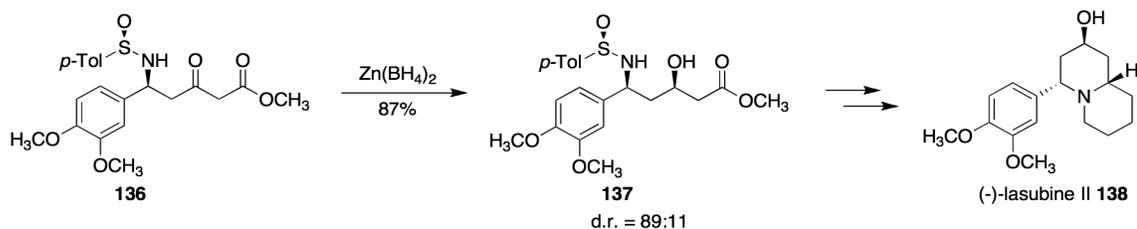
1,3-Amino alcohols have been described in several racemic syntheses which include reductions of β -amino ketones,⁶⁶⁻⁶⁹ reductions of β -hydroxy imines and oximes,⁷⁰⁻⁷² as well as the addition of organometallic reagents to β -amino aldehydes and ketones.⁷³ On the other hand, even with 1,3-amino alcohols being an important functionality, few general methods exist in the literature for their asymmetric synthesis.⁷⁴⁻⁷⁹ This lack of general methodology most likely arises from a lack of enantiomerically pure precursors. The published methodology for the synthesis of enantiomerically enriched 1,3-amino alcohols starting from acyclic precursors will be briefly described below.

In a published review by Tramontini on the stereoselective reductions of various chiral amino ketones, few examples are reported that describe the reduction of acyclic precursors.⁷⁴ The examples that are reported describe reductions of 1,3-amino ketones of type **133** to produce 1,3-amino alcohols **134** and **135** (Scheme 2.1). However, these contain chiral substitutions alpha to the carbonyl and no examples are reported whereby a methylene group is present. In addition, there are no examples that contain an elongation of the carbon chain alpha to the tertiary amine.



Scheme 2.1

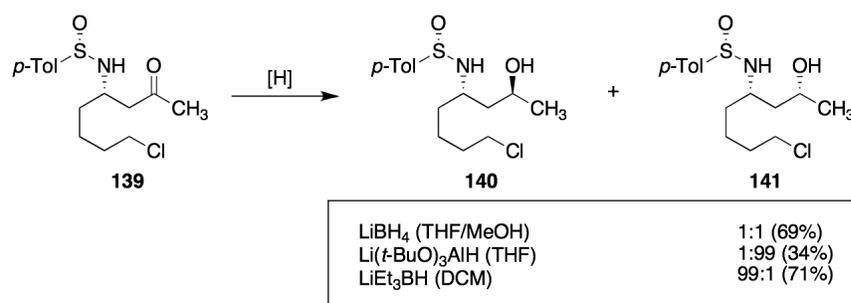
In the synthesis of the quinolizidine alkaloid, (-)-lasubine II (**138**), Davis and coworkers utilized a chelation-controlled stereoselective reduction of an *N*-sulfinyl α -amino β -keto ester **136** with zinc borohydride (Scheme 2.2). This chemoselective reaction yielded the *syn* 1,3-amino alcohol **137** in a 89:11 diastereomeric ratio.⁷⁵ The *syn* isomer was isolated and carried on to the natural product.



Scheme 2.2

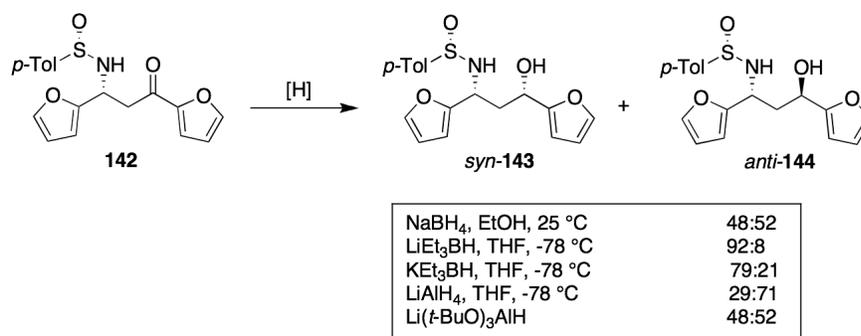
Again in the Davis laboratory, both *syn* and *anti* 1,3-amino alcohols were prepared from *N*-sulfinyl 1,3-amino ketones for the total synthesis of (+)-sedridine and (-)-

allosedridine.⁷⁶ In this procedure, the *anti* 1,3-amino alcohol **140** was produced through the reduction of the 1,3-amino ketone **139** with lithium triethyl borohydride (Super Hydride™) and the *syn* product **141** was produced through the reduction with lithium tri-*tert*-butoxy aluminumhydride in tetrahydrofuran, albeit in low yields (Scheme 2.3).



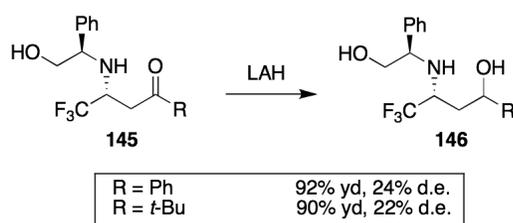
Scheme 2.3

Kennedy and coworkers described the stereoselective reduction of enantiopure difuran *N*-sulfinyl β -amino ketones **142** to give **143** and **144** as the corresponding *syn* and *anti* 1,3-amino alcohols, respectively (Scheme 2.4).⁷⁸ They reported here that lithium triethylborohydride gave the *syn* product predominantly while lithium aluminum hydride was selective for the *anti* product. The outcome of these experiments were opposite to what had been reported in other literature examples.^{67,75,76}



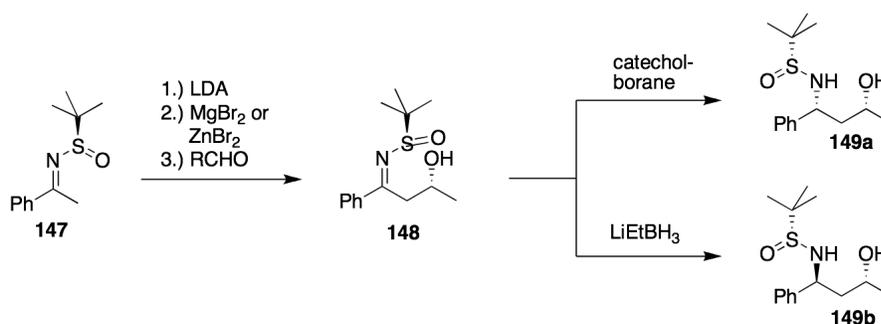
Scheme 2.4

Lastly, a report by Huguenot and coworkers describing the reductions of enantiopure β -trifluoromethyl β -amino ketones **145** with lithium aluminum hydride produced good yields but showed only moderate selectivity (Scheme 2.5).⁷⁹ Although the *syn* and *anti* diastereomers of **146** were separable, the authors were unable to determine the exact configuration of each isomer.



Scheme 2.5

In an analogous reaction, Ellman and co-workers found that the stereoselective reduction of enantiopure sulfinimine-derived β -hydroxyl *N*-sulfinyl imines **148** gives *syn* and *anti*-1,3-amino alcohols **149** in high diastereomeric ratio (Scheme 2.6).⁸⁰ Because the β -hydroxyl *N*-sulfinyl imines **148** must be prepared by aza-enolate addition of ketone-derived sulfinimines **147** to aldehydes, this procedure may be limited when an aliphatic chain containing additional functionalities is utilized in place of the phenyl group.^{80,81}

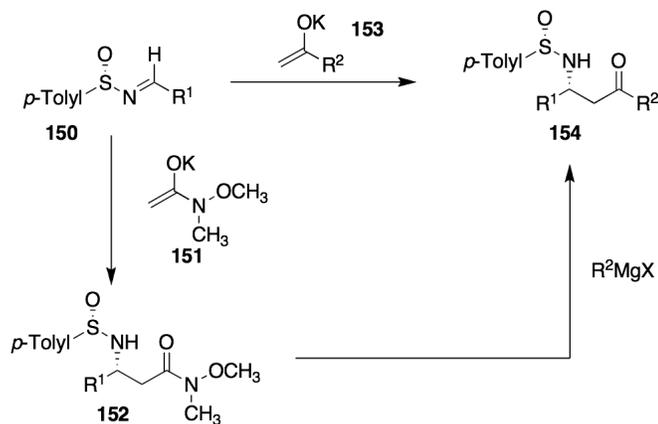


Scheme 2.6

Due to its ease of synthesis, β -amino ketone reductions offer the highest potential for the asymmetric synthesis of acyclic *syn* and *anti* 1,3-amino alcohols. Again, the advantages are in its ease of preparation and that they can be derived from a common precursor. However this procedure has not found general utility because there is a lack of diverse and enantiopure β -amino ketones.⁷⁵⁻⁷⁷ Acyclic enantiopure β -amino ketones **154** are readily available by the addition of Grignard reagents to sulfinimine-derived β -amino Weinreb amides **152**^{75,76,174,175} or by the addition of methyl ketone enolates **153** to sulfinimines (*N*-

sulfinyl imines) **150** (Scheme 2.7).¹⁶³ It is through this methodology that enantiopure β -amino ketones were produced for the investigation of asymmetric 1,3-amino alcohol synthesis

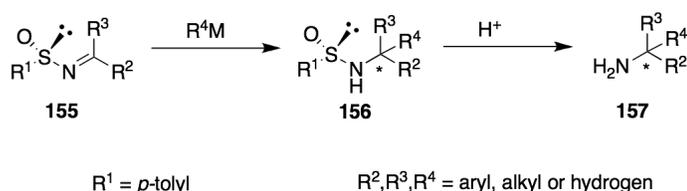
In order to obtain chiral *N*-sulfinyl β -amino ketones, the relevant chiral *N*-sulfinyl β -amino Weinreb amide precursors must first be synthesized. These β -amino Weinreb amides are sulfinimine-derived chiral building blocks that are prepared by the addition of a Weinreb amide enolate **151** to a sulfinimine **150** or by the reaction of lithium *N,O*-dimethylhydroxylamine with *N*-sulfinyl β -amino esters.^{85,86,169} In this chapter, the synthesis of enantiopure 1,3-amino alcohols from *N*-sulfinyl β -amino ketones and their application to the synthesis of (-)-pinidinol and (+)-epipinidinol are described.



Scheme 2.7

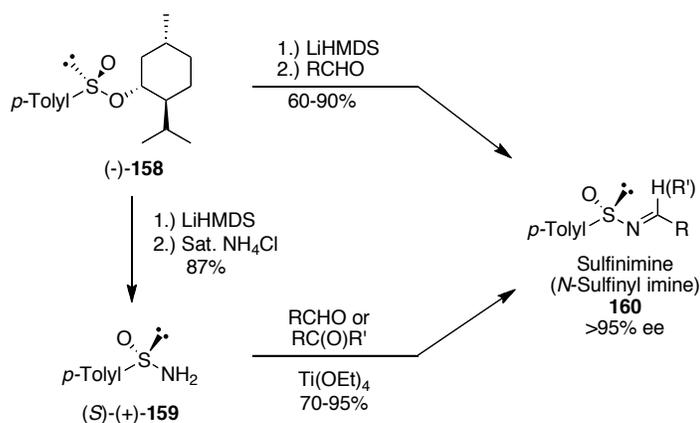
2.2 Sulfinimine (*N*-Sulfinyl Imine) Chemistry

A major component of modern, biologically relevant molecules is that of a chiral, nonracemic amine group.¹³⁰ It has been reported in the MDL drug library at Stanford University that 294 out of 1168 total drugs launched in the past 100 years contain chiral amines.¹³¹ Therefore, it is of great importance to develop new methodologies for the synthesis of chiral amine-containing compounds. Enantiopure sulfinimines (*N*-sulfinyl imines) **155**, developed by Davis and coworkers, have been shown to be excellent electrophiles for organo metallic additions (Scheme 2.8).¹³² The electron-withdrawing ability of the chiral *N*-sulfinyl auxiliary promotes stereospecific addition as well as increased electrophilicity of the imine carbon. The sulfinamide products **156** are quite stable and are also unlikely to undergo epimerization since the sulfinyl group stabilizes a nitrogen anion. Furthermore, because of the *N*-sulfinyl group's ability to stabilize nitrogen anions, it therefore acts as a protecting group, which can be removed under mild conditions without causing epimerization or decomposition of the amine products **157**.



Scheme 2.8

Sulfinimines **160** are prepared in a facile manner from (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl-4-methylbenzenesulfinate (Andersen's reagent) (**158**) in a one-pot procedure (Scheme 2.9).¹³³ From *para*-toluenesulfonamide **159**, which is derived from Andersen's reagent in one step, an improved synthetic route can be obtained that gives greater yields of the sulfonamide in fewer steps. This is due, in part, to the ease at which the Andersen's reagent diastereomers can be purified via recrystallization in cold acetone. Sulfonamide **159** reacts with a multitude of different aldehydes and ketones in the presence of titanium(IV) ethoxide or molecular sieves to give sulfinimines **160** in good to excellent yields.^{134,135} Enantiopure sulfinimines have been utilized in numerous asymmetric syntheses. These include the asymmetric synthesis of amines,¹³⁶⁻¹³⁸ α - and β -amino acids,¹³⁹⁻¹⁴⁸ α - and β -amino phosphonates,¹⁴⁹⁻¹⁵¹ aziridine carboxylates,¹⁵²⁻¹⁵⁸ δ -amino β -keto esters,¹⁵⁹⁻¹⁶² β -amino ketones,¹⁶³ isoquinolines,¹⁶⁴⁻¹⁶⁶ and *syn* and *anti*- α,β -diaminoesters (Figure 2.2).^{167,168}



Scheme 2.9

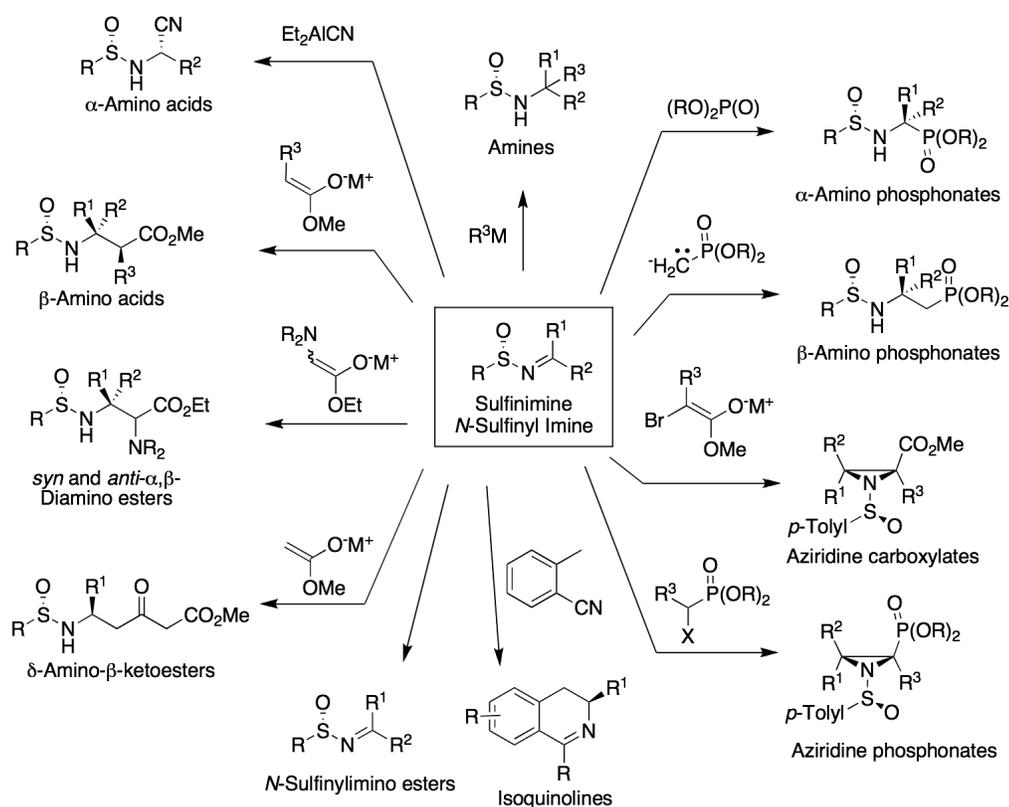
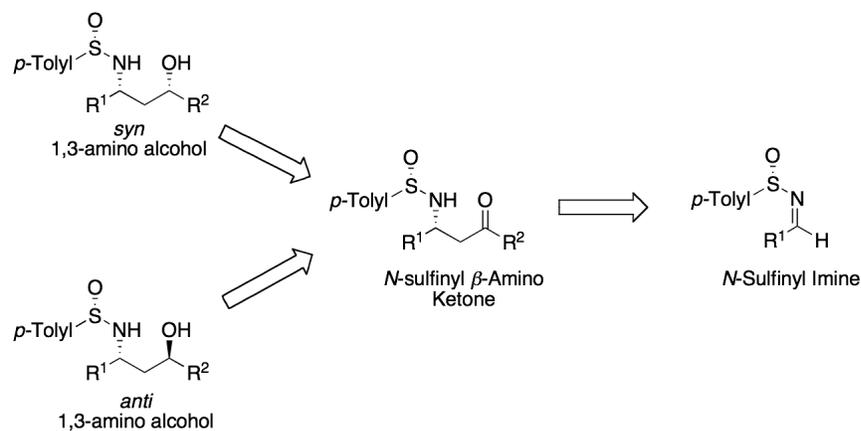


Figure 2.2: Applications of Sulfinimines

2.3 Present Study

The general features of 1,3-amino alcohol synthesis from sulfinimines is outlined in Scheme 2.10. This strategy involves the synthesis of chiral β -amino ketones, which are stereoselectively reduced to give either the *syn* or *anti* 1,3-amino alcohol. Chiral β -amino ketones are synthesized through reaction of a *N*-sulfinyl β -amino Weinreb amide with a Grignard reagent or through ketone enolate addition to a sulfinimine.



Scheme 2.10

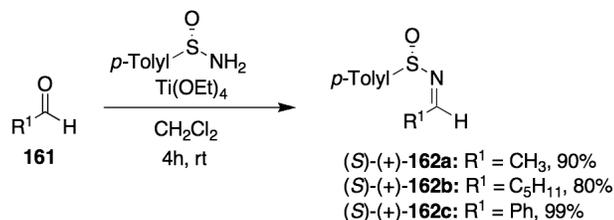
2.3.1 Synthesis of Chiral *Syn* and *Anti* 1,3-Amino Alcohols

2.3.1.1 Preparation of Sulfinimines

To obtain chiral *N*-sulfinyl β -amino ketones, the corresponding sulfinimine precursors need to be synthesized from their respective aldehydes. In addition, a general procedure for the synthesis of chiral 1,3-amino alcohols must allow for easy derivatization of R^1 since its effect on the diastereoselective reduction of β -amino ketones must be investigated (Scheme 2.11). For example, a methyl and a longer pentyl chain will be used to study the effect of aliphatic groups and a phenyl group will also be used for R^1 to study the effect of aryl groups on the diastereoselective reductions.

Acetaldehyde (**161a**) was reacted in the usual fashion with (*S*)-(+)-*p*-toluene sulfinamide and $\text{Ti}(\text{OEt})_4$ to yield (*S*)-(+)-**162a** in a 90% yield (Scheme 2.11).^{87,88} A sulfinimine derivative bearing an aliphatic pentyl chain for R^1 , (*S*)-(+)-**162b**, was likewise

synthesized from *n*-hexanal (**161b**) in 80% yield after chromatography. Finally aryl sulfinimine derivative (*S*)-(+)-**162c** where R¹ = Ph was synthesized from benzaldehyde (**161c**) in a 99% yield.^{87,88}

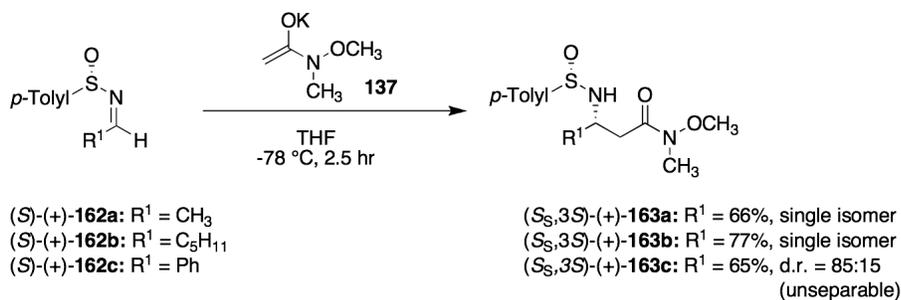


Scheme 2.11

2.2.1.2 Synthesis of *N*-Sulfinyl β -Amino Weinreb Amides

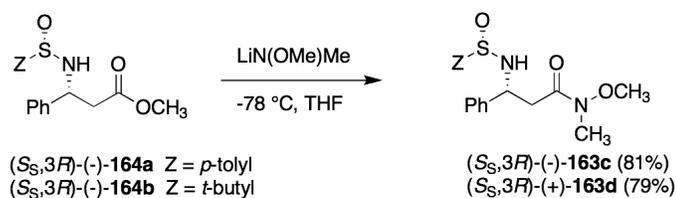
As previously mentioned, the synthesis of *N*-sulfinyl β -amino ketone derivatives requires that the *N*-*para*-toluenesulfinyl Weinreb amides must first be prepared (Scheme 2.12). In general, this task was accomplished by adding a solution of sulfinimine to a cooled solution of the potassium enolate of *N*-methoxy-*N*-methylacetamide (**151**) in THF at -78 °C for 2.5 hours. When R¹ is a methyl group or aliphatic chain, sulfinimine (*S*)-(+)-**162a** and (*S*)-(+)-**162b** both give the product as a single diastereomer in 66% and 77% yields, respectively. However, when R¹ = phenyl, this reaction produces the product with a d.r. of 80:20 in 65% yields with the diastereomers not being able to be separated.¹⁷⁴ An alternate procedure from the β -amino ester was used to prepared this Weinreb amide and is given below (Scheme 2.13). The configuration of the new chiral centers of the Weinreb amides

was assumed through previous established work on the addition of Weinreb amide enolates¹⁷⁴ to sulfinimines and also through the later synthesis of known compounds, (-)-pinidinol and (+)-epipinidinol.



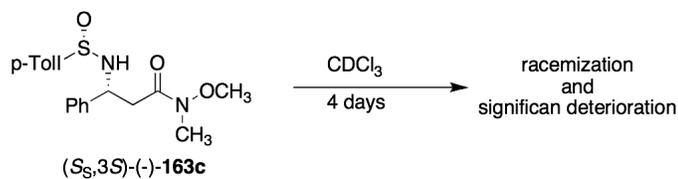
Scheme 2.12

As previously reported, Weinreb amide $(S_S,3S)$ -(+)-**163c** and $(S_S,3R)$ -(+)-**163d** can be alternately prepared by the reaction of lithium *N,O*-dimethylhydroxylamine with methyl esters and $(S_S,3R)$ -(+)-**164a** and $(S_S,3R)$ -(-)-**164b** (Scheme 2.13).^{76,174} This is because in these cases, the addition of the enolate of methyl acetate to the sulfinimine produces a pure diastereomer whereas the addition of the Weinreb enolate produces an inseparable mixture of diastereomers. The Weinreb amide bearing the *tert*-butyl sulfinimine, $(S_S,3R)$ -(+)-*N*-(2-methylpropanesulfinyl)-3-amino-3-*N*-methoxy-*N*-methyl-3-phenylpropionamide (**163d**) was prepared to test the sulfinyl groups' ability in directing the stereoselective reductions of β -amino ketones.



Scheme 2.13

It was found that care must be taken when handling the Weinreb amide ($S_S, 3S$)-(-)-**163c** which was derived from benzaldehyde. It was discovered that ($S_S, 3S$)-(-)-**163c** was especially unstable towards unpurified stock deuterated chloroform when performing NMR analyses. Significant racemization and deterioration occurred with the appearance of both diastereomer peaks on NMR as well as the development of multiple spots on thin-layer chromatography (Scheme 2.14). This problem was corrected when fresh deuterated chloroform was passed through a column of basic alumina and the chloroform was subsequently stored over fresh alumina. Although the mechanism of this racemization and deterioration occurring is unknown, it is believed that residual ethyl chloroformate, chlorine and/or phosgene, which are known contaminants of chloroform, could perhaps catalyze these side reactions.



Scheme 2.14

2.3.1.3 Synthesis of *N*-Sulfinyl β-Amino Ketones

In order to optimize conditions for the stereoselective reductions, a variety of ketones need to be synthesized bearing various aryl and aliphatic groups at both the 1 and 3 positions of the corresponding *N*-sulfinyl β-amino ketones (Figure 2.3). As previously mentioned, changing the size of these substituents will provide information regarding the mechanism of *N*-sulfinyl 1,3-amino alcohol synthesis and of hydride addition to the carbonyl. Derivatizing the nitrogen protecting group as the *p*-toluenesulfinyl or *t*-butane sulfinyl group will provide data on how increasing the size of the *Z* group will affect *syn* or *anti* selectivity. Finally, installing a more polar *para*-toluenesulfonyl protecting group will demonstrate the importance of any electronic effects at the nitrogen atom by decreasing electron density.

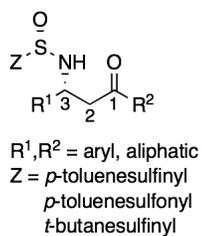
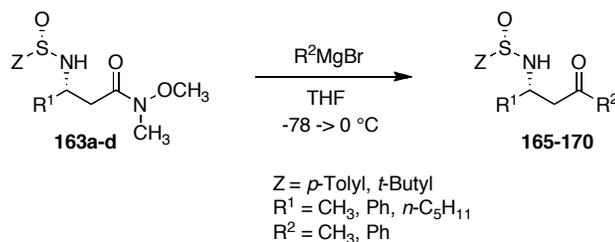


Figure 2.3: β -Amino Ketones

Treatment of *N*-sulfinyl- β -amino Weinreb amides **163a-d** with either five equivalents of phenyl magnesium bromide or methyl magnesium bromide gave the corresponding β -amino ketones **165-170** in good to excellent yields (Scheme 2.15). The results are summarized in Table 2.1 and Figure 2.4. The product, (*S_S*,3*S*)-(+)-*N*-(*para*-toluenesulfinyl)-3-amino-1-phenyl-3-methyl propanone (**165**) was obtained in 79% yield upon the reaction of phenylmagnesium bromide with Weinreb amide (*S_S*,3*S*)-(+)-**163a** (Table 2.1, entry 1). Likewise, methylmagnesium bromide was reacted with the pentyl-substituted Weinreb amide (*S_S*,3*S*)-(+)-**163b** to give the ketone (*S_S*,3*S*)-(+)-**166** in similar yields (Table 2.1, entry 2). This derivative will show how a long aliphatic chain might affect hydride addition with respect to a smaller methyl group. Varying R^2 as methyl or phenyl gives (*S_S*,3*R*)-(+)-**167** and (*S_S*,3*R*)-(+)-**168** from the phenyl substituted Weinreb amide (*S_S*,3*R*)-(+)-**163c**, respectively (Table 2.1, entries 3 & 4). Amino ketone (*S_S*,3*R*)-(+)-**169**, which contains the *t*-butanesulfinyl group as well as a phenyl group at R^1 and R^2 , was synthesized from (*S_S*,3*R*)-(+)-*N*-(2-methylpropanesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-3-phenylpropionamide (**163d**) in 83% yield by Peng Xu (Table 2.1, entry 5). Likewise, where R^1 is a phenyl group

but R² is methyl, the *tert*-butanesulfinyl containing amino ketone (S_S,3*R*)-(+)-**170** was similarly prepared from methylmagnesium bromide (Table 2.1, entry 6).



Scheme 2.15

Table 2.1: Synthesis of β -Amino Ketones By Reaction of Grignard Reagents with the Corresponding β -Amino Weinreb Amides^a

Entry	Weinreb amide	Grignard reagent ^b	β -amino ketone (% yield isolated)	R ¹	R ²	Z
1	(S _S ,3 <i>S</i>)-(+)- 163a (R = Me)	PhMgBr	(S _S ,3 <i>S</i>)-(+)- 165 (79)	CH ₃	Ph	<i>p</i> -tolyl
2	(S _S ,3 <i>S</i>)-(+)- 163b (R = <i>n</i> -C ₅ H ₁₁)	MeMgBr	(S _S ,3 <i>S</i>)-(+)- 166 (77)	C ₅ H ₁₁	CH ₃	<i>p</i> -tolyl
3	(S _S ,3 <i>R</i>)-(+)- 163c (R = Ph)	MeMgBr	(S _S ,3 <i>R</i>)-(+)- 167 (92) ^c	Ph	CH ₃	<i>p</i> -tolyl
4	(S _S ,3 <i>R</i>)-(+)- 163c (R = Ph)	PhMgBr	(S _S ,3 <i>R</i>)-(+)- 168 (84) ^c	Ph	Ph	<i>p</i> -tolyl

5	(<i>S</i> _S ,3 <i>R</i>)-(+)- 163d	PhMgBr	(<i>S</i> _S ,3 <i>R</i>)-(+)- 169	Ph	Ph	<i>t</i> -butyl ^d
	(R = Ph)		(83)			
6	(<i>S</i> _S ,3 <i>R</i>)-(+)- 163d	MeMgBr	(<i>S</i> _S ,3 <i>R</i>)-(+)- 170	Ph	CH ₃	<i>t</i> -butyl ^d
	(R = Ph)		(81) ^c			

^a All reactions were performed in THF as solvent at -78 to 0 °C for 2 hours. ^b Five equivalents of Grignard reagent were used. ^c Reference 128 ^d Synthesized by Peng Xu.

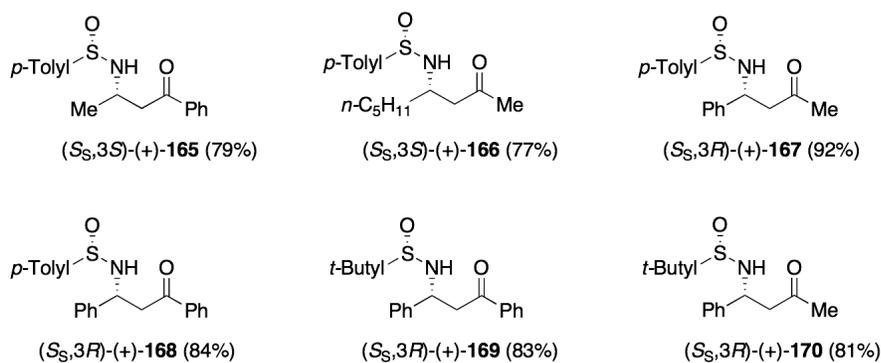
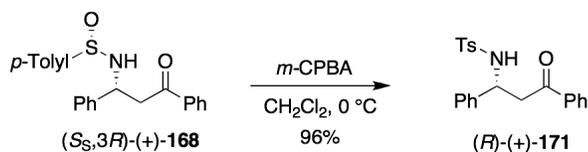


Figure 2.4: Ketones from the Reactions of *N*-Sulfinyl Weinreb Amides with Grignard Reagents

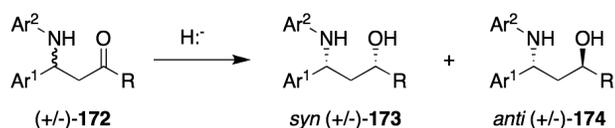
Oxidation of (*S*_S,3*R*)-(+)-*N*-(*para*-toluenesulfinyl)-3-amino-1,3-diphenylpropan-1-one (**168**) with *meta*-chloroperoxybenzoic acid produces (*R*)-(+)-*N*-(*p*-toluenesulfonyl)-3-amino-1,3-diphenylpropan-1-one (**171**) as a crystalline solid in 96% yield. This derivative contains a more electron-withdrawing nitrogen protecting group which is useful in studying transition state electronic effects of the nitrogen atom (Scheme 2.16).



Scheme 2.16

2.2.1.4 Reductions of *N*-Sulfinyl β -Amino Ketones

Pilli and coworkers performed an analysis of the stereoselective reductions of various racemic 1,3-amino ketones in 1990 using Super Hydride™ to yield *anti* 1,3-amino alcohols and zinc borohydride to yield *syn* 1,3-amino alcohols.⁶⁷ These racemic amino ketones contained a phenyl or a *para*-nitrophenyl at Ar¹, a phenyl or *para*-chloro phenyl group on the nitrogen (Ar²) and various aliphatic substituents at R (Scheme 2.17). Several examples are shown below which highlighted the scope of their results (Table 2.2). The variation of Ar¹ and Ar² did not change the diastereoselectivities, but variation in the R group did produce a noticeable change in the diastereomeric ratios. For example, when R is a large *t*-butyl group, good selectivities were observed for both the *anti* and *syn* products (Table 2.2, entry 1). The best results for *anti* selectivities were seen when R and Ar¹ are both phenyl and Ar² is a *para*-chloro phenyl group (Table 2.2, entry 2). Interestingly, *anti* selectivity suffered the most when R was changed to an isobutyl group but good *syn* selectivity still remained (Table 2.2, entry 3). When R was changed to a small methyl group, *syn* selectivity was diminished however decent *anti* selectivity remained (Table 2.2, entry 4).



Scheme 2.17

Table 2.2: Reduction of Racemic β -Amino Ketones by Pilli and Coworkers⁶⁷

entry	Ar ¹	Ar ²	R	LiEt ₃ BH ^{a,b}	Zn(BH ₄) ₂ ^{a,b}
1	Ph	Ph	<i>t</i> -Bu	18:82	82:18
2	Ph	<i>p</i> -ClPh	Ph	13:87	86:14
3	Ph	Ph	<i>i</i> -Bu	34:66	86:14
4	Ph	<i>p</i> -ClPh	CH ₃	20:80	66:34

^a Ratio of **159:160** ^b Performed in THF at -78 °C for 2 h.
 Performed in THF at 0 °C for 2 h.

They rationalized that the stereoselectivities depended only upon the bulk of the R group and they also proposed transition state models to explain their findings (Figure 2.5). Their findings supported their hypothesis that *anti* selectivity was observed when the reductive species poorly coordinated to the carbonyl and was left as an open chain (**TS 2.1**). The aryl group, which is covalently bound to the nitrogen, as well as the borane complex most likely blocks the approach of the hydride from one face. In the other model (**TS 2.2**), the R group has a repulsive steric interaction with Ar¹, which makes approach of the hydride from this face less favorable. By using a chelating reducing agent, such as zinc borohydride, which can coordinate strongly to the nitrogen anion and the carbonyl oxygen, a six-

membered cyclic transition state is formed whereby hydride attack occurs on the carbonyl face opposite to the nitrogen protecting group (**TS 2.3**).

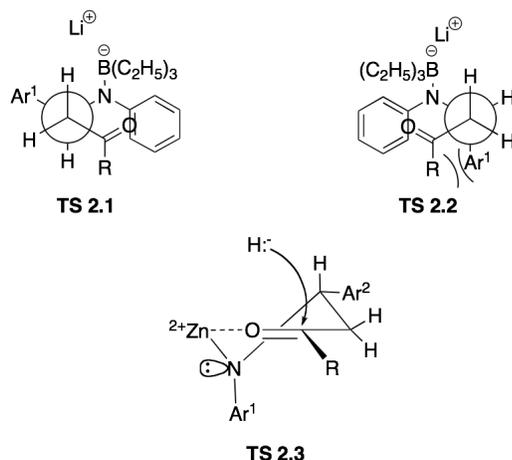


Figure 2.5: Proposed Transition States for *Syn* and *Anti* Reductions

It is noteworthy that similar cyclic chelated intermediates have been proposed to explain the *syn*-selectivity in the reductions of β -hydroxy oximes,⁷⁰ β -hydroxy imines,⁷² δ -hydroxy- β -keto esters⁸⁹ and β -hydroxy *N*-sulfinyl imines.⁸⁰ As mentioned above, there is literature precedence whereby several reductions of *N*-sulfinyl- β -amino ketones with Superhydride™ are reported to give *anti-N*-sulfinyl 1,3-amino alcohols.^{76,89} With zinc borohydride and lithium tri-*tert*-butoxyaluminumhydride, these amino ketones were shown to yield the *syn* products. However, zinc borohydride produced acceptable yields while the yields from lithium tri-*tert*-butoxyaluminumhydride suffered.^{76,159} It is likely that the transition states for asymmetric reductions of *N*-sulfinyl β -amino ketones are more complicated due to

the presence of the *N*-sulfinyl group. These corresponding transition states are proposed and shown below as **T.S.-2.4** and **T.S.-2.5**, which can be evoked to explain the observed selectivities (Figure 2.6). Here, the *Z* group (*para*-toluene or *tert*-butyl) blocks one face of the carbonyl giving *anti* selectivity (**TS-2.4**) and the six-membered transition state leading to the *syn* diastereomer could be enhanced by additional coordination of the sulfinyl oxygen (**TS-2.5**).

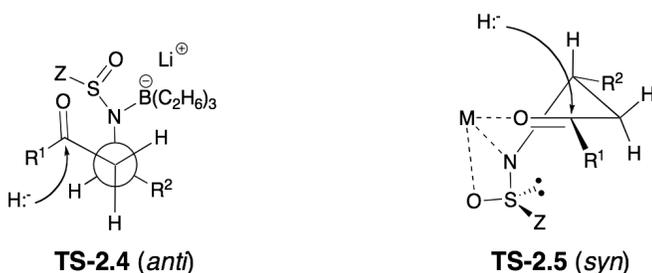
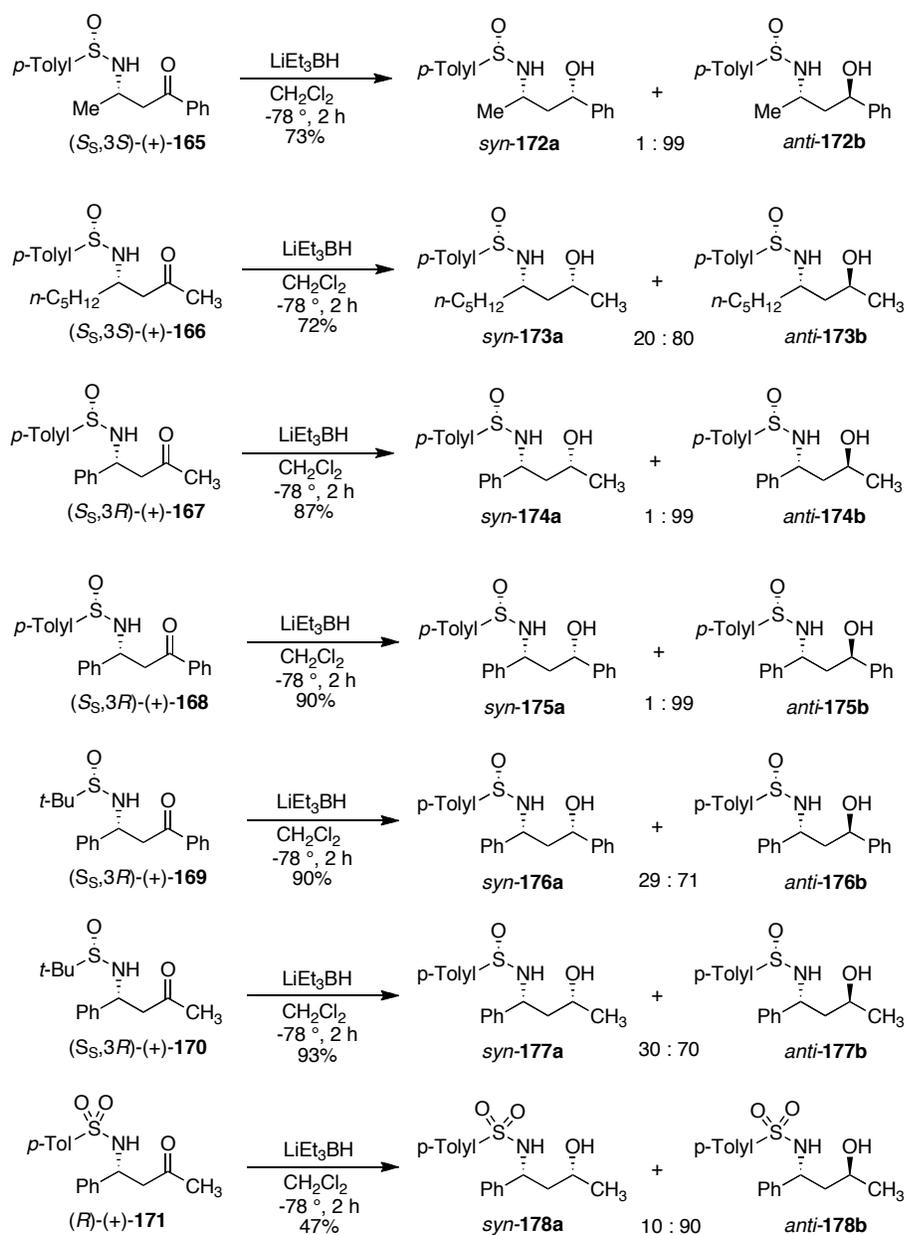


Figure 2.6: Transition states for reduction of β -amino ketones to either *anti* or *syn* 1,3-amino alcohols.

When *N*-(*p*-toluenesulfinyl)- β -amino ketones ($S_S,3S$)-(+)-**165**, ($S_S,3S$)-(+)-**166**, ($S_S,3R$)-(+)-**167** and ($S_S,3R$)-(+)-**168** were reduced with lithium triethyl borohydride at -78 °C in methylene chloride, the *anti* 1,3-amino alcohols **173** were obtained as the major diastereomer, consistent with **T.S. 2.4** (Scheme 2.18) (Figure 2.6). When lithium triethyl borohydride was used as the reducing agent and either R^1 or R^2 was a phenyl group, a single diastereomer was obtained in good yields (Table 2.3, entries 1, 3 and 4). The diastereomeric

ratio of the *syn/anti* selectivity was reduced to 20:80 when both R¹ and R² are aliphatic groups such as with (S_S,3S)-(+)-**166** (R¹ = *n*-C₅H₁₂, R² = CH₃) (Table 2.3, entry 2). Although these selectivities are better than those reported by Pilli and coworkers, the fact that a reduced diastereomeric ratio was observed when R¹ and R² are smaller groups agrees with proposed transition state (TS 2.1 & TS 2.4). Lower *anti* selectivity is also observed when the substituent on nitrogen is the more bulky *N*-(2-methylpropane)sulfinyl or the more electron withdrawing *N*-*p*-toluenesulfonyl group as in (S_S,3R)-(+)-**169** (Z = *t*-butanesulfinyl, R¹ = Ph, R² = Ph), (S_S,3R)-(+)-**170** (Z = *t*-butanesulfinyl, R¹ = Ph, R² = CH₃) and (R)-(+)-**171** (Z = *p*-toluenesulfonyl, R¹ = Ph, R² = CH₃) which were synthesized by Peng Xu (Table 2.3, entries 5, 6 and 7). The diastereomeric ratios for these reactions are 29:71, 30:70 and 1:9, respectively. The increased bulk of the *N*-(2-methylpropane)sulfinyl group might cause a greater Z-R steric interaction (TS-2.4) which could force the transition state increasingly to the other conformation (TS-2.2). In addition, the increased electron-withdrawing capability of the *N*-*p*-toluenesulfonyl group may retard the coordination ability of lithium triethylborohydride to the nitrogen atom, which would allow for delivery of the hydride from both the *Re* and *Si* faces of the carbonyl group. If it is truly both the nitrogen protecting group and the triethylborane complex that blocks hydride attack from one face (TS 2.1 & TS 2.4), then the lack of the nitrogen-borane complex, which is due to nitrogen's inability to donate its anionic character to the boron atom, would reduce the overall blocking effect.



Scheme 2.18

Table 2.3: Reduction of *N*-Sulfinyl β -Amino Ketones with Lithium Triethyl Borohydride (Super Hydride™)



entry	β -amino ketone	solvent	R ¹	R ²	product <i>syn/anti</i> (dr) ^a	% yield ^b
1	(<i>S</i> _S ,3 <i>S</i>)-(+)- 165	CH ₂ Cl ₂	CH ₃	Ph	172a:172b (1:99)	73
	<i>Z</i> = <i>p</i> -toluenesulfinyl					
2	(<i>S</i> _S ,3 <i>S</i>)-(+)- 166	CH ₂ Cl ₂	C ₃ H ₁₁	CH ₃	173a:173b (20:80)	72
	<i>Z</i> = <i>p</i> -toluenesulfinyl					
3	(<i>S</i> _S ,3 <i>R</i>)-(+)- 167	CH ₂ Cl ₂	Ph	CH ₃	174a:174b (1:99)	87
	<i>Z</i> = <i>p</i> -toluenesulfinyl					
4	(<i>S</i> _S ,3 <i>R</i>)-(+)- 168	CH ₂ Cl ₂	Ph	Ph	175a:175b (1:99)	90
	<i>Z</i> = <i>p</i> -toluenesulfinyl					
5	(<i>S</i> _S ,3 <i>R</i>)-(+)- 169	CH ₂ Cl ₂	Ph	Ph	176a:176b (29:71)	90 ^{c,d}
	<i>Z</i> = <i>t</i> -butanesulfinyl					
6	(<i>S</i> _S ,3 <i>R</i>)-(+)- 170	CH ₂ Cl ₂	Ph	CH ₃	177a:177b (30:70)	93 ^d
	<i>Z</i> = <i>t</i> -butanesulfinyl					
7	(<i>R</i>)-(+)- 171	CH ₂ Cl ₂	Ph	CH ₃	178a:178b (10:90)	47 ^d
	<i>Z</i> = <i>p</i> -toluenesulfonyl					

^a Determined by ¹H NMR on the crude reaction mixture. ^b Isolated yield of major diastereomer unless otherwise noted. ^c Inseparable and represents a Combined yield of both diastereomers. ^d Synthesized by Peng Xu.

High *syn* selectivity was more difficult to achieve via asymmetric reductions of *N*-sulfinyl β -amino ketones as compared to *anti* selectivities. In this case, the best *syn* selectivities for *N*-*p*-toluenesulfinyl β -amino ketones were achieved with lithium tri-*tert*-butoxy aluminumhydride in diethyl ether, regardless of the size of R¹ or R² (Scheme 2.19) (Table 2.4). The *syn/anti* selectivities for these reductions ranged from 4:1 to 9:1 and yields ranged from 60-90% (Table 2.19, entries 1-4). The worst selectivity for an *N*-*p*-toluenesulfinyl β -amino ketone again was seen when R¹ and R² are both small aliphatic groups (R¹ = *n*-C₅H₁₁, R² = CH₃) (Table 2.19, entry 2). This highlights the importance of the size of R² in directing hydride addition; when R¹ is a small methyl group but R² is a larger phenyl group as with (*S*₈,*3S*)-(+)-**165**, the diastereomeric ratio is 9:1 (Table 2.19, entry 1). Also, when R¹ is a phenyl group and R² is a methyl high *syn* selectivity is maintained (Table 2.19, entry 3). However, when both R¹ and R² are large phenyl groups, the diastereoselectivities were reduced to 85:15. Excellent *syn* selectivity (d.r. = 99:1) is obtained when the nitrogen protecting group was a *t*-butyl sulfinamide no matter if R¹ is methyl or phenyl (Table 2.19, entries 5 & 6). This increase of *syn* selectivity is most likely produced directly from the bulkier *N*-sulfinyl protecting group and gives evidence for a steric effect of the nitrogen protecting group in directing *syn* attack. It is highly probable that the sulfinyl group primarily dictates the approach of the hydride as the bulkier *tert*-butyl group effectively blocks hydride approach from one side (Figure 2.4). As for the *N*-*para*-toluenesulfonyl group, the selectivity is greatly diminished and has a d.r. of 55:45 as a mixture of inseparable isomers (Table 2.19, entry 7). These results most likely arise from the decreased electron density on the nitrogen anion. As electron density decreases at the

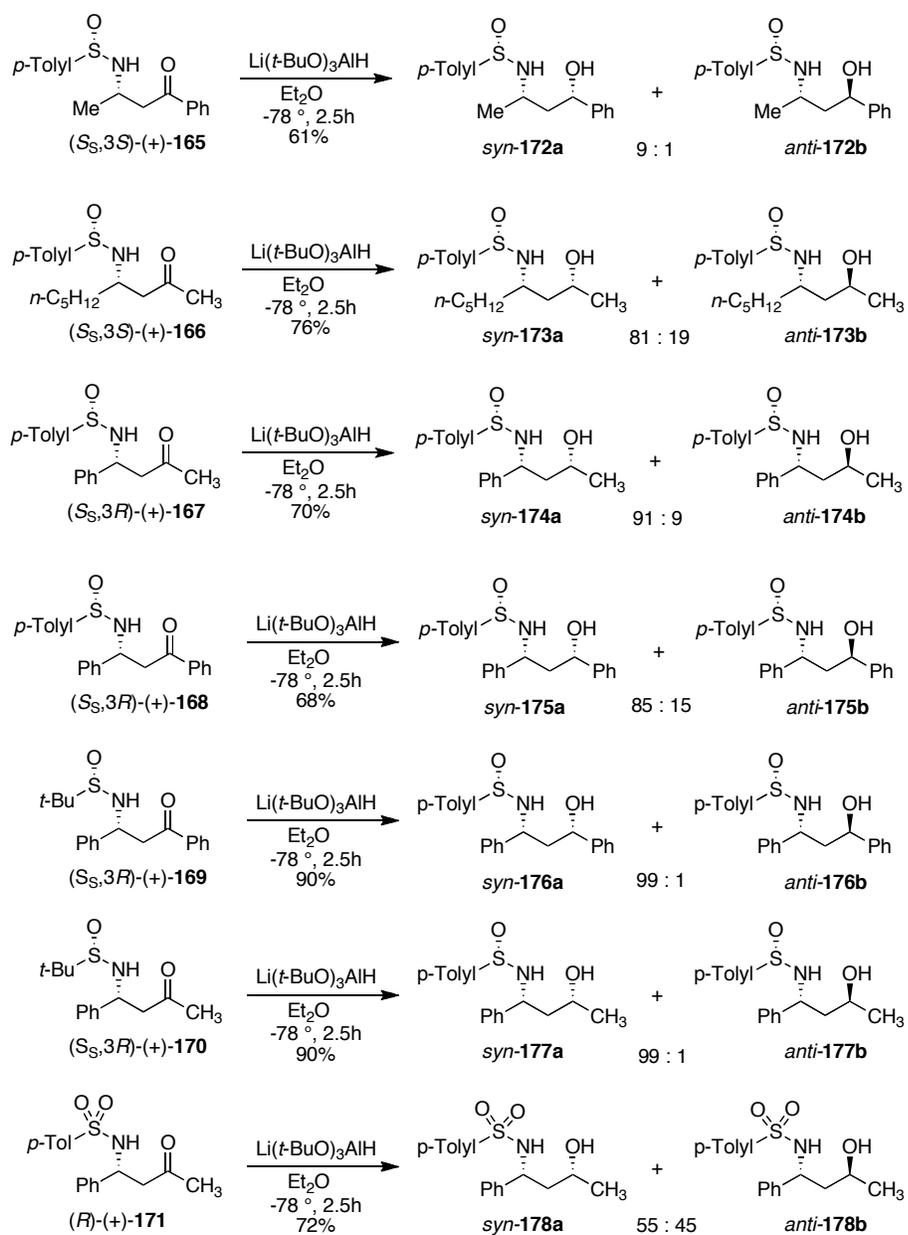
nitrogen anion, its ability to coordinate to the lithium or aluminum atom in the six-membered transition state also decreases (**TS-2.5**).

Table 2.4: Reduction of β -Amino Ketones at $-78\text{ }^{\circ}\text{C}$ with $\text{Li}(t\text{-BuO})_3\text{AlH}$



entry	β -amino ketone	solvent	R ¹	R ²	product <i>syn/anti</i> (dr) ^a	% yield ^b
1	(<i>S</i> _S ,3 <i>S</i>)-(+)- 165 <i>Z</i> = <i>p</i> -toluenesulfinyl	Et ₂ O	CH ₃	Ph	172a:172b (9:1)	61
2	(<i>S</i> _S ,3 <i>S</i>)-(+)- 166 <i>Z</i> = <i>p</i> -toluenesulfinyl	Et ₂ O	C ₅ H ₁₁	CH ₃	173a:173b (81:19)	76
3	(<i>S</i> _S ,3 <i>S</i>)-(+)- 167 <i>Z</i> = <i>p</i> -toluenesulfinyl	Et ₂ O	Ph	CH ₃	174a:174b (91:9)	70
4	(<i>S</i> _S ,3 <i>R</i>)-(+)- 168 <i>Z</i> = <i>p</i> -toluenesulfinyl	Et ₂ O	Ph	Ph	175d:175d (85:15)	68 ^c
5	(<i>S</i> _S ,3 <i>R</i>)-(+)- 169 <i>Z</i> = <i>t</i> -butanesulfinyl	Et ₂ O	Ph	Ph	176d:176d (99:1)	90 ^c
6	(<i>S</i> _S ,3 <i>R</i>)-(+)- 170 <i>Z</i> = <i>t</i> -butanesulfinyl	Et ₂ O	Ph	CH ₃	177c:177c (99:1)	90
7	(<i>R</i>)-(+)- 171 <i>Z</i> = <i>p</i> -toluenesulfonyl	Et ₂ O	Ph	CH ₃	178:178 (55:45)	72 ^{c,d}

^a Determined by ¹H NMR on the crude reaction mixture. ^b Isolated yield of major diastereomer unless otherwise noted. ^c Synthesized by Peng Xu. ^d Inseparable and represents a combined yield of both diastereomers.



Scheme 2.19

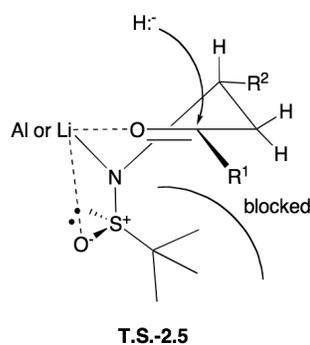
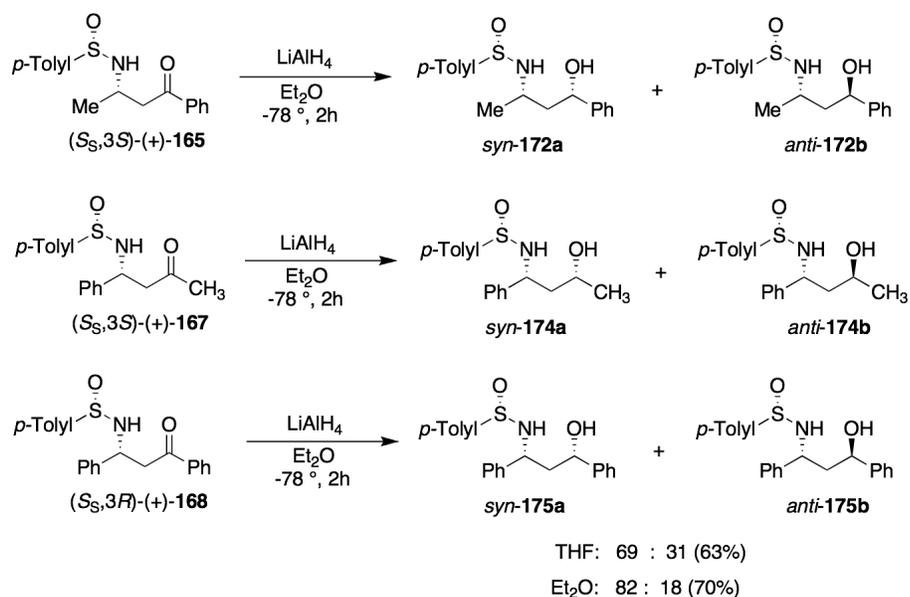


Figure 2.7: Proposed transition state **T.S.-2.5** for *syn* reductions of *N-t*-butanesulfinyl β -amino ketones

An interesting phenomena was observed when the solvent was varied for the *syn* selective reduction of (*S*_s,3*S*)-(+)-**167** with lithium tri-*tert*-butoxyaluminum hydride (Table 2.5). It appears that as the dielectric constant of a coordinating ether solvent was increased, such as with diethyl ether ($\epsilon = 4.33$) versus tetrahydrofuran ($\epsilon = 7.58$), the diastereomeric ratio decreased (Table 2.5, entries 1 & 2). Tetrahydrofuran produced only a 2:1 *syn/anti* ratio of inseparable isomers instead of the 9:1 ratio produced in diethyl ether. Methylene chloride, although having a higher dielectric constant than tetrahydrofuran, again produced a 9:1 ratio of *syn/anti* isomers (Table 2.5, entry 3).¹⁸² Toluene, also being an organic solvent with a low dielectric constant, produced consistent results with a 9:1 *syn/anti* ratio. Selectivities of lithium tri-*tert*-butoxy aluminumhydride to produce the *syn* isomer most likely depend upon the ability of the nitrogen anion and carbonyl oxygen to coordinate to the lithium cation and therefore maintain the six-membered transition state. Tetrahydrofuran molecules most likely solvate the lithium cation and prevent this intramolecular chelation thereby reducing *syn* selective hydride attack.

sulfinyl β -amino ketone ($S_S,3S$)-(+)-**165** or ($S_S,3R$)-(+)-**166**, respectively (Table 2.6, entries 1 & 2) with ($S_S,3R$)-(+)-**167** giving less overall yield (50%) (Table 2.6, entry 2). These results suggest that the size of R^1 and R^2 group must play a role in directing hydride attack. A bulky R^1 group most likely assists in blocking the hydride delivery from the *re* face. When R^2 is small, as with a methyl group in ($S_S,3S$)-(+)-**166**, the six-membered transition state could achieve two conformations which successfully receive delivery of the hydride in theory (Figure 2.8). Since lithium aluminum hydride is a smaller reducing agent than lithium tri-*tert*-butoxyaluminum hydride, it might possess a greater chance of delivering the hydride from the *re* face when the methyl group is in a pseudoaxial position (**TS-2.8**). Hydride delivery from the *si* face gives the expected *syn* product. Again, using a coordinating solvent with a higher dielectric constant produces a mixture of diastereomers with diminished *syn* selectivity (Table 2.6, entry 4). Tetrahydrofuran was shown to be a poor solvent for performing *syn* selective reductions with both lithium aluminum hydride as well as lithium tri-*tert*-butoxyaluminumhydride.



Scheme 2.20

Table 2.6: Reduction of β -Amino Ketones at $-78\text{ }^{\circ}\text{C}$ with LiAlH_4

entry	β -amino ketone	reducing agent (eq)	solvent	product <i>syn/anti</i> (dr) ^a	% yield ^b
1	(<i>S_S,3S</i>)-(+)- 165	LAH (3)	Et ₂ O	172a:172b (65:35)	70 ^c
2	(<i>S_S,3S</i>)-(+)- 167	LAH (3)	Et ₂ O	174a:174b (65:35)	50 ^c
3	(<i>S_S,3R</i>)-(+)- 168	LAH (3)	Et ₂ O	175a:175b (82:18)	70 ^c
4	(<i>S_S,3R</i>)-(+)- 168	LAH (3)	THF	175a:175b (69:31)	63 ^c

^a Determined by ¹H NMR on the crude reaction mixture. ^b Isolated yield of major diastereomer unless otherwise noted. ^c Inseparable and represents a combined yield of both diastereomers.

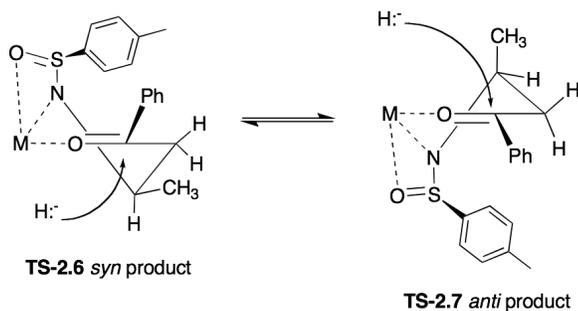
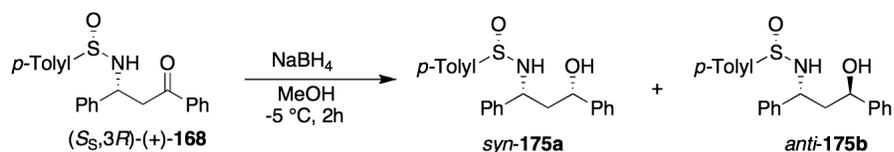


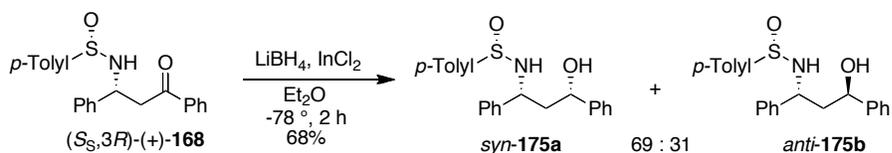
Figure 2.8: Six-Membered Transition States of ($S_S,3S$)-(+)-**165** Leading to *Syn* and *Anti* Products

Other reducing agents such as sodium borohydride, diisobutyl aluminum hydride and lithium borohydride/indium chloride were used with *N*-*para*-toluenesulfinyl β -amino ketone, ($S_S,3R$)-(+)-**168** ($R^1, R^2 = \text{Ph}$) but gave poorer results. These results are listed below in Table 2.7. Sodium borohydride gave nearly a 1:1 diastereomeric ratio with a slight preference of the *syn* isomer in methanol as the solvent. (Scheme 2.21)(Table 2.7, entry 1). This result most likely reflects sodium borohydride's small size and its inability to discriminate between either face of the carbonyl.



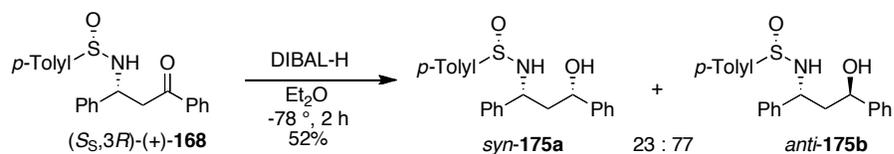
Scheme 2.21

A reduction of the same substrate ($S_S,3R$)-(+)-**168** with lithium borohydride and indium chloride favored the *syn* isomer in a 3:7 ratio (Scheme 2.22)(Table 2.7, entry 2).¹⁷⁹ The indium atom most likely acts as the chelating agent to maintain the six-membered intermediate **TS-2.5**.



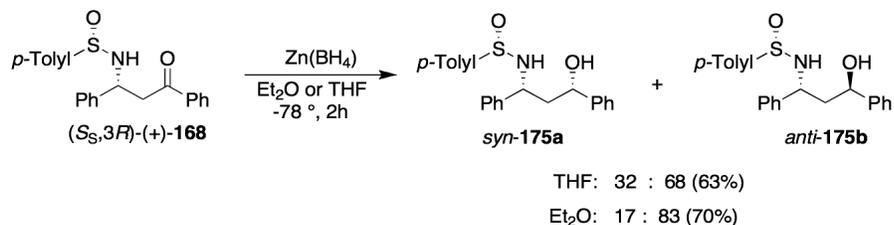
Scheme 2.22

Interestingly, five equivalents of diisobutyl aluminum hydride in diethyl ether favored the *anti* diastereomer (Scheme 2.23)(Table 2.7, entry 3). This is in contrast to the *syn* selectivity of lithium aluminum hydride. This most likely suggests that it is the lithium cation, which is responsible for maintaining the six-membered transition state leading the *syn* isomer. This would allow ($S_S,3R$)-(+)-**168** to react through an acyclic transition state which would be governed by **TS-2.4**.



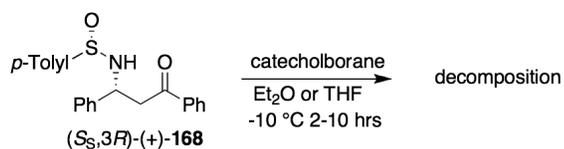
Scheme 2.23

In a surprising result, zinc borohydride, which favors *syn* selectivity in the literature^{67,76}, gave the *anti* diastereomer in both THF (*syn/anti* = 32:68) as well as Et₂O (*syn/anti* = 17:83) (Scheme 2.24)(Table 2.7, entries 4 and 5). The difference in selectivity could arise from the zinc atom coordinating with the polar sulfinyl group rather than the amino and carbonyl groups. As seen with *syn* selectivity, when the reaction was performed in a more coordinating solvent, preference for the *anti* diastereomer was also reduced to a modest 3:7 ratio (Table 2.7, entry 4). However, when diethyl ether was used, the diastereomeric ratio was roughly 2:8 *syn/anti*.



Scheme 2.24

As mentioned previously, Ellman and coworkers found that high *syn* selectivity was found in the reduction of β -hydroxy *N*-sulfinyl imines with catechol borane.⁸⁰ This reagent was also tested with *N*-*para*-toluenesulfinyl β -amino ketone (*S*_S,3*R*)-(+)-**168** (Table 2.7, entry 6) but decomposition of the starting material occurred rapidly under these conditions (Scheme 2.25). This could be due to the fact that catecholboranes are known to deoxygenate a wide range of sulfoxides.¹⁸⁰



Scheme 2.25

Table 2.7: Reduction of β -Amino Ketones with Various Reducing Agents

entry	β -amino ketone	reducing agent (eq)	solvent	product	% yield ^b
				<i>syn/anti</i> (dr) ^a	
1	(<i>S</i> _S ,3 <i>R</i>)-(+)- 168	NaBH ₄ (7)	MeOH	175a:175b (55:45)	65
2	(<i>S</i> _S ,3 <i>R</i>)-(+)- 168	LiBH ₄ /InCl ₃	Et ₂ O	175a:175b	68 ^{c,d,e}

				(69:31)	
3	(<i>S_S,3R</i>)-(+)- 168	DIBAL-H (5)	Et ₂ O	175a:175b (23:77)	52 ^c
4	(<i>S_S,3R</i>)-(+)- 168	Zn(BH ₄) ₂ (5)	THF ^d	175a:175b (32:68)	48 ^b
5	(<i>S_S,3R</i>)-(+)- 168	Zn(BH ₄) ₂ (5)	Et ₂ O ^d	175a:175b (17:83)	65
6	(<i>S_S,3R</i>)-(+)- 168	catecholborane (5)	THF ^d	n/a	decomp.

^a Determined by ¹H NMR on the crude reaction mixture. ^b Isolated yield of major diastereomer unless otherwise noted. ^c Inseparable and represents a combined yield of both diastereomers. ^d Reaction carried out at 0 °C ^e Synthesized by Brad Nolt

In summary, the best *anti* selectivity is seen for *N-para*-toluene sulfinamides where either R¹ or R² is a large group like phenyl. The *anti* selectivity is decreased when an *N-tert*-butane sulfinamide is used. The best results for *syn* selectivity were observed when lithium tri-*tert*-butoxy aluminumhydride was used in a solvent that lacks strong coordinating ability (ex: diethyl ether, methylene chloride and toluene) to reduce *N*-sulfinyl *tert*-butane sulfinamides. This is most likely because polar coordinating solvents form a solvation shell around the lithium cation and therefore prevent its ability to coordinate to the nitrogen anion and carbonyl oxygen giving the required six-membered transition state **TS-2.5**. The increased bulk of the *tert*-butane sulfinamide provides more steric hindrance on one face of the six-membered transition state increasing *syn* selectivity **TS-2.5** (Figure 2.7). However, larger nitrogen protecting groups disfavored *anti* approach and therefore disrupted the ideal conformation **TS-2.1** and **TS-2.2**. Surprisingly, zinc borohydride produced *anti* selectivity, which is opposite to what is recorded in the literature.^{67,74}

Stereochemical configurations of the 1,3-amino alcohol products were assigned by analogy to earlier stereoselective reduction studies of *N*-*para*-toluenesulfinyl β -amino ketones⁷⁶ as well as β -hydroxy ketones.⁹⁰ In the synthesis of (-)-sedridine by Davis and coworkers, ¹³C NMR studies of the C-2(OH) chemical shifts show that this signal appears at a lower chemical shift for *anti* 1,3-amino alcohols ($\delta = 63.86$) with respect to a higher chemical shift for *syn* 1,3-amino alcohols ($\delta = 67.63$).⁷⁶ These same results were seen for the stereoselective reductions of β -hydroxy ketones to 1,3-diols. Kathiawar and coworkers reported that the stereoselectivities for reduction of β -hydroxy ketones with zinc borohydride and other chelating reducing agents or Lewis acids produced *syn* 1,3-diols. Their group determined diastereomeric ratios by comparing the height of the C-OH ¹³C peak at the newly created stereogenic center. The present study confirmed this phenomena. For example, the C-2(OH) ¹³C NMR signal for (*S*_s,1*S*,3*R*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol, *anti*-(**174**) and (*S*_s,1*R*,3*R*)-(+)-3-(*p*-toluenesulfinylamino)-1,3-diphenylpropan-1-ol, *anti*-(**175**), has a range of δ 63-65 ppm while the signal for (*S*_s,1*R*,3*R*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol, *syn*-(**172**), and (*S*_s,1*S*,3*S*)-(+)-*N*-(*p*-toluenesulfinyl)-3-amino-1,3-diphenyl-propan-1-ol, *syn*-(**173**), appears at δ 67-71 ppm. From this standpoint, it is suggested that an incorrect configurational assignment was made by Kennedy and coworkers regarding the examples of asymmetric reduction of an difuryl *N*-sulfinyl- β -amino ketones.⁷⁸ Here, the authors reduced *N*-sulfinyl-1,3-difuryl- β -amino ketones with lithium triethyl borohydride but claimed *syn* selectivity (see Scheme 2.4). They also reported *anti* selectivity using lithium aluminum hydride, which is also contradictory with what was observed here. Upon review of their data, it was reported that

the C-2(OH) ^{13}C NMR signal for the *syn* and *anti* 1,3-amino alcohols are δ 64.4 ppm and δ 66.4 ppm, respectively, although no proof was given to verify these structures. This is the opposite of what was seen in this investigation as well as other examples.⁶⁶⁻⁶⁸ As mentioned above, the synthesis of (-)-lasubine II by Davis and coworkers show a *syn* selective reduction with zinc borohydride and an *N*-sulfinyl δ -amino β -keto ester which is contrary to the results of this investigation into reductions of *N*-sulfinyl β -amino ketones. The C-OH ^{13}C signal reported is δ 66.32 which falls closely near the range for *syn* *N*-sulfinyl 1,3-amino alcohols, but since data is not reported for the minor *anti* isomer, it is impossible to compare with the current results. This observation may also indicate a special case in the reactivities of *N*-sulfinyl δ -amino β -keto esters versus *N*-sulfinyl β -amino ketones.

2.3.2 Asymmetric Synthesis of (-)-Pinidinol and (+)-Epipinidinol

2.3.2.1 Introduction

(-)-Pinidinol (**179**) is an alkaloid found in North American conifers of the *Lobelia* and *Sedum* species which belong to the *Pinaceae* family. C-2 epimer, (+)-epipinidinol (**180**) is the unnatural synthetic isomer of (-)-**179**. These two alkaloids contain a 2 or 2,6-disubstituted piperidine moiety with a functionalized 2-propanol side chain (Figure 2.9).^{61,92} Pinidinol has been shown to act as an anti-feedent towards Eastern spruce budworms and therefore new syntheses might give access to novel pest deterrents.⁹³ There have been only four asymmetric syntheses of (-)-**179**⁹⁴⁻⁹⁷ and three of these are multi-step procedures with

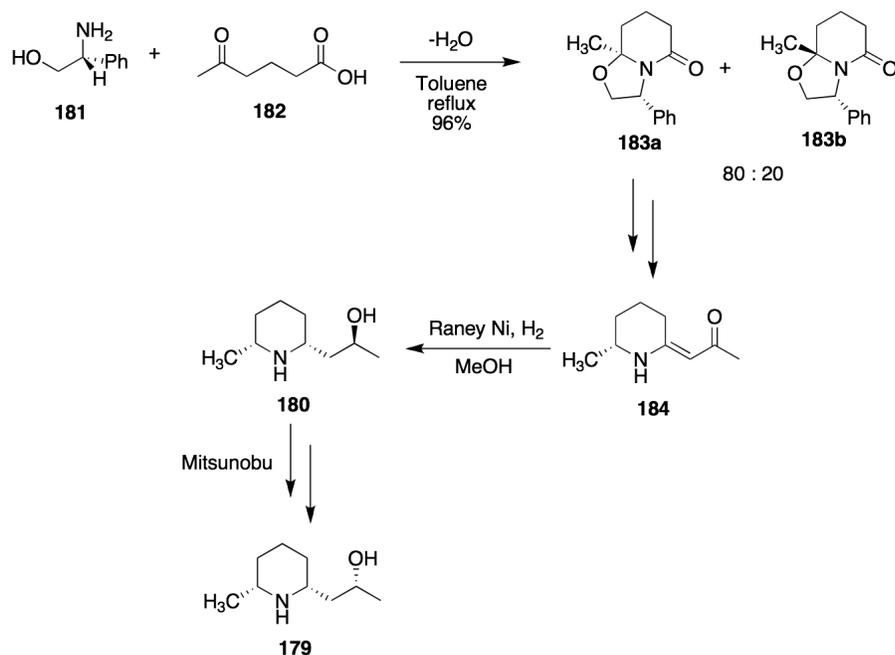
low overall yields.^{94,95,97} Three of the syntheses also use non-chiral amine starting materials.^{94,96,97} A brief review of these syntheses are described below.



Figure 2.9: Structures of (-)-Pinidinol and (+)-Epipinidinol

A synthesis by Takahata and coworkers utilized several Sharpless asymmetric dihydroxylations to install the chiral centers needed to complete the synthesis. This route was very cumbersome with fourteen steps needed to complete the synthesis of (-)-pinidinol (**179**).⁹⁷ In addition, this route produced mixtures of diastereomers in several steps, each requiring separation.

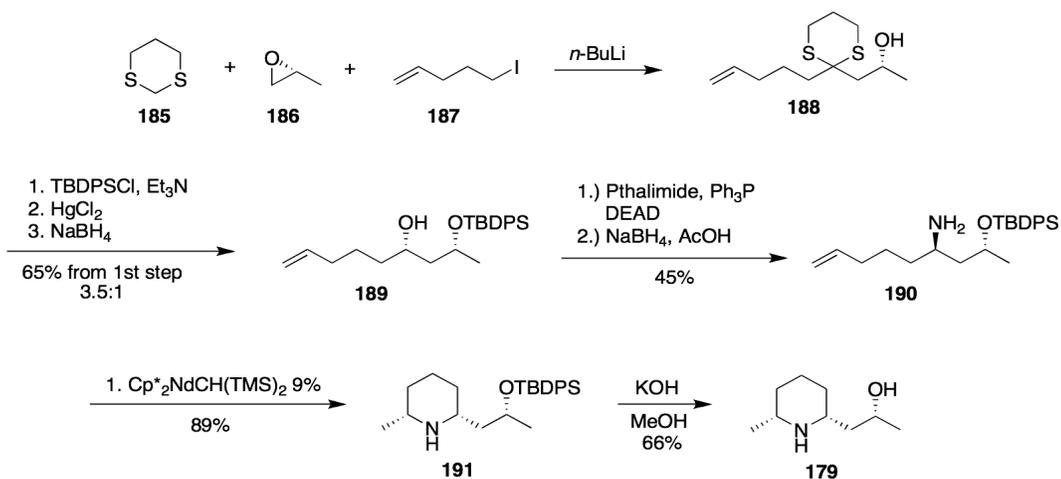
Lhommet and coworkers described the enantioselective synthesis of pinidinol and epipinidinol with their source of chirality coming from the condensation of (-)-phenylglycinol (**181**) and a δ -keto acid **182**.⁹⁵ This produced the separable oxazolopiperidin-2-ones **183a** and **183b** in a 4:1 ratio (Scheme 2.26).¹⁸¹ Through a series of manipulations, the β -enamino ketone **184** was produced which was catalytically reduced with Raney nickel to for epipinidinol (**180**). A Mitsunobu reaction was used to produce the natural (-)-pinidinol (**179**).



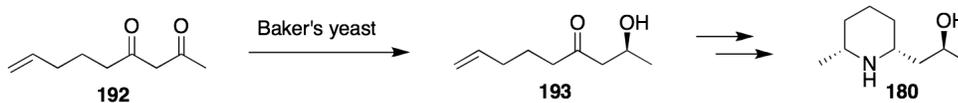
Scheme 2.26

The procedure by Molander and coworkers is the most efficient to date and utilizes a chiral epoxide and the diastereoselective lanthanocene-catalyzed intramolecular hydroamination to produce the chiral piperidine (Scheme 2.27).⁹⁶ Through a linchpin reaction of dithiane (**185**), epoxide **186** and 5-iodo-1-pentene (**187**), they synthesized the alcohol **188** which contained a dithiane as a masked keto functionality. The alcohol was then subsequently protected and the dithiane was removed leaving the ketone to be reduced to the *syn* diol in only a 3.5:1 ratio. **179**. A Mitsunobu reaction gave amine **190** which underwent intramolecular hydroamination to give piperidine **191**. The alcohol moiety was finally deprotected to yield natural (-)-pinidinol (**179**) as the only isomer. The chiral center needed

the epipinidinol (**180**) building block **193** was introduced via the chemoselective and asymmetric reduction of 1-nonen-6,8-dione (**192**) with Baker's yeast (Scheme 2.28).



Scheme 2.27



Scheme 2.28

The synthesis presented here would be the first using a β -amino ketone as a synthetic intermediate. For example, being able to access both (-)-pinidinol (**179**) and (+)-epipinidinol (**180**) from a common precursor via stereoselective reduction is an advantage to using β -

amino ketones in the synthesis of these compounds. A common precursor would also allow for enantiomers as well as ring C-2 and C-5 epimers to be theoretically constructed. In addition, a common precursor can provide the facile construction of an analog library for biological studies. Groups marked with an R can easily be varied with a multitude of groups in the synthesis, which is described below, if needed (Figure 2.10). Another question that will be answered by this total synthesis is whether a cascade cyclization to form the piperidine ring from an *N*-sulfinyl 1,3-amino alcohol is a feasible synthetic approach to these alkaloids (Figure 2.11). It is envisaged that a double deprotection (of the ketone and amine functionalities), followed by a tandem intramolecular condensation will provide a cyclic hexylimine that can be reduced in a 2,5-*syn* fashion.

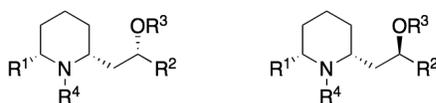


Figure 2.10: Approach to Analogs of (-)-Pinidinol and (+)-Epipinidinol

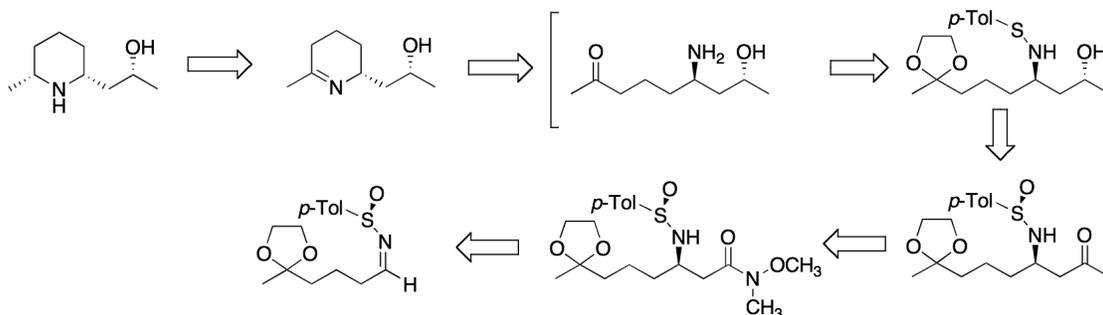


Figure 2.11: Retrosynthetic Analysis of (-)-Pinidinol

2.3.2.2 Preparation of (-)-Pinidinol and (+)-Epipinidinol

Masked oxo sulfinimines are useful polyfunctionalized chiral amine building blocks that contain a protected ketone moiety that can be further modified after nucleophilic addition to the imine (Figure 2.12).^{151,172} The R¹ substituent can therefore be a hydrogen, aryl or alkyl group. To obtain the required keto-protected sulfinimine, the keto-protected aldehyde must first be synthesized. A common way towards the synthesis of the aldehyde is through the corresponding ester, either through diisobutyl aluminum hydride reduction of the corresponding ester or via a reduction/oxidation through the intermediate alcohol.

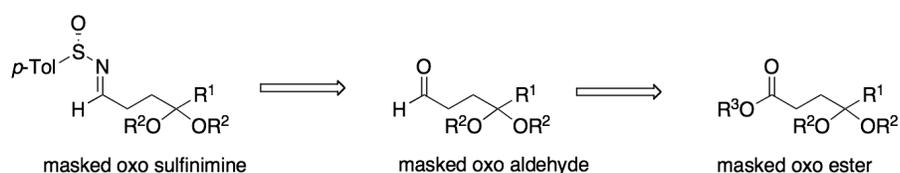
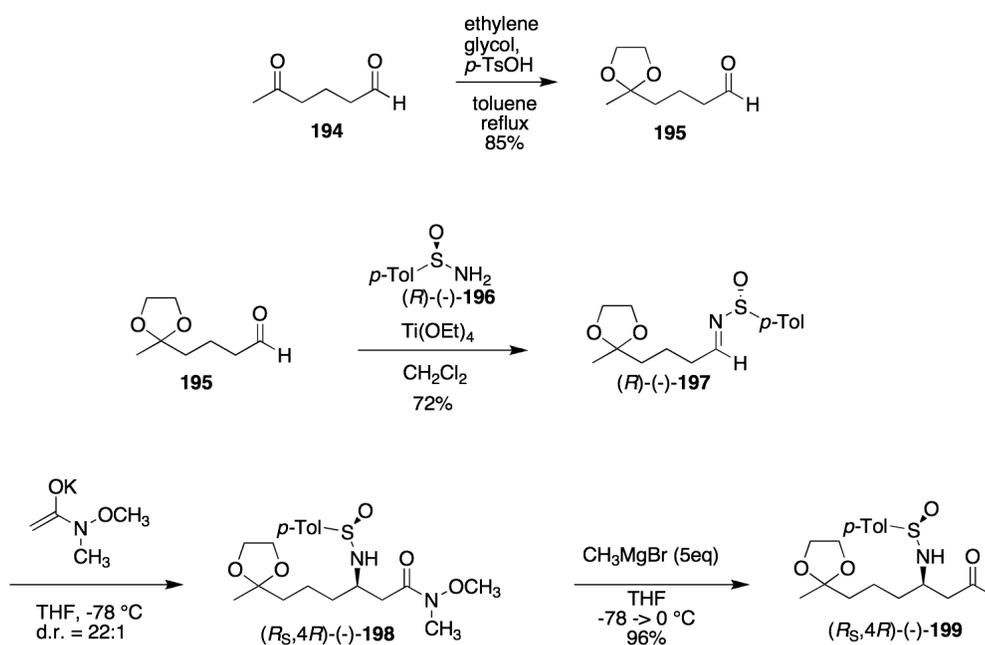


Figure 2.12: Synthesis of Masked Oxo Sulfinimines

The ketal-protected 2-oxohexanal **195** was prepared from commercially available 2-oxo-hexanal (**194**). Sulfinimine (*R*)-(-)-**196** was synthesized in 72% yield from the ketal-protected hexanal (**195**) and (*R*)-(-)-*p*-toluenesulfinamide (**197**) using titanium(IV) ethoxide as the Lewis acid (Scheme 2.29). The sulfinimine (-)-**196** was reacted with the potassium Weinreb amide enolate **137** to produce a 74% yield of *N*-sulfinyl- β -amino Weinreb amide (*R*_S,3*R*)-(-)-**198** as a pair of inseparable isomers with a d.r. of 22:1 after purification. The

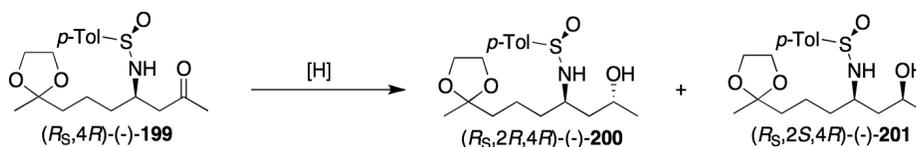
diastereomeric ratio was analyzed using ^1H NMR and the peaks at δ 3.64 and 3.68 corresponding to the O-CH_3 and N-CH that were used to obtain this ratio. The 22:1 N -sulfinyl- β -amino Weinreb amide mixture ($R_S,3R$)-(-)-**198** in THF was reacted with methylmagnesium bromide and gave a clean, high yielding conversion to the methyl ketone ($R_S,4R$)-(-)-**199** without the need for further purification.



Scheme 2.29

As expected, reduction of ($R_S,4R$)-(-)-**199** with lithium triethylborohydride gave the N -sulfinyl 1,3-amino alcohol ($R_S,2R,4R$)-(-)-**200** in 90% yield as a single isomer having the required *anti*-geometry for the synthesis of (-)-pinidinol (**179**) (Scheme 2.30) (Table 2.10,

entry 1). This assignment is based on this compound's later conversion to (-)-pinidinol (**179**) as well as the fact that the C-OH ^{13}C NMR chemical shift appears at δ 64.8 ppm as compared to δ 67.6 for the *syn* isomer (see below). Disappointingly, when lithium tri-*tert*-butoxyaluminumhydride was used as the reducing agent, a 54:46 (*syn:anti*) ratio of diastereomers as obtained (Table 2.10, entry 4). These results were unexpected as lithium tri-*tert*-butoxyaluminumhydride was a good *syn* selective reducing agent for the model ketones **165-170**. This prompted a search for improved reaction conditions that would favor the *syn* product in the presence of an *N-p*-toluenesulfinyl protecting group. It was hypothesized that the oxygens of the ketal protecting group of (*R*_S,4*R*)-(-)-**199** might be interfering with formation of the six-membered transition state **TS-2.5** since the reduction of *N*-(*p*-toluenesulfinyl)-4-amino-nonan-2-one (*S*_S,3*S*)-(+)-**166** produced acceptable results. Several reaction conditions were tried. Zinc borohydride again gave a preference for the *anti* product (Table 2.10, entry 2). Samarium iodide was investigated because Keck and coworkers could produce *syn* 1,3-amino alcohols from racemic β -amino ketones with a trifluoroacetyl protecting group on the nitrogen atom.¹⁸³ However, because of the presence of either the ketal, the sulfinyl group or both, these conditions resulted in decomposition of the starting material (Table 2.10, entry 3).



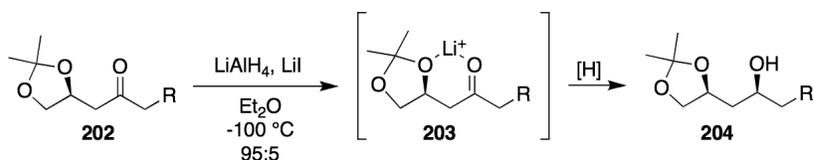
Scheme 2.30

Table 2.8: Reduction of β -Amino Ketone Ketal ($R_S,4R$)-(-)-**199** at $-78\text{ }^\circ\text{C}$

entry	reducing agent	solvent	d.r. (<i>syn/anti</i>) 200:201 ^a	% yield
1	LiEt ₃ BH	CH ₂ Cl ₂	1:99	90 ^b
2	Zn(BH ₄) ₂ (5 eq)	Et ₂ O	35:65	73
3	SmI ₂	CH ₂ Cl ₂	n/a	decomp.
4	Li(<i>t</i> -BuO) ₃ AlH (3 eq)	Et ₂ O	54:46	87

^a Determined by ¹H NMR on the crude reaction mixture. ^b Separated by column chromatography

To find alternative *syn* selective reduction conditions, the topic of stereoselective reductions of the analogous β -hydroxy ketones was researched in the literature. Work reported by Mori and coworkers on the reductions of ketal protected ketones with lithium aluminum hydride reagents and excess lithium iodide favored the formation of *syn* diols at low temperatures (Scheme 3.31).⁹⁸ Their group observed that reductions in the absence of LiI resulted in poor selectivities⁹⁹ and it was hypothesized that the addition of excess lithium cation would help induce selectivity through the chelation of the ketal and carbonyl functions via β -alkoxy induction.⁹⁸ They therefore found that reduction of compound **202** with lithium aluminum hydride and added lithium iodide at $-100\text{ }^\circ\text{C}$ produced the *syn* product **204** in high d.r. and was speculated to occur through **203** as a six-membered chelated intermediate.



Scheme 2.31

Although the pinidinol precursor 1,3-amino ketone ($R_S,4R$)-(-)-**199** contains a ketal alkoxy group that is six carbons away from the ketone moiety, it was thought that the lithium cation might be coordinating preferentially with the ketal oxygens, and therefore disrupting the six-membered intermediate **TS-2.5**. It was envisioned that by adding lithium salts to the reaction mixture, one might precoordinate the lithium cations with the ketal oxygens and therefore facilitate the formation of the six-membered chelated structure **TS-2.5** (Figure 2.13).

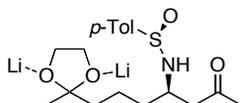
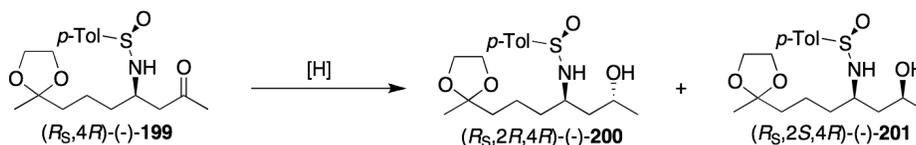


Figure 2.13: Precoordinating Ketal Oxygens with Lithium Cations

When lithium iodide used in the reduction of 1,3-amino ketone ($R_S,4R$)-(-)-**199** with lithium tri-*tert*-butoxyaluminumhydride, the *syn/anti* selectivity was increased from roughly 1:1 to 2:1 (Table 2.9, entry 1). The gain in selectivity was encouraging and prompted a

further study of analogous lithium salts although yields were initially low (54%). The low yields could be attributed to the difficulty in drying the hygroscopic lithium salts which were used in conjunction with the moisture-sensitive reducing agent. Lithium bromide produced lower selectivity than lithium iodide and also gave low yields (Table 2.9, entry 2). Again, these low yields were attributed to the highly hygroscopic nature of the lithium salt. Lithium chloride gave the best results with sufficiently high selectivity (9:1 *syn/anti*) and good yields (72%) (Table 2.9, entry 3). A reaction with lithium triflate was also attempted but provided modest selectivity (Table 2.9, entry 4).

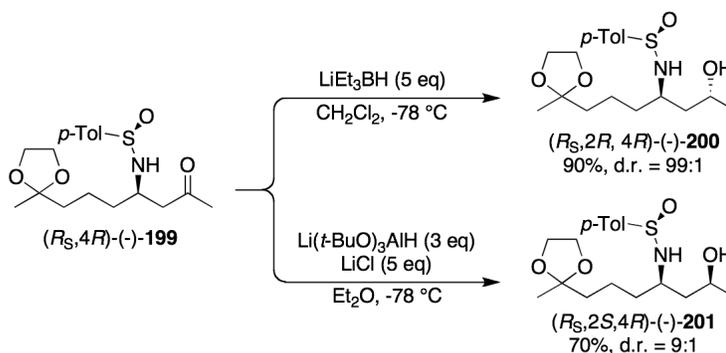
Table 2.9: Reduction of β -Amino Ketone Ketal ($R_S,4R$)-(-)-**199** with $\text{Li}(t\text{-BuO})_3\text{AlH}$ and Lithium Salts at $-78\text{ }^\circ\text{C}$



entry	reducing agent	solvent	d.r. (<i>syn/anti</i>) 200:201 ^a	% yield
1	$\text{Li}(t\text{-BuO})_3\text{AlH}$ (3 eq) LiBr (10 eq)	Et_2O	60:40	58
2	$\text{Li}(t\text{-BuO})_3\text{AlH}$ (3 eq) LiCl (10 eq)	Et_2O	89:11	72 ^b
3	$\text{Li}(t\text{-BuO})_3\text{AlH}$ (3 eq) LiI (10 eq)	Et_2O	67:33	54
4	$\text{Li}(t\text{-BuO})_3\text{AlH}$ (3 eq) LiOTf (10 eq)	Et_2O	70:30	63

^a Determined by ^1H NMR on the crude reaction mixture. ^b Separated by column chromatography

A facile synthesis for the *anti* and *syn* 1,3-amino alcohol is now available for the reduction of ketal-protected *N*-sulfinyl β -amino ketones. Efforts toward the synthesis of pinidinol and epipinidinol can now be undertaken with the use of lithium triethylborohydride and lithium tri-*tert*-butoxyaluminum hydride/lithium chloride to produce the *anti* and *syn* *N*-sulfinyl 1,3-amino alcohols (Scheme 2.32). In addition, the diastereomers produced from the Weinreb amide addition to the sulfinimine could now be separated via column chromatography.

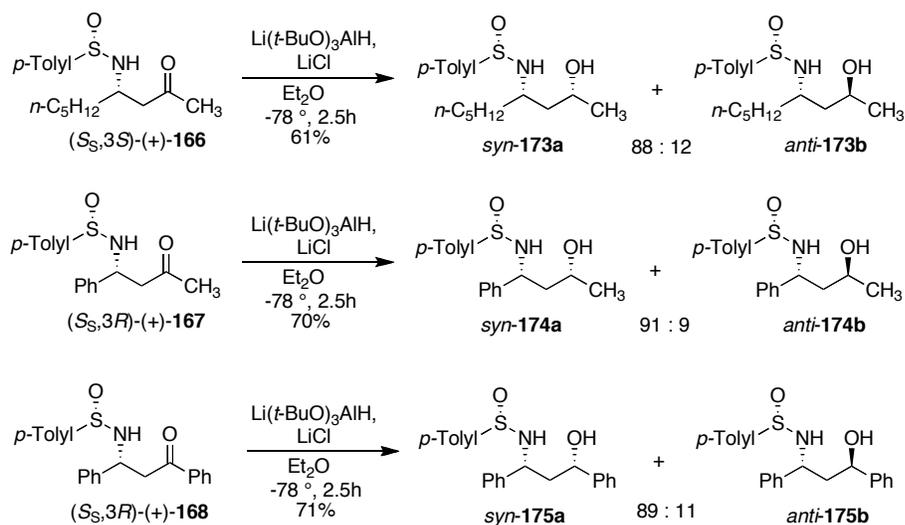


Scheme 2.32

The fact that the lithium salts produce a noticeable change in *syn* selectivity when used in conjunction with lithium tri-*tert*-butoxyaluminumhydride in the stereoselective reduction of *N*-*para*-toluenesulfinyl β -amino ketone ketal (*R_S*,4*R*)-(-)-**199** prompted an investigation into whether this combination could enhance the selectivities of the model *N*-sulfinyl- β -amino ketones **166-168** (Scheme 2.33) (Table 2.10). It was interesting that only a

slight difference in the diastereomeric ratio was seen with these model *N*-sulfinyl β -amino ketones. For example, the use of lithium chloride produced a diastereomeric ratio of 88:12 *syn/anti* (from 81:19) using model ketone (*S_S,3S*)-(+)-**166** as the substrate (Table 2.12, entry 1). When R¹ is methyl and R² is phenyl as in (*S_S,3R*)-(+)-**167**, there was no change in selectivity when lithium chloride was used as an additive (Table 2.10, entry 2). Also, with (*S_S,3R*)-(+)-**168** (R¹ = Ph, R² = Ph), only a slight increase in diastereoselectivity was seen (89:11 vs. 85:15) (Table 2.10, entry 3).

These results give further evidence that the ketal protecting group of (*R_S,4R*)-(-)-**199** has an interfering effect in formation of the six-membered intermediate leading to the *syn* 1,3-amino alcohol. Precoordination of the ketal oxygens with the lithium cation most likely enhances diastereoselectivity allowing the six-membered intermediate to form.



Scheme 2.33

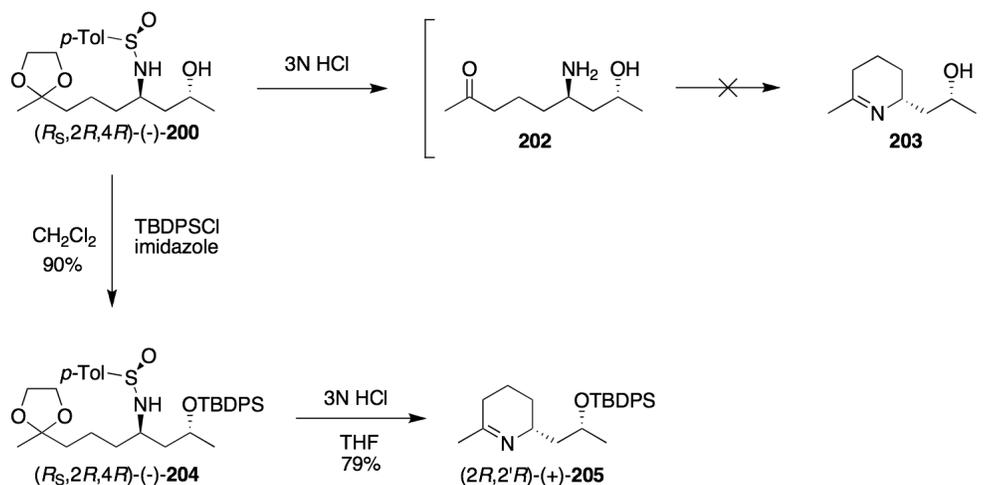
Table 2.10: Reduction of β -Amino Ketones at -78 °C

entry	β -amino ketone	reducing agent (eq)	solvent	product <i>syn/anti</i> (dr) ^a	% yield ^b
1	(<i>S</i> _S ,3 <i>S</i>)-(+)- 166	Li(<i>t</i> -BuO) ₃ AlH (3), LiCl (10)	Et ₂ O	158b:160b (88:12)	61 ^b
2	(<i>S</i> _S ,3 <i>R</i>)-(+)- 167	Li(<i>t</i> -BuO) ₃ AlH (3), LiCl (10)	Et ₂ O	158c:160c (91:9)	70 ^b
3	(<i>S</i> _S ,3 <i>R</i>)-(+)- 168	Li(<i>t</i> -BuO) ₃ AlH (3), LiCl (10)	Et ₂ O	158d:160d (89:11)	71 ^b

^a Determined by ¹H NMR on the crude reaction mixture. ^b Separated by column chromatography

A cascade reaction is one in which several chemical transformations can take place in a single step in a defined order. The benefits of cascade reactions include the minimization of excess solvent and waste generation as well as a reduction of time and labor. With both *anti* and *syn* 1,3-amino alcohols (*R*_S,2*R*,4*R*)-(-)-**200** and (*R*_S,2*S*,4*R*)-(-)-**201** in hand, cascade reaction leading to imine **203** could be tested (Scheme 2.34). The treatment of the *anti* *N*-sulfinyl protected 1,3-amino alcohol (*R*_S,2*R*,4*R*)-(-)-**200** with 3N HCl was expected to cyclize to the imine **203** via the intermediate keto amine **202**. However, when (*R*_S,2*R*,4*R*)-(-)-**200** was treated with 3N HCl in THF, the reaction led to decomposition which could easily be detected by thin-layer chromatography or ¹H NMR analysis of the crude reaction mixture. It was thought that the free hydroxyl group could be interfering with the intramolecular cyclization and it was therefore protected as the *tert*-butyldiphenylsilyl ether as in (*R*_S,2*R*,4*R*)-(-)-**204** (Scheme 2.34). At this point, treatment of (*R*_S,2*R*,4*R*)-(-)-**204** with 3N HCl for a short time produced the imine (2*R*,2'*R*)-(+)-**205** in 79% yield. This compound was

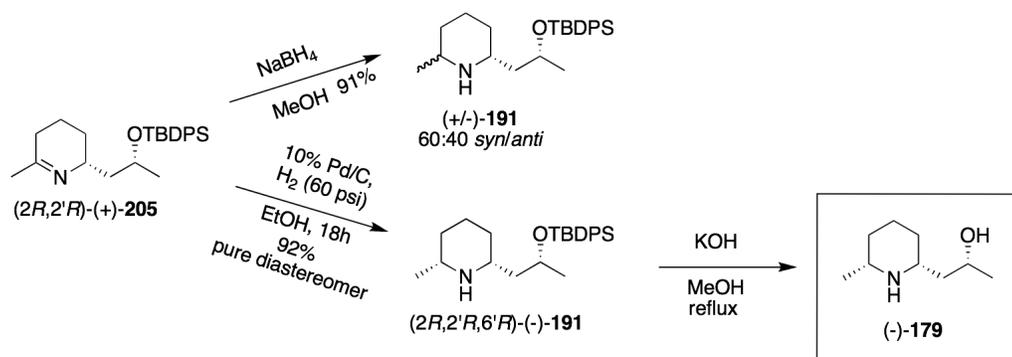
immediately carried onto the next step although this imine proved to be quite stable for over a week if kept in a freezer.



Scheme 2.34

A small amount of imine $(2R, 2'R)\text{-}(+)\text{-}205$ was first reacted with sodium borohydride in methanol in order to test the reactivity of the imine (Scheme 2.35). This produced an inseparable mixture of diastereomers in a 60:40 ratio. It was later determined that most predominant isomer was the *syn* isomer. The imine **205** was hydrogenated at atmospheric pressure, but there was no reaction. The pressure of hydrogen was then increased to 60 psi and the pinidinol silyl ether $(2R, 2'R, 6'R)\text{-}(-)\text{-}206$ was produced as a single diastereomer in high yields. This therefore completes a formal synthesis of $(-)$ -pinidinol (**179**) as this *O*-silylated pinidinol derivative $(2R, 2'R, 6'R)\text{-}(-)\text{-}206$ was also produced by Molander and coworkers.⁹⁶ Regardless, the *tert*-butyl diphenylsilyl protected pinidinol $(2R, 2'R, 6'R)\text{-}(-)\text{-}$

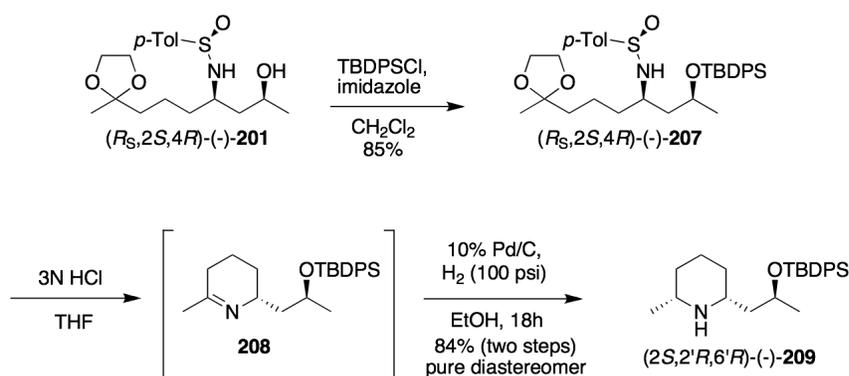
206 was deprotected to give (-)-pinidinol (**179**) which also matched the spectral data in the literature. This further proves the proper configuration of Weinreb enolate addition to the sulfinimine which is the key step for installing chirality into this synthesis.



Scheme 2.35

Similarly, the *syn* *N*-sulfinyl 1,3-amino alcohol ($R_S,2S,4R$)-(-)-**201** was protected with *tert*-butyl diphenylsilyl chloride and imidazole to yield the silyl ether ($R_S,2S,4R$)-(-)-**207** in 85% yield (Scheme 2.36). Treatment with 3N HCl in THF gave imine **208**. However, this imine oxidized quickly in the air and could not be characterized due to rapid degradation on column chromatography. Evidence of air oxidation can be seen by the crude material turning to a deep orange color. Instead it was therefore carried on as the crude material and quickly reduced to give *epi*-pinidinol silyl ether ($2S,2'R,6'R$)-(-)-**209** in 85% yield. Although this imine was unstable to column chromatography as well as air, 60 psi of hydrogen resulted in very little conversion of starting material. To obtain the desired product, the hydrogen

pressure must be increased to 100 psi which allows for complete conversion to the piperidine. Gratifyingly, this reduction also produces a single diastereomer in 84% yield. This therefore completes a formal synthesis of (+)-epipinidinol as this compound was also synthesized by Molander and coworkers.⁹⁶



Scheme 2.36

2.4 Conclusions

In conclusion, a general asymmetric synthesis of *syn* and *anti* 1,3-amino alcohols has been developed via the reduction of chiral *N*-sulfinyl β -amino ketones using lithium tri-*tert*-butoxyalumino hydride and lithium triethyl borohydride, respectively. Good yields and high diastereoselectivities were observed for reductions of diverse *N*-*p*-toluenesulfinyl β -amino ketones producing both *syn* and *anti* 1,3-amino alcohols. When this methodology was used in conjunction with the reduction of an *N*-sulfinyl β -amino ketone having a ketal group, poor *syn* selectivity resulted. This situation was resolved by the hypothesized precoordination of

lithium cations to the ketal oxygens so that the six-membered intermediate leading to the *syn* diastereomer is maintained. This methodology was expressed in the concise and asymmetric synthesis of the natural product, (-)-pinidinol (**179**) and its unnatural isomer, (+)-epipinidinol (**180**).

CHAPTER 3

SYNTHESIS OF ENANTIOMERICALLY PURE BRIDGEHEAD-SUBSTITUTED TROPINONES VIA MASKED OXO SULFINIMINES

3.1 Introduction

Tropane (**212**) and its related tropinone (**213**) derivatives which contain an 8-azabicyclo[3.2.1]octane ring system possess a wide range of bioactivities and are widely found in nature as plant alkaloids.^{100,101} Several well-known members of this family include (-)-cocaine (**214**), (-)-scopolamine (**215**) and atropine (**216**) (Figure 3.1). Cocaine, which is isolated from the South American *Erythroxylum coca*, is a highly addictive and potent dopamine reuptake inhibitor that acts as a locomotor stimulant. Coca leaves have been used for thousands of years in South America to aid in long strenuous journeys by foot and to simultaneously ward off hunger. Atropine and scopolamine, on the other hand, are anticholinergics and muscarinic antagonists that are found in *Atropa belladonna* as well as other plants.^{102,103} The preparation of these plants containing these chemicals have found traditional uses in the treatment of inflammation, menstrual cramps and motion sickness.¹⁸⁴ In higher dosages, these compounds can produce vivid hallucinations and death.

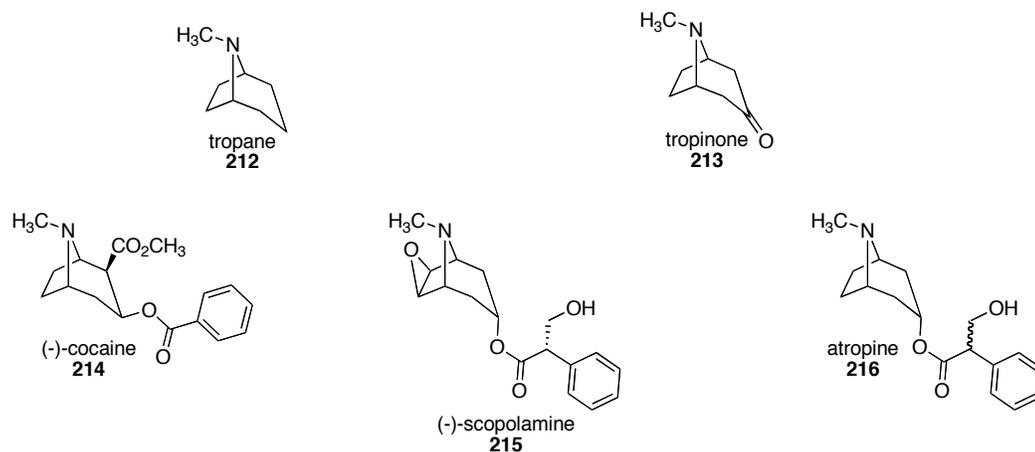
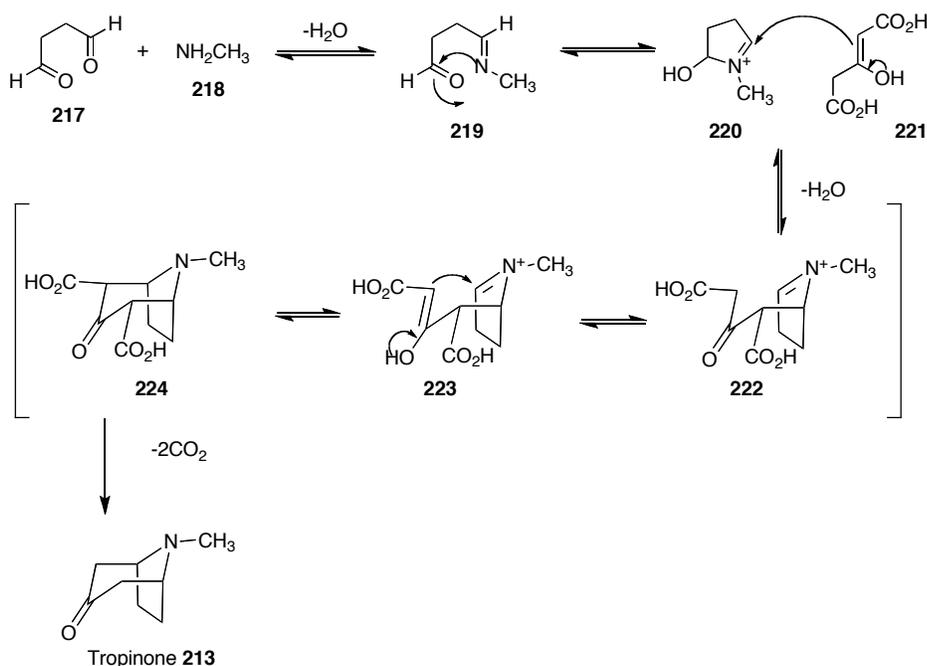


Figure 3.1: Examples of Tropane Alkaloids

The tropane skeleton is such an effective scaffold for drug development that several efforts have been directed towards the medicinal applications of tropane derivatives in the past year alone.¹⁰⁴⁻¹⁰⁸ Efforts towards the production of (-)-cocaine analogs have driven much of this chemistry.¹⁰² Since tropinone (**213**) is often used as a precursor for the synthesis of tropane alkaloid derivatives, the asymmetric synthesis of tropinone derivatives would prove quite useful for future drug development studies.¹⁰²

Several syntheses exist in the literature for preparing natural tropinone (**213**)¹⁰⁹⁻¹¹³ with the most recognized and widely used being that of Sir Robert Robinson's, whose famous multicomponent cascade reaction earned him a Nobel prize for in 1947.¹⁰⁹ The proposed mechanism his ground-breaking synthesis is as follows (Scheme 3.1): In a buffered acidic medium, succinaldehyde **217** was condensed with one equivalent of methylamine **218** to produce the intermediate imine **219**. This undergoes intramolecular nucleophilic attack by

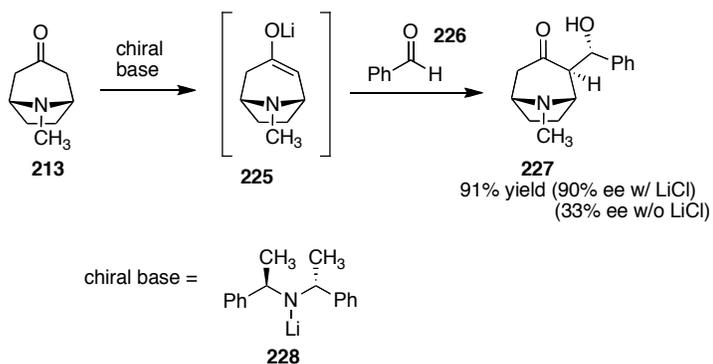
the nitrogen atom to produce hydroxy imine **220** after protonation. This undergoes a reaction with the acid-catalyzed enol of acetone dicarboxylic acid (**221**) to produce the carbon-carbon bond of **222**. Another loss of water and intramolecular nucleophilic attack of the enol **223** gives tropinone precursor **224** which gives tropinone **213** upon decarboxylation.



Scheme 3.1

Very few examples exist for the synthesis of asymmetric tropinone derivatives and desymmetrization of natural tropinone (**213**) via use of a chiral base is the most prevalent method (Scheme 3.2).¹¹⁴⁻¹¹⁷ It was first reported by Majewski and coworkers in 1995 that a chiral amine base **228** could selectively deprotonate tropinone to produce the desymmetrized

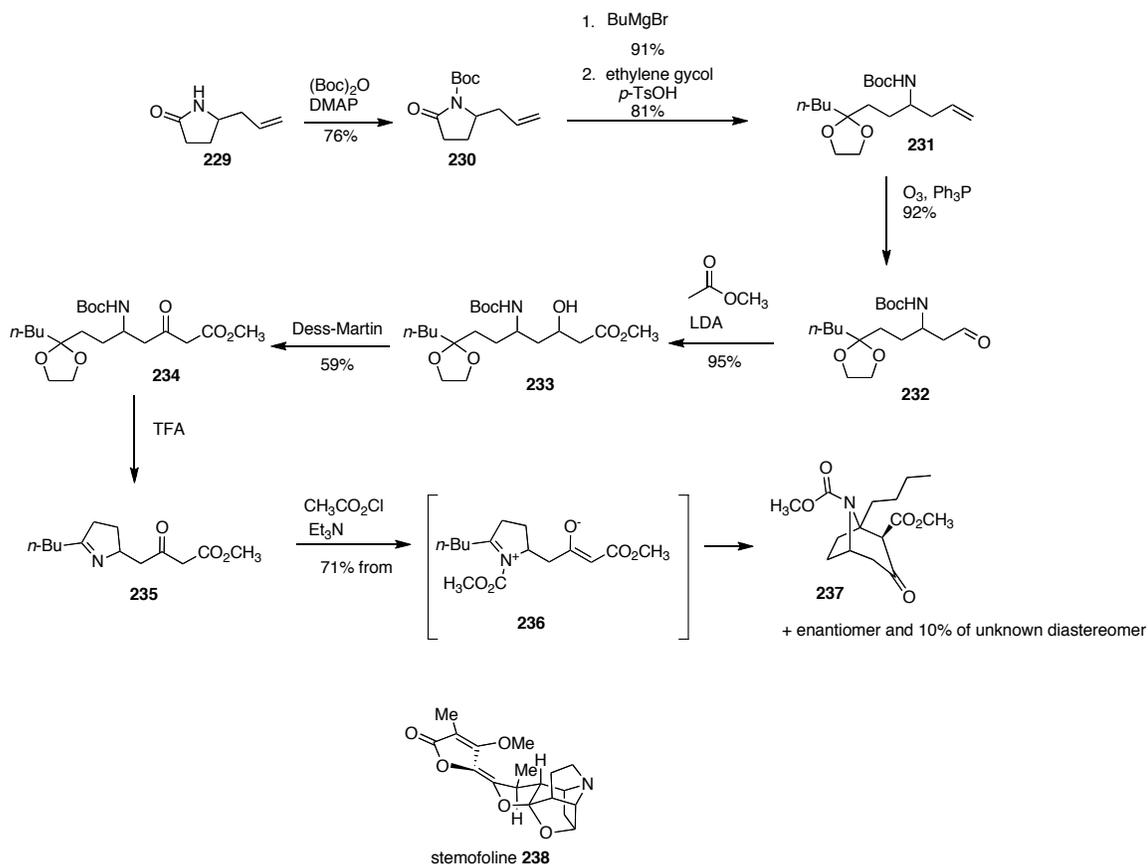
lithium enolate **225**.¹¹⁴ When this enolate is reacted with benzaldehyde **226** to give the aldol product **227**, the aldol product is produced as a single diastereomer in enantiomeric excess. Interestingly the ee suffers when the reaction is performed in the absence of lithium chloride as additive.



Scheme 3.2

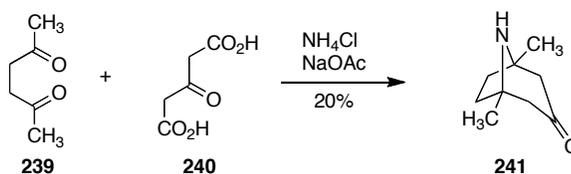
Stemofoline (**238**), is a natural product found in traditional Asian medicinal extracts of *Stemonacea* leaves. Aside from as single route towards the racemic synthesis of this alkaloid, no examples existed of tropinones with monosubstituted bridgehead substituents (Scheme 3.3).^{118,119,185} Here, Thomas and coworkers prepared a Boc-protected pyrrolidinone **230** from the allyl pyrrolidinone **229**. They then reacted **230** with butyl magnesium bromide to open the ring to **231** and then subsequently protected the newly formed ketone moiety as the ketal with ethylene glycol. Ozonolysis under reductive conditions formed the aldehyde **232** which was subjected to a reaction of the sodium enolate of methyl acetate to give aldol

product **233**. Oxidation of the alcohol with Dess-Martin periodinane gave the ketone **234** in only 59% yield. Acid hydrolysis of **234** produced the cyclic imine **235** which was reacted with acetyl chloride to give racemic C-1 substituted tropinone **236**. This tropinone existed with the C-2 carbomethoxy substituent mainly in the axial position. There was 10% of an unknown isomer also present in the product which was assumed to be the C-2 epimer of **236**. Although this group never achieved a total synthesis of stemofoline (**238**), this is the first and only example of a C-1 monosubstituted tropinone.



Scheme 3.3

A synthesis for making disubstituted nortropinones is reported in the literature (Scheme 3.4).^{186,187} Using a one-pot cascade reaction as reported by Sir Robert Robertson (Scheme 3.1), a symmetrical 1,5-dimethylated nortropinone **241** was synthesized by reacting 2,5-hexadione (**239**) (rather than succinaldehyde) with acetone dicarboxylic acid (**240**) and ammonium chloride. This nortropinone was a precursor which utilized in the diastereoselective synthesis of pyrrolidines.¹⁸⁷

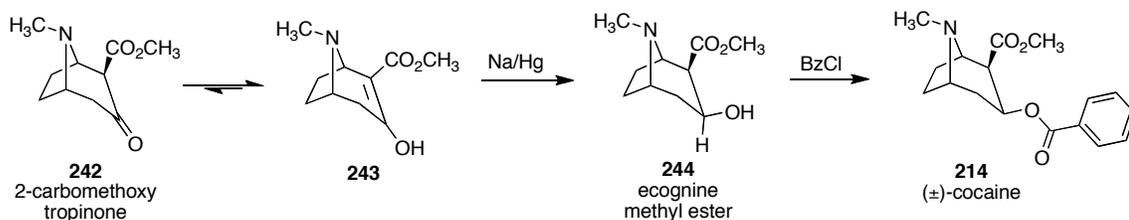


Scheme 3.4

Despite the large amount of research on the structure-activity relationships of (-)-cocaine and related tropane derivatives, no analogs exist in the literature whereby a substitution of the C-1 bridgehead position occurs, even in racemic form.¹⁰² Therefore, being able to access these novel analogs through tropane derivative in an asymmetric fashion would be pharmacologically useful and open doors to completely uncharted areas of (-)-cocaine SAR studies (and other biologically active tropane derivatives). These novel analogs

could be used as potential addiction therapeutics as well as unique ligands to the dopamine reuptake transport.

As previously mentioned, accessing (-)-cocaine (**215**) from tropinone (**184**) is readily achievable and is published in the literature (Scheme 3.5).^{102,188} The first example of the racemic total synthesis of (+/-)-cocaine **185** was reported by Willstätter in 1923.¹⁸⁸ Tropinone (**212**), which was synthesized according to Robertson's procedure, was derivatized to 2-carbomethoxy tropinone (**242**), which happened to be in equilibrium with the more abundant enol form **243**. Reduction with sodium mercury amalgam produced the desired diastereomer in abundance with the C-2 carbomethoxy group in the axial position of ecognine methyl ester (**244**) and benzylation gives cocaine (+/-)-**214**.



Scheme 3.5

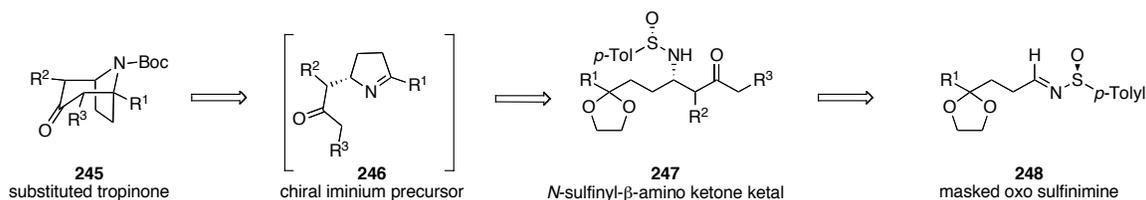
Accessing cocaine analogs through natural (-)-cocaine and tropinone as precursors¹⁰² are not the only methods available. Others include Michael additions, nucleophilic substitution reactions, cycloadditions, iminium ion cyclizations and ring-closing metathesis with relatively few of these being asymmetric.^{103,104} Asymmetric syntheses of (-)-**214**

include a nucleophilic substitution reaction by Rapoport starting from glutamic acid¹²² and a desymmetrization of tropinone with a chiral lithium amide base by Cha and coworkers.¹²³ However, most asymmetric syntheses of (-)-**214** occur through cycloadditions.^{120,121,124-129} For example, Mans and Pearson accessed the unnatural isomer of cocaine (+)-**214** using a 2-azaallyl lithium [3 + 2] cycloaddition to produce a *meso*-pyrrolidine dialdehyde which underwent a proline catalyzed intramolecular aldol reaction. Reddy and Davies produced an enantioselective synthesis of substituted tropanes through a rhodium catalyzed [4 + 3] cycloaddition of *N*-Boc pyrroles with vinyl diazoacetates.¹²⁸ Besides these examples, many syntheses are multistep and low yielding with none giving substitution of tropane at the bridgehead carbon. It is therefore of great importance to develop methods to access these novel structures.

3.2 Present Study

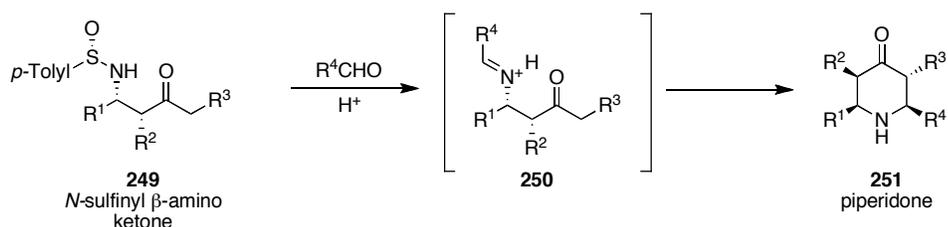
Wanting to develop the methodology which was used for the synthesis of (-)-pinidinol further (Chapter 2), a synthesis leading to an asymmetric C-1, C-2 and C-4 substituted tropinone **245** was envisioned and is shown below (Scheme 3.6). This strategy involves the diastereoselective addition of an enolate to a masked oxo-sulfinimine **248** to produce the desired *N*-sulfinyl- β -amino ketone ketal **247**. Upon acid hydrolysis, tandem deprotections and cyclization give the chiral imine **246** which could undergo intramolecular cyclization to the substituted tropinone **245**. The methodology developed here also happens to be strikingly similar to that which was reported by Thomas and coworkers in their efforts

to synthesize stemofoline (Scheme 3.3).¹⁸⁵ However, the current methodology has several advantages which include higher yields and of course, control of enantioselectivity.



Scheme 3.6

Also, a similar intramolecular technique has been used to synthesize asymmetric substituted piperidines **251** by Davis and coworkers (Scheme 3.7).¹⁶⁹ The intramolecular Mannich reaction has been employed in the efficient synthesis of (-)-nupharmine,¹⁷⁰ (-)-209B¹⁶³ and (-)-223A.¹⁷¹ Here, the condensation of the free amine generated from **249** with an aldehyde produced the acyclic imine **250** as an intermediate that underwent a tandem, acid-catalyzed intramolecular Mannich reaction.

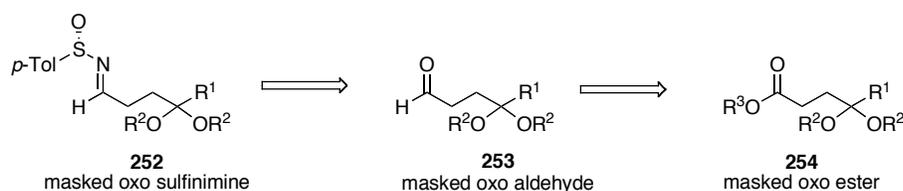


Scheme 3.7

3.2.1 Synthesis of Enantiomerically Pure Bridgehead Substituted Tropinones

3.2.1.1 Preparation of Masked Oxo Sulfinimines

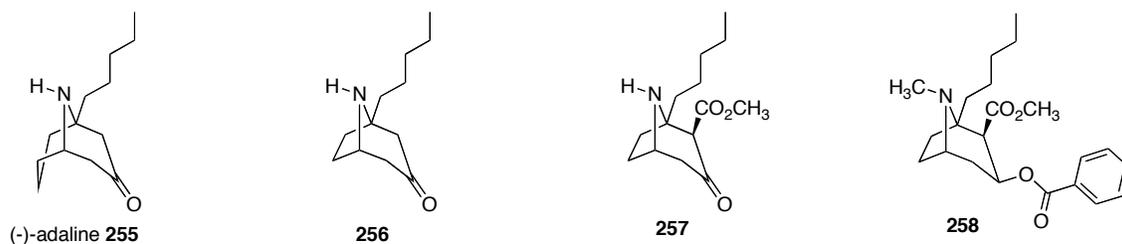
Masked oxo sulfinimines are useful polyfunctionalized chiral amine precursors which contain a protected ketone moiety that can be further modified after nucleophilic addition to the imine (Scheme 3.8).^{151,172} The R¹ substituent can therefore be a hydrogen, aryl or alkyl group depending on the needs of the target bridgehead-substituted tropinone. To obtain the required masked oxo sulfinimine **252**, the masked oxo aldehyde **253** must be synthesized. A common way towards the synthesis of the aldehyde is through the corresponding ester **254**, either through DIBAL reduction or via a reduction/oxidation through the intermediate alcohol.



Scheme 3.8

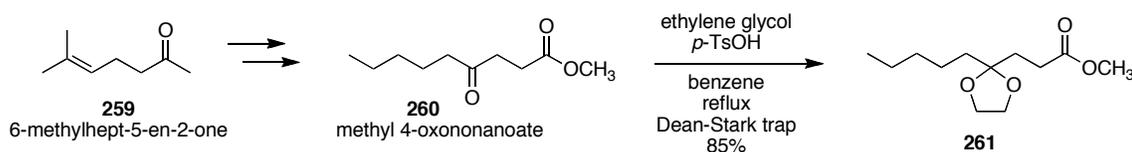
In order to test this methodology, it is important to vary the substituent at the bridgehead C-1 position of tropinone (R¹) (Scheme 3.9). First, building blocks that would provide a pentyl chain at C-1 would give an interesting derivative of tropinone **256** which would be also resemble a ring-contracted derivative of the ladybug alkaloid, (-)-adaline

(255). Its 2-carbomethoxy derivative would look like **257** and the corresponding cocaine analog as **258**.



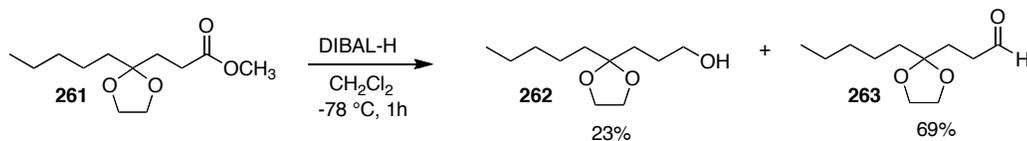
Scheme 3.9

The commercially available ketone, 6-methylhept-5-en-2-one (**259**) was taken through several manipulations that ended with an ozonolysis to yield methyl 4-oxononanoate (**260**) as reported by Geraghty and coworkers (Scheme 3.10).¹⁷⁸ The keto ester **261** was protected with ethylene glycol in the presence of *p*-toluene sulfonic acid through the azeotropic removal of water. After purification with Kügelrohr distillation, this afforded the ketal-protected ester in 85% yield.



Scheme 3.10

This ketal-protected keto ester **261** was subjected to an attempted reduction with diisobutyl alumino hydride in methylene chloride as solvent at $-78\text{ }^{\circ}\text{C}$ (Scheme 3.11). However, even with slow, careful addition of the reducing agent at $-78\text{ }^{\circ}\text{C}$, an inseparable mixture of alcohol **262** and aldehyde **263** resulted. Several conditions were tried and the conditions for these reductions can be found below (Table 3.1). The best results for this reaction were as outlined in Scheme 3.10 (Table 3.1, entry 1). As the equivalents of diisobutylalumino hydride were reduced, the yield of **263** suffered significantly and even the appearance of alcohol **262** was not eliminated (Table 3.1, entry 2). When the reaction time was changed, results were nearly identical with those obtained in entry 1 (Table 3.1, entry 3). Finally the use of other solvents, such as diethyl ether, tetrahydrofuran and toluene, was attempted (Table 3.1, entries 4, 5 & 6). With diethyl ether and tetrahydrofuran, the ratio of **262** to **263** suffered significantly (Table 3.1, entries 4 & 5). With toluene, the reaction was nearly identical to that of methylene chloride (Table 3.1, entry 6). This procedure was therefore abandoned and an alternate route to the aldehyde was undertaken.



Scheme 3.11

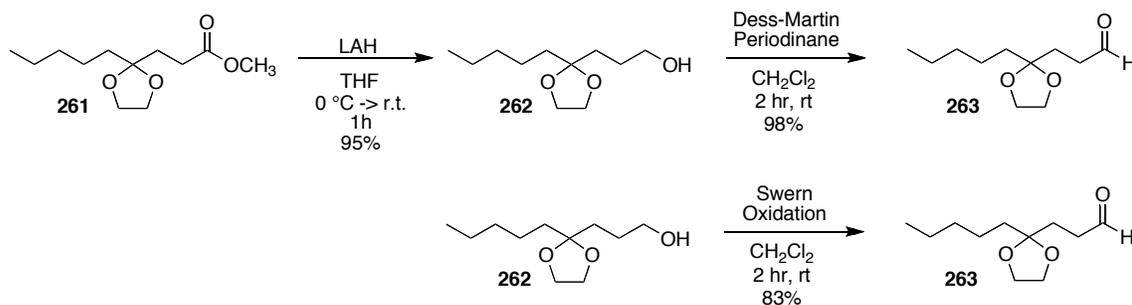
Table 3.1: Conditions for the Reduction of **261** with DIBAL-H

Entry	Solvent	Equiv [H]	Temp.	Time (hr)	Ratio (262:263) ^a	% Yield ^b
1	CH ₂ Cl ₂	1	-78 °C	1	1:3	92
2	CH ₂ Cl ₂	0.85	-78 °C	1	1:4	65
3	CH ₂ Cl ₂	1	-78 °C	0.5	1:3	89
4	Et ₂ O	1	-78 °C	1	2:3	90
5	THF	1	-78 °C	1	1:1	91
6	toluene	1	-78 °C	1	1:3	89

^a Ratio determined by ¹H NMR analysis of the reaction mixture. ^b Combined yield of **262** and **263**

The reduction of keto ester **261** with diisobutylaluminum hydride to yield only the aldehyde **263** proved to be unsuccessful. Therefore, the complete reduction of **261** to the corresponding alcohol **262** using lithium aluminum hydride and subsequent oxidation was necessary to obtain the desired aldehyde in high purity and yield (Scheme 3.12). Reduction of **261** with lithium aluminum hydride produced **262** cleanly and in 95% yield. Oxidation of **262** using Dess-Martin periodinane was found to be the most successful as the aldehyde **263** was obtained efficiently in 98% yield and without the need for purification. Oxidation of **262** using the Swern oxidation gave aldehyde **263** in only 83% yield with significant

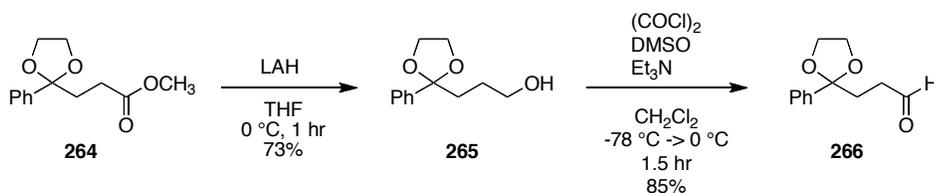
contamination that could not be removed due to aldehyde **263** being sensitive to degradation upon column chromatography.



Scheme 3.12

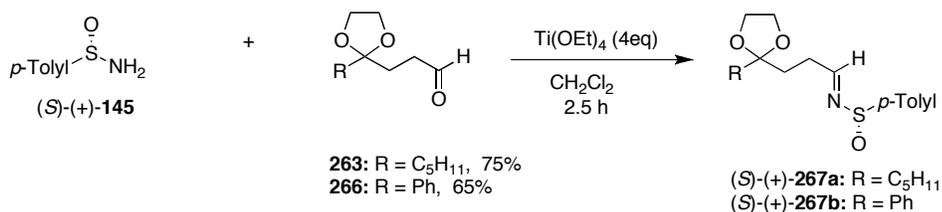
Synthesis of a masked oxo ester bearing a phenyl group rather than a pentyl chain was also synthesized using a previously known procedure.¹⁷³ Varying this group will provide information on any possible steric effects of the final iminium ion cyclization. The authors used a diisobutylaluminum hydride reduction of **264** to produce aldehyde **266** which was used *in situ* with a Wittig reagent to produce an alkene. However, it was found that reduction of **264** with diisobutylaluminum hydride produced poor yields of aldehyde **265** when using diisobutylaluminum hydride. This was again due to the production of inseparable mixtures of both aldehyde and alcohol. In addition, this Aldehyde was even more susceptible to degradation than its pentyl equivalent **263** and decomposed quickly (overnight) at room temperature. Therefore, reduction of **264** with lithium aluminum hydride to give the more stable alcohol intermediate **265** followed by a Swern oxidation cleanly produced the phenyl-

substituted aldehyde **266** which was used immediately in the next step (Scheme 3.13). Some care must also be taken with both the phenyl-substituted alcohol **265** because this compound is also prone to degradation at room temperature.



Scheme 3.13

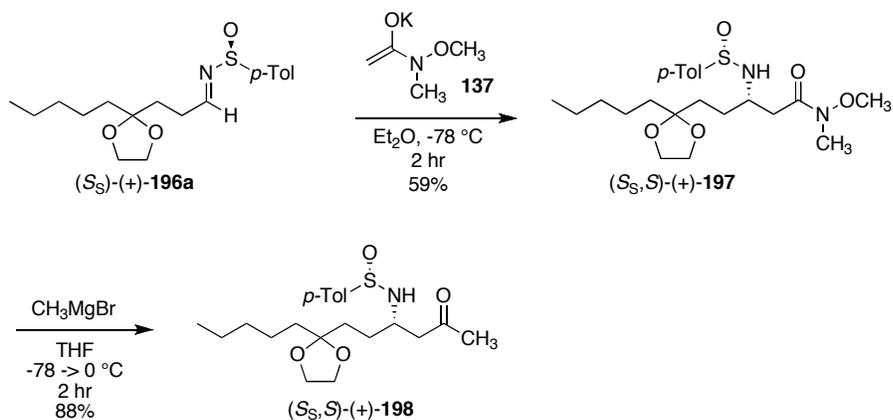
Masked oxo-aldehydes **263** and **266** were condensed with (*S*)-(+)-*p*-toluenesulfonamide (**145**) and titanium ethoxide as the Lewis acid in methylene chloride to give sulfinimines (*S_S*)-(+)-**267a** and (*S_S*)-(+)-**267b** in 75% and 65% yields, respectively (Scheme 3.14). Both of these sulfinimines were much more stable than their aldehyde counterparts and can be stored in the freezer (-20 °C) for extended periods of time.



Scheme 3.14

3.2.1.2 Addition of Enolates to Sulfinimines

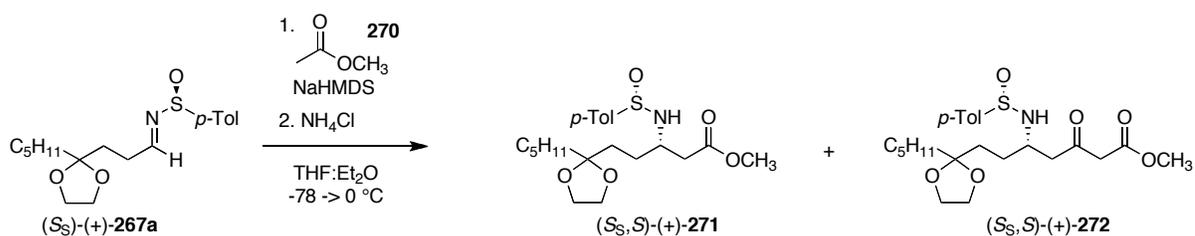
A solution of *N*-*para*-toluenesulfinyl 4,4-ethylenedioxy-1-nonan-1-imine (S_S)-(+)-**267a** was carefully added to a stirring solution of the potassium enolate of *N*-methoxy, *N*-methyl acetamide (**137**) to yield the *N*-sulfinyl β -amino Weinreb amide (S_S,S)-(+)-**268** in 65% yield but in a 8:1 ratio of rotamers (Scheme 3.15). Although the ^1H and ^{13}C NMR of this amide suggested a single diastereomer, this fact was not verified until the conversion of amide (S_S,S)-(+)-**268** to methyl ketone (S_S,S)-(+)-**269** with methyl magnesium bromide was accomplished. The *N*-sulfinyl β -amino ketone, (S_S,S)-(+)-**269**, was prepared in 88% yield and allowed for the disappearance of any rotamer peaks and their related confusion in determining a diastereomeric ratio. This chiral building block can give rise to the pentyl bridgehead-substituted tropinone **261** which is also a ring-contracted homologue of (-)-adalinone (Scheme 3.8).



Scheme 3.15

When *N*-*para*-toluenesulfinyl imine (*S_S*)-(+)-**267a** was added to a solution of five equivalents of the sodium enolate of methyl acetate (**270**) at -78 °C it produced a separable mixture of the *N*-sulfinyl monoester (*S_S*)-(+)-**271** and *N*-sulfinyl β -keto ester (*S_S*)-(+)-**272** which was also a pure diastereomer by ¹H and ¹³C NMR (Scheme 3.16).¹⁶⁰⁻¹⁶² Because it is the *N*-sulfinyl β -keto ester (*S_S*)-(+)-**272** that is the desired product for conversion into tropinone cocaine analog precursor **262**, several conditions were investigated for this transformation which are listed below (Table 3.2). When sulfinimine (*S_S*)-(+)-**267a** was reacted with five equivalents of the sodium enolate of methyl acetate at -78 °C, incomplete conversion occurred and the monoester (*S_S*)-(+)-**271** and β -keto ester (*S_S*)-(+)-**272** were formed in 30% and 40% yield, respectively (Table 3.2, entry 1). However, when this reaction mixture was raised to -45 °C, only a slight increase in *N*-sulfinyl β -keto ester (*S_S*)-(+)-**272** was seen (Table 3.2, entry 2). Also, very little was gained when the reaction time was held for six hours (Table 3.2, entry 3). Because the ambient conditions of a Pennsylvania summer was hot and humid at the time, it was believed that some enolate was being quenched by the excess humidity and therefore preventing full conversion of monoester (*S_S*)-(+)-**271** to *N*-sulfinyl β -keto ester (*S_S*)-(+)-**272**. In order to drive the reaction forward, six equivalents of the sodium enolate of methyl acetate were reacted with *N*-sulfinimine (*S_S*)-(+)-**267a** (Table 3.2, entries 4, 5 & 6). Even though the reaction time was reduced again to three hours, another slight increase in the desired *N*-sulfinyl β -keto ester (*S_S*)-(+)-**272** occurred (Table 3.2, entry 4). The best results were found when the reaction was warmed to 0 °C after stirring at -78 °C for two hours (Table 3.2, entry 5). Complete conversion of the monoester (*S_S*)-(+)-**271** was accomplished with the *N*-sulfinyl

β -keto ester (S_S,S)-(+)-**272** being obtained in a 68% yield. No change in diastereoselectivity was seen and indicates that all of the sulfinimine (S_S,S)-(+)-**267a** was consumed at -78 °C with only the conversion of monoester (S_S,S)-(+)-**271** to β -keto ester (S_S,S)-(+)-**272** requiring higher temperatures in this case. Likewise, it was important to maintain the reaction temperature at 0 °C no longer than one hour since the appearance of multiple undesired products could be seen through the use of thin-layer chromatography.



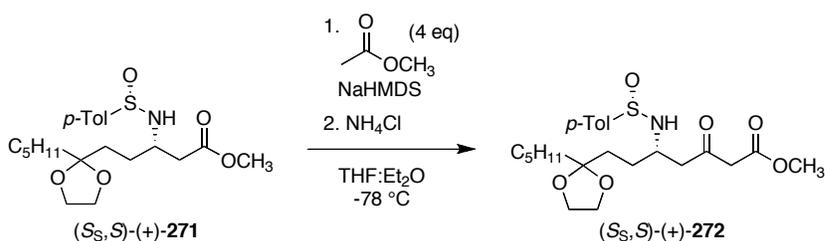
Scheme 3.16

Table 3.2: Conditions for the One-Pot Synthesis of *N*-Sulfinyl β -Keto Ester (S_S,S)-(+)-**272**

entry	enolate equiv.	temp. (°C)	time	% Yield of recovered 267a	% Yield (S_S,S)-(+)- 271 ^b	% Yield (S_S,S)-(+)- 272 ^b
1	5	-78	3	12	30	40
2	5	-78 to -40	3	8	28	45
3	5	-78 to -40	6	5	25	48
4	6	-78 to -40	3	5	15	52

^a Determined by ¹H NMR analysis of the chromatographed reaction mixture.

In an analogous reaction, several conditions were tried for converting the obtained monoester (*S,S,S*)-(+)-**271** to the *N*-sulfinyl β-keto ester (*S,S,S*)-(+)-**272** (Scheme 3.17) (Table 3.3). The results of these reactions verify the conclusions made from the optimized conditions of synthesizing β-keto ester (*S,S,S*)-(+)-**272** directly from sulfinimine (*S,S,S*)-(+)-**267a** in that full conversion of monoester (*S,S,S*)-(+)-**271** to β-keto ester (*S,S,S*)-(+)-**272** could only be accomplished at more elevated temperatures (Table 3.3, entry 3). When reacting the enolate of methyl acetate at only -78 °C (Table 3.3, entry 1) or with elevation to -45 °C (Table 3.3 entry 2), only a partial conversion of the monoester was observed. This confirms that the reason for the one-pot conversion (Scheme 3.10) not going to completion was due to reaction temperature and not the high ambient humidity.



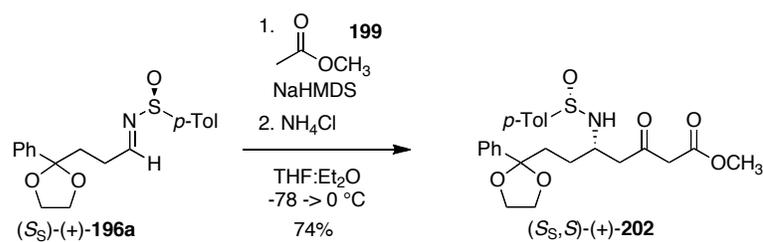
Scheme 3.17

Table 3.3: Conditions for the Two-Step Synthesis of *N*-Sulfinyl β -Keto Ester (*S_S*)-(+)-**272**^a

entry	temp. (°C)	Time (hr)	% Yield	
			(<i>S_S</i>)-(+)- 271	(<i>S_S</i>)-(+)- 272
1	-78	3	40%	49%
2	-78 to -40	3	30%	55%
3	-78 to 0	3	0%	82%

^a All reactions performed using 4 equivalents of methyl acetate.

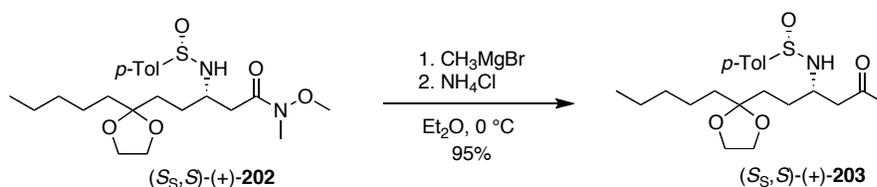
Utilizing the optimized conditions for the one-pot conversion of the *N*-sulfinimine to the *N*-sulfinyl β -keto ester, the phenyl-substituted masked oxo sulfinimine (*S*)-(+)-**267b** was easily converted to the keto ester (*S_S*)-(+)-**273** in 74% yield (Scheme 3.18). The product was obtained as a single diastereomer and showed no signs of instability as with some of its precursors (ex: **266**).



Scheme 3.18

3.2.1.3 Synthesis of β -Amino Ketone Ketals

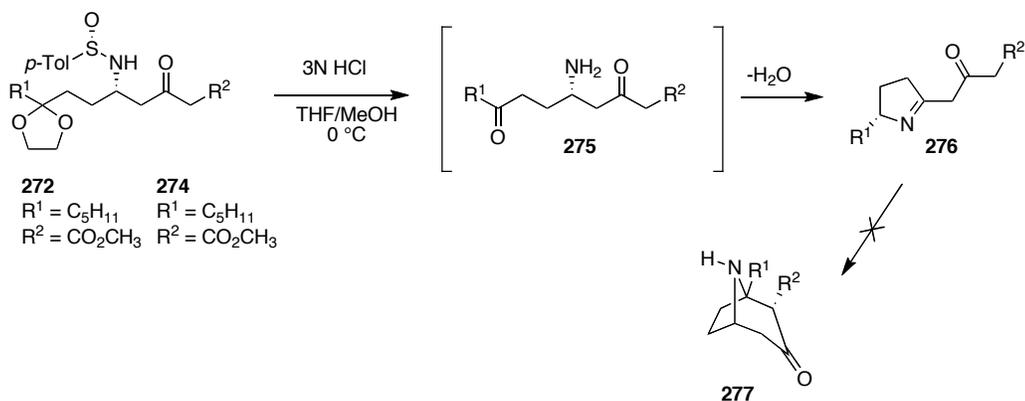
With Weinreb amide (S_S,S)-(+)-**268** in hand, the methyl ketone (S_S,S)-(+)-**274** could be synthesized using five equivalents methyl magnesium bromide in diethyl ether at 0 °C (Scheme 3.19). This produced the methyl ketone cleanly and in very high yields and could be used in cyclization studies to make a novel ring-truncated derivative of (-)-adaline (**260**).



Scheme 3.19

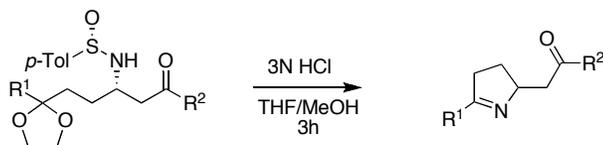
3.2.1.4 Formation of Dehydropyrrolidines (Imines)

The masked *N*-sulfinyl- δ -amino- β -keto esters and the β -amino ketone ketals **273** and **274** were subjected to hydrolysis in aqueous hydrochloric acid in methanol and THF (Scheme 3.20) (Table 3.4). The imine precursor underwent complete deprotection of the ketal and *N*-*para*-toluenesulfinyl protecting groups to give a non-isolated intermediary amino ketone **275** which undergoes a ring-closing condensation that gave only production of the 5-membered imine **276** (Scheme 3.19). No tropinone derivative **277** formation was detected in any of these cases.



Scheme 3.20

Table 3.4: Formation of 5-Membered Imines^a

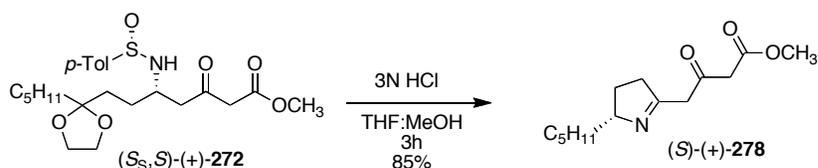


Entry	Imine Precursor	R ¹	R ²	Product	Yield%
1	(<i>S,S,S</i>)-(+)- 272	C ₅ H ₁₁	CO ₂ CH ₃	(<i>S</i>)-(+)- 278	85
2	(<i>S,S,S</i>)-(+)- 273	Ph	CO ₂ CH ₃	(<i>S</i>)-(-)- 279	69
3	(<i>S,S,S</i>)-(+)- 274	C ₅ H ₁₁	CH ₃	(<i>S</i>)-(+)- 280	71

^a All reactions were carried out with 3 N HCl/MeOH in THF at rt for 5 h.

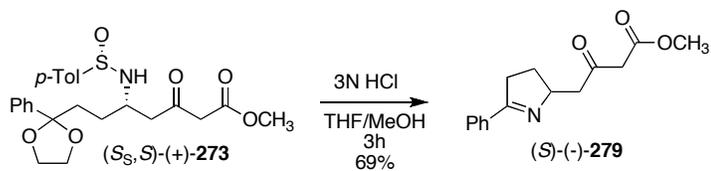
The *N*-*para*-toluenesulfinyl β-amino ketone, (*S,S,S*)-(+)-**272** was reacted with 3N hydrochloric acid in tetrahydrofuran and methanol. Here, methanol was chosen as the cosolvent because it had been reported that 2-carbomethoxy tropinone **242**, as well as

ecognine methyl ester **243**, can undergo saponification to the carboxylic acid in the presence of water.¹⁸⁹ However, dehydropyrrolidine (*S*)-(+)-**278** was formed in 85% yield with no sign of epimerization by NMR (Scheme 3.21) (Table 3.4, entry 1). The presence of the imino carbons at δ 176.5 ppm in ¹³C NMR, as well as the appearance of a peak in the infrared spectrum at 1680 cm⁻¹ corresponding to the C=N stretch was indicative of the imine and not the cyclized nortropinone product.



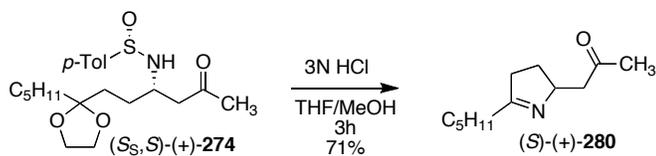
Scheme 3.21

Likewise, phenyl substituted *N*-sulfinyl β -keto ester (*S_{S,S}*)-(+)-**273** was treated in the same conditions to yield dehydropyrrolidine (*S*)-(-)-**279** in 69% yield (Scheme 3.22) (Table 3.4, entry 2). Again, no evidence of nortropinone formation was detected and only complete conversion to the cyclic imine was observed. Carbons at δ 200-210 and δ 165 ppm, respectively, provided evidence for the formation of (*S*)-(-)-**279** over the nortropinone derivative.



Scheme 3.22

With the pentyl substituted *N*-sulfinyl β -amino ketone $(S,S,S)\text{-}(+)\text{-274}$, treatment with HCl gave the imine cyclization product $(S)\text{-}(+)\text{-280}$ with no appearance of the nortropinone which would appear as the ring-truncated analog of $(-)$ -adaline (Scheme 3.23) (Table 3.4, entry 3). Cyclization to this imine product occurred in 71% yield.

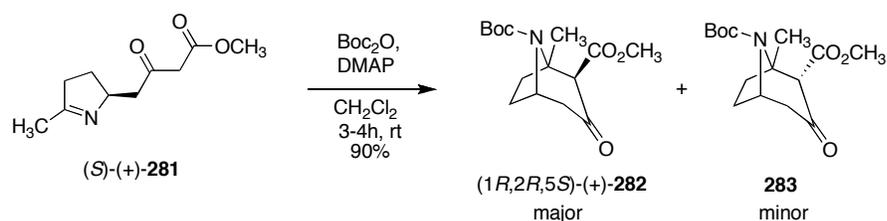


Scheme 3.23

3.2.1.5 Cyclization of *N*-Acyl Iminium Ion

It was later discovered by Naresh Theddu that treatment of an analogous dehydropyrrolidine $(+)\text{-281}$, which contains a bridgehead methyl substituent, with di-*tert*-butyl dicarbonate produced the Boc-protected tropinone $(+)\text{-282}$ in 90% yield (Scheme 3.24).¹⁹⁰ Although the starting material dehydropyrrolidine **281** was used as a pure

diastereomer, the product tropinone **282** was obtained as a 10:1 mixture of inseparable diastereomers. This minor diastereomer was assumed to be the C-2 epimer as reported by Thomas and coworkers.¹⁷⁶ The major epimer is assigned as axial because in their paper, a similar assignment was made regarding an analogous intermediate in a racemic synthesis towards stemofoline.¹⁷⁶ Also, the methyl ¹H NMR signal of the tropinone shifts upfield to δ 1.0-1.3 with respect to δ 2.0 for the imine **281**.



Scheme 3.24

It is probable that the major diastereomer (1*R*,2*R*,5*S*)-(+)-**282** is formed through the cyclic iminium ion **TS-3.2** whereby the enol achieves a thermodynamically stable *E* geometry which gives the major product with the C-2 carbomethoxy group in the thermodynamically unfavorable axial position (Figure 3.2). When the nucleophilic enol is in the *Z* geometry, it is likely that a steric interaction between the methyl ester and the bridgehead substituent occurs and therefore minimizes formation of the equatorial C-2 carbomethoxy group.

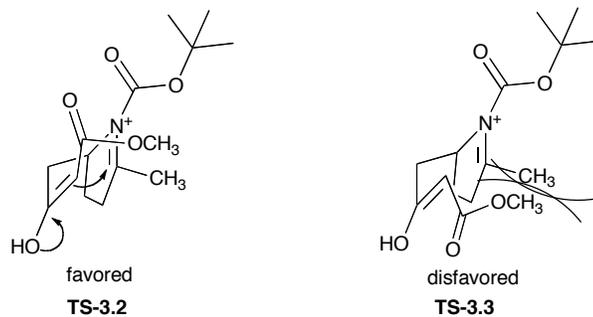
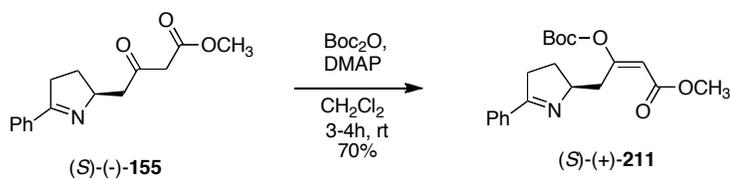


Figure 3.2: Cyclization Transition State of *N*-Acyl Iminium Ion to Tropinones

Also shown by Naresh Theddu, when (*S*)-(-)-**155b** was reacted under the same conditions, enol carbonate (*S*)-(+)-**211** formed in 70% yields (Scheme 3.25).



Scheme 3.25

3.4 Conclusions

Although this methodology has not been, fully developed, *N*-sulfinyl- β -amino ketones have been shown to be valuable sulfinimine-derived intermediates that can be used in the intramolecular Mannich reaction to produce chiral, bridgehead-substituted tropinones.

By accessing these unique bridgehead-substituted tropinones, novel derivatives of tropane alkaloids such as (-)-cocaine and scopolamine can possibly be formed through this route. The synthesis and biological analyses of chiral, bridgehead-substituted tropane derivatives, such as (-)-cocaine, would provide new data on the structure-activity-relationships of these bioactive natural products. Since no bridgehead-substituted derivatives of (-)-cocaine have been made, a new class of compounds which act at the dopamine reuptake transporter could await. These compounds could possibly be used as addiction therapeutics or novel stimulants devoid of any addictive behavior.

CHAPTER 4

EXPERIMENTAL SECTION

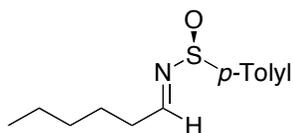
4.1 General Methods

Reagents and solvents were purchased from Sigma-Aldrich or Acros Organics and were used without additional purification unless otherwise noted. Glassware was oven-dried at 120 °C and cooled to ambient temperature in desiccators prior to use. Reactions involving air sensitive substances and/or requiring anhydrous reaction conditions were flame-dried and performed under an argon atmosphere. Reagent grade tetrahydrofuran (THF), diethyl ether (Et₂O) and methylene chloride (CH₂Cl₂) were purified by filtration on a Glass Contour Solvent Dispensing System. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). Analytical and preparative thin-layer chromatography was performed on precoated silica gel plates (250 and 1000 microns) purchase from Analtech Inc. TLC plates were visualized with UV, in an iodine chamber or with a potassium permanganate stain.

Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer using NaCl plates for liquid and KBr discs for solids. ¹H and ¹³C NMR spectra were obtained in CDCl₃ or CD₃OD solution and were referenced to TMS (0.00 ppm), CHCl₃ (7.26 ppm for ¹H NMR and 77.36 ppm for ¹³C NMR), methanol (3.35 ppm for ¹H NMR and 49.86 ppm for ¹³C NMR using GE Omega 500 MHz,

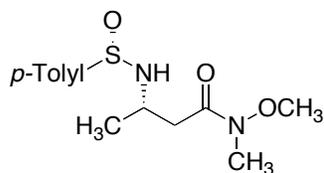
Bruker 400 MHz or Varian 300 MHz NMR spectrometer. High resolution mass spectra were collected at the Department of Chemistry, Drexel University, Philadelphia, PA, or Michigan State University Mass Spectrometry Facility, East Lansing, MI. Elemental analyses were performed at the Department of Chemistry, University of Pennsylvania, Philadelphia PA.

4.2 CHAPTER 2: ASYMMETRIC SYNTHESIS OF ACYCLIC 1,3-AMINO ALCOHOLS. FORMAL SYNTHESIS OF (-)-PINIDINOL AND (+)-EPIPINIDINOL



(*S*)-(+)-**162b**

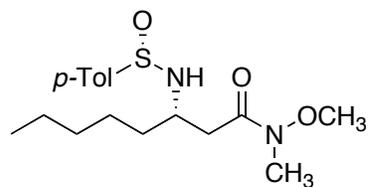
(*S*)-(+)-*N*-(Hexylidene)-*p*-toluenesulfonamide (162b): In a 250 mL, flame-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed (*S*)-(+)-*p*-toluenesulfonamide (**159**) (1.55 g, 10 mmol) and *n*-hexanal (1.23 mL, 10 mmol) in CH₂Cl₂ (62 mL) at 0 °C. To the mixture was added Ti(OEt)₄ (0.114 g, 50 mmol) at 0 °C, and the solution was stirred for 4 h at rt. At this time, the reaction was quenched with H₂O (10 mL) and filtered through a Celite pad, and the Celite was washed with CH₂Cl₂ (50 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were combined, dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc, 92:8) gave 1.9 g (80%) of a slightly yellow oil: [α]_D²⁰ = +328.6 (*c* 0.982, CHCl₃); IR (neat) 1597, 1458, 1096 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.31 (4 overlapping H), 1.61 (m, 2H), 2.41 (s, 3H), 2.49 (m, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 8.23 (t, *J* = 4.8 Hz, 1H); δ 14.1, 21.7, 22.6, 25.4, 31.6, 36.1, 124.9, 130.1, 141.9, 142.3, 167.6; HRMS calcd for C₁₃H₂₀NOS (M + H) 238.1272, found 238.1265.



(*S,S,S*)-(+)-**163a**

(*SS,3S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methylpropionamide

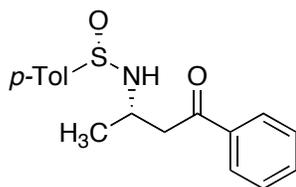
(163a): In a two-neck, oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed *N*-methoxy-*N*-methylacetamide (0.16 mL, 1.5 mmol) in THF (20 mL). The solution was cooled to -78 °C, KHMDS (1.5 mmol, 3 mL of 0.5 M solution in toluene) was added, and the reaction mixture was stirred at this temperature for 1 h. A solution of (*S*)-(+)-**162a** (0.25 g, 1.0 mmol) in THF (10 mL) was added, and the solution was stirred at this temperature for 2.5 h. At this time, the reaction mixture was quenched with saturated NH₄Cl (5 mL), slowly warmed to rt, and diluted with H₂O (10 mL). The solution was extracted with Et₂O (2 x 30 mL), and the organic phases were washed with brine (25 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc 1:9) yielded 0.19 g (66%) of a clear oil: [α]_D²⁰ = +154.8 (*c* 2.73, CHCl₃); IR (neat) 3482, 3220, 1652 cm⁻¹; ¹H NMR (CDCl₃) δ 1.42 (d, *J* = 6.6 Hz, 3H), 2.42 (s, 3H), 2.67 (d, *J* = 5.5 Hz, 2H), 3.16 (s, 3H), 3.66 (s, 3H), 3.85 (m, 1H), 5.06 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.61 (q, *J* = 4.9, 8.2 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.8, 22.7, 32.2, 33.2, 39.7, 40.3, 47.9, 61.6, 126.1, 126.4, 129.9, 141.5, 142.6, 172.5; HRMS calcd for C₁₃H₂₀O₃N₂SNa (M + Na) 307.1092, found 307.1090.



(*S_s,3S*)-(+)-163b

(*S_s,3S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyloctanamide

(163b). Flash chromatography (hexanes:/EtOAc, 2:3) gave 1.1 g (77%) of a clear oil: $[\alpha]_D^{20} = +105.7$ (*c* 1.07, CHCl₃); IR (neat) 3019, 1216 cm⁻¹; ¹H NMR (CDCl₃) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.4-1.8 (8 overlapping H), 2.41 (s, 3H), 2.78 (m, 2H), 3.16 (s, 3H), 3.67 (s, 3H overlapped with 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.4, 21.7, 22.9, 26.3, 31.9, 36.1, 37.9, 53.6, 61.6, 125.9, 129.8, 141.4, 143.3, 173.5; HRMS calcd for C₁₇H₂₉N₂O₃S (M + H) 341.1899, found 341.1903.

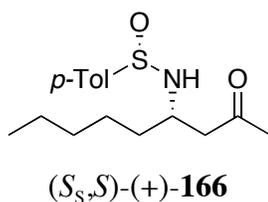


(*S_s,3S*)-(+)-165

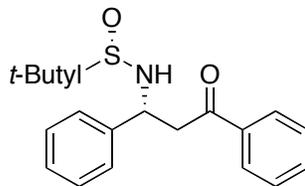
(*SS,3S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-phenyl-3-methylpropan-

1-one (165): In an oven-dried, singleneck, 50-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (*S_s,R*)-(+)-**163a** (0.284 g, 1.0 mmol) in THF (20 mL) under an argon atmosphere. The solution was cooled to -78 °C, PhMgBr (5.0 mmol, 5.0 mL of 1.0 M solution in THF) was added via syringe, and the reaction mixture was warmed to rt. After being stirred for 1 h, the solution was cooled to -78

°C, quenched with satd NH₄Cl (6 mL), and warmed to rt. The solution was diluted with H₂O (10 mL) and extracted with Et₂O (3 x 10 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc 1:1) gave 0.257 g (79%) of a clear oil: $[\alpha]_D^{20} = +75.1$ (*c* 0.8, CHCl₃); IR (neat) 3197, 1675, 1568 cm⁻¹; ¹H NMR (CDCl₃) δ 1.36 (d, *J* = 6.6 Hz, 3H), 2.33 (s, 3H), 3.09 (dq, *J* = 5.4 Hz, *J* = 16.8 Hz, 1H), 3.89-3.95 (m, 2H), 4.62 (d, *J* = 7.8 Hz, 1H), 7.34 (m, 7H), 7.77 (d, *J* = 7.4 Hz, 2H). ¹³C NMR (CDCl₃) δ 21.7, 22.5, 22.9, 46.7, 47.7, 125.8, 128.5, 129.0, 129.9, 133.8, 137.1, 141.6, 142.4, 198.0; HRMS calcd for C₁₇H₁₉NO₂SNa (M + Na) 324.1034, found 324.1030.



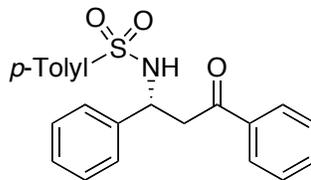
(*SS,4S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-one (166). Chromatography (hexanes/EtOAc, 7:3) gave 74% of a clear oil: $[\alpha]_D^{20} = +101.6$ (*c* 1.36, CHCl₃); IR (neat) 3053, 1712, 1265, 1063 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (t, *J* = 6.8 Hz, 3H), 1.27-1.71 (8 overlapping H), 2.11 (s, 3H), 2.42 (s, 3H), 2.77 (d, *J* = 5.2 Hz, 2H), 3.66 (m, 1H), 4.42 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.3, 21.6, 22.8, 26.2, 31.1, 31.8, 36.1, 49.5, 52.9, 125.8, 129.8, 141.5, 143.0, 207.8; HRMS calcd for C₁₆H₂₆NO₂S (M + H) 296.1684, found 296.1691.



(*S,S,3R*)-(+)-**169**

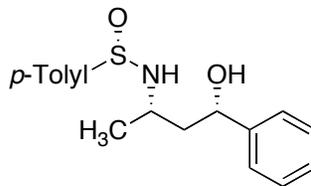
(*S,S,3R*)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1,3-diphenylpropan-

1-one (169): In a single-neck, oven-dried, 50-mL round-bottomed flask equipped with a magnetic stirring bar, a rubber septum and an argon inlet were placed THF (10 mL) and KHMDS (1.8 mmol, 3.6 mL of a 0.5 M solution in THF) under argon atmosphere. The solution was cooled to -78 °C, acetophenone (0.21 mL, 1.8 mmol) was added via syringe, and the solution was stirred for 1 h. A cooled -78 °C solution of (*S*)-(-)-*N*-(benzylidene-2-methylpropane) sulfinamide³¹ (0.209 g, 1.0 mmol) in THF (10 mL) was added dropwise via cannula to the enolate solution followed by THF (5 mL) to rinse the flask. The reaction mixture was stirred at -78 °C for 2 h and cautiously quenched with saturated NH₄Cl (4 mL). The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (2 x 15 mL), and the combined organic phases were combined. Chromatography (30:70, hexanes/EtOAc) gave 0.273 g (83%) of a clear oil which solidified on standing: mp 68-70 °C; [α]_D²⁰ = +123.6 (*c* 0.25, CHCl₃); IR (neat) 3270, 3202, 1629 cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (s, 9H), 3.47 (dd, *J* = 8.0 Hz, *J* = 17.2 Hz, 1H), 3.59 (dd, *J* = 17.2 Hz, *J* = 4.0 Hz, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.96 (m, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 7.35 (m, 7H), 7.55 (m, 1H), 7.91 (m, 2H); ¹³C NMR (CDCl₃) δ 23.0, 46.3, 55.7, 55.9, 127.9, 128.3, 128.5, 129.0, 134.0, 136.9, 141.4, 198.9; HRMS calcd for C₁₉H₂₃NO₂SNa (M + Na) 352.1347, found 352.1348.



(*R*)-(+)-171

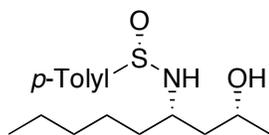
(*R*)-(+)-*N*-(*p*-Toluenesulfonyl)-3-amino-1,3-diphenylpropan-1-one (171). In a single-neck, 25-mL round-bottom flask equipped with magnetic stirring bar, rubber septum, and argon inlet were placed (*S_S,3R*)-(+)-**168** (0.363 g, 1.0 mmol) and CH₂Cl₂ (15 mL) under an argon atmosphere. The solution was cooled to 0 °C, *m*CPBA (0.6 g, 3.5 mmol, 77%) was added, and the solution was stirred at this temperature for 3.5 h. At this time, NaHCO₃ (1 N aqueous solution) was added to the reaction mixture until pH 8 was reached. The solution was extracted with EtOAc (2 x 10 mL), and the organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc 1:1) gave 0.364 g (96%) of a clear oil: $[\alpha]_D^{20} = +18.3$ (*c* 1.0, CHCl₃); IR (neat) 3050, 1629, 1410, 1250 cm⁻¹; ¹H NMR (CDCl₃) δ 2.35 (s, 3H), 3.45 (dd, *J* = 6.0 Hz, *J* = 17.2 Hz, 1H), 3.59 (dd, *J* = 6.0 Hz, *J* = 17.2 Hz, 1H), 4.87 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 5.81 (d, *J* = 6.4 Hz, 1H), 7.16 (m, 7H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.54 (t, 1H), 7.61 (d, *J* = 8 Hz, 2H), 7.80 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.8, 45.1, 54.8, 127.1, 127.6, 128.0, 128.4, 128.9, 129.0, 129.8, 133.9, 136.7, 137.6, 140.3, 143.6, 198.1. HRMS could not be obtained due to decomposition in the instrument.



(*S_s*,1*R*,3*R*)-(+)-**172a**

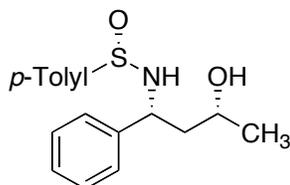
(*S_s*,1*R*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol

(172a). Typical Procedure for the Reduction of β -Amino Ketones with Li(*t*-Bu)₃AlH and LiCl in Et₂O To Give *syn*-1,3-Amino Alcohols. In a flame-dried, 50-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (+)-**151** (0.054 g, 0.179 mmol) and LiCl (0.076 g, 1.8 mmol) in Et₂O (9 mL). The reaction mixture was sonicated for 5-10 min and cooled to -78 °C, and Li(*t*-BuO)₃AlH (0.895 mmol, 0.895 mL of a 1.0 M solution in THF) was added dropwise. The solution was stirred at this temperature for 2 h and quenched with satd aqueous NH₄Cl (0.5 mL) and H₂O (0.5 mL). The organic phases were separated; the aqueous phase was washed with EtOAc (2 x mL), and the combined organic phases were dried (MgSO₄) and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 0.014 g (61%) of a clear oil: $[\alpha]_D^{20} = +76.5$ (*c* 4.5, CHCl₃); IR (neat) 3309, 3223, 1270 cm⁻¹; ¹H NMR (CDCl₃) δ 1.35 (d, *J* = 6.5 Hz, 3H), 1.74 (m, 1H), 1.88 (m, 1H), 2.41 (s, 3H), 3.71 (m, 1H), 3.84 (d, *J* = 3.5 Hz, 1H), 4.79 (m, 1H), 5.03 (d, *J* = 4.5 Hz, 1H), 7.26 (m, 7H), 7.61 (m, 2H); ¹³C NMR (CDCl₃) δ 21.9, 24.2, 47.7, 48.9, 50.8, 71.2, 74.2, 126.2, 127.9, 128.1, 129.1, 130.2, 145.3; HRMS calcd for C₁₇H₂₁NO₂SNa (M + Na) 326.1191, found 326.1195.



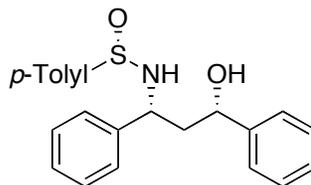
(*S_S,2*S*,4*R)-(+)-173a**

(*S_S,2*S*,4*R)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-ol (173a).** Chromatography (hexanes/EtOAc, 6:4) gave 61% of a clear oil: $[\alpha]_D^{20} = +107.6$ (*c* 0.341, CHCl₃); IR (neat) 3054, 1422, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 0.92 (t, *J* = 10.4 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.45 (m, 10H), 2.41 (s, 3H), 3.53 (m, 1H), 3.60 (br d, *J* = 2.8 Hz, 1H), 4.04 (m, 1H), 4.30 (d, *J* = 6.8 Hz, 1H), 7.29 (d, *J* = 8 Hz, 2H), 7.59 (d, *J* = 8 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.4, 21.7, 22.9, 24.7, 25.5, 32.0, 38.1, 45.5, 56.4, 67.6, 125.6, 129.9, 141.8, 142.8; HRMS calcd for C₁₆H₂₈NO₂S (M + H) 298.1762, found 297.1831.



(*S_S,1*S*,3*R)-(+)-174a**

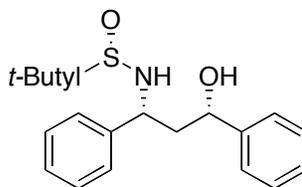
(*S_S,1*R*,3*R)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (174a):** Chromatography (hexanes/EtOAc, 40:60) gave 0.040 g (70%) of a clear oil: $[\alpha]_D^{20} = +16.6$ (*c* 0.295, CHCl₃); IR (neat) 3054, 1422, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 1.16 (d, *J* = 6 Hz, 3H), 1.85 (m, 2H), 2.40 (s, 3H), 3.45 (d, *J* = 4.8 Hz, 1H), 4.01 (m, 1H), 4.74 (m, 1H), 5.51 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8 Hz, 2H), 7.35 (m, 5 overlapping H), 7.54 (d, *J* = 8 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.7, 25.0, 47.5, 58.8, 125.6, 127.5, 128.0, 129.1, 129.9, 141.7, 143.1, 143.2; HRMS calcd for C₁₇H₂₁NO₂SNa (M+ H) 326.1190, found 326.1182.



(*S_s,1*S*,3*R)-(+)-175a**

(*SS,1*S*,3*R)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenylpropan-1-ol (175a).**

Chromatography (hexanes/EtOAc, 65:35) gave 74% of a white solid: mp 46-47 °C; $[\alpha]_D^{20} = +12.1$ (*c* 1.0, CHCl₃); IR (CHCl₃) 3268, 1246 cm⁻¹; ¹H NMR (CDCl₃) δ 1.95 (m, 1H), 2.14 (m, 1H), 2.33 (s, 3H), 3.27 (d, *J* = 2.8 Hz, 1H), 4.79 (dt, *J* = 2.8 Hz, *J* = 9.2 Hz, 2H), 5.45 (d, *J* = 2.4 Hz, 1H), 7.16 (m, 2H), 7.23 (m, 6H), 7.30 (t, *J* = 8 Hz, 2H), 7.37 (t, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.8, 47.7, 58.7, 125.7, 125.9, 127.7, 128.0, 128.1, 128.9, 129.0, 129.9, 141.7, 142.8, 144.9; HRMS calcd for C₂₂H₂₃NO₂SNa (M + Na) 388.1347, found 388.1345.

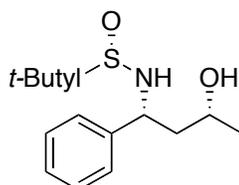


(*SS,1*S*,3*R)-(+)-176a**

(*S_s,1*S*,3*R)-(+)-*N*-(2-Methylpropanesulinylyl)-3-amino-1,3-diphenyl-1-ol (176a):**

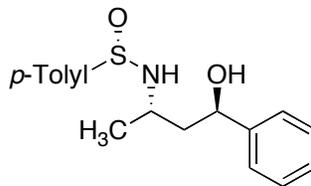
Chromatography (hexane/EtOAc, 3:1) gave 90% of white solid: mp 158-162 °C; $[\alpha]_D^{20} = +66.3$ (*c* 0.3, CHCl₃); IR (neat) 3231, 1651, 1280 cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (s, 9H), 1.98 (dq, *J* = 2.4 Hz, *J* = 3.2 Hz, *J* = 14.4 Hz, 1H), 2.19 (dt, *J* = 4.4 Hz, *J* = 10.4 Hz, *J* = 14.4

Hz, 1H), 4.02 (br, 1H), 4.74 (m, 1H), 5.00 d, $J = 10.4$ Hz, 1H), 5.44 (s, 1H), 7.26 (m, 2H), 7.35 (m, 8H); ^{13}C NMR (CDCl_3) δ 23.1, 46.3, 55.7, 56.0, 127.9, 128.3, 128.5, 129.0, 134.0, 136.9, 141.4, 198.9; HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{SNa}$ ($\text{M} + \text{Na}$) 354.1504, found 354.1517.



($S_S,1S,3R$)-(+)-177a

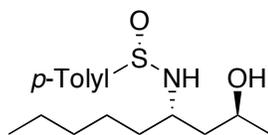
($S_S,1S,3R$)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1-methyl-3 phenylpropan-1-ol (177a). Chromatography (EtOAc/hexanes 2:1) gave 90% of a white solid: mp 145-6 °C; $[\alpha]_D^{20} = +181.9$ (c 0.8, CHCl_3); IR (neat) 3100, 1210 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.13 (s, 9H), 1.23 (d, $J = 6.1$ Hz, 3H), 1.70 (m, 1H), 1.83 (m, 1H), 2.06 (br, 1H), 4.09 (m, 1H), 4.30 (m, 1H), 4.52 (d, $J = 9.6$ Hz, 1H), 7.16 (m, 1H), 7.23 (m, 4H); ^{13}C NMR (CDCl_3) δ 23.1, 25.2, 47.1, 55.8, 59.2, 68.8, 127.5, 127.83, 137.84, 143.6; HRMS calcd for $\text{C}_{14}\text{H}_{24}\text{NSO}_2$ ($\text{M} + \text{H}$) 270.1538, found 270.1521.



(*S_s,1S,3R*)-(+)-**172b**

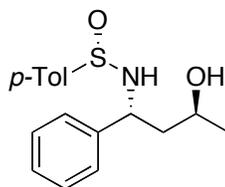
(*S_s,1S,3R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-phenyl-3-methylpropan-1-ol

(172b): Typical Procedure for the Reduction of β -Amino Ketones with LiEt₃BH To Give *anti*-1,3-Amino Alcohols. In a single-neck, oven-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (*SS,3S*)-(+)-**165** (0.036 g, 0.1 mmol) in CH₂Cl₂ (10 mL) under an argon atmosphere. The solution was cooled to -78 °C, and LiEt₃BH (0.5 mmol, 0.5 mL of 1.0M solution in THF) was added dropwise via syringe. After being stirred at -78 °C for 2 h, the reaction mixture was cautiously quenched with saturated NH₄Cl (1 mL) and warmed to rt. The solution was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL), and the combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 73% of a clear oil. $[\alpha]_D^{20} = +88.4$ (*c* 2.6, CHCl₃); IR (neat) 3322, 2963, 1248 cm⁻¹; ¹H NMR (CDCl₃) δ 1.35 (d, *J* = 6.5 Hz, 3H), 1.80 (m, 1H), 1.89-1.95 (m, 2H), 2.42 (s, 3H), 2.97 (d, *J* = 4.5 Hz, 1H), 3.53 (m, 1H), 4.35 (d, *J* = 7.5 Hz, 1H), 7.29 (m, 7H), 7.61 (d, *J* = 8.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.3, 24.0, 47.3, 48.7, 126.0, 127.7, 128.8, 129.9, 141.8, 142.4, 144.9; HRMS calcd for C₁₇H₂₁NO₂SNa (M + Na) 326.1191, found 326.1198.



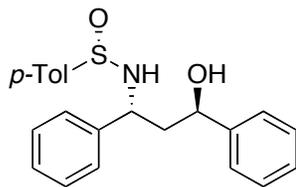
(*S*_S,2*S*,4*S*)-(+)-**173b**

(*S*_S,2*S*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-aminononan-2-ol (173b): Chromatography (hexanes/EtOAc, 6:4) gave 72% of a clear oil: $[\alpha]_D^{20} = +89.6$ (*c* 0.341 CHCl₃); IR (CH₂Cl₂) 3054, 1422, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ (major diastereomer) 0.89 (m, 7 overlapping H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.31-1.78 (m, 6 overlapping H), 2.42 (s, 3H), 3.23 (m, 1H), 3.62 (m, 1H), 3.98 (m, 1 H), 4.48 (br s, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.4, 21.7, 23.0, 23.9, 26.1, 32.0, 37.8, 45.1, 54.1, 63.9, 125.7, 129.9, 141.9, 142.7; HRMS calcd for C₁₆H₂₈NO₂S (M + H) 298.1841, found 298.1840.



(*S*_S,1*S*,3*R*)-(+)-**174b**

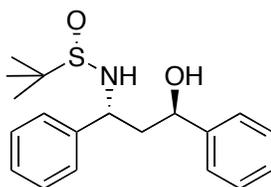
(*S*_S,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (174b): Chromatography (petroleum ether/EtOAc, 1:1) provided 84% of a clear oil: $[\alpha]_D^{20} = +65.2$ (*c* 1.0, CHCl₃); IR (neat) 3339, 3214, 1263 cm⁻¹; ¹H NMR (CDCl₃) δ 1.15 (d, *J* = 6.3 Hz, 3H), 1.73 (m, 1H), 1.88 (m, 1H), 2.34 (s, 3H), 2.86 (d, *J* = 4.4 Hz, 1H), 4.65 (d, *J* = 6.3 Hz, 1H), 4.74 (m, 1H), 4.88 (br, 1H), 7.25 (m, 7H), 7.53 (d, *J* = 5.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.8, 23.8, 45.7, 55.7, 64.7, 126.5, 127.5, 127.7, 128.8, 129.7, 137.9, 141.1, 143.5; HRMS calcd for C₁₇H₂₂NO₂S (M + H) 304.1371, found 304.1365.



(*S_s*,1*R*,3*R*)-(+)-175b

(*S_s*,1*R*,3*R*)-(+)-3-(*p*-Toluenesulfinylamino)-1,3-diphenylpropan-1-ol (175b).

Chromatography (petroleum ether/EtOAc 1:1) gave 0.033 g (90%) of a white solid: mp 123-126 °C; $[\alpha]_D^{20} = +130.8$ (*c* 1.0, CHCl₃); IR (neat) 3260, 3030, 1262 cm⁻¹; ¹H NMR (CDCl₃) δ 1.99 (dq, *J* = 4.4 Hz, *J* = 4.8 Hz, *J* = 7.2 Hz, *J* = 18.8 Hz, m, 1H), 2.16-2.23 (dq, *J* = 4.4 Hz, *J* = 4.8 Hz, *J* = 7.2 Hz, *J* = 18.8 Hz, m, 1H), 2.32 (s, 3H), 3.06 (d, *J* = 4.0 Hz, 1H), 4.68-4.73 (m, 2H), 4.76 (d, *J* = 6.4 Hz, 1H), 7.15 (m, 1H), 7.22 (m, 7H), 7.29 (d, *J* = 4.0 Hz, m, 4H), 7.50 (d, *J* = 8.0 Hz, m, 2H); ¹³C NMR (CDCl₃) δ 21.7, 47.4, 56.5, 70.9, 125.9, 126.2, 127.2, 127.85, 127.90, 128.9, 129.1, 130.0, 141.9, 142.6, 143.0, 144.2. Anal. calcd for C₂₂H₂₃NO₂S: C, 72.30; H, 6.34; N, 3.83. Found: C, 72.46; H, 6.82; N, 3.89.

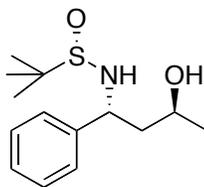


176b

(*S_S*,1*S*,3*R*)-(+)-*N*-(2-Methylpropanesuliny1)-3-amino-1,3-diphenyl-1-ol (176b).

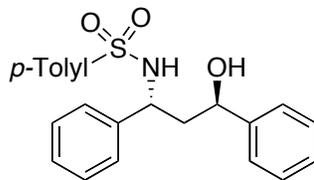
Chromatography (hexane/EtOAc, 3:1) gave 90% of white solid: mp 158-162 °C; $[\alpha]_D^{20} = +66.3$ (*c* 0.3, CHCl₃); IR (neat) 3231, 1280 cm⁻¹; ¹H NMR (CDCl₃) δ 1.22 (s, 9H), 1.98 (dq,

$J = 2.4$ Hz, $J = 3.2$ Hz, $J = 14.4$ Hz, 1H), 2.19 (dt, $J = 4.4$ Hz, $J = 10.4$ Hz, $J = 14.4$ Hz, 1H), 4.02 (br, 1H), 4.74 (m, 1H), 5.00 (d, $J = 10.4$ Hz, 1H), 5.44 (s, 1H), 7.26 (m, 2H), 7.35 (m, 8H); ^{13}C NMR (CDCl_3) δ 23.1, 46.3, 55.7, 56.0, 127.9, 128.3, 128.5, 129.0, 134.0, 136.9, 141.4, 198.9; HRMS calcd for $\text{C}_{19}\text{H}_{25}\text{NO}_2\text{SNa}$ ($\text{M} + \text{Na}$) 354.1504, found 354.1517.



(*Ss,1S,3R*)-(+)-**177b**

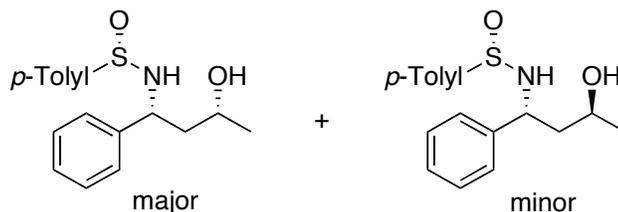
(*SS,1S,3R*)-(+)-*N*-(2-Methylpropanesulfinyl)-3-amino-1-methyl-3-phenylpropan-1-ol (177b). Chromatography (EtOAc/hexanes 2:1) gave 90% of a white solid: mp 145-6 °C; $[\alpha]_{\text{D}}^{20} = +181.9$ (c 0.8, CHCl_3); IR (neat) 3100, 1210 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.13 (s, 9H), 1.23 (s, 3H), 1.70 (m, 1H), 1.83 (m, 1H), 2.06 (br, 1H), 4.09 (m, 1H), 4.52 (d, $J = 9.6$ Hz, 1H), 5.55 (s, 1H), 7.16 (m, 1H), 7.23 (m, 4H); ^{13}C NMR (CDCl_3) δ 23.1, 25.2, 47.1, 55.8, 59.2, 68.8, 127.5, 127.83, 137.84, 143.6; HRMS calcd for $\text{C}_{14}\text{H}_{24}\text{NO}_2\text{S}$ ($\text{M} + \text{H}$) 270.1538, found 270.1521.



(1*R*,3*R*)-(+)-**178b**

(1*R*,3*R*)-(+)-*N*-(*p*-Toluenesulfonyl)-3-amino-1,3-diphenylpropan-

1-ol (178b). Chromatography (petroleum ether/EtOAc, 1:1) provided 58% of a colorless oil: IR (neat) 3600, 3300, 1400, 1250 cm^{-1} ; $[\alpha]_{\text{D}}^{20} = +110.6$ (c 0.15, CHCl_3); ^1H NMR (CDCl_3) δ 2.03 (m, 2H), 2.37 (s, 3H), 2.54 (br, 1H), 4.61 (dt, $J = 4.4$ Hz, $J = 8.0$ Hz, 1H), 4.82 (t, $J = 5.6$ Hz, 1H), 5.66 (d, $J = 8.0$ Hz, 1H), 7.03 (m, 2H), 7.16 (m, 2H), 7.25 (m, 6H), 7.33 (m, 2H), 7.63 (d, $J = 8$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 21.5, 45.7, 55.4, 70.9, 125.7, 126.3, 127.2, 127.4, 127.8, 128.57, 128.60, 129.5, 137.7, 140.5, 143.2, 143.7. A satisfactory HRMS could not be obtained because of decomposition in the instrument.

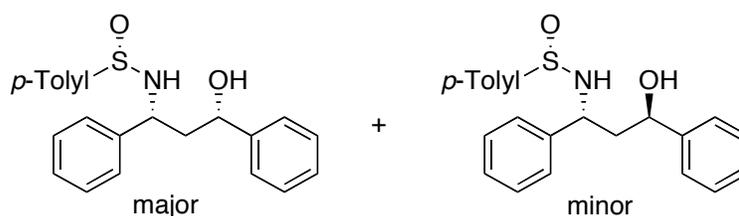


(*S*_s,1*S*,3*R*)-(+)-**174a** and (*S*_s,1*S*,3*R*)-(+)-**174b**

(*S*_s,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfonyl)-3-amino-1-methyl-3-phenylpropan-1-ol

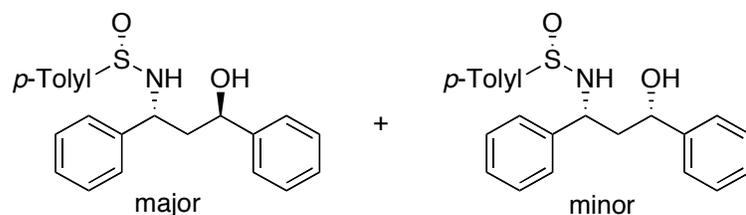
(174b): Typical Procedure for the Reduction of β -Amino Ketones with Lithium Aluminum Hydride. In a single-neck, oven-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (*S*_s,3*R*)-(+)-**167** (0.036 g, 0.1 mmol) in diethyl ether (10 mL) under an argon atmosphere. The solution was

cooled to $-78\text{ }^{\circ}\text{C}$, and lithium aluminum hydride (0.3 mmol, 0.3 mL of 1.0M solution in diethyl ether) was added dropwise via syringe. After being stirred at $-78\text{ }^{\circ}\text{C}$ for 2 h, the reaction mixture was cautiously quenched with H_2O (1 mL) and warmed to room temp. The reaction was then filtered through a pad of Celite and the flask was rinsed with hot THF which was also passed over the Celite (3 x 5mL). The combined organic phases were washed with brine (5 mL), dried (MgSO_4), and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 50% of a unseparable clear oil (dr = 65:35):



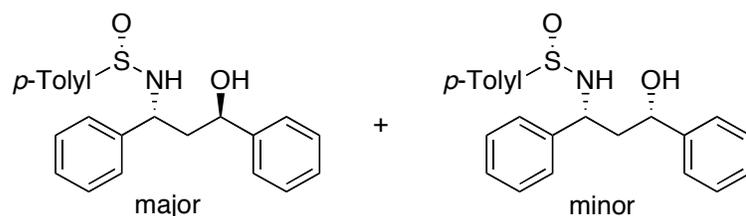
$(S_S,1S,3R)$ -(+)-**175a** and $(S_S,1R,3R)$ -(+)-**175b**

$(S_S,1S,3R)$ -(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenyl-1-ol (175a): Typical Procedure for the Reduction of β -Amino Ketones with Sodium Borohydride. In a single-neck, oven-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum and an argon inlet was placed (+)-**154** (0.036 g, 0.1 mmol) in methanol (8 mL). The solution was cooled to $-5\text{ }^{\circ}\text{C}$, and sodium borohydride (0.02 g, 0.7 mmol) was added portionwise. After being stirred at $-5\text{ }^{\circ}\text{C}$ for 2 h, the reaction mixture was quenched with H_2O (2 mL) and diluted with diethyl ether (10 mL) and warmed to room temperature. The aqueous layer was separated and washed with diethyl ether (3 x 2 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO_4), and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 65% of a clear oil (dr = 55 : 45)



(*S_s*,1*S*,3*R*)-(+)-**175a** and (*S_s*,1*R*,3*R*)-(+)-**175b**

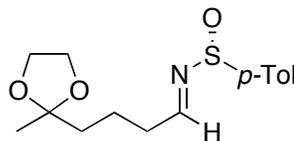
(*S_s*,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenyl-1-ol (175a): Typical Procedure for the Reduction of β -Amino Ketones with Zinc Borohydride. In a single-neck, flame-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar was placed (+)-**168** (0.036 g, 0.1 mmol) in diethyl ether (10 mL) under an argon atmosphere. The solution was cooled to 0 °C, and zinc borohydride (0.5 mmol, 3.3 mL of a 0.15M solution in diethyl ether) was added dropwise. After being stirred at 0 °C for 4 h, the reaction mixture was quenched with saturated NH₄Cl (2 mL) and warmed to room temperature. The aqueous layer was separated and washed with diethyl ether (3 x 2 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 86% of an unseparable clear oil: dr (17 : 83)



(*S_s*,1*S*,3*R*)-(+)-**175a** and (*S_s*,1*R*,3*R*)-(+)-**175b**

(*S_s*,1*S*,3*R*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-1,3-diphenyl-1-ol (160d): Typical Procedure for the Reduction of β -Amino Ketones with Diisobutyl Aluminohydride. In a single-neck, flame-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar

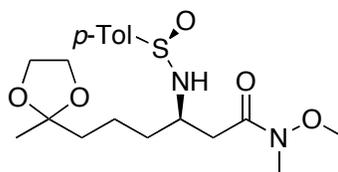
was placed (+)-**154** (0.036 g, 0.1 mmol) in tetrahydrofuran (10 mL) under an argon atmosphere. The solution was cooled to -78 °C, and diisobutyl aluminumhydride (0.5 mmol, 0.5 mL of a 1.0 M solution in tetrahydrofuran) was added dropwise. After being stirred at -78 °C for 4 h, the reaction mixture was quenched with saturated NH₄Cl (2 mL) and warmed to room temperature. The aqueous layer was separated and washed with diethyl ether (3 x 2 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (petroleum ether/EtOAc, 1:1) provided 52% of a clear oil: dr (23 : 77)



(*R*)-(-)-**197**

(*R*)-(-)-*N*-[5,5-(Ethylenedioxy)hexanylidene]-*p*-toluenesulfinamide (197). In a 250 mL, flame-dried, single-necked, round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed (*R*)-(-)-*p*-toluenesulfinamide (1.55 g, 10 mmol) and **195** (1.23 mL, 10 mmol) in CH₂Cl₂ (62 mL) at 0 °C. To the mixture was added Ti(OEt)₄ (0.114 g, 50 mmol) at 0 °C, and the solution was stirred for 4 h at rt. At this time, the reaction was quenched with H₂O (10 mL) and filtered through a Celite pad, and the Celite was washed with CH₂Cl₂ (50 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL), and the combined organic phases were combined, dried (MgSO₄), and concentrated. Flash chromatography (hexanes/EtOAc 8:2) provided 1.06 g (83%) of a colorless oil: [α]_D²⁰ = -279.7 (*c* 0.52, CHCl₃); IR (CH₂Cl₂) 3051, 1635, 1214 cm⁻¹; ¹H NMR (CDCl₃) δ 1.30 (s, 3H),

1.66 (m, 4 overlapping H), 2.41 (s, 3H), 2.50 (m, 2 overlapping H), 3.92 (m, 4H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 7.8$ Hz, 2H), 8.23 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 20.2, 21.7, 24.1, 36.2, 38.7, 65.0, 124.9, 130.1, 142.0, 167.2; HRMS calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_3\text{S}$ ($\text{M} + \text{H}$) 296.1320, found 296.1326.

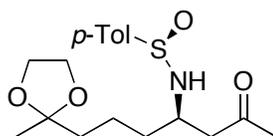


($R_S,3R$)-(-)-198****

($R_S,3R$)-(-)- N -(p -Toluenesulfinyl)-3-amino- N -methoxy- N -methyl-7,7-

(ethylenedioxy)octamide (198**):** In a two-neck, oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed N -methoxy- N -methylacetamide (0.16 mL, 1.5 mmol) in THF (20 mL). The solution was cooled to -78 $^{\circ}\text{C}$, KHMDS (1.5 mmol, 3 mL of 0.5 M solution in toluene) was added, and the reaction mixture was stirred at this temperature for 1 h. A solution of (R)-(+)-**197** (0.25 g, 1.0 mmol) in THF (10 mL) was added, and the solution was stirred at this temperature for 2.5 h. At this time, the reaction mixture was quenched with satd NH_4Cl (5 mL), slowly warmed to rt, and diluted with H_2O (10 mL). The solution was extracted with Et_2O (2 x 30 mL), and the organic phases were washed with brine (25 mL), dried (MgSO_4), and concentrated. Chromatography (hexanes/ EtOAc , 2:3) gave 0.619 g (74%) of a pale yellow oil: $[\alpha]_{\text{D}}^{20} = -44.5$ (c 0.951, CHCl_3); IR (neat) 3101, 1652, 1215 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.31 (s, 3H), 1.63 (m, 6H), 2.38 (s, 3H), 2.76 (m, 2H), 3.13 (s, 3H), 3.64 (s, 3H), 3.68 (m, 1H), 3.92 (m, 4H), 4.94 (d, $J = 8.8$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR

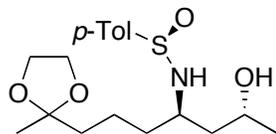
(CDCl₃) δ 21.0, 21.5, 24.0, 32.1, 36.0, 37.8, 38.9, 53.4, 61.5, 64.9, 110.2, 125.8, 129.7, 141.3, 143.0, 172.5; HRMS calcd for C₁₉H₃₁N₂O₅S (M + H) 399.1954, found 399.1987.



(*R_S*,4*R*)-(-)-**199**

(*R_S*,4*R*)-(-)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)-nonan-2-one

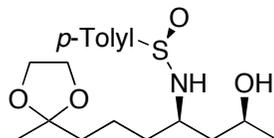
(199): In a flame-dried, 100-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (-)-**198** (0.472 g, 1.18 mmol) in THF (38 mL). The solution was cooled to -78 °C, and methylmagnesium bromide (5.9 mmol, 1.97 mL of a 3.0 M solution in Et₂O) was added. The reaction mixture was warmed to 0 °C, stirred for 30 min, and quenched with saturated aqueous NH₄Cl (3 mL). At this time, H₂O (5 mL) was added, the aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic phases were combined, dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc, 2:3) gave 0.401 g (96%) of a clear oil: $[\alpha]_D^{20} = -78.1$ (*c* 0.547, CHCl₃); IR (neat) 3210, 1712, 1063 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (s, 3H), 1.4-1.7 (m, 6H), 2.10, (s, 3H), 2.40 (s, 3H), 2.77 (d, *J* = 4.8 Hz, 2H), 3.67 (m, 1H), 3.94 (m, 4H), 4.39 (d, *J* = 9.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (CDCl₃) δ 20.8, 21.4, 23.9, 30.9, 35.9, 38.7, 49.3, 52.6, 64.8, 110.0, 125.6, 129.6, 141.4, 142.7, 207.5; HRMS calcd for C₁₈H₂₈NO₄S (M + H) 354.1739, found 354.1737.



(*R_S,2R,4R*)-(-)-200

(*R_S,2R,4R*)-(-)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy) nonan-2-ol

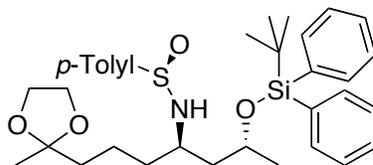
(200): In a flame-dried, 100-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (-)-**199** (0.120 g, 0.34 mmol) in CH₂Cl₂ (34 mL). The solution was cooled to -78 °C, lithium triethylborohydride (2.04 mmol, 2.04 mL of a 1.0 M solution in THF) was added dropwise, and the solution was stirred at this temperature for 2.5 h. At this time, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl (2 mL) and H₂O (2 mL). The phases were separated, and the aqueous phase was saturated with NaCl and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic phases were dried (MgSO₄) and concentrated. Chromatography (hexanes/EtOAc, 2:3) gave 0.102 g (85%) of a clear oil: $[\alpha]_D^{20} = -132.6$ (*c* 0.941, CHCl₃); IR (neat) 3416, 3240, 1375, 1087 cm⁻¹; ¹H NMR (CDCl₃) δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.33 (s, 3H), 1.57 (m, 8H), 2.40 (s, 3H), 3.23 (d, *J* = 5.4 Hz, 1H), 3.61 (m, 2H), 3.95 (m, 4H), 4.05 (d, *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (CDCl₃) δ 20.7, 21.5, 23.8, 24.0, 37.7, 39.0, 44.9, 53.7, 63.7, 64.8, 110.2, 125.6, 129.8, 141.7, 142.6; HRMS calcd for C₁₈H₃₀NO₄S (M + H) 356.1896, found 356.1898.



(*R_S*,2*S*,4*R*)-(-)-201

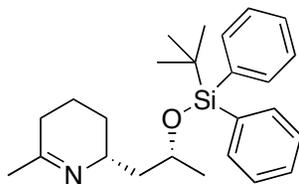
(*R_S*,2*S*,4*R*)-(-)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)-nonan-2-ol

(201): In a flame-dried, 50-mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (-)-**199** (0.093 g, 0.262 mmol) and LiCl (0.111 g, 2.62 mmol) in Et₂O (10 mL). The solution was sonicated for 5-10 min and cooled to -78 °C. Li(*t*-BuO)₃AlH (0.95 mL, 0.895 mmol of a 1.0M solution in THF) was added dropwise, and the reaction mixture was stirred at -78 °C for 2 h. At this time, the reaction was quenched by addition of satd aqueous NH₄Cl (0.5 mL) and H₂O (0.5 mL). The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 x 1 mL). The combined organic phases were dried (MgSO₄) and concentrated. Chromatography (hexanes/EtOAc, 40:60) gave 0.049 g (90%) of a clear oil: $[\alpha]_D^{20} = 43.1$ (*c* 0.237, CHCl₃); IR (neat) 3053, 1421, 1263 cm⁻¹; ¹H NMR (CDCl₃) δ 1.15 (d, *J* = 6.4 Hz, 2H), 1.34 (s, 3H), 1.51-1.71 (9 overlapping H), 2.40 (s, 3H), 3.55 (m, 1H), 3.70 (m, 1H), 3.96 (m, 4H), 4.05 (m, 1H), 4.39 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (CDCl₃) δ 20.4, 21.7, 24.1, 24.7, 38.2, 39.2, 45.5, 56.3, 65.0, 67.6, 110.3, 125.6, 129.9, 141.8, 142.7; HRMS calcd for C₁₈H₃₀NO₄S (M + H) 356.1896, found 356.1905.



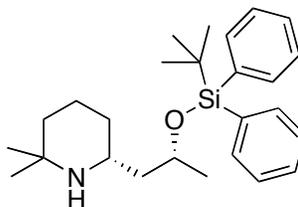
(*R_S*,2*R*,4*R*)-(-)-**204**

(*R_S*,2*R*,4*R*)-(-)-*N*-(*p*-Toluenesulfinyl)-2-(*tert*-butyldiphenylsilyloxy)-4-amino-7-(2-methyl-1,3-dioxolan-2-yl)heptane (**204**): In a flame-dried 5-mL vial, equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (-)-**200** (0.030 g, 0.084 mmol) and imidazole (0.014 g, 0.21 mmol) in CH₂Cl₂ (1 mL). To the solution was added TBDPSCl (0.025 g, 0.092 mmol) in CH₂Cl₂ (0.5 mL), and the reaction was stirred for 8 h and quenched by addition of H₂O (0.5 mL). The phases were separated, the aqueous phase was extracted with CH₂Cl₂ (3 x 0.5 mL), and the combined organic phases were dried (MgSO₄) and concentrated. Chromatography (hexanes/EtOAc, 4:1) gave 0.047 g (90%) of a clear oil: $[\alpha]_D^{20} = -62.8$ (*c* 1.15, CHCl₃); IR (CH₂Cl₂) 3050, 1415, 1261 cm⁻¹; ¹H NMR (CDCl₃) δ 0.83 (s, 9H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.33 (s, 3H), 1.68 (m, 8H), 2.37 (s, 3H), 3.64 (m, 1H), 3.92 (m, 4H), 4.04 (m, 1H), 4.94 (d, *J* = 4.40 Hz, 1H), 7.44 (m, 14H); ¹³C NMR (CDCl₃) δ 19.2, 20.3, 21.6, 22.8, 24.1, 27.1, 30.0, 36.1, 39.3, 43.7, 51.9, 65.0, 68.6, 110.3, 125.9, 127.8, 127.9, 129.7, 129.9, 130.0, 133.9, 134.4, 136.2, 141.2, 143.2; HRMS calcd for C₃₄H₄₈NO₄SSi (M + H) 594.3073, found 594.3093.



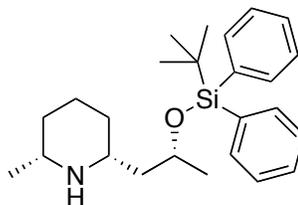
(2*R*,2'*R*)-(+)-**205**

(2*R*,2'*R*)-(+)-2',3',4',5'-Tetrahydro-6'-methylpyridinyl-2-(*tert*-butyldiphenylsilyloxy) propane (205): In a 50-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (-)-**204** (0.244 g, 0.41 mmol) in THF (19 mL). The solution was cooled to 0 °C, 3 N HCl (1.8 mL) was added, and the reaction mixture was stirred for 3 h at this temperature. The solution was neutralized to pH 7.0 by dropwise addition of satd aqueous NaHCO₃. The phases were separated, the aqueous phase was extracted with Et₂O (3 x 2 mL), and the combined organic extracts were dried (MgSO₄) and concentrated. Chromatography (3% MeOH/CH₂Cl₂) gave 0.128 g (79%) of a clear oil: $[\alpha]_D^{20} = +12.1$ (*c* 1.14, CHCl₃); IR (thin film) 3070, 3048, 1660, 1427, 1374 cm⁻¹; ¹H NMR (CDCl₃) δ 1.05 (s, 9H), 1.12 (d, *J* = 6 Hz, 3H), 1.41-1.61 (m, 4 overlapping H), 1.76 (m, 1H), 1.88 (d, *J* = 1.6 Hz, 3 H), 2.00 (m, 2H), 3.24 (br m, 1H), 4.14 (m, 1H), 7.39 (m, 5H), 7.72 (m, 5H); ¹³C NMR (CDCl₃) δ 19.0, 19.6, 24.0, 27.4, 27.9, 30.3, 48.1, 55.1, 67.9, 127.7, 129.7, 135.0, 135.4, 136.3, 167.1; HRMS calcd for C₂₅H₃₅NOSi (M + H) 394.2566, found 394.2555.



(2*R*,2'*R*)-(+)-**205a**

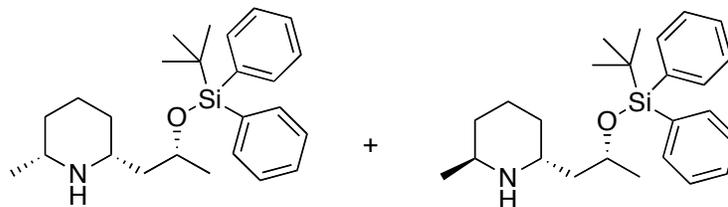
(2*R*,2'*R*)-(+)-1-(6'-Dimethylpiperidin-2'-yl)-2-(*tert*-butyldiphenylsilyloxy) propane (205a): In a 50-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (-)-**205** (0.039 g, 0.1 mmol) in THF (10 mL). The solution was cooled to 0 °C, and a solution of BF₃•Et₂O was added (0.021 g, 0.15 mmol). After stirring for 5 minutes, methylmagnesium bromide was added (0.15 mmol, 0.15 mL, 1.0 M solution in diethyl ether) and the reaction was stirred at 0 °C for 1.5 hours. The reaction was then quenched with saturated NH₄Cl solution (1 mL) and brine (1mL) and the mixture was allowed to warm to room temperature. The aqueous layer was separated and was washed with diethyl ether (2 x 1 mL). The pooled organic extracts were dried (MgSO₄), filtered and reduced to yield an orange oil. Chromatography (3% MeOH/CH₂Cl₂) yielded 0.023g (56%) of a clear oil: [α]_D²⁰ = +25.8 (*c* 0.95, CHCl₃); ¹H NMR (CDCl₃) δ 0.99 (s, 9H), 1.18 (s, 6H), 1.29 (m, 6H), 1.53 (m, 5H); 2.37 (m, 1H), 2.61 (m, 1H); 3.89 (m, 1H); 7.34 (m, 6H), 7.63 (m, 4H); ¹³C NMR (CDCl₃) δ 19.4, 24.1, 27.5, 29.0, 33.2, 33.8, 39.4, 43.4, 50.3, 61.7, 69.6, 128.2, 130.2, 130.3, 134.3, 135.1, 136.5, 136.8; HRMS: (M + H) calcd for C₂₆H₄₀NOSi, 410.2879; found, 410.2893.



(2*R*,2'*R*,6'*R*)-(-)-**191**

(2*R*,2'*R*,6'*R*)-(-)-1-(6'-Methylpiperidin-2'-yl)-2-(*tert*-butyldiphenylsilyloxy)

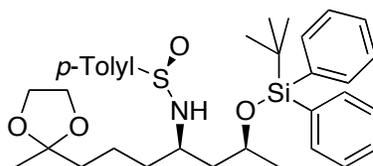
propane (191): In a 2-dram vial equipped with a loose fitting lid were placed (+)-**205** (0.040 g, 0.1 mmol) and 10% Pd/C (0.001 g) in methanol (2 mL). The vial was placed in a Parr bomb and pressurized with hydrogen (60 psi), and the solution was stirred for 8 h. The bomb was depressurized, the reaction mixture was filtered through Celite, and the Celite washed with MeOH (1 mL). The filtrate was concentrated to give 0.036 g (92%) of a clear oil: $[\alpha]_D^{20} = -1.5$ (*c* 0.735 CHCl₃) [lit. $[\alpha]_D^{20} = -1.4$ (*c* 0.55, CHCl₃)]; IR (neat): 3344, 3070, 1589 cm⁻¹; ¹H NMR (CDCl₃) δ 0.96 (d, *J* = 6.3 Hz, 3H), 0.99 (m, 1H), 1.07 (m, 12H), 1.28 (m, 1H), 1.51 (m, 5H), 1.70 (m, 2H), 2.46 (m, 1H), 2.73 (m, 1H), 3.95 (m, 1H), 7.37 (m, 6H), 7.67 (m, 4H); ¹³C NMR (CDCl₃) δ 19.9, 23.2, 24.6, 25.4, 27.7, 33.1, 34.3, 47.1, 53.1, 54.2, 67.5, 128.1, 128.3, 130.2, 130.3, 134.7, 135.3, 136.5, 136.6; HRMS: (M + H) calcd for C₂₅H₃₈NOSi, 396.2722; found, 396.2705



191

(2*R*,2'*R*,6'*R*)-(-)-1-(6'-Methylpiperidin-2'-yl)-2-(*tert*-butyldiphenylsilyloxy)

propane (191): In a single-neck, oven-dried, 25-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum and an argon inlet was placed (+)-**175** (0.039 g, 0.1 mmol) in methanol (8 mL). The solution was cooled to 0 °C, and sodium borohydride (0.02 g, 0.7 mmol) was added portionwise. After being stirred at 0 °C for 2 h, the reaction mixture was quenched with H₂O (2 mL) and diluted with diethyl ether (10 mL) and warmed to room temperature. The aqueous layer was separated and washed with diethyl ether (3 x 2 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (3 % MeOH/CH₂Cl₂) provided 35 mg (91%) of a clear oil: dr (60 : 40) inseparable

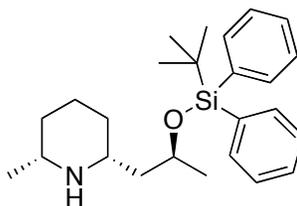


(*RS*,2*S*,4*R*)-(-)-207

(*RS*,2*S*,4*R*)-(-)-*N*-(*p*-Toluenesulfinyl)-2-(*tert*-butyldiphenylsilyloxy)-

4-amino-7-(2-methyl-1,3-dioxolan-2-yl)heptane (207): In a flame-dried 5-mL vial, equipped with a magnetic stirring bar, rubber septum, and argon inlet were placed (-)-**171**

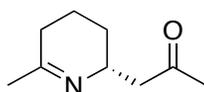
(0.030 g, 0.084 mmol) and imidazole (0.014 g, 0.21 mmol) in CH₂Cl₂ (1 mL). To the solution was added TBDPSCl (0.025 g, 0.092 mmol) in CH₂Cl₂ (0.5 mL), and the reaction was stirred for 8 h and quenched by addition of H₂O (0.5 mL). The phases were separated, the aqueous phase was extracted with CH₂Cl₂ (3 x 0.5 mL), and the combined organic phases were dried (MgSO₄) and concentrated. Chromatography (hexanes/EtOAc, 4:1) gave 0.047 g (90%) of a clear oil: $[\alpha]_D^{20} = -46.8$ (*c* 1.03, CHCl₃); IR (CH₂Cl₂) 3054, 1421, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (d, *J* = 6.0 Hz, 3H), 1.02 (s, 9H), 1.31 (s, 3H), 1.51 (8 overlapping H), 2.39 (s, 3H), 3.23 (m, 1H), 3.49 (d, *J* = 8.0 Hz, 1H), 3.78 (m, 1H), 3.93 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.38 (8 overlapping H), 7.68 (4 overlapping H); ¹³C NMR (CDCl₃) δ 19.5, 20.3, 21.6, 23.5, 24.1, 27.3, 37.4, 39.2, 46.1, 52.5, 65.0, 67.4, 110.3, 126.0, 127.8, 128.0, 129.7, 129.9, 130.0, 134.9, 136.3, 141.3, 142.5; HRMS calcd for C₃₄H₄₈NO₄SSi (M + H) 594.3073, found 594.3093.



(2*S*,2'*R*,6'*R*)-(-)-**209**

(2*S*,2'*R*,6'*R*)-(-)-1-(6'-Methylpiperidin-2'-yl)-2-(tert-butyl-diphenylsilyloxy)propane (209): In a 50-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (+)-**207** (0.244 g, 0.41 mmol) in THF (19 mL). The solution was cooled to 0 °C, 3 N HCl (1.8 mL) was added, and the reaction mixture was stirred for 3 h at this temperature. The solution was neutralized to pH 7.0 by dropwise

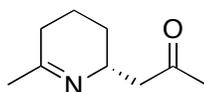
addition of saturated aqueous NaHCO₃. The phases were separated, the aqueous phase was extracted with Et₂O (3 x 2 mL), and the combined organic extracts were dried (MgSO₄), concentrated and chromatographed (3% MeOH/CH₂Cl₂) to give a clear oil which was used immediately. In a 2-dram vial equipped with a loose fitting lid were placed imine and 10% Pd/C (0.001 g) in methanol (2 mL). The vial was placed in a Parr bomb and pressurized with hydrogen (60 psi), and the solution was stirred for 18 h. The bomb was depressurized, the reaction mixture was filtered through Celite, and the Celite washed with methanol (1 mL). The filtrate was concentrated to give 0.136 g (84%) of a clear, viscous oil: $[\alpha]_D^{20} = -6.5$ (*c* 0.499, CHCl₃) [lit. $[\alpha]_D^{20} = -6.5$ (*c* 0.51, CHCl₃)]; IR (neat): 3349.3, 3071.0, 1589.8 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06 (14 overlapping H), 1.25 (m, 2 overlapping H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.64 (m, 4 overlapping H), 2.24 (m, 1H), 2.94 (m, 1H), 3.15 (m, 1H), 3.86 (m, 1H), 7.40 (m, 6 overlapping H), 7.67 (m, 4 overlapping H); ¹³C NMR (CDCl₃) δ 19.4, 19.7, 23.0, 24.4, 27.2, 27.6, 30.9, 42.6, 54.5, 56.0, 66.6, 127.7, 128.0, 129.9, 130.0, 133.7, 134.1, 136.0, 136.1. HRMS: (M + H) calcd for C₂₅H₃₈NOSi, 396.2723; found 396.2721.



(*R*)-(+)-**210**

1-((*R*)-(-)-2,3,4,5-Tetrahydro-6-methylpyridin-2-yl)propan-2-one (210): In a 25-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (-)-**199** (0.071 g, 0.2 mmol) in THF (10 mL). The solution was cooled to 0 °C, 3 N HCl (1.8 mL) was added, and the reaction mixture was stirred for 1 h at this temperature and allowed to warm to room temperature. The solution was then neutralized to pH 7.0 by the dropwise

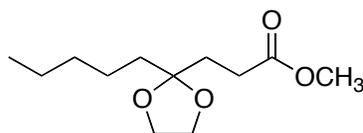
addition of saturated aqueous NaHCO₃. The phases were separated, the aqueous phase was extracted with Et₂O (3 x 2 mL), and the combined organic extracts were dried (MgSO₄) and concentrated. Chromatography (3% MeOH/CH₂Cl₂) gave 0.025 g (81%) of a clear oil: $[\alpha]_D^{20} = +40.2$ (*c* 1.19, CHCl₃); IR (neat) 2950, 1715, 1660 cm⁻¹; ¹H NMR (CDCl₃) δ 1.06 (m, 1H), 1.56 (m, 1H), 1.72 (m, 2H), 1.86 (d, *J* = 1.9, 3H), 2.05 (m, 2H), 2.14 (s, 3H), 2.44 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.77 (dd, *J* = 16.2, 6.0 Hz, 1H), 3.71 (m, 1H); ¹³C NMR (CDCl₃) δ 18.6, 27.0, 27.4, 29.9, 30.7, 51.4, 54.2, 168.3, 208.1. HRMS calcd for C₉H₁₆NO (M + H) 154.1226. Found 154.1229.



(*R*)-(+)-**210**

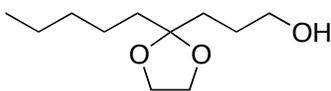
1-((*R*)-(-)-2,3,4,5-Tetrahydro-6-methylpyridin-2-yl)propan-2-one (210): General Procedure for the Cyclization of (-)-199 with *p*-Toluene Sulfonic Acid Monohydrate. In a 50-mL, round-bottom flask equipped with magnetic stirring bar and rubber septum was placed (-)-**199** (0.102 g, 0.29 mmol) and *p*-toluene sulfonic acid monohydrate (0.181 g, 0.95 mmol) in benzene (20 mL). The solution was refluxed under a condenser for 2 hours. The reaction was allowed to cool and then neutralized by the addition of saturated aqueous NaHCO₃ (5 mL). The phases were separated, the aqueous phase was extracted with Et₂O (3 x 2 mL), and the combined organic extracts were washed with brine (5 mL), dried (MgSO₄) and then concentrated. Chromatography (3% MeOH/CH₂Cl₂) gave 0.027 g (60%) of a clear oil.

4.3 CHAPTER 3: SYNTHESIS OF ENANTIOMERICALLY PURE BRIDGEHEAD-SUBSTITUTED TROPINONES VIA MASKED OXO SULFINIMINES



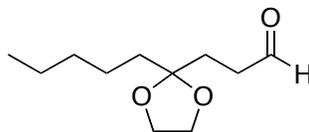
261

Methyl 3-(2-pentyl-1,3-dioxolan-2-yl)propanoate (261): To a 50 mL round-bottomed flask equipped with a Dean-Stark trap and a condenser was placed methyl 4-oxononanoate (931 mg, 5.0 mmol), ethylene glycol (0.418 mL, 0.75 mmol) and *p*-toluenesulfonic acid monohydrate (11 mg, 0.06 mmol) in toluene (10 mL). This was refluxed for 18 hours or until evolution of H₂O ceases. The reaction was cooled to r.t. and the reaction was washed with satd. NaHCO₃ (2mL) and H₂O (2 mL). The organic layer was dried (MgSO₄) and volatiles were removed to yield an amber oil. This was distilled (100-125 °C, 1 mmHg) to yield 0.967 g (84%) of a clear oil. IR (neat) 2874, 1689, 1438, 901 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.29 (6 overlapping H), 1.57 (t, *J* = 8.0 Hz, 2H), 2.00 (t, *J* = 8.0 Hz, 2H), 2.36 (t, *J* = 8.0 Hz, 2H), 3.68 (s, 3H), 3.94 (s, 4H); ¹³C NMR (CDCl₃) 14.3, 22.9, 23.8, 29.0, 32.4, 37.7, 51.9, 65.4, 111.2, 174.5; HRMS calcd for C₁₂H₂₂O₄Na (M + Na) 253.1415. Found 253.1408.



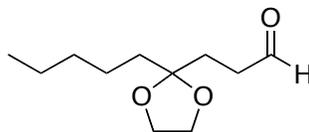
262

3-(2-Pentyl-1,3-dioxolan-2-yl)propan-1-ol (262): In a flame-dried, round-bottomed 25 mL flask under argon was placed lithium aluminum hydride (152 mg, 4.0 mmol) in anhydrous THF (5 mL). The slurry was cooled to 0 °C with an external ice bath and a solution of **261** (461 mg, 2.0 mmol) in THF (2 mL) was added dropwise to avoid an overly vigorous reaction. After addition, the ice bath was removed and the reaction was stirred at r.t. for 2 hours. At this point the reaction was again cooled to 0 °C and then quenched with H₂O (1 mL). The solids were filtered through Celite® and the filter cake was washed with hot THF. The filtrate was dried (MgSO₄), filtered and had volatiles removed to give 392 mg (97%) of a yellow oil. An analytical sample could be obtained by chromatography (hexanes:EtOAc 3:1). IR (neat) 3460, 3054, 2955, 1437, 1265, 1058 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.23-1.40 (6 overlapping H), 1.60-1.74 (6 overlapping H), 2.01 (br s, 1H), 3.65 (t, *J* = 6.4 Hz, 2H), 3.96 (s, 4H); ¹³C NMR (CDCl₃) 13.8, 22.4, 23.3, 26.8, 31.8, 33.4, 36.8, 62.9, 64.6, 111.5; HRMS calcd for C₁₁H₂₃O₃ (M + H) 203.1647. Found 203.1642.



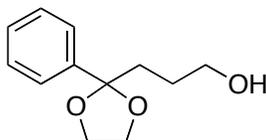
263

3-(2-Pentyl-1,3-dioxolan-2-yl)propanal (263): General Procedure for the Oxidation of 262 with Dess-Martin Periodinane. A 50 mL round-bottomed flask was charged with **262** (404 mg, 2 mmol), Dess-Martin periodinane (1.27 g, 3 mmol) in CH₂Cl₂ (10 mL) and the solution was stirred for 2 hours. Upon completion of the reaction a 1:1 mixture of saturated Na₂S₂O₃ and saturated NaHCO₃ solution (5 mL) was added and the mixture was vigorously stirred for 15 minutes or until two clear layers appear. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 3 mL). The pooled organic extracts were dried (MgSO₄), filtered and had volatiles removed to yield 393 mg (98%) of a slightly yellow oil. IR (neat) 3054, 2957, 2305, 1721, 1421, 1264 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.26-1.38 (6 overlapping H), 1.59 (m, 2H), 2.05 (t, *J* = 7.2 Hz, 2H), 2.45 (dt, *J*₁ = 2.4 Hz, *J*₂ = 7.2 Hz, 2H), 3.94 (m, 4H), 9.72 (t, *J* = 2.0 Hz, 1H); ¹³C NMR (CDCl₃) 13.8, 22.3, 23.4, 29.6, 31.8, 37.4, 38.1, 64.8, 110.7, 201.9; HRMS calcd for C₁₁H₂₁O₃ (M + H) 201.1490 Found 201.1493.



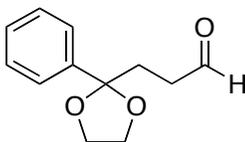
263

3-(2-Pentyl-1,3-dioxolan-2-yl)propanal (263): General Procedure for the Oxidation of 262 under Swern Oxidation Conditions. In a flame-dried 250 mL round-bottomed flask equipped with rubber septum and argon inlet was placed oxalyl chloride (1.27 g, 10 mmol) in CH₂Cl₂ (50 mL). The solution was then cooled to -78 °C with external dry-ice/acetone bath and ultrapure DMSO (0.780 g, 10 mmol) was added. The reaction was maintained at this temperature for 1 hr. A solution of **262** (1.01 g, 5 mmol) in CH₂Cl₂ (10 mL) was added dropwise and the reaction was maintained at -78 °C for an additional hour. Then, ultrapure Et₃N (2.02 g, 20 mmol) was added and the reaction was stirred for 30 min. The temperature of the reaction was then raised to 0 °C and was subsequently checked by TLC to check for consumption of starting material. Upon completion, H₂O (10 mL) was added to the reaction to quench and the mixture was poured into a separatory funnel. The layers were separated and the aqueous layer was washed with CH₂Cl₂ (3 x 5 mL). The pooled organic extracts were washed with brine (10 mL), dried (MgSO₄) filtered and had volatiles removed to yield 1.01 g of a yellow oil. This crude aldehyde was taken onto subsequent steps due to its instability towards heat and silica gel.



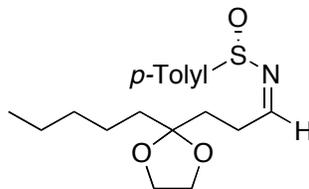
265

3-(2-Phenyl-1,3-dioxolan-2-yl)propan-1-ol (265): In a flame-dried, round-bottomed 25 mL flask under argon was placed lithium aluminum hydride (152 mg, 4.0 mmol) in anhydrous THF (5 mL). The slurry was cooled to 0 °C with an external ice bath and a solution of **264** (416 mg, 2.0 mmol) in THF (2 mL) was added dropwise to avoid an overly vigorous reaction. After addition, the ice bath was removed and the reaction was stirred at r.t. for 1 hour. At this point the reaction was again cooled to 0 °C and then quenched with H₂O (1 mL). The solids were filtered through Celite® and the filter cake was washed with hot THF. The filtrate was dried (MgSO₄), filtered and had volatiles removed to give 387 mg (95%) of a clear oil. IR (neat) 3460, 3121 cm⁻¹; ¹H NMR (CDCl₃) δ 1.50 (m, 2H), 1.83 (t, *J* = 7.2 Hz, 2H), 3.53 (3 overlapping H), 4.02 (m, 4H), 7.35 (m, 5H); ¹³C NMR 20.1, 35.3, 63.9, 119.2, 125.9, 127.1, 128.5, 139.7; HRMS calcd for C₁₂H₁₇O₃ (M + H) 209.1177 Found 209.1493.



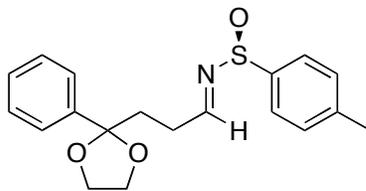
266

4,4-Ethylenedioxy-4-phenylbutanal (266): In a flame-dried 50 mL round-bottomed flask equipped with rubber septum and argon inlet was placed oxalyl chloride (0.127 g, 1 mmol) in CH₂Cl₂ (5 mL). The solution was then cooled to -78 °C with external dry-ice/acetone bath and ultrapure DMSO (0.078 g, 1 mmol) was added. The reaction was maintained at this temperature for 1 hr. A solution of **265** (0.104 g, 0.5 mmol) in CH₂Cl₂ (1 mL) was added dropwise and the reaction was maintained at -78 °C for an additional hour. Then, ultrapure Et₃N (0.202 g, 2 mmol) was added and the reaction was stirred for 30 min. The temperature of the reaction was then raised to 0 °C and was subsequently checked by TLC to check for consumption of starting material. Upon completion, H₂O (1 mL) was added to the reaction to quench and the mixture was poured into a separatory funnel. The layers were separated and the aqueous layer was washed with CH₂Cl₂ (3 x 1 mL). The pooled organic extracts were washed with brine (10 mL), dried (MgSO₄) filtered and had volatiles removed to yield 0.108 g of a pale yellow oil which was sufficiently pure. The aldehyde was taken onto subsequent steps due to its instability towards heat and silica gel. IR (CH₂Cl₂) 3154, 2957, 1715, cm⁻¹; ¹H NMR (CDCl₃) δ 2.15 (t, *J* = 7.3 Hz, 2H), 2.45 (q, *J* = 4.9, 7.3 Hz, 2H), 4.00 (m, 4H), 7.37 (m, 5H), 9.81 (t, *J* = 2.0 Hz, 1H); ¹³C NMR (CDCl₃) 31.3, 33.9, 63.9, 122.4, 126.0, 127.0, 128.8, 139.0, 202.2; HRMS calcd for C₁₂H₁₅O₃ (M + H) 207.1021 Found 207.1032.



(*S*)-(+)-**267a**

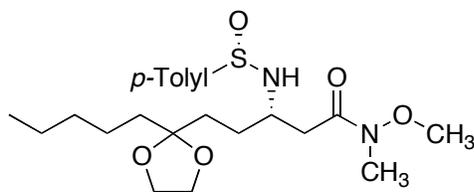
(+)-(*S*)-(2-pentyl-1,3-dioxolan-2-yl)propylidene-*p*-toluene sulfinamide (**267a**). A 100 mL round-bottomed flask was charged with (*S*)-*p*-toluenesulfinamide (775 mg, 5 mmol), **263** (1.00 g, 5 mmol), Ti(OEt)₄ (4.56 g, 20 mmol) in CH₂Cl₂ (50 mL). The reaction was stirred for 4 hours at room temperature and the reaction was quenched with H₂O (20 mL) at 0 °C. The reaction was filtered through Celite® and dried (MgSO₄). Removal of the volatiles yielded a crude yellow oil. Chromatography (hexanes:EtOAc, 4:1) yielded 1.11 g (75%) of a clear oil as a 6:1 unseparable mixture of *E/Z* isomers. $[\alpha]_D^{25} = +216.6^\circ$ (*c* = 0.705); IR (CH₂Cl₂) 2951, 2360, 1620, 1097 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.23-1.34 (6 overlapping H), 1.57 (m, 2H), 1.96 (m, 2H), 2.40 (s, 3H), 2.55 (m, 2H), 3.87 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 8.24 (t, *J* = 4.4 Hz, 1H); ¹³C NMR δ (CDCl₃) 13.8, 21.2, 22.3, 23.3, 30.4, 31.8, 32.3, 37.3, 64.7, 110.7, 124.4, 129.5, 141.3, 141.7, 167.1; HRMS calcd for C₁₈H₂₈NO₃S (M + H) 338.1790. Found 338.1783.



(*S*)-(+)-**267b**

(*S*)-(+)-3-(2-Phenyl-1,3-dioxolan-2-yl)propylidene-*p*-toluenesulfonamide (267b).

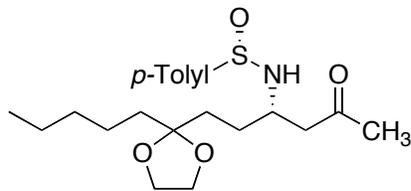
To a 250 mL round-bottomed flask equipped with magnetic stirring bar and argon inlet was placed 4,4-ethylenedioxy-4-phenylbutanal (**266**) (1.140 g, 5.5 mmol) in dry CH₂Cl₂ (55 mL). To this was added (*S*)-(+)-*p*-toluenesulfonamide (0.900 g, 5.8 mmol) followed by Ti(OEt)₄ (5.02 g, 22 mmol) and the reaction was stirred for 4 h. The reaction mixture was cooled to 0 °C with an external ice bath and then quenched with H₂O (30 mL). After stirring for 5 min, the solids were filtered through Celite™ and the filter cake was washed with CH₂Cl₂ (20 mL). The mother liquor was dried (MgSO₄), filtered and concentrated to yield a crude brown oil. Flash chromatography (12% EtOAc/hexanes) yielded 0.710 g (65%) of a slightly yellow oil; [α]_D²⁵ = +206.0° (*c* 1.30, CHCl₃); IR (neat) 3051, 1635, 1213 cm⁻¹; ¹H NMR (CDCl₃) δ 2.16 (m, 2H) 2.33 (s, 3H), 2.53 (dt, *J* = 7.6 Hz, 4.4 Hz, 2H), 3.66 (m, 2H), 3.88 (m, 2H), 7.24 (m, 5H), 7.35 (m, 2H), 7.48 (d, *J* = 10.0 Hz, 2H), 8.18 (t, *J* = 5.5 Hz, 1H); ¹³C NMR (CDCl₃) δ 21.4, 30.6, 35.9, 64.5, 109.5, 124.6, 125.6, 128.0, 128.2, 129.7, 141.5, 142.1, 167.1. HRMS calcd for C₁₉H₂₁NO₃SNa (M+Na) 366.1140. Found 366.1139.



(*S_s,3S*)-(+)-**268**

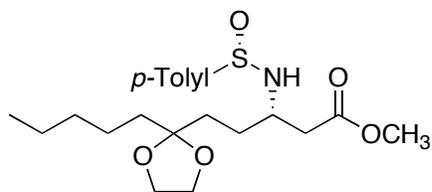
(*S_s,3S*)-(+)-*N*-Methoxy-*N*-methyl-3-(*p*-toluene sulfinamido)-5-(2-pentyl-1,3-

dioxolan-2-yl)pentanamide (268). In a 50 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed *N*-methoxy, *N*-methyl acetamide (0.13 mL, 1.2 mmol) in Et₂O (10 mL). The solution was cooled to -78 °C, and KHMDS (1.2 mmol, 2.4 mL of 0.5 M solution in toluene) was added and the reaction mixture was stirred at this temperature for 1 h. A solution of (*S*)-(+)-**267a** (0.20 g, 0.58 mmol in Et₂O (2 mL) was added and the solution was stirred at this temperature for 2.5 h. At this time the reaction mixture was quenched with sat. NH₄Cl (2 mL), slowly warmed to rt, and diluted with H₂O (3 mL). The solution was extracted with Et₂O (2 x 30 mL), the organic phases were washed with brine (25 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc 2:3) yielded 0.143 g (59%) of a clear oil; [α]_D²⁰ +72.4° (c = 1.19); IR (neat) 3053, 1421, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.32 (m, 7H), 1.70 (m, 6H), 2.40 (s, 3H), 2.79 (m, 2H), 3.15 (s, 3H), 3.66 (s, 3H), 3.70 (m, 1H), 3.89 (s, 3H), 5.00 (d, *J* = 8.8 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.0, 21.3, 22.6, 23.5, 30.0, 31.8, 32.0, 33.6, 37.1, 37.6, 53.5, 61.2, 64.9, 111.5, 125.4, 129.4, 141.0, 142.8, 172.1; HRMS calcd. for C₂₂H₃₇N₂O₅S (M + H) 441.2432. Found 441.2389.



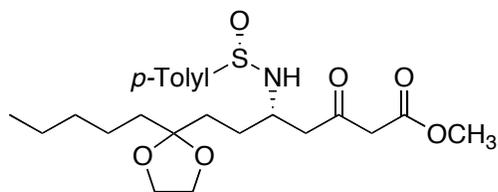
(*S_S,3S*)-(+)-**269**

(*S_S,4S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-6-(2-pentyl-1,3-dioxolan-2-yl)pentan-**2-one (269)**. In an oven-dried, single-neck, 50-mL round-bottom flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet was placed (*S_S,3S*)-(+)-**268** (0.441 g, 1.0 mmol) in THF (20 mL) under an argon atmosphere. The solution was cooled to -78° C, and PhMgBr (5.0 mmol, 5.0 mL of 1.0 M solution in THF) was added via syringe and the reaction mixture was warmed to rt. After stirring for 2 h, the solution was cooled to -78° C, quenched with sat. NH₄Cl (6 mL), and warmed to rt. The solution was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with brine (5 mL), dried (MgSO₄), and concentrated. Chromatography (hexanes/EtOAc 1:1) gave 0.348 g (88%) of a clear oil; [α]_D²⁵ +56.1; (*c* 0.750, CHCl₃); IR (neat) 3053, 1714, 1286, 738 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.29 (m, 7H), 1.65 (m, 6H), 2.09 (s, 3H), 2.41 (s, 3H), 2.80 (d, *J* = 5.2 Hz, 2H), 3.68 (m, 1H), 3.94 (s, 3H), 4.54 (d, *J* = 9.2 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 13.9, 21.3, 22.6, 23.5, 29.9, 30.7, 32.0, 33.5, 37.1, 49.3, 52.7, 64.8, 111.5, 125.4, 129.4, 141.2, 142.6, 207.3; HRMS calcd for C₂₁H₃₄NO₄S (M + H) 396.2209. Found 396.2213.



(*S_S*,*3S*)-(+)-**271**

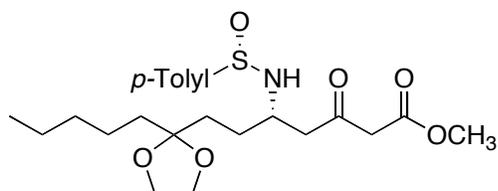
(*S_S*,*3S*)-(+)-Methyl 3-(4-methylphenylsulfinamido)-5-(2-pentyl-1,3-dioxolan-2-yl)pentanoate (271): Two-Step Method from (*S_S*)-(+)-267a**.** In a flame-dried, single-necked, 50 mL round-bottomed flask equipped with magnetic stirbar and argon inlet was placed NaHMDS (1.5 mmol, 1.5 mL of a 1 M soln in THF) in 10 mL anhydrous THF. The solution was cooled to -78 °C and anhydrous methyl acetate (0.111 g, 1.5 mmol) in THF (1mL) was added dropwise. To the cooled reaction was added (+)-**196a** (0.337 g, 1 mmol) in THF (3 mL) was then added dropwise and the reaction was stirred for 3 hr. The reaction was then quenched with satd. NH₄Cl solution (1 mL) followed by H₂O (1 mL). After warming to room temperature, the layers were separated and the aqueous layer was washed with EtOAc (3 x 2mL). The pooled organic extracts were washed with brine (1mL) and dried (MgSO₄). Filtration followed by removal of volatiles yielded a crude yellow oil. Chromatography (hexanes/EtOAc, 1:1) yielded 337 mg (82%) of a clear oil. $[\alpha]_D^{25} = +74.5$ (*c* 1.19, CHCl₃); IR (neat) 3050, 1716 cm⁻¹; ¹H NMR (CDCl₃) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.28 (m, 6 overlapping H), 1.71 (m, 7 overlapping H), 2.36 (m, 1H), 2.40 (s, 3H), 2.60 (m, 1H), 3.25 (m, 1H), 3.68 (s, 3H), 4.00 (m, 4H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 14.1, 21.3, 22.5, 22.7, 23.3, 30.7, 32.4, 37.7, 41.5, 49.5, 51.9, 64.3, 121.5, 129.3, 129.5, 137.9, 173.1; HRMS calcd for C₂₁H₃₄NO₅S (M + H) 412.2158. Found 412.2161.



(*S_s,3S*)-(+)-**272**

(*S_s,5S*)-(+)-Methyl 5-(4-methylphenylsulfonamido)-3-oxo-7-(2-pentyl-1,3-dioxolan-2-yl)heptanoate (272): Two-Step Method from (*S_s,3S*)-(+)-271**.** In a flame-dried, single-necked, 50 mL round-bottomed flask equipped with magnetic stirbar and argon inlet was placed NaHMDS (5 mmol, 5 mL of a 1 M soln in THF) in 10 mL anhydrous THF. The solution was cooled to -78 °C and anhydrous methyl acetate (0.370 g, 5 mmol) in THF (1mL) was added dropwise. The reaction was allowed to stir for 1 h before adding anhydrous Et₂O (3 mL). To the cooled reaction was added (*S_s,3S*)-(+)-**271** (0.411 g, 1 mmol) in THF (3 mL) was then added dropwise to the reaction. The reaction was monitored by TLC. If after 2.5 h there is remaining (+)-**271** in the reaction, the reaction is warmed up to 0 °C with an external ice/salt bath until the disappearance of starting material is observed. The reaction was then quenched with satd. NH₄Cl soln (1 mL) followed by H₂O (1 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 2 mL). The pooled organic extracts were washed with brine (1 mL) and dried (MgSO₄). Filtration followed by removal of volatiles yielded a crude yellow oil. Chromatography (hexanes/EtOAc, 1:1) yielded 368 mg (81%) of a clear oil. $[\alpha]_D^{25} = +99.4$ (*c* 1.02, CHCl₃); IR (neat) 3050, 1723 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 7.2 Hz, 3H), 1.29 (m, 6 overlapping H), 1.69 (m, 6 overlapping H), 2.41, (s, 3H), 2.80 (m, 2H), 2.85 (m, 1H), 3.42 (s, 2H), 3.93 (s, 3H), 4.01 (m, 4H), 4.48 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H); ¹³C NMR

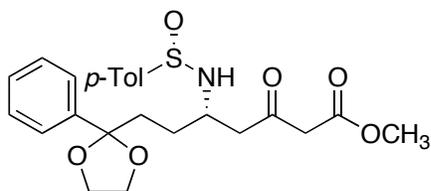
(CDCl₃) δ 14.1, 21.3, 22.6, 22.7, 23.3, 30.7, 32.4, 47.5, 47.7, 48.6, 51.6, 64.3, 121.5, 129.3, 129.5, 137.9, 168.1, 201.1; HRMS calcd for C₂₃H₃₆NO₆S (M + H) 454.2263. Found 454.2281.



(*S*_S,3*S*)-(+)-**272**

(*S*_S,5*S*)-(+)-Methyl 5-(4-methylphenylsulfonamido)-3-oxo-7-(2-pentyl-1,3-dioxolan-2-yl)heptanoate (272): One-Pot Method from (*S*_S)-(+)-267a**.** In a flame-dried, single-necked, 50 mL round-bottomed flask equipped with magnetic stirbar and argon inlet was placed NaHMDS (6.4 mmol, 6.42 mL of a 1 M soln in THF) in 4.3 mL anhydrous THF. The solution was cooled to -78 °C and anhydrous methyl acetate (0.476 g, 6.42 mmol) in THF (1mL) was added dropwise. The reaction was allowed to stir for 1 h before adding anhydrous Et₂O (4.3 mL). To the cooled reaction was added (*S*_S)-(+)-**267a** (0.194 g, 0.574 mmol) in THF (1 mL) was then added dropwise to the reaction. The reaction was monitored by TLC. If, after 2.5 h, there is remaining (+)-**267a** in the reaction, the reaction is warmed up to 0 °C with an external ice/salt bath until the disappearance of starting material is observed. The reaction was then quenched with satd. NH₄Cl soln (1 mL) followed by H₂O (1 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 2mL). The pooled organic extracts were washed with brine (1 mL) and dried (MgSO₄). Filtration followed by

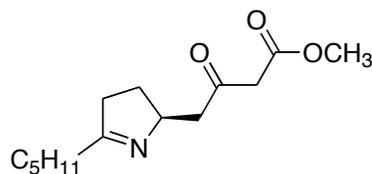
removal of volatiles yielded a crude yellow oil. Chromatography (hexanes/EtOAc, 1:1) yielded 177 mg (68%) of a clear oil. $[\alpha]_D^{25} = +99.4$ (c 1.02, CHCl_3); IR (neat) 3050, 1723 cm^{-1} ; ^1H NMR (CDCl_3) δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.29 (m, 6 overlapping H), 1.69 (m, 6 overlapping H), 2.41, (s, 3H), 2.80 (m, 2H), 2.85 (m, 1H), 3.42 (s, 2H), 3.93 (s, 3H), 4.01 (m, 4H), 4.48 (d, $J = 8.7$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.57 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (CDCl_3) δ 14.1, 21.3, 22.6, 22.7, 23.3, 30.7, 32.4, 47.5, 47.7, 48.6, 51.6, 64.3, 121.5, 129.3, 129.5, 137.9, 168.1, 201.1; HRMS calcd for $\text{C}_{23}\text{H}_{36}\text{NO}_6\text{S}$ ($\text{M} + \text{H}$) 454.2263. Found 454.2281.



(*S*_s,5*S*)-(+)-**273**

(*S*_s,5*S*)-(+)-Methyl *N*-(*p*-toluenesulfinyl)-5-(amino-3-oxo-7-(2-phenyl-1,3-dioxolan-2-yl)heptanoate: In a flame-dried, single-necked, 50 mL round-bottomed flask equipped with magnetic stirbar and argon inlet was placed NaHMDS (6.0 mmol, 6.00 mL of a 1 M soln in THF) in 4.3 mL anhydrous THF. The solution was cooled to -78 °C and anhydrous methyl acetate (0.444 g, 6.00 mmol) in THF (1mL) was added dropwise. The reaction was allowed to stir for 1 h before adding anhydrous Et_2O (4.3 mL). To the cooled reaction was added (*S*_s)-(+)-**267b** (0.194 g, 1 mmol) in THF (2 mL) was then added dropwise to the reaction. The reaction was monitored by TLC. If, after 2.5 h, there is remaining)-(+)-

267b in the reaction, the reaction is warmed up to 0 °C with an external ice/salt bath until the disappearance of starting material is observed. The reaction was then quenched with satd. NH₄Cl soln (2 mL) followed by H₂O (2 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 4mL). The pooled organic extracts were washed with brine (1 mL) and dried (MgSO₄). Filtration followed by removal of volatiles yielded a crude yellow oil. Chromatography (hexanes/EtOAc, 1:1) yielded 362 mg (69%) of a clear oil. $[\alpha]_D^{25} = +43.8$ (*c* 2.52, CHCl₃); IR (neat) 1709, 1748 cm⁻¹; ¹H NMR (CDCl₃) δ 1.70 (q, *J* = 7.3 Hz, 2H), 2.00 (m, 1H), 2.08 (m, 1H), 2.41 (s, 3H), 2.83 (m, 2H), 3.39 (s, 2H), 3.71 (s, 3H), 3.74 (m, 3H), 4.01 (m, 2H), 4.42 (d, *J* = 9.1 Hz, 1H), 7.31 (m, 5H), 7.43 (m, 2H), 7.53 (m, 2H); ¹³C NMR (CDCl₃)δ 21.3, 29.6, 36.7, 48.8, 49.6, 52.0, 52.0, 52.3, 64.4, 64.5, 110.0, 125.4, 125.5, 125.6, 127.9, 128.1, 129.4, 141.3, 142.4, 167.2, 201.2. HRMS calcd for C₂₄H₂₉NO₆SNa (M+Na) 482.1613. Found 482.1606.



(4*S*)-(+)-**278**

(4*S*)-(+)-Methyl 3-oxo-4-(5-pentyl-3,4-dihydro-2*H*-pyrrol-2-yl)butanoate (278). In a 50 mL, round-bottomed flask equipped with a magnetic stirbar was placed (*S*₅,*3S*)-(+)-**272** (0.080 g, 0.176 mmol) dissolved in THF (17 mL). To this was added 1.25 M HCl in MeOH (1.7 mL) followed by 3M HCl (0.3 mL). The reaction was stirred at r.t. for 24 hrs. At this point, the reaction was quenched with NaHCO₃ and diluted with H₂O (10 mL). The layers were separated and the aqueous layer was washed with EtOAc (3 x 5 mL). The pooled

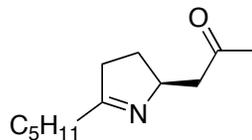
organic extracts were washed with brine (5 mL) and dried (MgSO₄). Filtration followed by removal of volatiles yielded a crude orange oil. Chromatography (MeOH/DCM, 1:99) yielded 36 mg (85%) as a slight orange oil. $[\alpha]_D^{25} = +69.1$ (*c* 1.52, CHCl₃); IR (neat) 3012, 1715 cm⁻¹; ¹H NMR (CDCl₃) δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.32 (m, 8 overlapping H), 2.19 (m, 1H), 2.31 (t, *J* = 8.4 Hz, 2H), 2.52 (m, 2H), 2.66 (dd, *J*₁ = 8.0 Hz, *J*₂ = 16.4 Hz, 1H), 3.04 (dd, *J*₁ = 5.2 Hz, *J*₂ = 16.8 Hz, 1H), 3.53 (s, 1H), 3.74 (s, 3H), 4.33 (m, 1H); ¹³C NMR (CHCl₃) δ 14.1, 22.4, 29.3, 31.9, 32.4, 32.7, 37.7, 45.9, 48.6, 51.6, 57.6, 168.1, 176.5, 206.4; HRMS calcd for C₁₄H₂₄NO₃ (M + H) 254.1756. Found 254.1756.



(4*S*)-(+)-**279**

(*S*)-(+)-Methyl (3,4-dihydro-5-phenyl-2*H*-pyrrol-2-yl)-3-oxobutanoate (279).

Chromatography (50% EtOAc/hexanes) yielded 0.230 g (80 %) of a colorless oil; IR (neat) 3054, 1746, 1717, 1422, cm⁻¹; $[\alpha]_D^{20} +37.5$ (*c* 1.35, CHCl₃); ¹H NMR (CDCl₃) δ 1.61 (m, 1H), 2.36 (m, 1H), 2.74 (q, *J* = 8.05 Hz, 1H), 2.93 (m, 1H), 3.08 (m, 2H), 3.59 (s, 2H), 3.74 (s, 3H), 4.58 (m, 1H), 7.42 (m, 3H), 7.82 (d, *J* = 6.7 Hz, 2H); ¹³C NMR (CDCl₃) δ 29.0, 35.1, 49.6, 52.3, 68.9, 127.7, 128.4, 130.6, 134.2, 167.6, 173.2, 201.6. HRMS calcd for C₁₅H₁₈NO₃ (M+H) 260.1287. Found 260.1297.



(S)-(+)-280

(S)-1-(5-pentyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-one (280).

Chromatography (1:99 MeOH/CH₂Cl₂) yielded 0.182 g (71 %) of a colorless oil; IR (neat) 3054, 1750, 1422, cm⁻¹; [α]²⁰_D +63.5 (*c* 1.10, CHCl₃); ¹H NMR (CDCl₃) δ 0.90 (t, *J* = 8.2 Hz, 3H), 1.34 (8 overlapping H), 2.14 (s, 3H), 2.35 (5 overlapping H), 2.61 (dd, *J*₁ = 7.9 Hz, *J*₂ = 16.2 Hz, 1H), 4.29 (m, 1H); ¹³C NMR (CDCl₃) δ 14.1, 22.4, 29.3, 29.8, 31.9, 32.4, 32.7, 37.7, 48.7, 57.6, 176.5, 207.7; HRMS calcd for C₁₂H₂₂NO (*M* + *H*) 196.1701. Found 196.1712.

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