2007

Controlling the diastereoselectivity in the microwave-assisted aza-cope rearrangement--mannich cyclization

Wesley A. Turley

Controlling the Diastereoselectivity in the Microwave-assisted aza-Cope Rearrangement—Mannich Cyclization

by

Wesley A. Turley

Thesis

Submitted to the Department of Chemistry

Eastern Michigan University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

in

Chemistry

Thesis Committee:

Harriet Lindsay, PhD, Chair

Cory Emal, PhD

Gregg Wilmes, PhD

November 27, 2007

Ypsilanti, Michigan

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank a number of people who have helped me during my time at Eastern Michigan University. First, I would like to thank Dr. Harriet Lindsay, who welcomed me into her research group and provided me with a platform to develop into an aspiring researcher. I would like to thank my thesis committee members, Dr. Cory Emal and Dr. Gregg Wilmes, for all their suggestions and support during my graduate studies. Also, I would like to thank the Chemistry Department Heads, Dr. Maria Milletti and Dr. Ross Nord, along with the Department Graduate Advisor, Dr. Krish Rengan, and the Chemistry faculty members for everything they have done for me. Thank you to the Graduate School at Eastern Michigan University for financial support. I would also like to thank the Lindsay Research Group, both former and present members, namely Edwin Marrero and Ben Johnson, who presented with me at the 2007 National A.C.S. meeting in Chicago. Thank you to my family because without them I would not be where I am at today.

ABSTRACT

The aza-Cope rearrangement—Mannich cyclization (ACM), pioneered by Larry Overman, is a powerful tool in synthesizing pyrrolidines and pyrrolizidine alkaloids. The ACM reaction is a highly efficient process in which three different reactions occur in a single synthetic step (**Scheme**). An amino alcohol reacts with an aldehyde to form an iminium cation. The iminium cation undergoes [3,3]-sigmatropic rearrangement with subsequent cyclization to provide pyrrolidine diastereomers. Traditional ACM reactions require reaction times between 10 and 72 hours under reflux conditions. We have developed the first microwave-assisted version of the tandem aza-Cope rearrangement—Mannich cyclization. This provides acylpyrrolidine diastereomers in a single step while drastically reducing the reaction times. We have found increasing the size of the nitrogen protecting group (R_1) on the amino alcohol can improve the diastereoselectivity in the ACM reaction. We have observed in some instances that lowering the reaction temperature can also improve the diastereoselectivity in the reaction.

Scheme

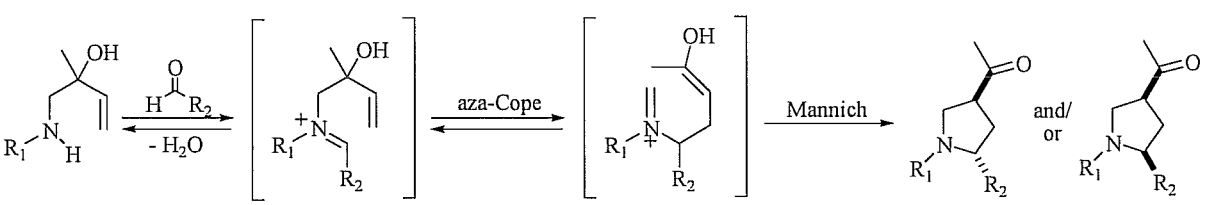


TABLE OF CONTENTS

LIST OF TABLES

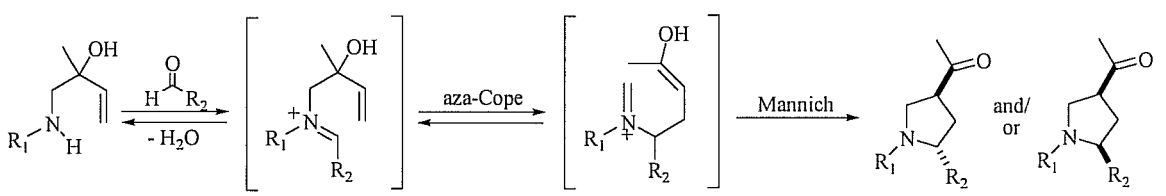
LIST OF FIGURES

Introduction

I. Background on the aza-Cope Rearrangement—Mannich Cyclization

The aza-Cope rearrangement—Mannich cyclization (ACM) reaction, pioneered by Overman, is a powerful method to synthesize pyrrolidines and similar compounds.[1] This reaction consists of a [3,3]-sigmatropic rearrangement that allows for the formation of a new carbon-carbon bond. The rearrangement is followed by an intramolecular ring closure, known as a Mannich cyclization, resulting in the formation of a pyrrolidine. A typical aza-Cope—Mannich reaction is shown in **Scheme 1**. Here, amino alcohol **1** reacts with an aldehyde resulting in iminium ion **2**. Iminium ion **2** undergoes aza-Cope rearrangement to provide iminium ion **3**. Mannich cyclization occurs and iminium ion **3** is transformed into acylpyrrolidine diastereomers **4** and **5**. Not shown in this scheme but vital to the reaction is the need of a drying agent and an acid catalyst. An equivalent of water is produced in a reversible step when amino alcohol **1** forms iminium ion **2**. The drying agent is needed to absorb this mole of water, ensuring the formation of iminium ion **2** occurs irreversibly.

Scheme 1



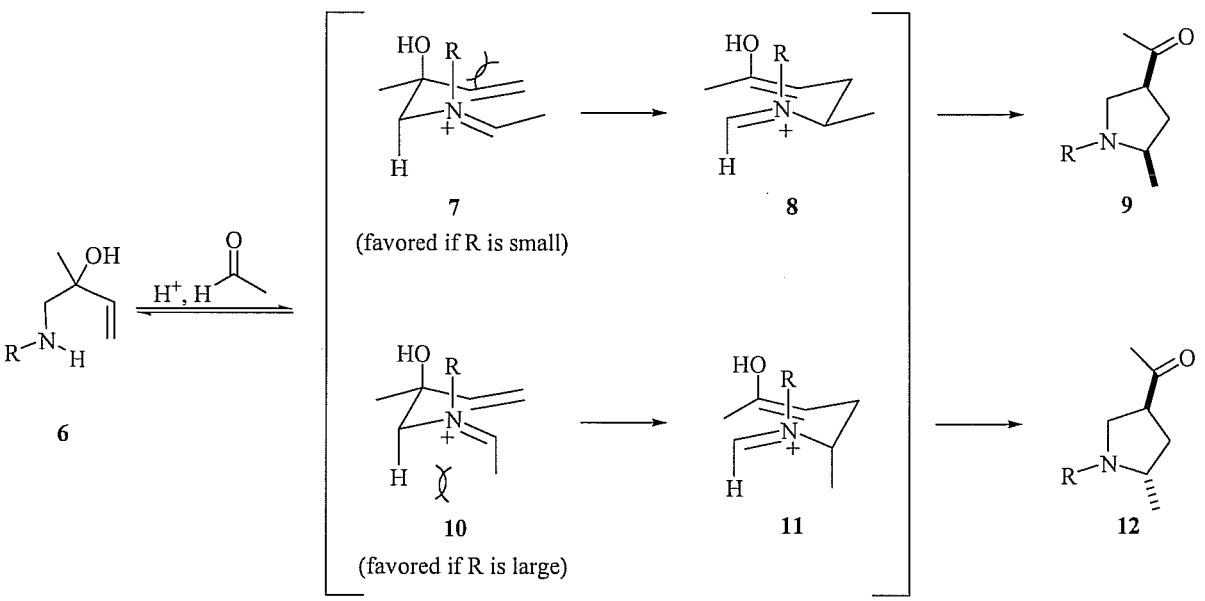
1 **2** **3** **4** **5**

II. Controlling Diastereoselectivity Using Amine Protecting Group Size

As shown in **Scheme 1**, the result of an aza-Cope—Mannich reaction is two acylpyrrolidine diastereomers. Many factors affect the diastereoselectivity in the reaction. We hypothesize the major factor controlling the diastereoselectivity is the size of the nitrogen protecting group on amino alcohol **6** (**Scheme 2**). This is due to allylic strain dictating the

iminium cation geometry.[2-4] When the nitrogen protecting group is large (e.g. R=$CHPh_2$), the allylic strain in iminium ion 7 between the methyl iminium substituent and the protecting group is rather large. In this case, iminium cation **10** is favored, resulting in higher selectivity for *trans*-acylpyrrolidine **12**. The opposite is seen when the nitrogen protecting group is small (e.g. R=Me) because the interaction between the alkyl substituent and the protecting group is not as significant. In that case, pseudo 1,3-diaxial interactions in iminium cation **10** cause cation **7** to be favored. Thus, aza-Cope—Mannich reaction via iminium ion **7** occurs to a greater extent, which increases diastereoselectivity for *cis*-acylpyrrolidine **9**. Controlling the diastereoselectivity by changing the steric demand of the nitrogen protecting group is not without precedence. Although a more structurally rigid amino alcohol was investigated, Overman showed that steric influences of the alkyl substituent on the nitrogen protecting group played a role in controlling the diastereoselectivity via iminium ion geometry control.[3]

Scheme 2



III. Microwave Chemistry

One disadvantage of the ACM is that the reaction typically takes from 10 to 72 hours to be completed.[5] Thus, microwave-assisted organic synthesis was utilized in our efforts to reduce the time requirement for the aza-Cope—Mannich reaction. Microwave ovens have been used by organic chemists since the 1980s due to their ability to produce faster reaction rates, improve yields, and use more environmentally-friendly conditions.[6-8] Microwaves are electromagnetic energy that occur with a frequency between 300 and 300,000 MHz. Most commercial microwave reactors produce energy with a frequency of 2,450 MHz. Magnetic energy is composed of two fields: electric and magnetic. The electric field is responsible for delivering energy used as a heating source whereas the magnetic field usually is not involved in chemical interactions.[6-8] Microwaves do not affect the chemical structure of molecules because the energy range of their photons is not high enough to cleave bonds.

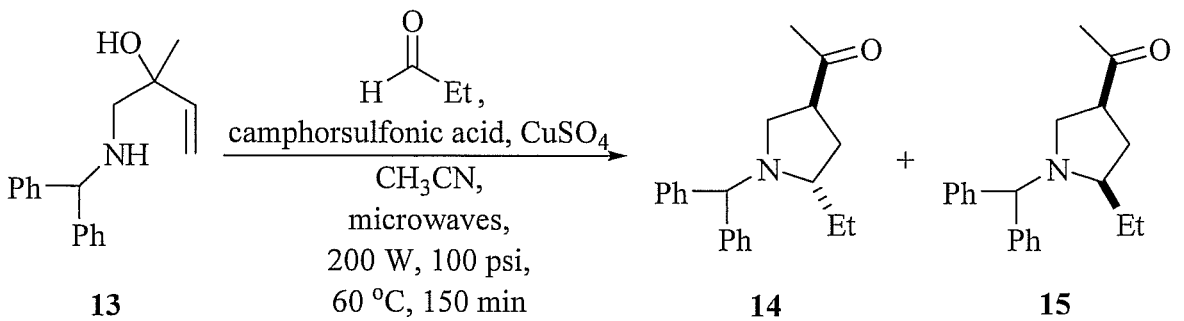
Microwaves heat a substance differently than traditional heating methods. Traditional methods utilize conductive heating from an external source, which requires driving heat through vessel walls before reaching the reactants and solvent. This method is inefficient because it is slow and the energy transfer depends on the thermal conductivity of the reaction vessel and reaction mixture. This leads to two specific drawbacks.[6-8] The reaction mixture needs time to reach thermal equilibrium with the vessel. Also, maintaining a constant reaction temperature involves adjusting the applied heating source throughout the course of the reaction. By comparison, microwave heating is a more efficient heating method and does not depend on thermal conductivity. Heating occurs as a result of the microwaves interacting directly with the components of the reaction mixture.

There are two ways in which microwave heating can be generated: dipolar polarization and ionic conduction.[6-8] Dipolar polarization is observed in reactions occurring in polar solvents (water, methanol, ethanol, etc.) and is the more common process. Molecules align their dipoles with the magnetic field. The magnetic field oscillates, which causes the molecules to oscillate as well. This generates friction, which is the energy source that heats the reaction. The greater the molecular dipole, the greater the molecule's susceptibility to motion and therefore to microwave heating.

IV. Microwave-Assisted Aza-Cope—Mannich Reaction

We were interested in developing a microwave assisted version of the aza-Cope—Mannich reaction for the synthesis of pyrrolidine alkaloids (**Scheme 3**). To our knowledge, ours is the first example of a microwave-assisted version of this reaction.[2b] Based on our hypothesis and Overman's earlier investigations,[3,9] we anticipated being able to control diastereoselectivity in the aza-Cope—Mannich reaction by varying the size of the amine protecting group. Specifically, our investigation examined amino alcohols with nitrogen protecting groups ranging in size from R=H to R=CPh_3.

Scheme 3

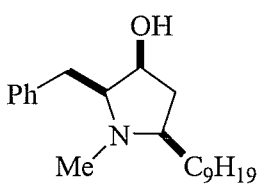


13 **14** **15**

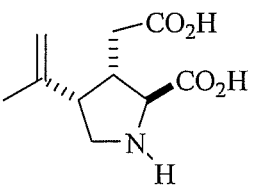
82%, 7:1 (**14**:**15**)

V. Applications of the Aza-Cope—Mannich Reaction

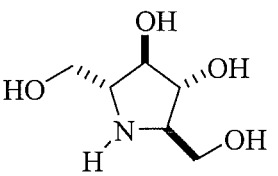
Ultimately, this reaction could be applied to the synthesis of a number of natural products. For example, (+)-preussin (**16**) is an antifungal agent that is isolated from the fermentations of *Preussia* sp. and has shown antifungal activity against yeasts and filamentous fungi. [10] (-)-(α)-Kainic acid (**17**) is another example of a naturally occurring pyrrolidine alkaloid. This analogue of glutamic acid has exhibited potent neuroexcitatory and neurotoxic properties.[11] 2,5-Dihydroxymethyl-3,4-dihdroxypyrrolidine (**18**), commonly called DMDP, is a pyrrolidine alkaloid with glycosidase inhibitory properties.[12] First isolated from the leaves of *Derris elliptica*, DMDP has also been found in other disparate plant species and many microorganisms.



16



17



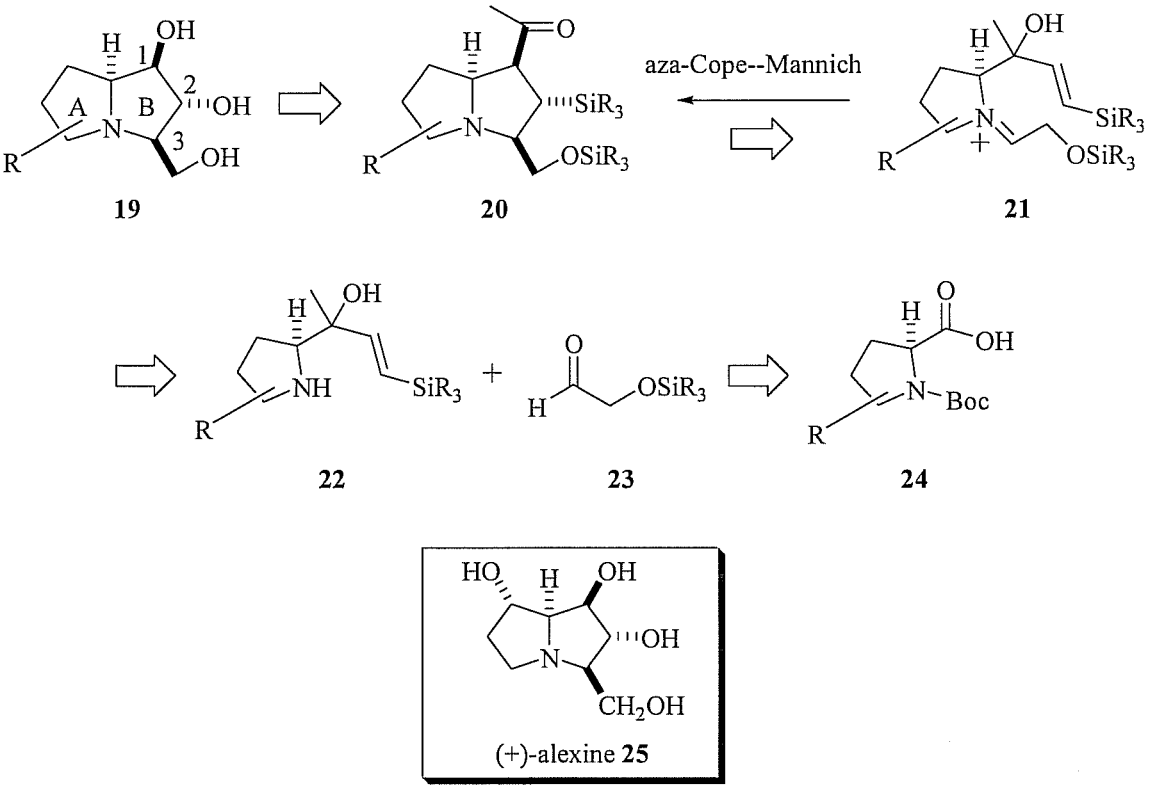
18

Figure 1. Examples of pyrrolidine alkaloids: (+)-preussin (**16**), (-)-(α)-kainic acid (**17**), and DMDP (**18**).

Upon successful synthesis of pyrrolidine alkaloids by the microwave assisted aza-Cope—Mannich reaction, we wanted to apply this reaction to the synthesis of pyrrolizidine alkaloids. One pyrrolizidine alkaloid target was (+)-alexine (**25**) (**Scheme 4**), a glycosidase inhibitor, which is structurally similar to DMDP **18**.[13] Our retrosynthetic analysis for the synthesis of polyhydroxylated pyrrolizidine **19** is shown in **Scheme 4**. The key step of the synthesis is an aza-Cope—Mannich reaction that would establish B-ring relative stereochemistry at C_1, C_2, and C_3. Polyhydroxylated pyrrolizidine **19** would be available from acylpyrrolizidine **20** after oxidation and deprotection. Acylpyrrolizidine **20** would be

the product of the aza-Cope—Mannich cyclization of iminium ion **21** formed from amino alcohol **22** and aldehyde **23**. Amino alcohol **22** can be prepared by methyl addition, deprotection, and vinyl addition to commercially available Boc-L-proline (**24**) (R=H) or a similar amino acid containing an A-ring substituent (R=OH).

Scheme 4

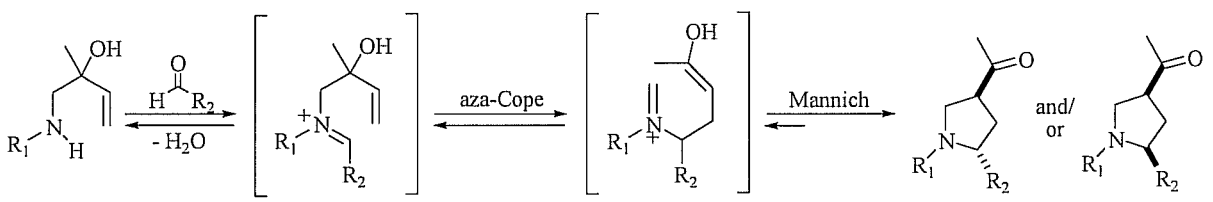


Literature Review

I. Overview of the Aza-Cope Rearrangement—Mannich Cyclization

In 1979, Overman and Kakimoto developed a 2-azonia-[3,3]-sigmatropic rearrangement method for forming carbon-carbon bonds and coupled it with a Mannich cyclization.[1] Mechanistically, this rearrangement occurs after the aldehyde undergoes condensation with an amine or ammonium salt to give an iminium cation. Once this occurs, a [3,3]-sigmatropic rearrangement takes place followed by an intramolecular Mannich ring closure. Ring closure results in an oxonium ion, which is then deprotonated to form an acylpyrrolidine (**Scheme 1**). In order for the [3,3]-sigmatropic (aza-Cope) rearrangement to be a viable synthetic method, the rearrangement needs to be irreversible in the preferred direction.[1] When water is present in the system, the iminium cation **2** can react reversibly to form the amino alcohol **1**. Water must be removed from this step to ensure the irreversible formation of **2** from **1**. The aza-Cope rearrangement of the iminium cations **2** and **3** is also a reversible step so cation **3** must undergo an energetically favored Mannich cyclization to produce the acylpyrrolidines **4** and/or **5**.

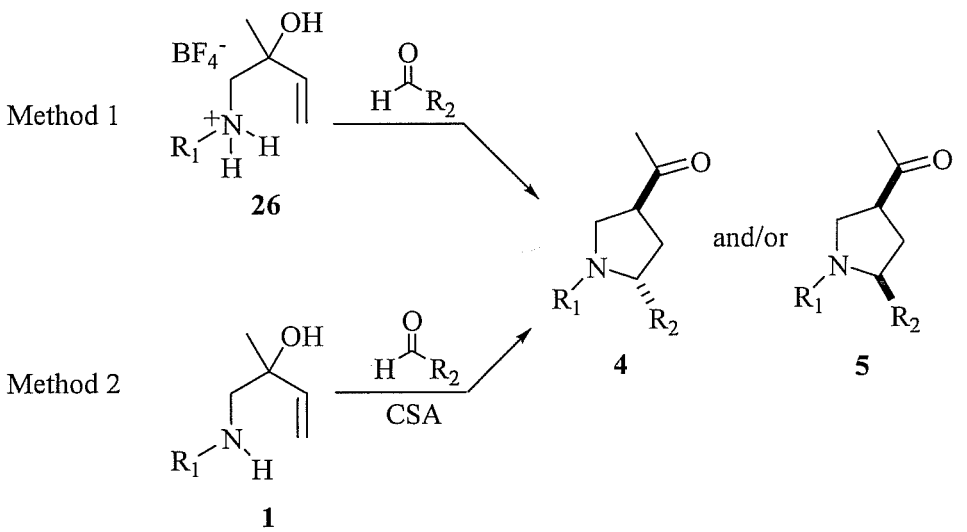
Scheme 1



Overman and Kakimoto found that substituted acylpyrrolidines can be formed in a single step by the reaction of aldehydes with salts of alkoxybutenamines.[1] This reaction takes place in a single synthetic step and high yields are obtainable. Alkyl, benzyl, and phenyl amines (R_1, **Scheme 1**) and aliphatic, aromatic, and heteroaromatic aldehydes (R_2,

Scheme 1) were used. Reactions required between 5 and 72 hours, and all products were obtained as a mixture of acylpyrrolidine diastereomers **4** and **5** in yields ranging from 54-97% (depending on aldehyde and nitrogen substituents and conditions). Two different methods for iminium cation formation were examined (**Scheme 5**).[1] Method 1 utilized a crystalline ammonium tetrafluoroborate salt, while Method 2 employed a free amine and approximately one equivalent of camphorsulfonic acid (CSA). The resulting products for both methods were the same acylpyrrolidines **4** and/or **5**. The relative stereochemistry of the products was not determined, and the reaction was limited to unhindered aldehydes.

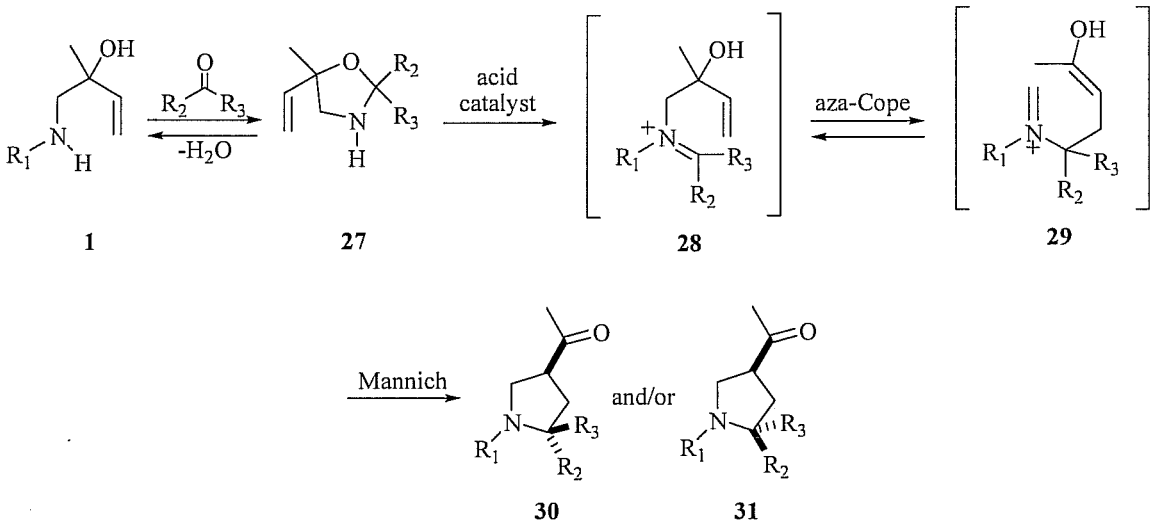
Scheme 5



Overman and co-workers examined generating the iminium cation via an oxazolidine intermediate as an alternate route to synthesize pyrrolidines.[5] They found that the one-step synthesis (**Scheme 1**) was limited to more reactive aldehydes. Consequently they developed a two-step procedure (**Scheme 6**) that utilized the same amino alcohol **1** as before, but unlike the one-step method, this procedure resulted in successful condensation with either an aldehyde or a ketone. The product of the first step was oxazolidine **27**, produced in yields ranging from 84-92% depending on the carbonyl compound and conditions. Oxazolidine **27**

then formed iminium cation **28** in the presence of an acid catalyst. Cation **28** underwent the aza-Cope rearrangement to form iminium cation **29** and then cyclized to produce acylpyrrolidines **30** and **31**. This method could be used for substituted cyclohexanones and more hindered aldehydes. Although the method has its advantages, the disadvantage is that isolation and in some cases purification of oxazolidine **27** are needed.

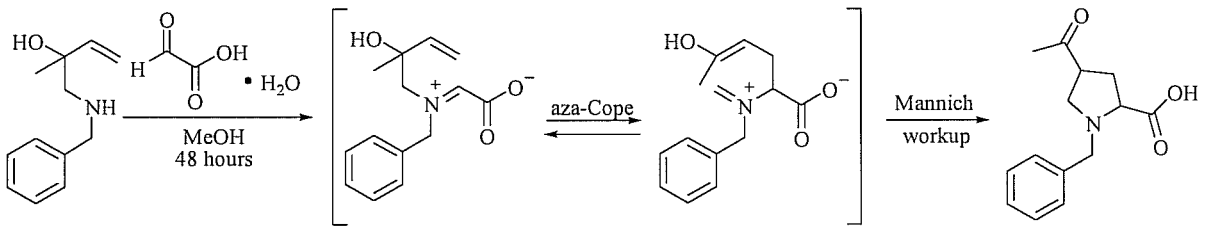
Scheme 6



Cooke utilized glyoxylic acid in the aza-Cope—Mannich reaction to generate *N*-benzyl-4-acetylproline.[14] In previous experiments performed by Overman and co-workers, an amino alcohol reacted with an aldehyde or ketone to form an iminium ion in the presence of an acid catalyst (**Schemes 1** and **5**). In Cooke's version of the ACM, the acid catalyst and aldehyde are contained on the same reactant. Specifically, benzylamine **32** reacted with glyoxylic acid monohydrate to form iminium ion **33**, which underwent aza-Cope rearrangement to form iminium ion **34**. Mannich cyclization of iminium ion **34** produced *N*-benzyl-4-acetylproline **35** as a mixture of diastereomers in 64% yield after 48 hours. The ratio of diastereomers varied between 80:20 and 96:4 depending on the reaction conditions, although the optimal conditions were not reported. The benefit of this type of aza-Cope—

Mannich reaction is that functionalized proline derivatives can form at room temperature with no required purification other than recrystallization.

Scheme 7

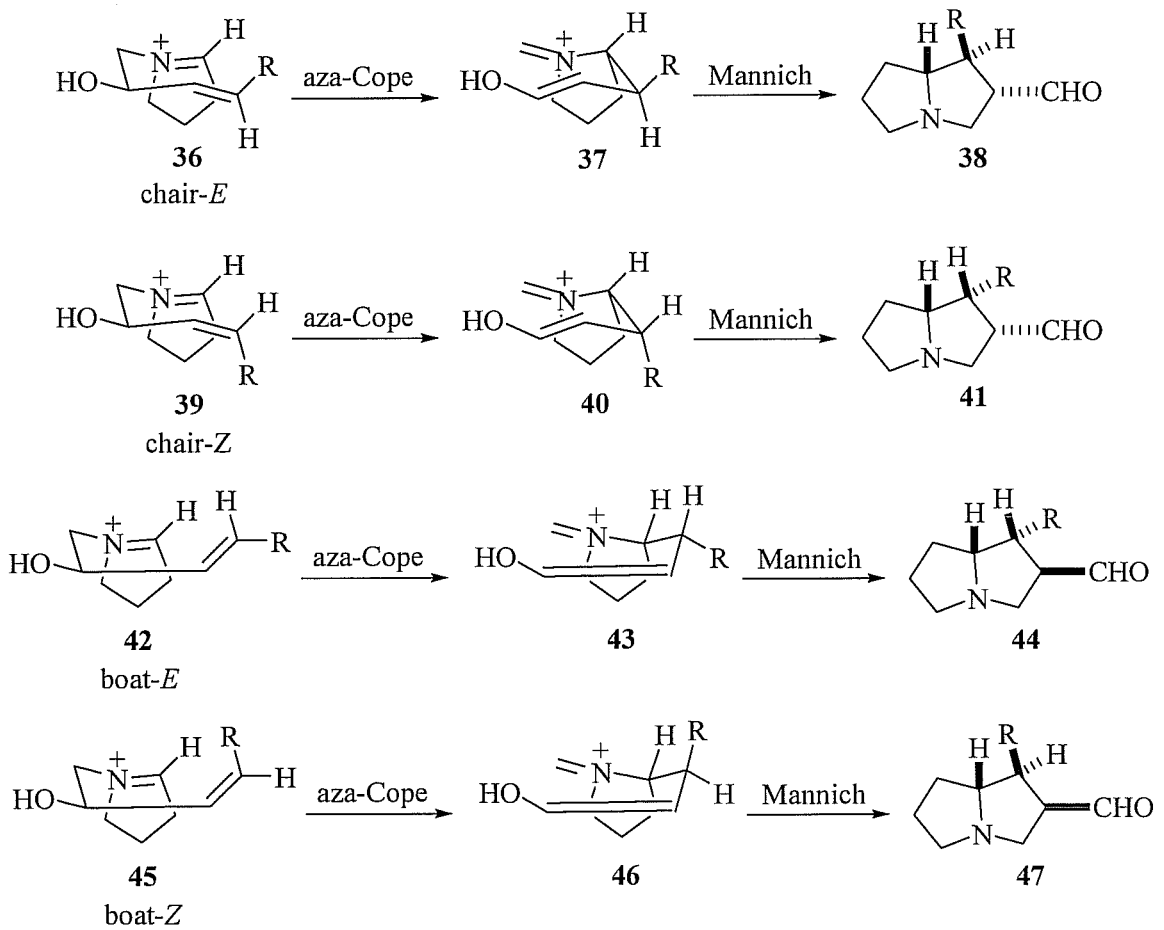


32 **33** **34** **35**

II. Stereochemistry of the Aza-Cope—Mannich reaction

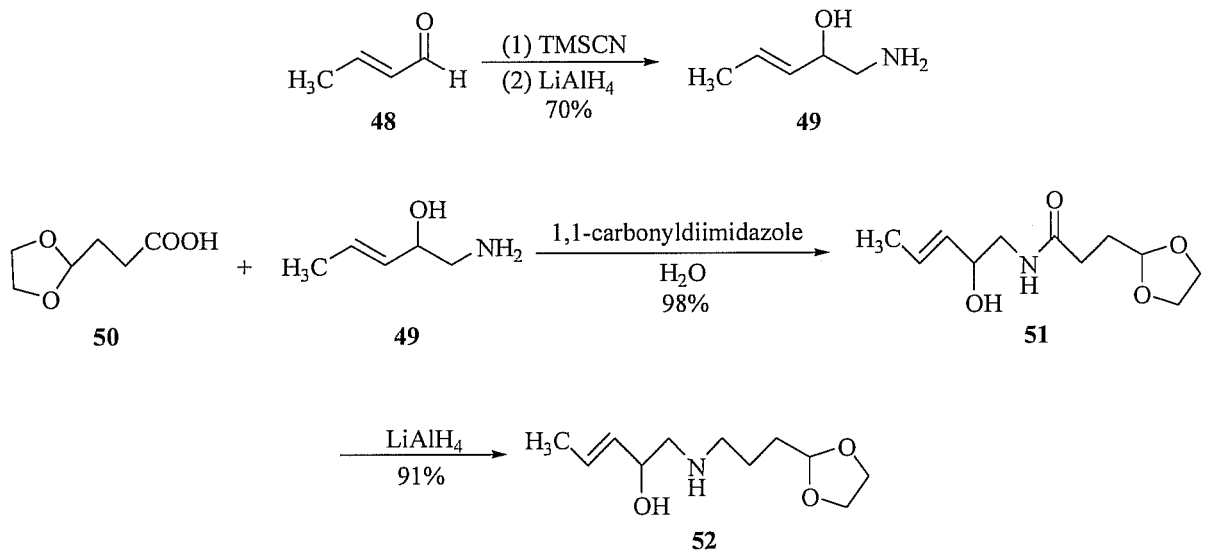
Predicting the stereochemical outcome of the aza-Cope—Mannich reaction was of interest to Overman. The basis of his predictions was the fact that the [3,3]-sigmatropic rearrangement most likely occurs via a chair configuration.[3] First, Overman examined the effect of the C=C geometry on acylpyrrolidine relative stereochemistry. He chose a substrate in which the iminium cation would be endocyclic, thus making the iminium cation geometry a non-issue (**Scheme 8**).[15] According to his predictions, when the starting C=C is set in the *E* configuration, formyl pyrrolizidine **38** would form via a chair transition state. Alternatively, if the boat conformation was adopted, then formyl pyrrolizidine **44** would form. By contrast, when the starting iminium ion is set in the *Z* configuration, formyl pyrrolizidine **41** would form from the chair conformation. Alternatively, formyl pyrrolizidine **47** would form from the boat conformation.

Scheme 8



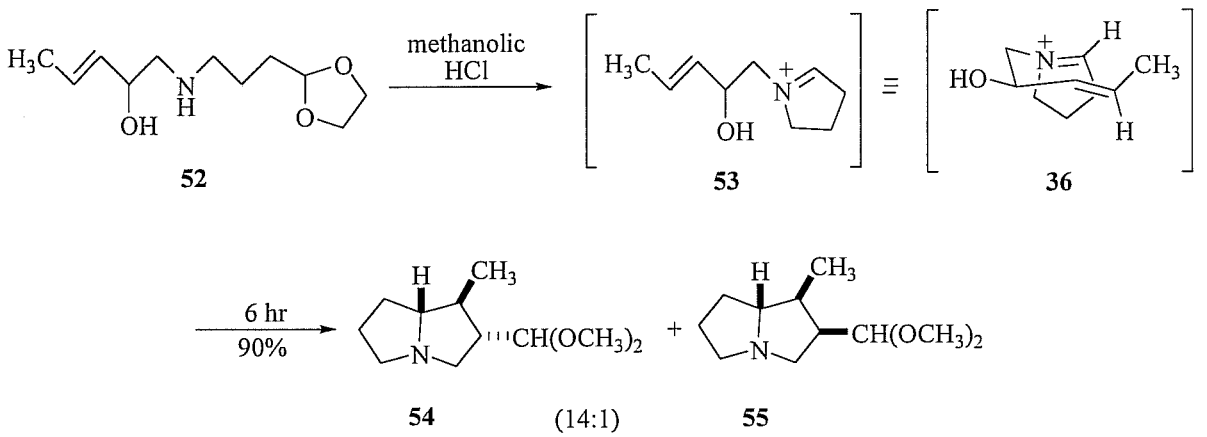
To test their predictions, an amino alcohol bearing an *E* carbon-carbon double bond was prepared and subjected to ACM conditions. Beginning with crotonaldehyde **48**, cyanohydrin formation and reduction led to amino alcohol **49**. Amino alcohol **52** was prepared by condensation of acid **50** with amine **49** followed by reduction of the resulting amide **51** (**Scheme 9**).

Scheme 9



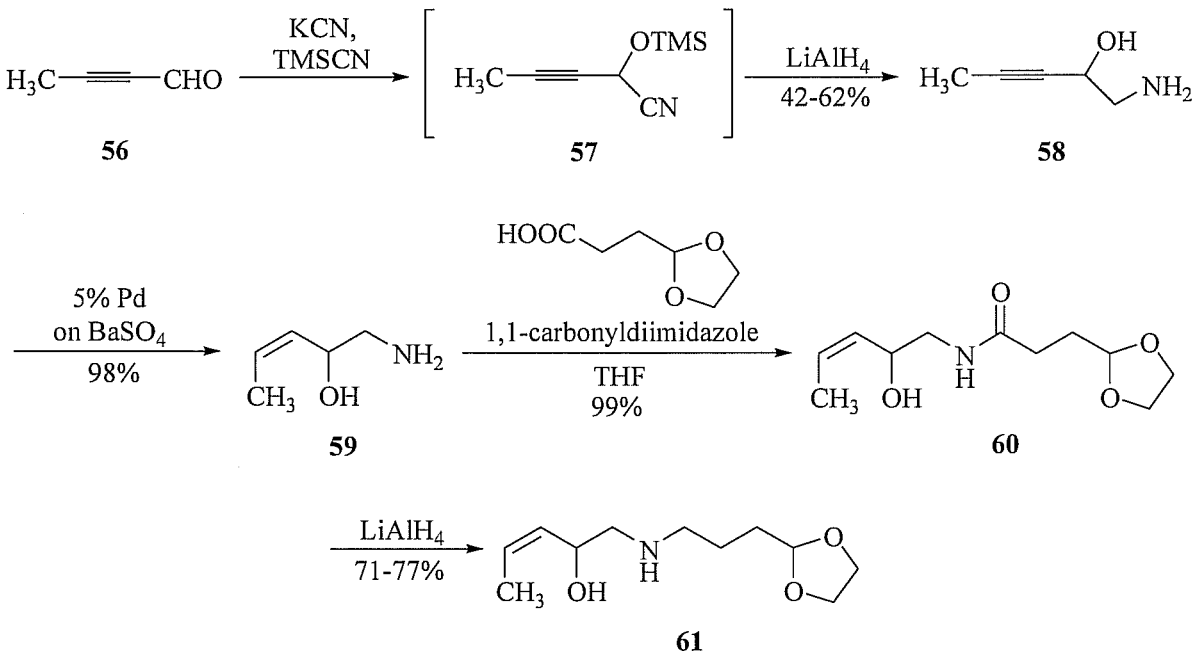
Heating amino alcohol **52** in 0.25 M methanolic HCl for 6 hours at 65°C induced the aza-Cope—Mannich rearrangement, resulting in epimeric pyrrolizidine acetals **54** and **55** with a combined yield of 90% (**Scheme 10**). Overman did not account for the remaining 10%. The ratio of pyrrolizidines **54**:**55** was determined to be 14:1 by GC analysis. Nuclear Overhauser effect difference spectroscopy (NOEDS) experiments were performed on each isomer, and the configuration of the acetal substituent was the only difference found. According to transition state analysis, the major isomer resulted from rearrangement and cyclization via chair topography. Epimerization following the ACM would lead to the formation of the minor isomer.

Scheme 10



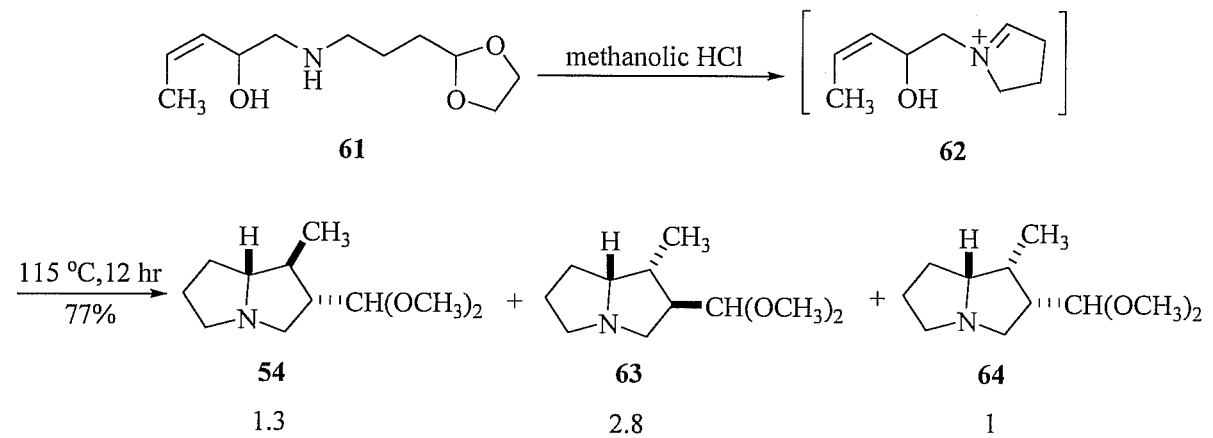
An analogous experiment was performed using amino acetal **61**, having *Z* C=C geometry (**Scheme 11**).[15] A catalytic amount of KCN was added to 2-butynal **56** to produce trimethylsilyl cyanohydrin **57**, which was then reduced with $LiAlH_4$ to form the alkynyl amino alcohol **58**. Alkynyl amino alcohol **58** underwent semihydrogenation with Pd-$BaSO_4$/pyridine, to produce the *Z* alkene **59**. As before, the amino acetal **61** was formed by condensation with a carboxylic acid followed by the reduction of the amide.

Scheme 11



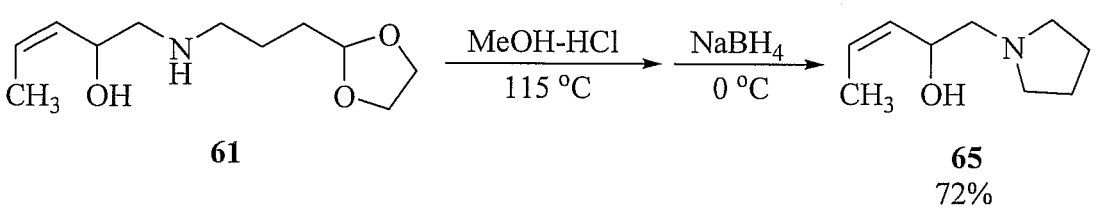
For the ACM, amino acetal **61** was treated with methanolic HCl at 65 °C for 6 hours. However, no reaction occurred. When more forcing reaction conditions were used (115 °C, 12 hours), a mixture of pyrrolizidines **54**, **63**, and **64** were formed (**Scheme 12**). The mixture of **54**, **63**, and **64** was separated by GC and was found to contain 20%, 42%, and 15% of each respective isomer. The composition of the remaining 23% was not reported. The acetal stereochemistries of pyrrolizidines **63** and **64** were assigned using spectra from ^{1}H NMR and NOEDS experiments. The stereochemistry of pyrrolizidine **54** was assigned from the previous experiment (**Scheme 10**). Using **Scheme 8**, the routes by which each pyrrolizidine stereoisomer formed may be rationalized. Pyrrolizidine **54** most likely formed through the boat conformation and subsequent epimerization. Pyrrolizidine **64** most likely formed through the chair conformation, whereas pyrrolizidine **63** likely formed through the chair conformation and subsequent epimerization.

Scheme 12



Another possibility is that pyrrolizidine **54** could have been formed by C=C isomerization followed by rearrangement via chair topography. The possibility of the *Z* alkene of amino acetal **61** undergoing *Z*→*E* isomerization prior to ACM was examined by submitting amino acetal **61** to the ACM rearrangement conditions, allowing partial completion and then quenching the reaction by reducing the iminium cation with $NaBH_4$ to form the *Z*-pyrrolidine alcohol **65** (**Scheme 13**).

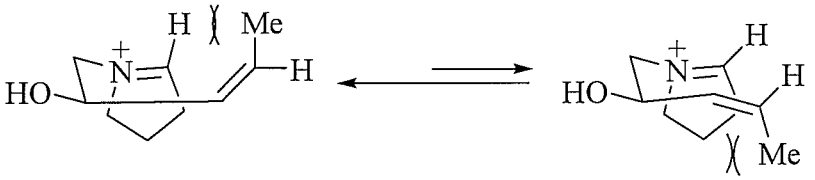
Scheme 13



GC analysis and ^1H NMR spectroscopy showed that *Z* pyrrolidine alcohol **65** was the only product that formed. This is consistent with the reaction occurring by competitive rearrangement via a boat transition state but does not rule out the possibility of isomerization occurring before rearrangement. This is due to the likelihood that iminium cation **53** with *E* C=C geometry undergoes 3,3-sigmatropic rearrangement faster than iminium cation **62** with *Z* C=C geometry. It is not unreasonable that iminium cation **62** would partially rearrange via

a boat conformation because of a destabilizing steric interaction between the azacyclopentene ring and the *Z*-methyl substituent in the chair conformation (**Scheme 14**).

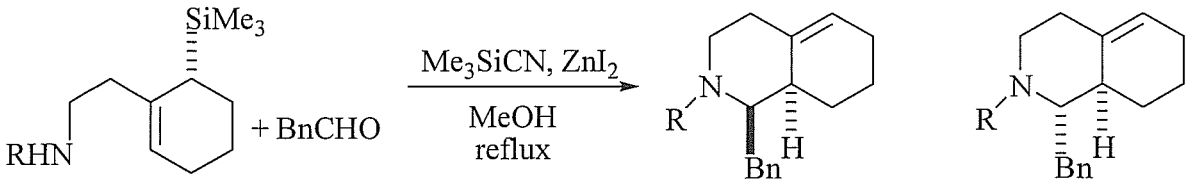
Scheme 14



66$_{boat}$ **66**$_{chair}$

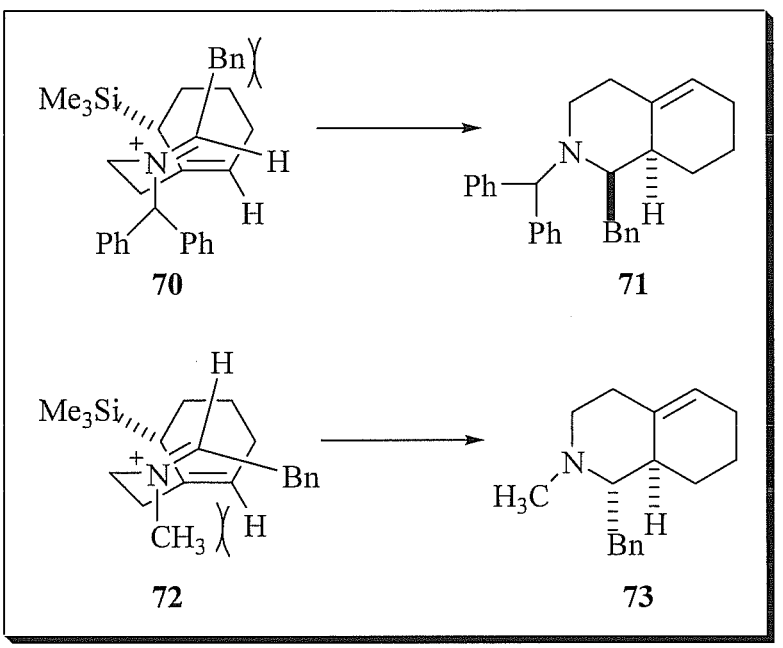
During Overman's development of a route to opium alkaloids he found that the size of the nitrogen protecting group controlled the stereochemistry in iminium ion-vinylsilane cyclizations (**Scheme 15**).[9,15,16] It was anticipated that when R was small (e.g. Me), cyclization through iminium cation **72** would be preferred where the iminium substituent has pseudo-axial orientation. This cyclization would lead to the octahydroisoquinoline **73**. By contrast, when R is large (e.g. Ph_2CH), interaction between R and the iminium substituent should destabilize the transition state leading to iminium cation **72** enough to cause the cyclization to go through iminium cation **70**. This cyclization would lead to the octahydroisoquinoline **71**. In the event, allylsilane amine **67** (R=Me) reacted with benzaldehyde, Me_3SiCN, ZnI_2, and MeOH under reflux conditions to provide an 88% yield of octahydroisoquinolines **68** and **69**. The diastereoselectivity of octahydroisoquinolines **68** and **69** was 11:89. However, when the amine-protecting group was larger in size (Ph_2CH) the reaction produced different results. A 73% yield was obtained of a single isomer, octahydroisoquinoline **68**. These results are wholly consistent with the chair transition state predictions.

Scheme 15



67 **68** **69**

R = Me, 11:89 (88%)
R = Ph_2Ch. 100:0 (73%)



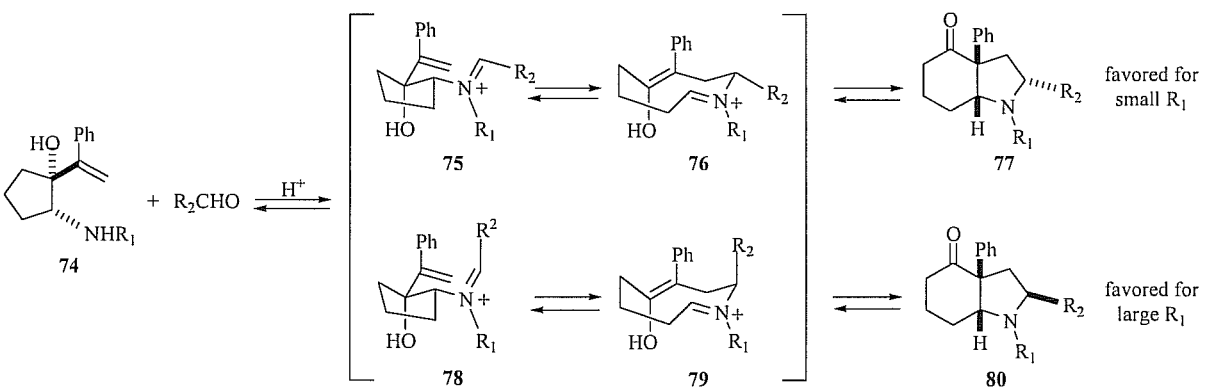
70 **71**

72 **73**

Overman and Trenkle applied this knowledge to try to control the stereochemistry in the aza-Cope—Mannich reaction of *N*-protected *cis*-2-amino-1-alkenylcyclopentanol **74** with different aldehydes.[3] As in the case of the iminium ion-vinylsilane cyclization, the stereoisomers of *cis*-octahydroindolone can be controlled depending on the size of the nitrogen protecting group (**Scheme 16**). When the nitrogen substituent (R_1) of amino alcohol **74** is small, such as a methyl group, the [3,3]-sigmatropic rearrangement goes through a transition state where the R_2 group from the reacting aldehyde is in a pseudo-equatorial orientation.[17] This orientation is likely adopted to avoid psuedo-1,3-diaxial interactions with

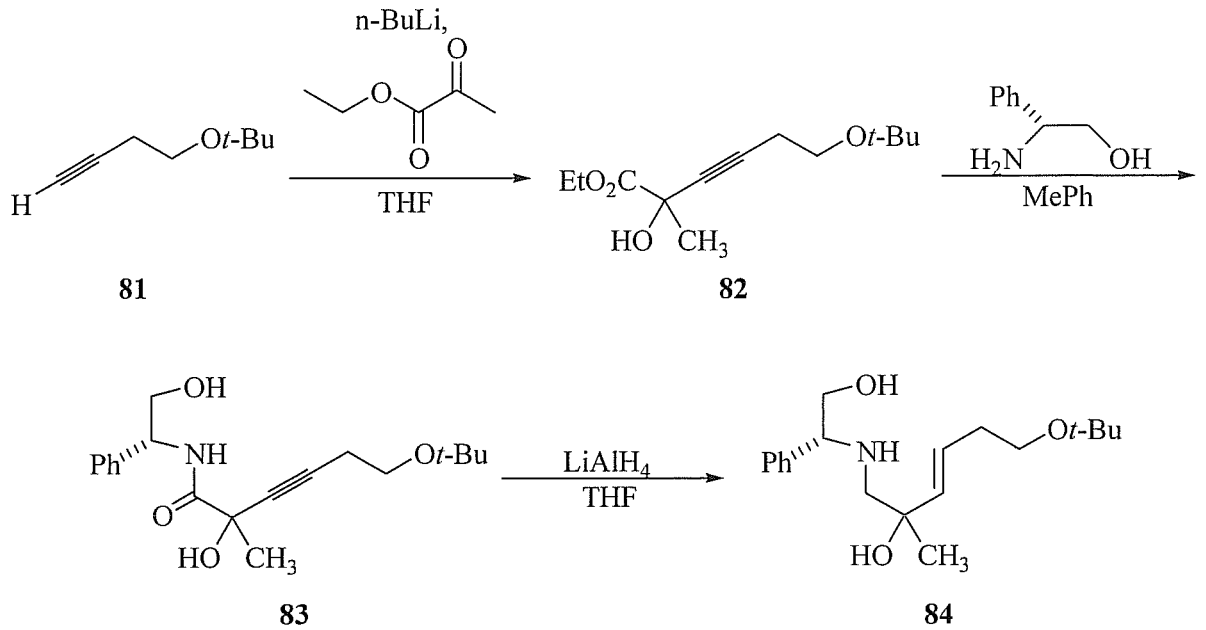
the pseudo-axial aromatic ring. Rearrangement via chair **75** would lead to the formation of indolizidinone **77**. Indeed, stirring amino alcohol **74** (R_1 = Me) with acetaldehyde and CSA (0.9 eq) in MeCN for 24 hours at 60 °C provided octahydroindolone **77** as a single isomer in 92% yield. However, when R_1 is a larger substituent, such as $CHPh_2$, the vicinal R_1 and R_2 groups are involved in allylic strain that raises the energy of the **75**→**76** transition state enough to cause the rearrangement to go through a transition state that orients the iminium substituent in a pseudo-axial position, leading to octahydroindolone **80**.[18] Stirring amino alcohol **74** (R_1 = $CHPh_2$) with acetaldehyde and CSA (0.9 eq) in MeCN for 40 hours at 60 °C provided octahydroindolone **80** as a single isomer in 92% yield.

Scheme 16



Agami used an aza-Cope—Mannich reaction en route to his enantioselective synthesis of (-)-α-allokainic acid.[19] The amino alcohol **84** needed for the aza-Cope—Mannich reaction was prepared by the carbonyl addition of alkyne **81** to ethyl pyruvate to give α-hydroxy ester **82**. Condensation with *R*-phenylglycinol produced amide **83**. Reduction of the amide provided amino alcohol **84** with an overall yield of 62% for three steps (**Scheme 17**).

Scheme 17

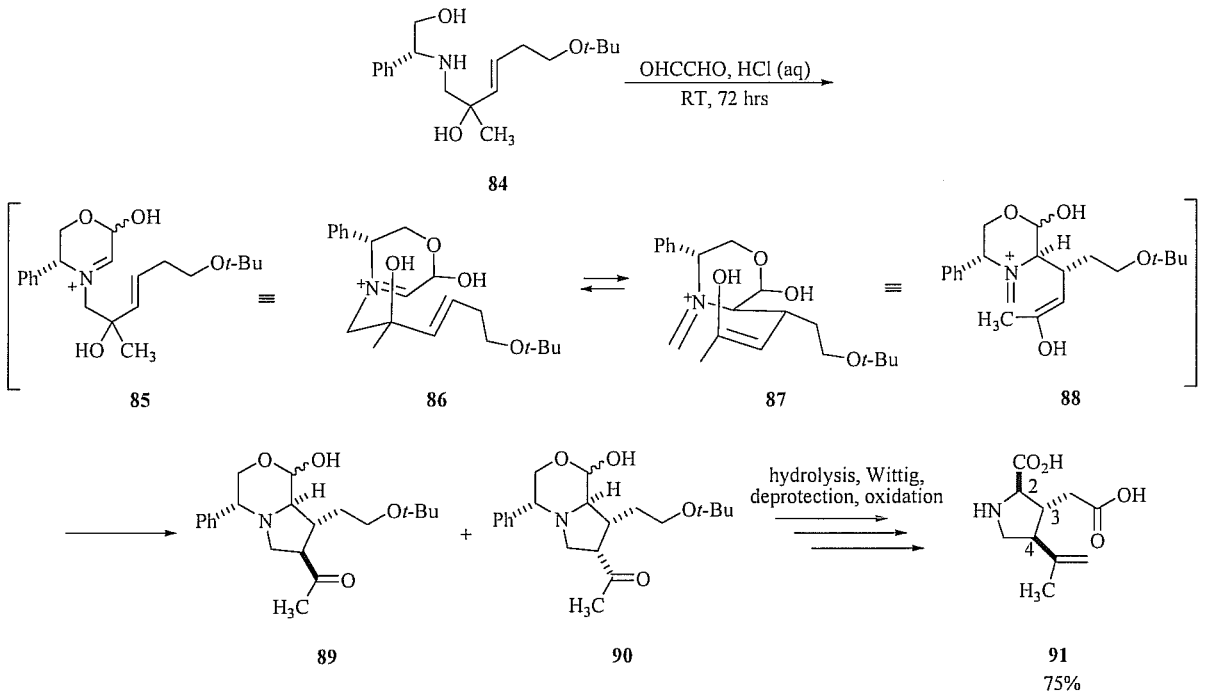


81 **82**

83 **84**

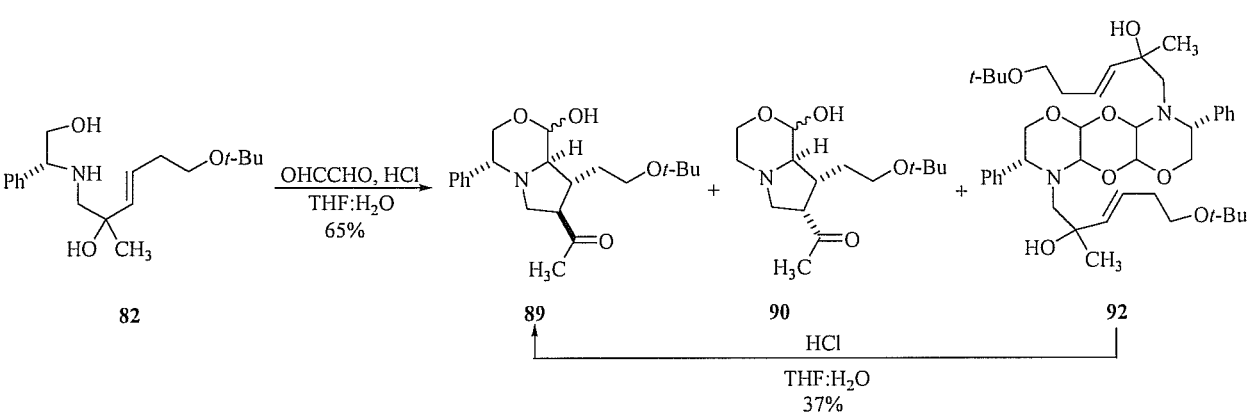
Agami then used the aza-Cope—Mannich reaction to form the bicyclic hemiacetal **89** as part of a synthetic route to (-)-α-allokainic acid (**91**)(**Scheme 18**).[19] Amino alcohol **84** underwent acid catalyzed condensation with glyoxal to form the iminium cation **85** (**Scheme 18**). Cation **85** underwent aza-Cope rearrangement to form iminium cation **88**. The bicyclic hemiacetal **89** was formed once iminium cation **88** underwent Mannich cyclization. The ACM required a reaction time of 72 hours, which provided a 45% yield of epimers **89** and **90** with a selectivity of 70:30. Both the C=C and iminium cation geometry are set, and the stereochemical outcome observed for the major isomer is consistent with rearrangement via chair topography. The mixture of epimers likely arose from epimerization. Acetal hydrolysis, a Wittig reaction, and deprotection of the t-butyl ether and oxidation of epimer **89** produced (-)-α-allokainic acid (**91**).

Scheme 18



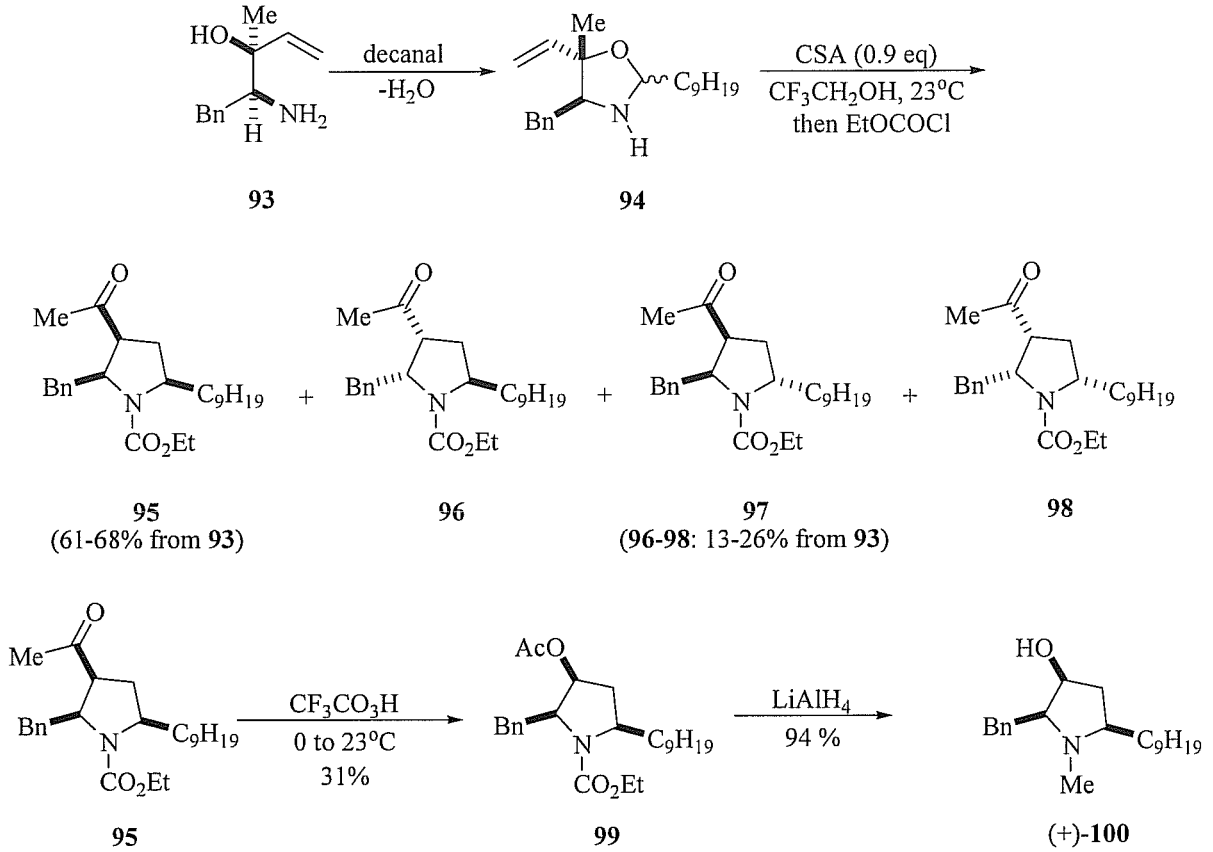
When amino alcohol **84** reacted with glyoxal under slightly acidic conditions, acetal trimer **92** formed along with the expected bicyclic hemiacetal diastereomers **89** and **90** (**Scheme 19**). The relative ratio of the mixture of the bicyclic hemiacetal **89** to the tricyclic compound **92** was 2.25:1. Acetal trimer **92** was separated by flash chromatography and, when resubjected to the initial reaction conditions, the bicyclic hemiacetal **89** reformed. The diastereoselectivity for this transformation was not reported.

Scheme 19



Deng and Overman used the aza-Cope—Mannich reaction to prepare enantioenriched substituted pyrrolidines for the first time.[18] They used this methodology to synthesize both enantiomers of preussin, an antifungal agent composed of a pyrrolidine skeleton. They also examined enantioselectivity and diastereoselectivity in the aza-Cope—Mannich reaction. Deng and Overman utilized the aza-Cope—Mannich reaction to rearrange oxazolidine **94** to form acetylpyrrolidine **95**, which is needed for the total synthesis of (+)-preussin (**100**) (**Scheme 20**). This sequence required the isolation of an intermediate. When amino alcohol **93** and decanal were refluxed in trifluoroacetic acid, decomposition occurred. However, oxazolidine **94** could be formed in the absence of acid. When oxazolidine **94** was treated with acid catalyst, aza-Cope rearrangement and Mannich cyclization readily occurred after 40 hours (**Scheme 6**) to form four pyrrolidine diastereomers. ^{1}H NMR analysis showed the all-*cis* pyrrolidine diastereomer to be the major product that contains all functionality of (+)-preussin (**100**). Due to their lack of stability, the pyrrolidine diastereomers were treated directly with ethyl chloroformate to provide pyrrolidine carbamates **95** through **98** (61% yield for carbamate **95** and 26% combined yield for carbamates **96**, **97**, and **98**). The enantiomeric excess (ee) of pyrrolidine **95** was found to be 80 ± 3% according to HPLC analysis. ^{1}H DNOE experiments confirmed the relative stereochemistry of pyrrolidines. Pyrrolidine **95** underwent a Baeyer-Villiger oxidation followed by a reduction to complete the enantioselective total synthesis of (+)-preussin (**100**).

Scheme 20



93 **94**

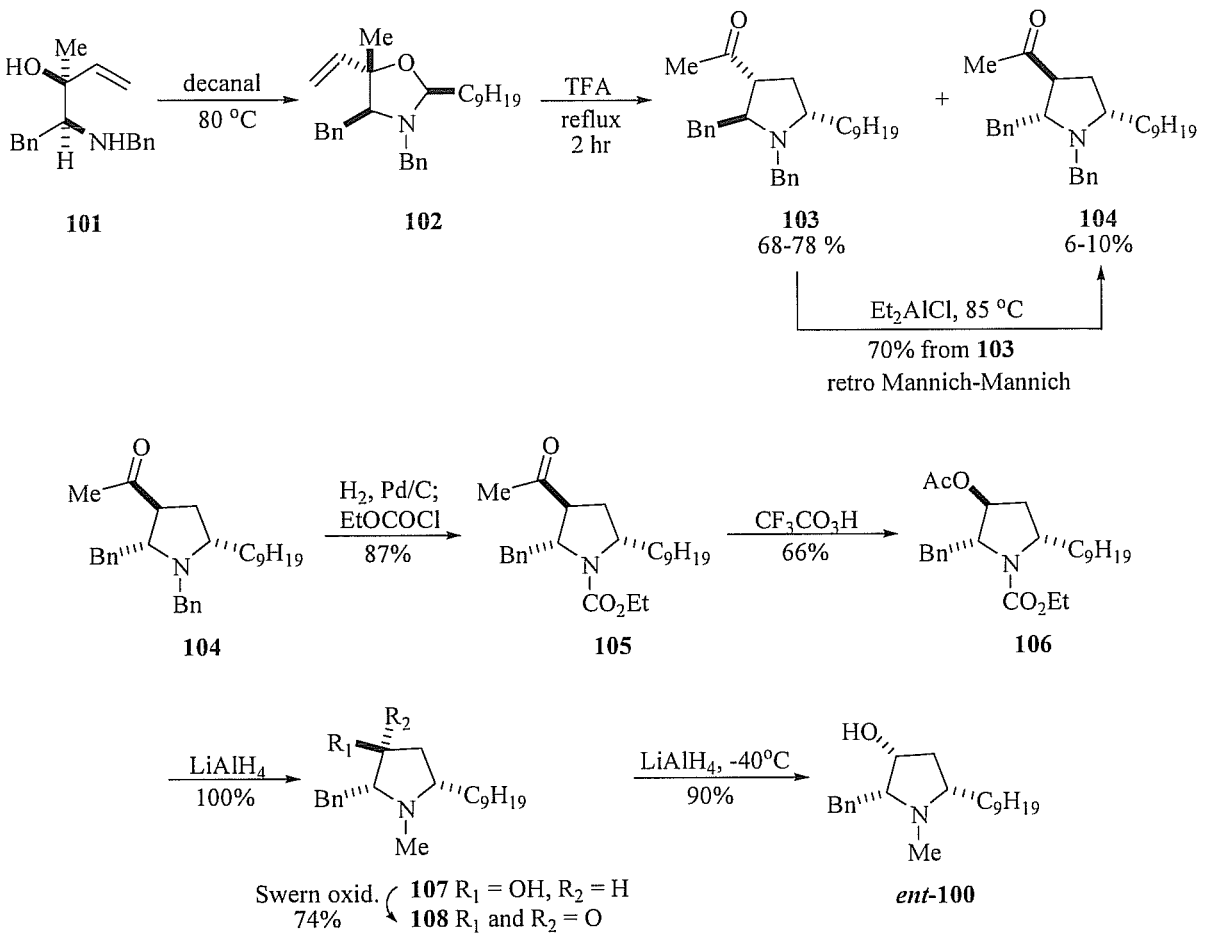
95 (61-68% from **93**) **96** **97** (**96-98**: 13-26% from **93**) **98**

95 **99** (+)-**100**

Deng and Overman used *N*-benzylamino alcohol **101** en route to the synthesis of *ent*-preussin (**100**) (**Scheme 21**). *N*-Benzylamino alcohol **101** was heated with decanal to form oxazolidine **102**, which underwent aza-Cope rearrangement and Mannich cyclization when refluxed in trifluoroacetic acid for 2 hours to produce pyrrolidines **103** and **104** in yields of 68-78% and 6-10%, respectively. HPLC analysis showed the ee of the major 2,5-*trans* isomer **103** to be 78-88% and the minor 2,5-*cis* isomer **104** to be 79 ± 1%. A retro-Mannich—Mannich sequence was used to convert pyrrolidine **103** to **104**. A toluene solution of Et_2AlCl was added dropwise to pyrrolidine **103** at 23 °C and then raised to 85 °C for 1 hr. After an aqueous workup and purification, a 70% yield of pyrrolidine **104** was obtained. Pyrrolidine **104** was ultimately used in the synthesis of *ent*-preussin **100**.

Pyrrolidine **104** was subjected to debenzylation, followed by ethoxycarbonylation to produce pyrrolidine **105**. Baeyer-Villiger oxidation, as before, resulted in acetate **106**. Acetate **106** underwent a reduction to produce 3-epi-*ent*-preussin **107**. *Ent*-preussin (**100**) could be accessed by a diastereoselective Swern oxidation/reduction sequence.

Scheme 21

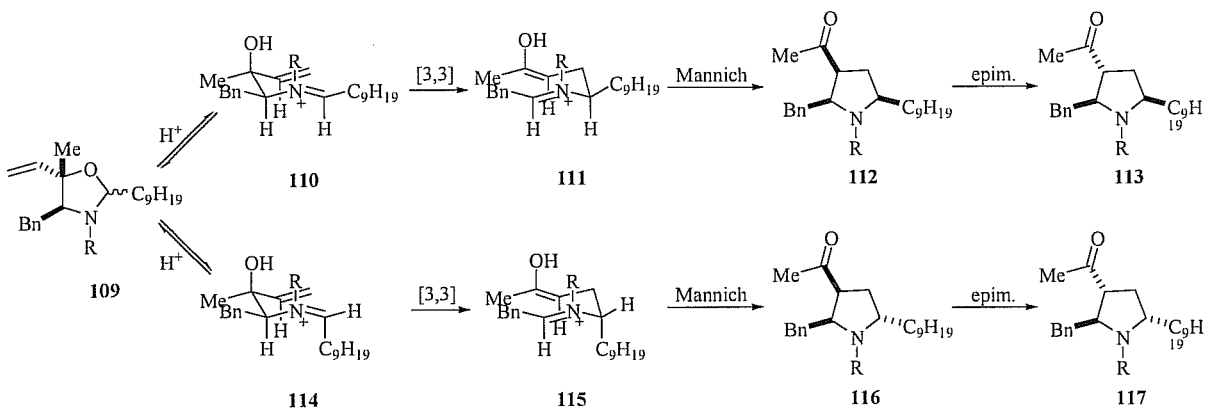


Several questions arose in the course of Overman and Deng's investigation. The first is why oxazolidines containing an NH substituent prefer to form 2,5-*cis* pyrrolidines, whereas N-substituted oxazolidines prefer to form 2,5-*trans* pyrrolidines. They made the assumptions that [3,3]-rearrangement prefers to react via a chair conformation, and intramolecular Mannich cyclization takes place without isomerization of the enol and

iminium cation. Also, they assumed the pyrrolidines that have *cis* acetyl and benzyl groups could undergo epimerization at the α-carbon (**Scheme 22**). The other possibility is for C-C sigma bond rotation to occur (**Scheme 23**).

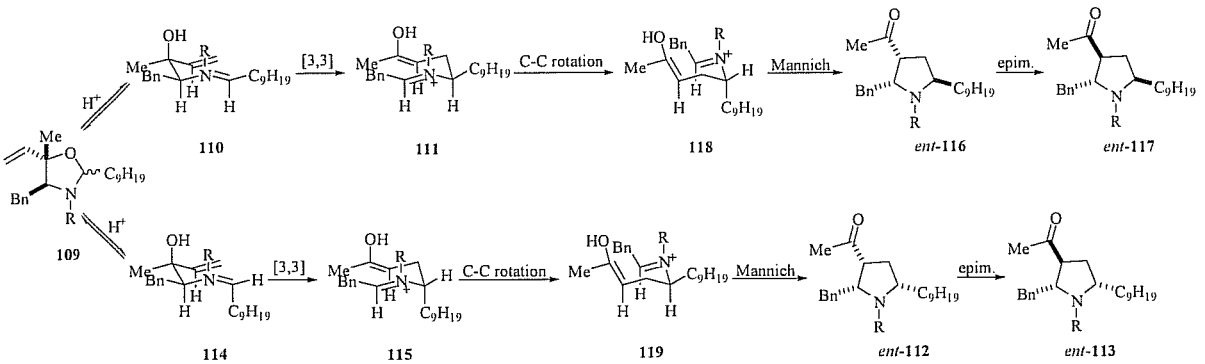
When oxazolidine **109** is subjected to an acid catalyst, iminium ions **110** and **114** can form (**Scheme 22**). Iminium ion **110** has *E* configuration whereas iminium **114** has *Z* configuration. Each iminium ion can undergo aza-Cope rearrangement to produce either iminium ion **111** or **115**. Once this occurs, Mannich cyclization provides pyrrolidines **112** and **116**, which can epimerize to form pyrrolidines **113** and **117**.

Scheme 22



Iminium ions **111** and **115** can also undergo C-C rotation to provide iminium ions **118** and **119** (**Scheme 23**). Mannich cyclization of these iminium ions would produce the enantiomers of pyrrolidines **112** and **116**. *Ent*-**116** and *ent*-**112** can also epimerize to form *ent*-**117** and *ent*-**113**. The ACM of amino alcohol **93** produced pyrrolidine **95** as the major product, likely via the *E* iminium cation. Alternatively amino alcohol **101** initially produced pyrrolidine **103** as the major isomer. This product was presumably formed via the *Z* iminium cation, ACM, and subsequent epimerization.

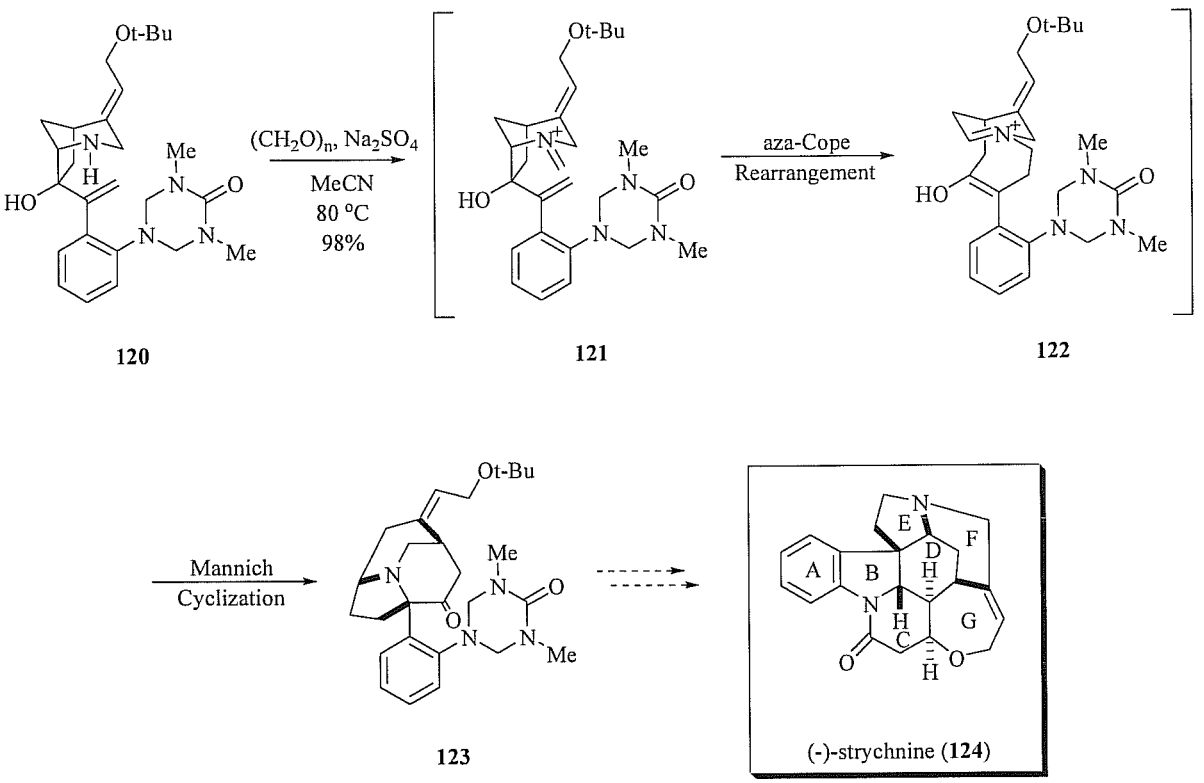
Scheme 23



III. Recent Applications of the Aza-Cope—Mannich reaction

In addition to allokainic acid and preussin, Overman applied the aza-Cope—Mannich reaction to key steps in the total synthesis of both enantiomers of strychnine (**124**) (**Scheme 24**).[20] Strychnine is a poison found mostly in Southeast Asia in plants such as the Indian poison nut and the Saint Ignatius bean. Although strychnine is lethal, even in milligram doses, it reportedly can increase skeletal muscle tone and stimulate appetite.[20] Strychnine has a molecular structure is composed of seven rings (A-G), containing 24 skeletal atoms and six stereogenic centers (**Scheme 24**). The key step in the synthesis of (-)-strychnine (**124**) was an aza-Cope rearrangement—Mannich cyclization. 2-Azabicyclooctane **120** was heated with Na_2SO_4, paraformaldehyde, and acetonitrile under reflux conditions for 10 minutes. After the mixture was concentrated and purified by flash chromatography, a 98% yield of pentacylic intermediate **123** was obtained. The conversion of 2-azabicyclooactane **120** to pentacylic intermediate **123** was responsible for establishing the stereochemistry of the D, E, and F rings (**Scheme 24**). Although Overman's overall synthetic route was only a few steps shorter than previous methods, his overall yield was 100,000 times greater. The procedure for synthesizing (-)-strychnine (**124**) was modified to synthesize (+)-strychnine.

Scheme 24

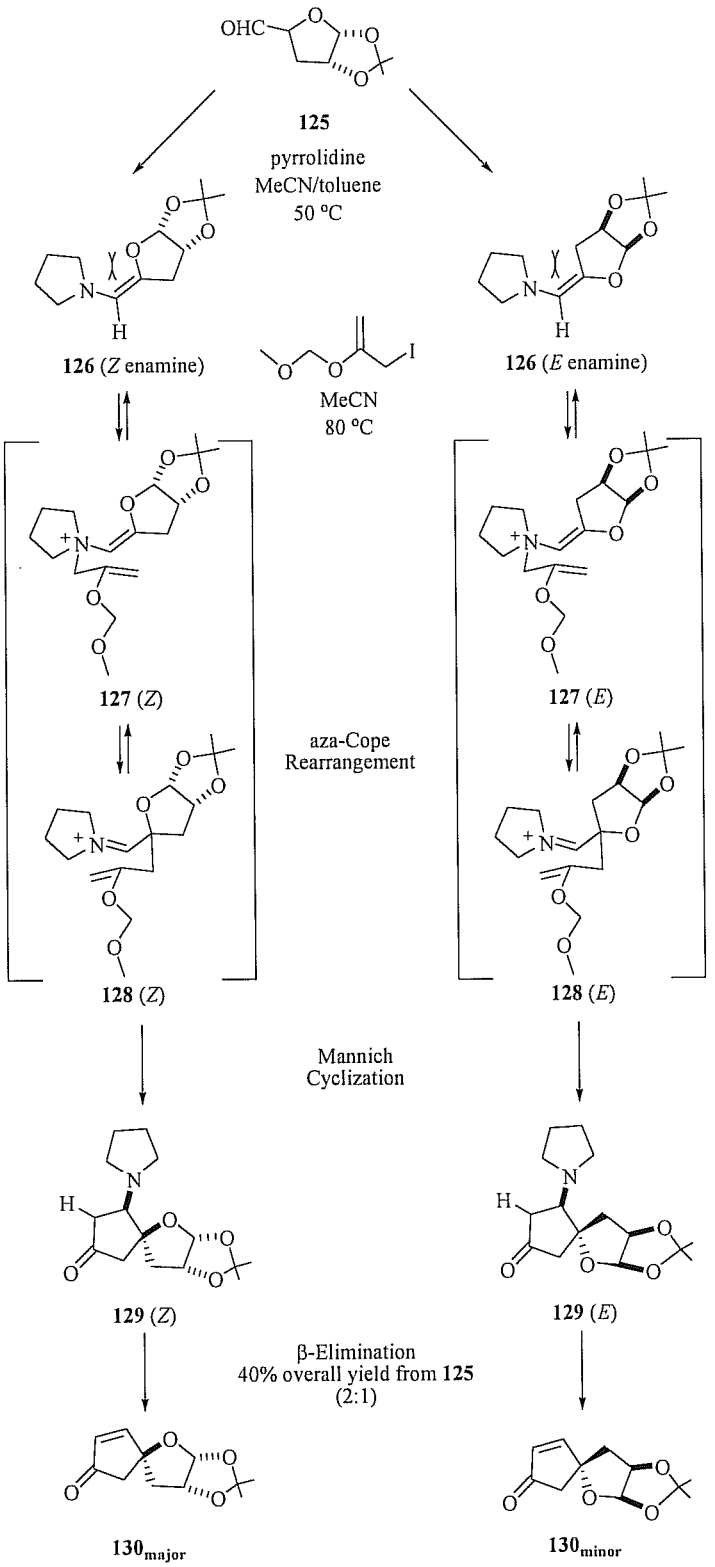


120 121 122 123

Florent developed a one-pot alkylation followed by an aza-Cope—Mannich reaction to synthesize polyfunctionalized cyclopentenoids.[21] Cyclopentenoids are present in a wide variety of natural products and have been used as effective therapeutic agents, especially as antineoplastic and antiviral compounds.[21] The aza-Cope—Mannich reaction was triggered by alkylation of a mixture of *E* and *Z* enamines **126** to form iminium cation **127** (**Scheme 25**). After the alkylation, the *E* and *Z* iminium ions **127** undergo aza-Cope rearrangement (80 °C, 24 hrs), which resulted in iminium ions **128**. Iminium ions **128** then undergo Mannich cyclization to produce cyclopentanone diastereomers **129**. After β-elimination, a 2:1 ratio of cyclopentanones $\mathbf{130}_{\mathbf{major}}$ and $\mathbf{130}_{\mathbf{minor}}$ formed in 40% overall yield from aldehyde **125**. The relative stereochemistry of cyclopentanones $\mathbf{130}_{\mathbf{major}}$ and $\mathbf{130}_{\mathbf{minor}}$ was determined by NOESY experiments. The authors state that the modest diastereoselectivity is due primarily

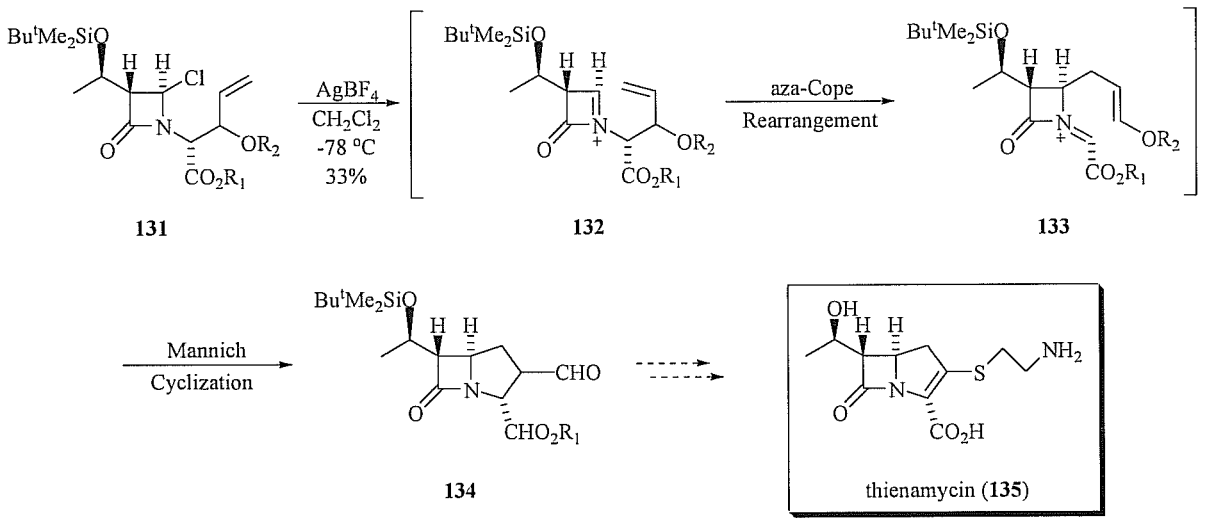
to two factors: the *Z*/*E* –*N*-alkyl olefin geometry determined during the formation of enamine and the contribution of the chair versus the boat conformation transition states. An alternate theory is that the modest diastereoselectivity could be a result of the *Z* and *E* enamines **126** having similar energy levels. *Z* enamine **126** is likely to be slightly lower in energy, which explains why cyclopentanone $\mathbf{130_{major}}$ is preferred. If the energy difference between *Z* and *E* enamines **126** were significantly larger, the diastereoselectivity would likely be greater.

Scheme 25


OHC
125
pyrrolidine
MeCN/toluene
50 °C
126 (Z enamine)
126 (E enamine)
MeCN
80 °C
127 (Z)
127 (E)
aza-Cope
Rearrangement
128 (Z)
128 (E)
Mannich
Cyclization
129 (Z)
129 (E)
β-Elimination
40% overall yield from 125
(2:1)
130major
130minor

Horikawa utilized the aza-Cope—Mannich reaction in the synthesis of carbapenem antibacterial agents (**Scheme 26**).[22] Carbapenems have a molecular core composed of a [3.2.0] ring system with a bridgehead nitrogen (e.g. thienamycin (**135**)). The formation of the five-membered ring is a key step in the synthesis. Horikawa's method generated the iminium cation intramolecularly by β–elimination of a chloride ion. In most aza-Cope—Mannich reactions, the iminium cation is generated by intermolecular condensation of an amino alcohol with an aldehyde. The first attempts to make carbapenam **134** were unsuccessful because the C-Cl bond did not cleave. To accomplish this, silver salts with non-nucleophilic counter anions were used to generate the iminium ion. When azetidinone **131** was treated silver tetrafluoroborate ($AgBF_4$), the C-Cl bond was cleaved, forming acyl iminium ion **132**, which underwent aza-Cope rearrangement—Mannich cyclization to give carbapenem **134** as a single isomer in 33% yield.

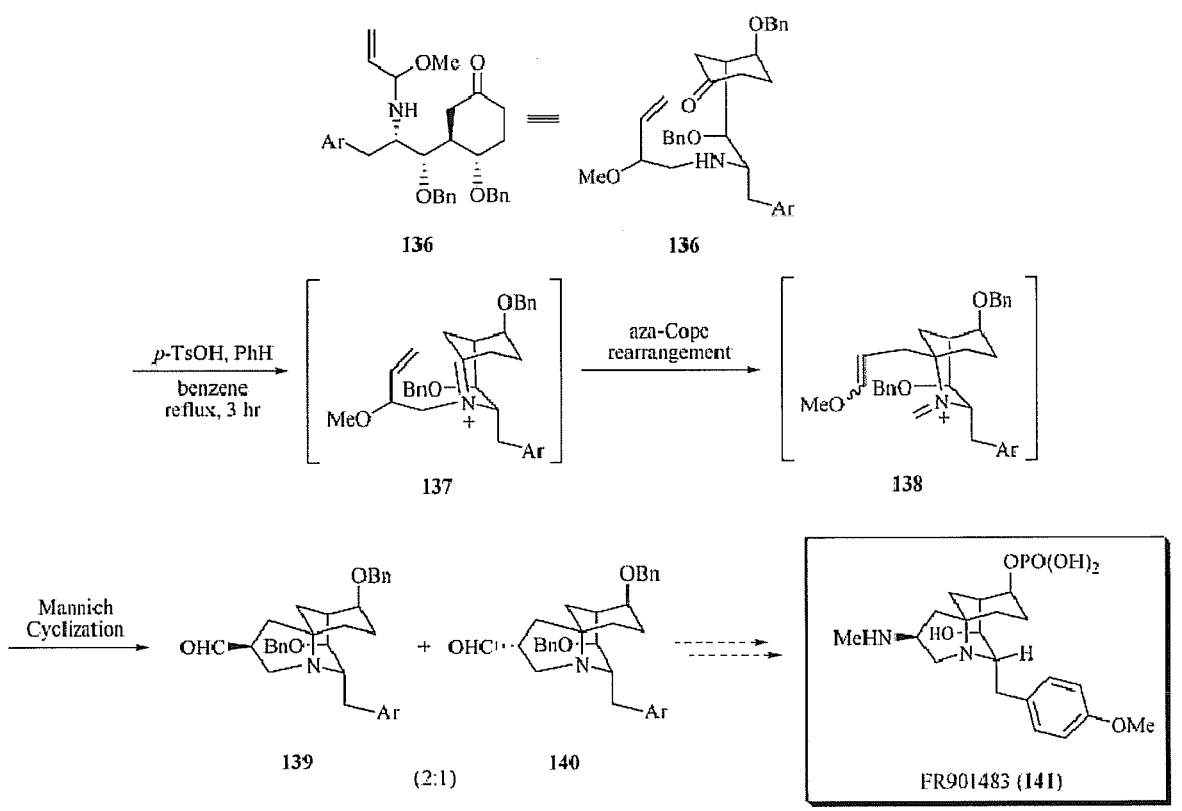
Scheme 26



Brummond and Hong utilized an aza-Cope—Mannich reaction in the total synthesis of the immunosuppressant (-)-FR901483 (**141**).[23] Their strategy for constructing the bridging tricyclic azaspirane FR901483 (**141**) core substructure was a tandem cationic aza-Cope

rearrangement—Mannich cyclization (**Scheme 27**). In this key step, the reaction proceeds through a bridgehead iminium ion, a violation of Bredt's rule.[24] Amino ketone **136** was subjected to 1.2 eq of *p*-TsOH in benzene for 3 hours under reflux conditions. This induced the formation of iminium cation **137**, which underwent aza-Cope rearrangement to provide iminium cation **138**. Iminium cation **138** underwent Mannich cyclization to provide diastereomeric amino aldehydes **139** and **140** in a 2:1 ratio in 63% yield. They found that the total synthesis of FR901483 (**141**) could be achieved in 18 steps with an overall yield of 2.5% from commercially available starting material.

Scheme 27



The aza-Cope rearrangement—Mannich cyclization reaction has been developed and applied to the synthesis of a variety of natural products. The stereochemistry of the ACM products is dependent on transition state topography and C=C geometry. Further, the

stereochemistry can be controlled by altering the iminium cation geometry. However, controlling the iminium cation geometry has not been successful in ACM reactions leading to monosubstituted acylpyrrolidines. The goal of this project was to develop a microwave-assisted version of the aza-Cope rearrangement—Mannich cyclization reaction to address the lack of stereocontrol in these systems and also to decrease the lengthy reaction times required for this transformation.

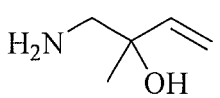
Results and Discussion

I. The Synthesis of Pyrrolidine Diastereomers Using the Aza-Cope—Mannich Reaction

A. Synthesis of Amino Alcohols

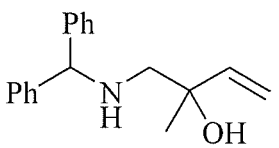
One goal of this project is to develop a microwave-assisted version of the aza-Cope Rearrangement—Mannich Cyclization (ACM). We are interested in what factors control the diastereoselectivity of the reaction and how we can improve the diastereoselectivity. Another goal is to apply this method to the synthesis of pyrrolidine and pyrrolizidine alkaloids that have known pharmalogical effects.

Several different amino alcohols, varying in the nitrogen protecting group size, were synthesized as ACM precursors. The role that the nitrogen protecting group size played in the pyrrolidine diastereoselectivity was of special interest (*vide infra*). Amino alcohols to be studied were free amino alcohol **142**, benzhydryl-protected amino alcohol **143**, and trityl-protected amino alcohol **144**.



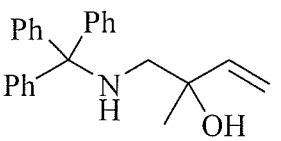
free amino alcohol

142



benzhydryl-protected amino alcohol

143



triphenylmethyl-protected amino alcohol

144

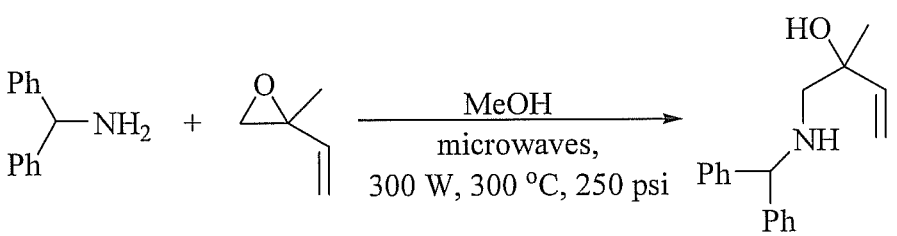
Figure 2. Amino alcohols: free amino alcohol **142**, benzhydryl-protected **143**, and trityl-protected **144**.

i. Synthesis of Benzhydryl-Protected Amino Alcohol

The first amino alcohol synthesized was the benzhydryl-protected amino alcohol **143**. Amino alcohol **143** was synthesized by allowing diphenylmethylamine **145** to react with methyl vinyl oxirane **146** in methanol under microwave conditions (300 W, 300 °C, and 250

psi) **Scheme 28**.[25] The first effort in synthesizing benzhydryl-protected amino alcohol **143** involved the reaction of 3.57 mmol each of amine **145** and epoxide **146** for 20 minutes under microwave conditions (300 W, 300 °C, and 250 psi) (**Table 1**, entry 1). A crude yield of 96% was found upon completion of this reaction, but the ^{1}H NMR spectrum showed the presence of unreacted diphenylmethylamine **145.** When the reaction scale was increased to 7.14 mmol of reactants **145** and **146** (**Table 1**, entry 2) and the reaction time was increased to 40 minutes, total conversion of starting material to product was achieved. A crude yield of 91% and purified yield of 71% were obtained. The reaction using 7.14 mmol of benzhydryl-protected amine **145** and methyl vinyl oxirane **146** provided the best results and was close to the maximum volume allowed in the microwave reaction vessels, precluding further scale-up. All future syntheses of diphenyl amino alcohol **143** would follow this scale and microwave conditions.

Scheme 28



145 **146** **143**

Table 1. Benzhydryl-Protected Amino Alcohol Data

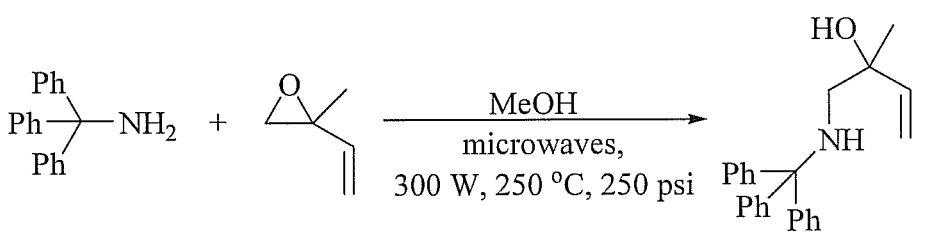
Entry	Scale (mmol)	Time (min)	Crude Yield (%)	Pure Yield (%)	Avg Max[a] (°C/psi/W)
1	3.57	20	96	46	151/129/300
2[b]	7.14	40	91	71	174/239/198

[a] Average value calculated after initial 1 min ramp time.
[b] Average value of multiple experiments.

ii. Synthesis of Triphenylmethyl-Protected Amino Alcohol

The second amino alcohol investigated was a triphenylmethyl-protected amino alcohol **144**. Triphenylmethyl-protected amino alcohol **144** was synthesized by the reaction of 3.77 mmol each of tritylamine **147** and methyl vinyl oxirane **146** in methanol under microwave conditions (300 W, 250 °C, and 250 psi) for 180 minutes **Scheme 29** (**Table 2**, entry1). When the reaction was complete, a crude yield of 98% was produced. The ^{1}H NMR spectrum of the crude reaction mixture was complex. However, purification by flash chromatography provided a 29% pure yield of triphenylmethyl-protected amino alcohol **144**. This reaction was not optimized because the ACM using this amino alcohol proved unsuccessful (*vide infra*).

Scheme 29



147 **146** **144**

Table 2. Triphenylmethyl-Protected Amino Alcohol Data

Scale (mmol)	Time (min)	Crude Yield (%)	Pure Yield (%)	Avg Max[a] (°C/psi/W)
3.77	180	98	29	192/237/184

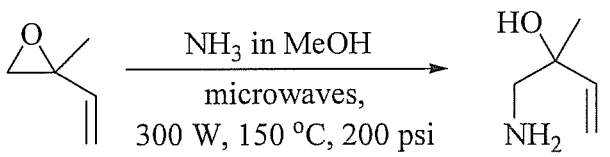
[a] Average value calculated after initial 1 min ramp time.

iii. Synthesis of Free Amino Alcohol

The final amino alcohol investigated was free amino alcohol **142**. Free amino alcohol **142** was synthesized by the reaction of 2 mmol of methyl vinyl oxirane **146** with over 200 molar equivalents of 7 N ammonia in methanol solution (3.0 mL) under microwave conditions (300 W, 150 °C, and 200 psi) for 20 minutes. A crude yield of 1% was obtained.

The low recovery of free amino alcohol **142** can be attributed to the product's low boiling point and difficulties isolating it from bis-alkylation products. This yield was not optimized, but several iterations of this reaction provided sufficient quantities of amino alcohol **142** to perform ACM reactions.

Scheme 30



146 **142**

Table 3. Free Amino Alcohol Data

Scale (mmol)	Time (min)	Crude Yield (%)	Avg Max[a] (°C/psi/W)
2.0	20	1[b]	124/204/15

[a] Average value calculated after initial 1 min ramp time.
[b] Average value of multiple experiments.

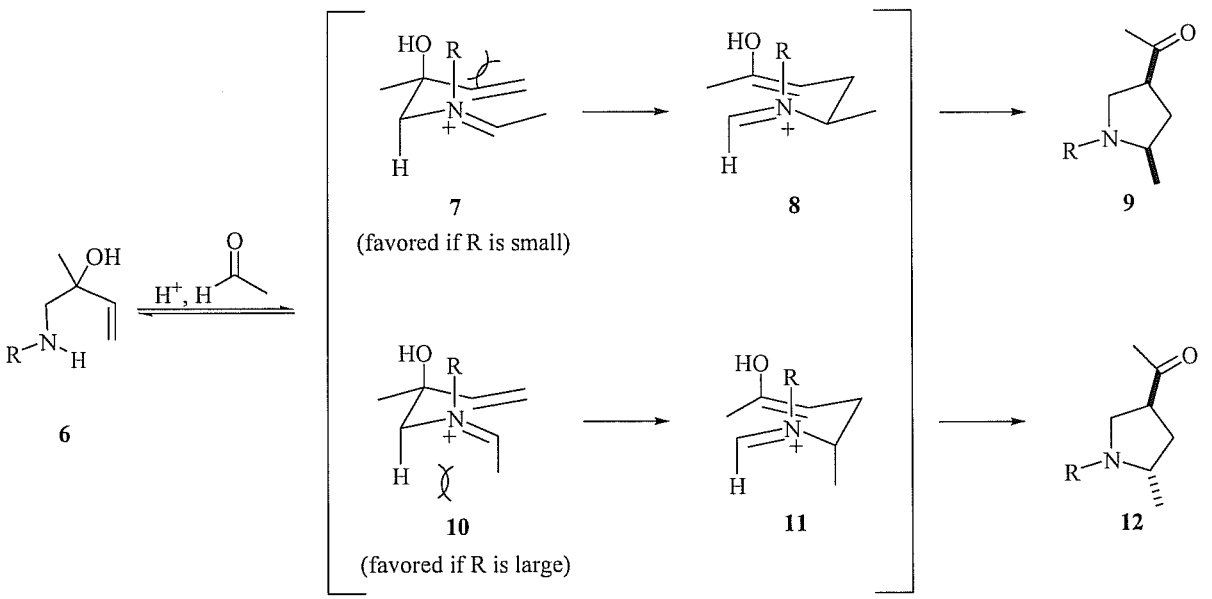
B. Microwave-assisted Aza-Cope—Mannich reactions

Once the amino alcohols were synthesized, different factors influencing the selectivity of the aza-Cope—Mannich reaction were studied, including size of the amine protecting group, solvent, reaction time, and temperature. Of primary interest was how changing the amine protecting group size affected the diastereoselectivity of the resulting methyl and ethyl acylpyrrolidines.

As discussed earlier, we hypothesized that the major factor controlling the diastereoselectivity was the size of the amine protecting group on amino alcohol **6** (**Scheme 2**). This is due to variability in allylic strain between two possible iminium cation isomers.[2,3,4] When the nitrogen protecting group is large (R=$CHPh_2$), the allylic strain in iminium ion **7** between the methyl iminium substituent and the protecting group is rather

large, resulting in the preferred formation of iminium cation **10**, which upon rearrangement and cyclization should form *trans*-acylpyrrolidine **12**. The opposite is expected when the nitrogen protecting group is small (R=Me) because the interaction of the alkyl substituent and the protecting group is not as significant. In that case, pseudo 1,3-diaxial interactions would cause cation **7** to be favored. Thus, aza-Cope—Mannich reaction via iminium ion **7** should occur to a greater extent, which would increase diastereoselectivity for *cis*-acylpyrrolidine **9**.

Scheme 2

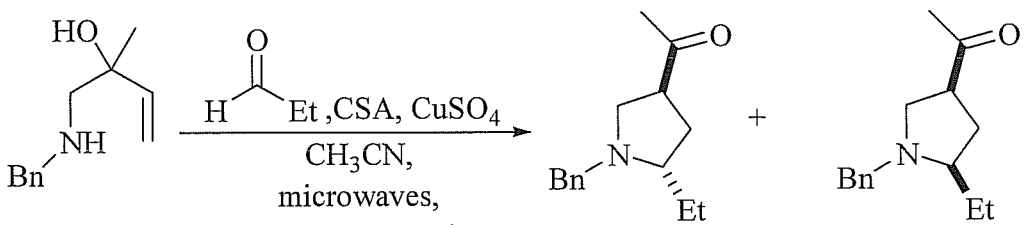


i. Benzyl-Protected Amino Alcohol ACM Reactions

A colleague, Edwin Marrero, studied the microwave assisted aza-Cope rearrangement—Mannich cyclization reaction using benzyl-protected amino alcohol **148** to produce acylpyrrolidines **149** and **150** (**Scheme 31**).[2b,26] This amino alcohol differs from the benzhydryl-protected amino alcohol **143** because of the smaller size of the benzyl protecting group. According to the analysis in **Scheme 2**, the smaller the nitrogen protecting group, the more prevalent the formation of *cis*-pyrrolidine. The aza-Cope—Mannich reaction of

benzyl-protected amino alcohol **148** revealed that under two different reaction times and temperatures the diastereoselectivity of acylpyrrolidines **149** and **150** was 3:1 according to ^1H NMR analysis. Since the benzhydryl-protected amino alcohol **143** used in this investigation has a larger protecting group, the diastereomeric mixture of acylpyrrolidines should be enriched in the *trans* isomer.

Scheme 31



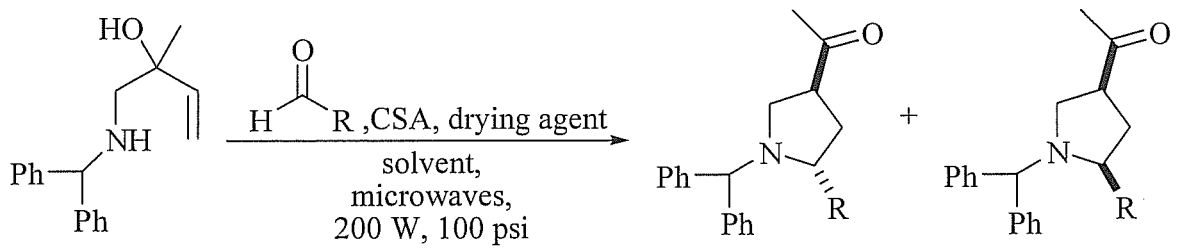
148 **149** **150**

63-84%
3:1 diastereoselectivity

ii. Optimization of Benzhydryl-Protected Amino Alcohol ACM

The first microwave assisted aza-Cope—Mannich reactions performed to synthesize methyl acylpyrrolidines **151** and **152** from benzhydryl-protected amino alcohol **143** focused on optimizing the reaction conditions (**Scheme 32**). Optimization experiments addressed finding the appropriate amount of aldehyde, amount of acid catalyst, best solvent, and most appropriate reaction time and temperature to provide the highest possible conversion to products with the best diastereoselectivity.

Scheme 32



Optimizing the amount of acid catalyst needed to provide the best yield and diastereoselectivity with complete conversion of amino alcohol starting material was examined first. Varied amounts of camphorsulfonic acid (CSA) were allowed to react with 0.28 mmol of benzhydryl-protected amino alcohol **143**, 5 eq of acetaldehyde, and 1 eq of $CuSO_4$ in CH_3CN under microwave conditions (200 W, 100 psi) at 90 °C for 15 minutes (**Scheme 33**). ^1H NMR analysis revealed that only 73% conversion to methyl acylpyrrolidines **153** and **154** was achieved when 0.5 eq of CSA was used. These conditions provided a diastereoselectivity of 5:1 (**Table 4**, entry 1). When the reaction was performed using 1 eq of CSA, ^1H NMR analysis showed complete conversion of benzhydryl-protected amino alcohol **143** to methyl acylpyrrolidines **153** and **154** with an overall crude yield of 75% (**Table 4**, entry 2). In that case, the diastereoselectivity of methyl acylpyrrolidines **153** and **154** was found to be 4:1. Although the diastereoselectivity decreased slightly (5:1 compared to 4:1) when 1 eq of acid catalyst was used, complete conversion of starting material to product was obtained providing methyl acylpyrrolidines in good yield (75%). All future ACM reactions would be performed using 1 eq of acid CSA. Since complete conversion of benzhydryl-protected amino alcohol **143** occurred, any amount above 1 eq of acid catalyst was not examined.

Scheme 33

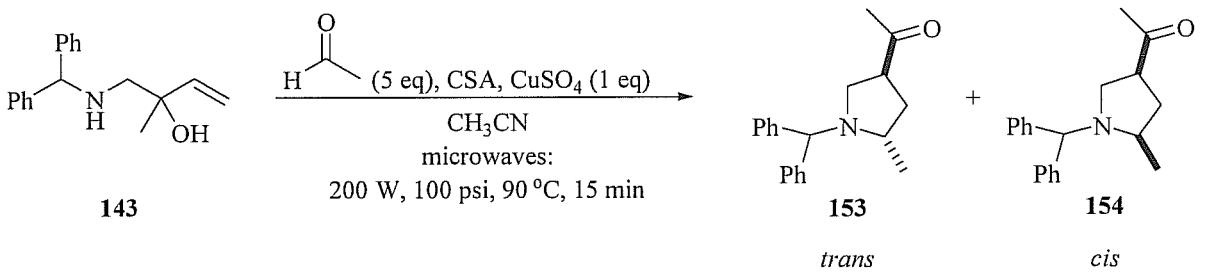


Table 4. Optimizing ACM: Effect of Acid Catalyst

Entry	CSA(eq)	% Conversion (yield)	DS[a] (**153**:**154**)	Avg Max[b] (°C/psi/W)
1	0.5	73	5:1	91/31/7
2[c]	1	100 (75%)	4:1	91/34/9

[a] Diastereoselectivity (DS) determined ^{1}H NMR.
[b] Average value calculated after initial 1 min ramp time.
[c] Average value of multiple experiments.

The next reaction condition optimized was the reaction solvent. Acetonitrile and methanol were the solvents used in the reactions of benzhydryl-protected amino alcohol **143** with 3 eq of acetaldehyde, 1 eq of CSA, and 1 eq of $CuSO_4$ under microwave conditions (200 W, 100 psi) (**Scheme 34**). When 0.28 mmol of the starting material was subjected to the reaction conditions in 0.4 mL of CH_3CN for 15 minutes at 90 °C (**Table 5**, entry 1), the ^{1}H NMR analysis revealed complete conversion to methyl acylpyrrolidines **153** and **154** with an overall yield of 77%. The diastereoselectivity of this reaction was 4:1. A similar reaction was performed in 0.4 mL of MeOH with the same time and temperature, using 0.42 mmol of benzhydryl-protected amino alcohol **143**. By contrast to the reactions using CH_3CN as the solvent, only 21% conversion to the methyl acylpyrrolidines **153** and **154** was achieved with an overall crude yield of 17% (**Table 5**, entry 2). However, the diastereoselectivity of the reaction increased to 10:1. In efforts to push for complete conversion of the starting material in MeOH, 0.34 mmol of benzhydryl-protected amino alcohol **143** in 0.4 mL of MeOH was allowed to react for 30 minutes at 110 °C (**Table 5**, entry 3). Similar to the previous reaction in MeOH, ^{1}H NMR analysis revealed the incomplete conversion to product. Only 53%

conversion to methyl acylpyrrolidines **153** and **154** was found with an overall crude yield of 33% and diastereoselectivity of 4:1. Increasing the reaction time and temperature in MeOH provided an increase in overall yield and conversion (**Table 5**, entry 3 vs. 2) but the diastereoselectivity decreased to 4:1. This value is the same that was found when the reaction was performed in CH_3CN, where complete conversion and a good overall yield were obtained. For this system, CH_3CN provided the best results (**Table 5**, entry 1). Thus CH_3CN was used in all future reactions at an approximate concentration of 0.7 mmol/mL.

Scheme 34

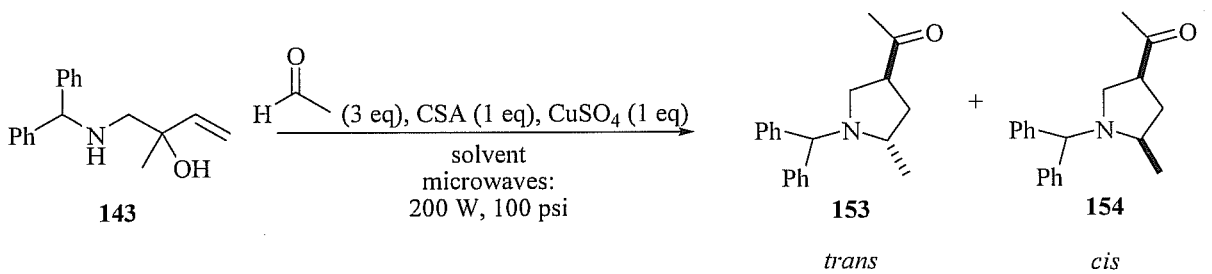


Table 5. Optimizing ACM: Effect of Solvent

Entry	Solvent	Time/Temp (min/°C)	% Conversion	% Yield[a]	DS[b] (**153**:**154**)	Avg Max[c] (°C/psi/W)
1	CH_3CN	15/90	100	77	4:1	97/15/0.5
2	MeOH	15/90	21	17	10:1	92/26/1
3	MeOH	30/110	53	33	4:1	110/52/9

[a] Combined crude yield of both diastereomers.
[b] Diastereoselectivity (DS) determined ^{1}H NMR.
[c] Average value calculated after initial 1 min ramp time.

After the optimized solvent and amount of acid catalyst were found, optimizing the amount of acetaldehyde needed to provide the best diastereoselectivity was undertaken. In these ACM reactions, 0.28 mmol of benzhydryl-protected amino alcohol **143** were allowed to react with varied amounts of acetaldehyde, 1 eq of CSA, and 1 eq of $CuSO_4$ in CH_3CN under microwave conditions (200 W, 100 psi) at 90 °C (**Scheme 35**). When 2 eq of acetaldehyde was used in a 15 minute reaction, ^{1}H NMR analysis revealed 85% conversion of starting material to methyl acylpyrrolidines **153** and **154** (**Table 6**, entry 1). An overall yield of 67%

was obtained along with a diastereoselectivity of 3:1. In an attempt to gain complete conversion, higher yield, and increased diastereoselectivity, 3 eq of acetaldehyde was allowed to react for 25 minutes, which provided 97% conversion, 77% overall crude yield, and a diastereoselectivity of 4:1 (**Table 6**, entry 2). Increasing the amount of acetaldehyde to 4 eq and the reaction time to 35 minutes did not affect the diastereoselectivity (4:1). However, complete conversion of benzhydryl-protected amino alcohol **143** to methyl acylpyrrolidines **153** and **154** in quantative yield was obtained (**Table 6**, entry 3).

Scheme 35

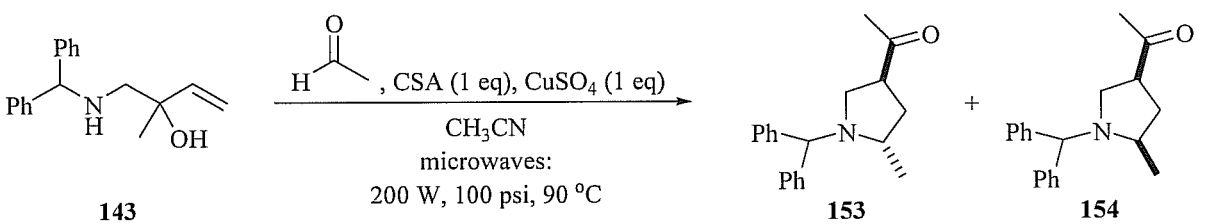


Table 6. Optimizing ACM: Aldehyde and Reaction Time

Entry	Aldehyde (eq)	Time (min)	% Conversion	% Yield[a]	DS[b] (**153**:**154**)	Avg Max[c] (°C/psi/W)
1	2	15	85	67	3:1	91/26/9
2	3	25	97	77	4:1	92/26/1
3[d]	4	35	100	Quantative	4:1	90/38/8

[a] Combined crude yield of both diastereomers.
[b] Diastereoselectivity (DS) determined ^{1}H NMR.
[c] Average value calculated after initial 1 min ramp time.
[d] Average value of multiple experiments.

The optimized ACM reaction conditions that provide methyl acylpyrrolidines **153** and **154** from benzhydryl-protected amino alcohol **143** were found to be 4 eq of acetaldehyde, 1 eq of CSA, and 1 eq of $CuSO_4$ in CH_3CN under microwave conditions (200 W, 100 psi) for 35 minutes at 90 °C. These reaction conditions were used initially in the synthesis of ethyl acylpyrrolidines from benzhydryl-protected amino alcohol **143**. Propionaldehyde was the aldehyde utilized in the synthesis.

Optimizing the amount of propionaldehyde needed to achieve complete conversion, high yield, and the greatest diastereoselectivity to provide ethyl acylpyrrolidines was examined first. In these ACM reactions, benzhydryl-protected amino alcohol **143**, 1 eq of CSA and 1 eq of $CuSO_4$ were allowed to react in CH_3CN under microwave conditions (200 W, 100 psi) at 90 °C (**Scheme 36**). When 3 equivalents of propionaldehyde were used and the reaction time was 25 minutes (**Table 7**, entry 1), ^1H NMR analysis revealed 95% conversion of benzhydryl-protected amino alcohol **143** to ethyl acylpyrrolidines **155** and **156** with an overall crude yield of 80%. The diastereoselectivity was found to be 2:1. Increasing the reaction time to 35 minutes increased the overall % conversion, % yield, and diastereoselectivity of the reaction to 96%, 89%, and 4:1, respectively for the ethyl acylpyrrolidines **155** and **156** (**Table 7**, entry 2). In efforts to achieve complete conversions, the reaction was performed using 4 eq of propionaldehyde with a reaction time of 35 minutes (**Table 7**, entry 3). ^1H NMR analysis showed total conversion of benzhydryl-protected amino alcohol **143** to ethyl acylpyrrolidines **155** and **156** with an overall crude yield of 94%. However, the diastereoselectivity remained 4:1. The reaction was performed with 5 eq of propionaldehyde, and only a slight increase in yield was obtained (**Table 7**, entry 4). Just as in the ACM reactions leading to methyl acylpyrrolidines **153** and **154**, 4 eq of aldehyde was found to provide the best results in the synthesis of ethyl acylpyrrolidines **155** and **156**.

Scheme 36

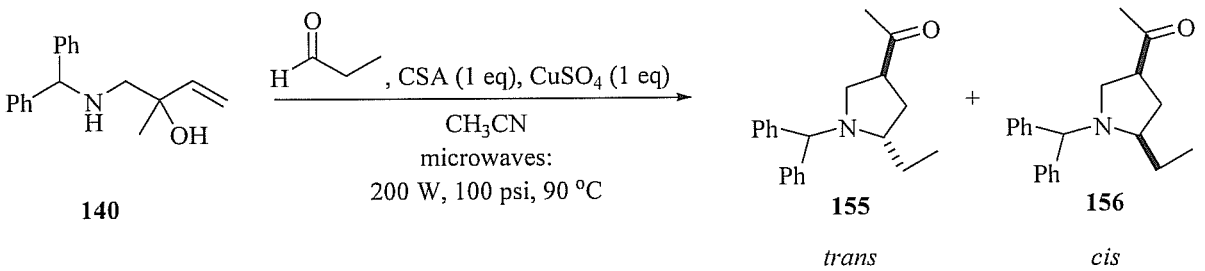


Table 7. Optimizing ACM: Aldehyde and Reaction Time

Entry	Aldehyde (eq)	Time (min)	% Conversion	% Yield[a]	DS[b] (**155**:**156**)	Avg Max[c] (°C/psi/W)
1	3	25	95	80	2:1	90/13/21
2[d]	3	35	96	89	4:1	91/27/7
3[d]	4	35	100	94	4:1	90/39/8
4	5	35	100	97	4:1	NA

[a] Combined crude yield of both diastereomers.
[b] Diastereoselectivity (DS) determined ^{1}H NMR.
[c] Average value calculated after initial 1 min ramp time.
[d] Average value of multiple experiments.

The reaction temperature was the next condition optimized for the synthesis of ethyl acylpyrrolidines **155** and **156**. These ACM reactions used 0.28 mmol of benzhydryl-protected amino alcohol **143**, 4 eq of propionaldehyde, 1 eq of CSA, and 1 eq of $CuSO_4$ in CH_3CN under microwave conditions (200 W, 100 psi) (**Scheme 37**). Earlier results indicated that complete conversion to ethyl acylpyrrolidines **155** and **156** could be obtained when the reaction was performed for 35 minutes at 90 °C (**Table 7**, entry 3, and **Table 8**, entry 1). These conditions provided an overall crude yield of 94% with a diastereoselectivity of 4:1. A similar reaction was performed for 60 minutes at 60 °C and provided an improved diastereoselectivity of 8:1 (**Table 8**, entry 2). Although the diastereoselectivity significantly increased, ^{1}H NMR analysis revealed incomplete conversion to ethyl acylpyrrolidines **155** and **156** with an overall yield of 57%. Also, the analysis showed the presence of oxazolidine **157** in a 7% yield. Oxazolidine **157** is presumably an early intermediate in the ACM

sequence. Thus, the reaction time likely needed to be increased in order to achieve complete conversion. Another reaction was performed at 60 °C but with a 150-minute reaction time (**Table 8**, entry 3). Total conversion to ethyl acylpyrrolidines **155** and **156** was achieved with an overall crude yield of 91%. The diastereoselectivity decreased slightly to 7:1. For comparison, a 60 °C reaction was performed with a 240-minute reaction time (**Table 8**, entry 4). Again, total conversion was observed, but the overall crude yield and diastereoselectivity of ethyl acylpyrrolidines **155** and **156** decreased to 84% and 6:1. Overall, lowering the reaction temperature from 90 °C to 60 °C was found to increase the diastereoselectivity of the reaction from 4:1 to 7:1.

Scheme 37

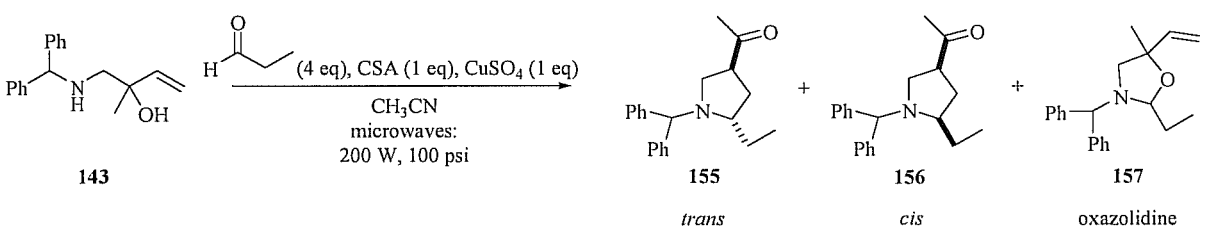


Table 8. Optimizing ACM: Reaction Temperature and Time

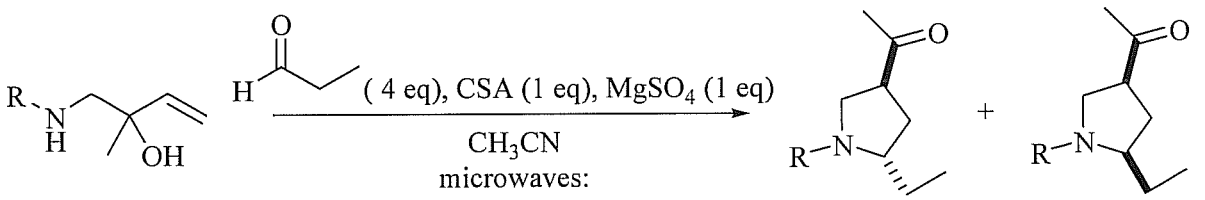
Entry	Time/Temp (min/°C)	% Conversion	% Yield[a]	% **157**	DS[b] (**155**:**156**)	Avg Max[c] (°C/psi/W)
1[d]	35/90	100	94	0	4:1	90/39/8
2	60/60	60	57	7	8:1	NA
3[d]	150/60	100	91	0	7:1	63/11/1
4	240/60	100	84	0	6:1	64/13/1

[a] Combined crude yield of both diastereomers.
[b] Diastereoselectivity (DS) determined ^{1}H NMR.
[c] Average value calculated after initial 1 min ramp time.
[d] Average value of multiple experiments.

ACM reactions were performed on the free amino alcohol **158a** and trityl-protected amino alcohol **158b** to synthesize acylpyrrolidines **159a,b** and **160a,b** (**Scheme 38**). We expected that ACM reactions using free amino alcohol **158a** would provide the lowest selectivity for *trans* acylpyrrolidine **159a** and quite possibly favor the formation of the *cis*

acylpyrrolidine **160a** as the major diastereomer. However, ACM reactions using free amino alcohol **158a** failed to produce resonances in the ^{1}H NMR spectra characteristic of acylpyrrolidines **159a** and **160a**. ACM reactions using trityl-protected amino alcohol **158b** were expected to provide the greatest selectivity for the *trans* acylpyrrolidine of all amino alcohols studied. Unfortunately, ACM reactions using trityl-protected amino alcohol **158b** were also unsuccessful due to the likely cleavage of the protecting group under the acidic conditions of the reaction.

Scheme 38



158a, R=H
158b, R=CPh_3

159a, R=H
159b, R=CPh_3
trans

160a, R=H
160b, R=CPh_3
cis

iii. Summary of Optimization of Microwave-Assisted ACM

In summary, a selectivity of around 4:1 was routinely seen in the aza-Cope—Mannich reaction of benzhydryl-protected amino alcohol **143** to produce methyl acylpyrrolidines diastereomers **153** and **154**. Optimized reaction conditions were found to require 4 eq of aldehyde, 1 eq of acid catalyst, 1 eq of drying agent in acetonitrile, with reaction temperature and time of 90 °C and 35 minutes. Using the same conditions, ethyl acylpyrrolidines **155** and **156** were routinely formed with 4:1 diastereoselectivity. Lowering the reaction temperature to 60 °C and increasing the reaction time to 150 minutes allowed for an increase in diastereoselectivity to 7:1. When these reaction conditions were used, the same increase was not observed for the formation of methyl acylpyrrolidines. Finally,

increasing the size of the nitrogen protecting group was shown to increase the selectivity for the *trans*-diastereomer. The 60 °C ACM reactions using benzhydryl-protected amino alcohol **143** produced a diastereoselectivity of 7:1 compared to 3:1 in reactions involving benzyl-protected amino alcohol **148**.[2b]

C. Identifying Diastereomers

The benzhydryl-protected *cis*-ethyl acylpyrrolidine **156** (minor diastereomer) was isolated by flash chromatography. TLC analysis was used to separate the diastereomers, and ^{1}H NMR confirmed the separation (**Figure 3**). NOE analysis was used to confirm the stereochemistry. A colleague, Edwin Marrero, isolated and confirmed the stereochemistry of the benzyl-protected *trans*-ethyl acylpyrrolidine **149** (major diastereomer). Although the nitrogen protecting groups of these products vary, the relative stereochemistry of the major diastereomers is the same for both benzyl- and benzhydryl-protected ethyl acylpyrrolidines.

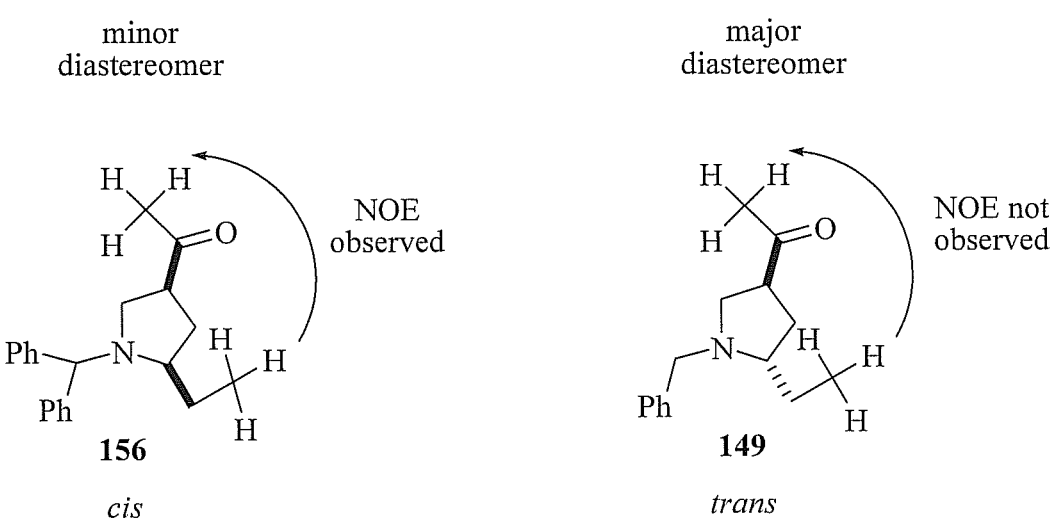
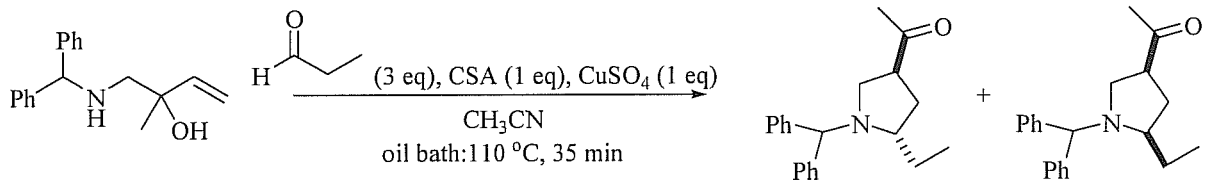


Figure 3. Identification of major and minor diastereomers.

D. Oil Bath ACM Study

An aza-Cope—Mannich reaction was performed in an oil bath to determine if microwave irradiation provides better conversion and/or diastereoselectivity than a conventional heating source (**Scheme 39**). Thus, 0.28 mmol of benzhydryl-protected amino alcohol **143**, 3 eq of propionaldehyde, and 1 eq of CSA were reacted in CH_3CN in a sealed vessel that was heated in an oil bath with a temperature of 110 °C for 35 minutes (**Table 9**, entry 1). An oil bath temperature of 110 °C was targeted because it was estimated that the reaction mixture temperature would be approximately 90 °C. The results from this reaction were to be compared to previous ACM reactions using the same reagent amounts that were heated to 90 °C using microwave irradiation. The microwave-assisted ACM provided 89% yield and 4:1 diastereoselectivity for ethyl acylpyrrolidines **155** and **156** (**Table 9**, entry 2). As the reaction time progressed, the oil bath temperature decreased to the low 70's. According to ^1H NMR analysis, complete conversion was obtained, providing an overall crude yield of 83% for ethyl acylpyrrolidines **155** and **156** with a diastereoselectivity of 6:1. The oil bath reaction provided an increase in diastereoselectivity most likely due to the lower reaction temperature. Although a direct data comparison between the 90 °C microwave and oil bath ACM could not be made, this experiment did provide valuable insight that lowering the reaction temperature in the microwave-assisted ACM could provide an increase in diastereoselectivity. It was this discovery that suggested optimization experiments involving reaction temperature (c.f. **Table 8**).

Scheme 39



143 **155** **156**

trans *cis*

Table 9. Oil Bath vs. Microwave ACM

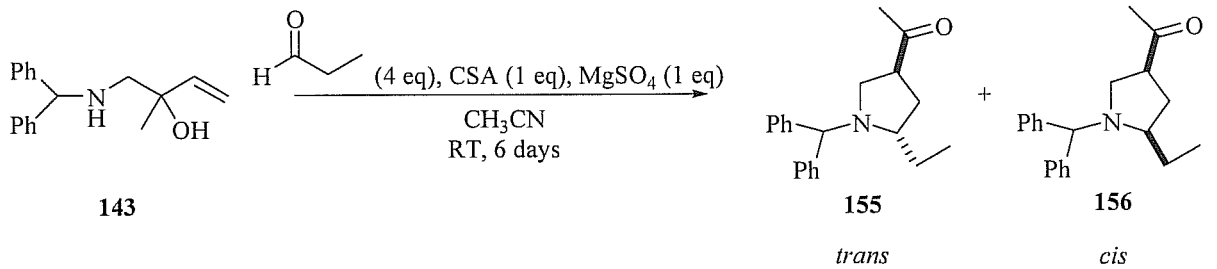
Entry	Conditions	Temp (°C)	% Yield[a]	DS[b] (**155**:**156**)
1	oil bath	70-110	83	6:1
2	microwave	90	89	4:1

[a] Combined crude yield of both diastereomers.
[b] Diastereoselectivity (DS) determined ^{1}H NMR.

E. Room Temperature ACM Study

Since lowering the reaction temperature provided better diastereoselectivity in the aza-Cope—Mannich reaction (**Table 8**), an ACM reaction performed at room temperature might provide even better diastereoselectivity (**Scheme 40**). Thus, 0.28 mmol of benzhydryl-protected amino alcohol **143**, 4 eq of propionaldehyde, and 1 eq of CSA in CH_3CN were stirred at room temperature for 6 days (**Table 10**, entry 1). According to ^{1}H NMR analysis, the reaction provided 91% conversion to ethyl acylpyrrolidines **155** and **156** with an overall crude yield of 67%. The diastereoselectivity of the reaction was 13:1, which was a significant increase compared to our optimized microwave-assisted results of 7:1 (**Table 10**, entry 2). However, the reaction time required to achieve comparable conversion to products was excessive.

Scheme 40



143 **155** *trans* **156** *cis*

Table 10. Room Temperature vs. Microwave ACM

Entry[a]	Conditions	Time	% Conversion	% Yield[b]	DS[c] (**155**:**156**)
1	room temperature	6 days	91	67	13:1
2	microwave, 60 °C	150 min	100	91	7:1

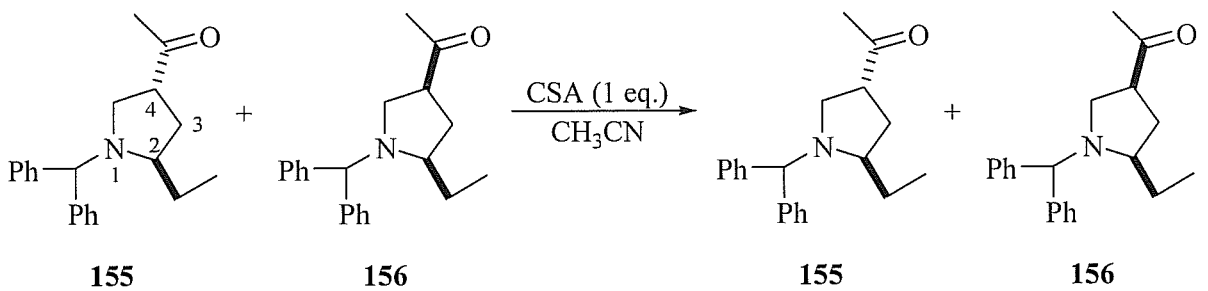
[a] Average value of multiple experiments.
[b] Combined crude yield of both diastereomers.
[c] Diastereoselectivity (DS) determined ^{1}H NMR.

F. Acid Catalyzed Epimerization: Effect on Diastereoselectivity

The possibility of acid-catalyzed C-4 epimerization altering diastereoselectivity following the ACM was examined by resubmitting ethyl acylpyrrolidines **155** and **156** to the reaction conditions (microwave settings of 200 W and 100 psi and 1 eq of CSA) (**Scheme 41**). An aliquot was taken from the reaction mixture at timed intervals and the selectivity was checked. Acetonitrile-D3 was used as the solvent so the aliquot could be placed directly in an NMR tube and ^{1}H NMR spectra recorded. An aliquot was taken from the reaction before submitting the sample to microwave irradiation. At t=0 min, the diastereoselectivity of ethyl acylpyrrolidines **155** and **156** was 4:1 (**Table 11**, entry 1). This selectivity was the same as seen after the initial aza-Cope—Mannich reaction. After 15 minutes of irradiation, the diastereoselectivity decreased from 4:1 to 2:1 (**Table 11,** entry 2). This suggests that prolonged exposure to the acidic reaction conditions was causing epimerization of the acylpyrrolidines. The mixture was irradiated for an additional 15 minutes to determine if the selectivity of ethyl acylpyrrolidines **155** and **156** would continue to decrease. After a total of 30 minutes of reaction time, an aliquot produced a diastereoselectivity of 2:1 (**Table 11**,

entry 3). This suggests that epimerization occurred within the first 15 minutes of reaction time. After this aliquot, the reaction was allowed to run for an additional two hours. The t=150 min aliquot again showed a diastereoselectivity of ethyl acylpyrrolidines **152** and **153** of 2:1 (**Table 11**, entry 4). These experiments demonstrated that acid-catalyzed epimerization causes a decrease in diastereoselectivity and that this occurs within the first 15 minutes of reaction time. Two possible mechanism for epimerization are keto-enol tautomerism and retro-Mannich—Mannich cyclization (**Scheme 42**).

Scheme 41



155 **156** **155** **156**

4 : 1 2 : 1

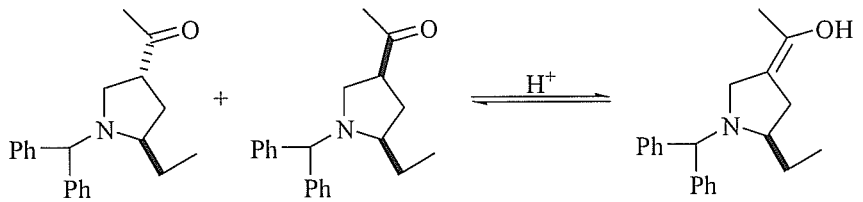
Table 11. Epimerization Study Data

Entry	Time (min)	Diastereoselectivity[a] **155** : **156**
1	0	4:1
2	15	2:1
3	30	2:1
4	150	2:1

[a] Diastereoselectivity determined ^{1}H NMR.

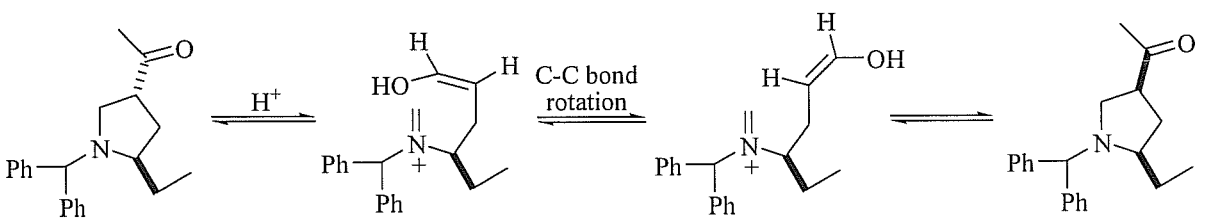
Scheme 42

Keto-Enol Tautomerism



155 **156** **161**

Retro-Mannich–Mannich Cyclization



155 **162** **163** **156**

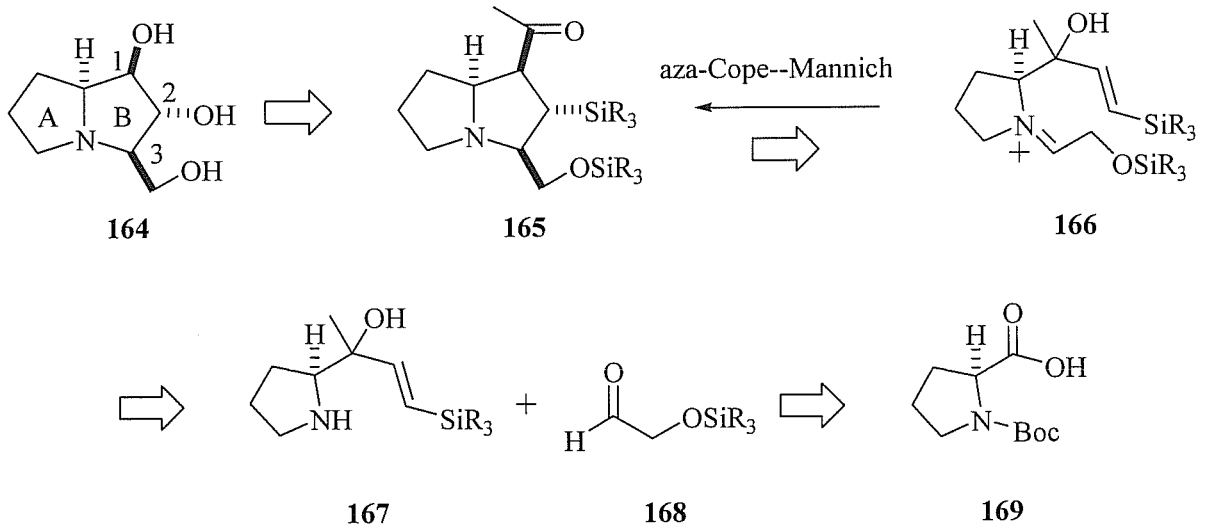
II. Synthesis of Pyrrolizidines using the Aza-Cope—Mannich Reaction

Once the microwave-assisted version of the tandem aza-Cope rearrangement—Mannich cyclization to provide acylpyrrolidines was optimized, the next step was to apply this reaction to the synthesis of pyrrolizidines. Pyrrolizidines presented a more complex target on which to test the methodology. In addition, they are core structures for a variety of important natural products.

The retrosynthetic analysis for polyhydroxylated pyrrolizidine **164** is shown in **Scheme 43**. An aza-Cope—Mannich reaction would establish B ring stereochemistry at C_1, C_2, and C_3. Polyhydroxylated pyrrolizidine **164** would be available from acylpyrrolizidine **165** after oxidation and deprotection. Acylpyrrolizidine **165** would be the product of the aza-Cope—Mannich cyclization of iminium ion **166** formed from a condensation between amino

alcohol **167** and aldehyde **168**. Amino alcohol **167** can be prepared by alkylation, deprotection, and vinyl addition to commercially available Boc-proline **169**.

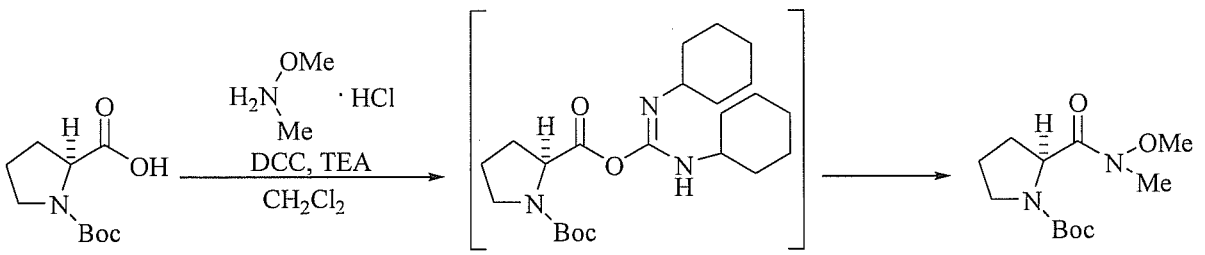
Scheme 43



A. Synthesis of the Weinreb Amide

Efforts to synthesize pyrrolizidines via a microwave-assisted aza-Cope rearrangement—Mannich cyclization focused initially on the formation of amino alcohol **167**, the ACM precursor. The first step in that process was to synthesize Weinreb amide **171** from Boc-proline **169** (**Scheme 44**).[27] Boc-proline **169** (4.6 mmol) was treated with 1.5 eq of hydroxylamine hydrochloride, 1.5 eq of 1,3-dicyclohexylcarbodiimide (DCC), and 4 eq of triethylamine (TEA) in dichloromethane at room temperature (**Table 12**, entry 1). The reaction was allowed to react for 24 hours. Although quantitative crude yields were obtained, only 58% conversion to products occurred. In addition to the desired amide **171**, the ^{1}H NMR spectrum showed resonances consistent with coupling intermediate **170** or a related degradation product. Another reaction was performed using the same scale (**Table 12**, entry 2). Following purification, a 55% yield was obtained.

Scheme 44



169 **170** **171**

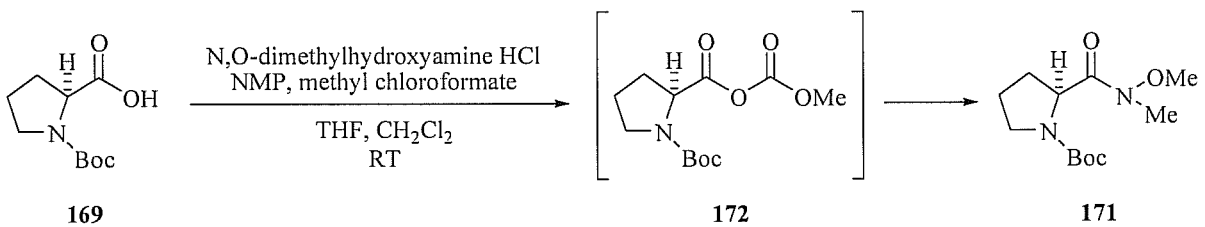
Table 12. First Weinreb Procedure Data

Entry	Conditions	% Yield
1[a]	RT, 24 hr	quantitative[b]
2	RT, 24 hr	55[c]

[a] Average value of multiple experiments.
[b] Crude yield with an average of 58% conversion to product observed.
[c] Purified yield

Goel developed a procedure that produced a Weinreb amide from Boc-leucine without the use of DCC.[28] This method utilized a two-pot procedure in which *N,O*-dimethylhydroxyamine hydrochloride, dichloromethane, and *N*-methylpiperidine were combined in one flask. That mixture was then added to a solution of Boc-proline **169**, *N*-methylpiperdine, and methyl chloroformate in THF and CH_2Cl_2 (**Scheme 45**). Adjusting the amounts of the amine hydrochloride and *N*-methylpiperdine in the first reaction flask was necessary to obtain satisfactory yields and complete conversion of Boc-proline **169** to Weinreb amide **171** (**Table 12**).

Scheme 45



169 **172** **171**

First, the procedure that Goel reported was followed exactly. This consisted of mixing 1 eq of *N,O*-dimethylhydroxyamine hydrochloride and 1.05 eq of *N*-methylpiperdine

in dichloromethane, then transferring the mixture to a flask containing 4.65 mmol of Boc-proline **169**, THF, dichloromethane, 1.1 eq of *N*-methylpiperidine, and 1 eq of methyl chloroformate (**Table 13**, entry 1). After stirring for 24 hours, the reaction produced a crude yield of 63%. ^{1}H NMR revealed that a 76% conversion to Weinreb amide **171** occurred. This percent conversion represents the conversion of Weinreb amide from an intermediate acyl carbonate **172**. This procedure's results were more promising than the previous procedure using DCC as the coupling agent.

In an effort to achieve total conversion to Weinreb amide **171**, the amounts of *N,O*-dimethylhydroxyamine hydrochloride and of *N*-methylpiperidine reacted in dichloromethane were doubled (2.06 eq and 2 eq, respectively) while keeping the rest of the reaction scale the same (**Table 13**, entry 2). The reaction time was also increased to 48 hours. Analysis by ^{1}H NMR showed total conversion to Weinreb amide **171** occurred, providing a crude yield of 62%. The low yield is presumably due to incomplete conversion of starting material to acyl carbonate **172**. Unreacted Boc-proline was likely removed during aqueous $NaHCO_3$ washes in the workup. Increasing the reaction time to 72 hours did not improve the yield of the reaction (**Table 13**, entry 3). Although the yield of this reaction was modest, it was easily reproducible and resulted in clean product that could be used without purification.

Table 13. Second Weinreb Procedure Data

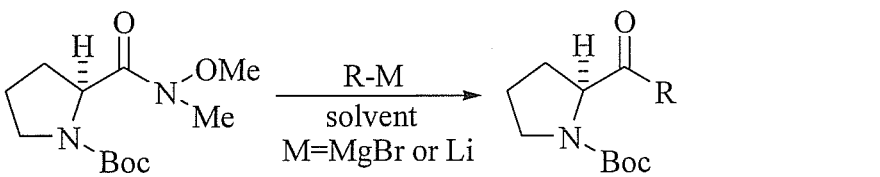
Entry	Amine HCl (eq)	Time (hr)	% Conversion	% Yield
1	1	24	76	63
2[a]	2	48	100	62
3[a]	2	72	100	60

[a] Average value of multiple experiments.

B. Carbonyl Addition to the Weinreb Amide

The next step in synthesizing the aza-Cope—Mannich precursor **167** was carbonyl addition to the Weinreb amide **171** using either methyl or butyl lithium or Grignard reagents (**Scheme 46**).

Scheme 46



171

173a, R=Me

173b, R=

Initially, methyl magnesium bromide ($MgBr\text{-}CH_3$) was used for the synthesis of methyl ketone **173a**. Weinreb amide **171** (7.28 mmol) was allowed to react with 3 eq of $MgBr\text{-}CH_3$ in THF at -78 °C, then warmed to room temperature and allowed to stir for 24 hours (**Table 14**, entry 1). The reaction provided an 80% crude yield and, according to ^1H NMR analysis, complete conversion of Weinreb amide **171** to methyl ketone **173a**. Another experiment was performed using 2.9 mmol of Weinreb amide **171** and 3 eq of $MgBr\text{-}CH_3$ (**Table 14**, entry 2). A crude yield of 34% was obtained, which contained only 46% conversion to methyl ketone **173a**. In order to achieve complete conversion and a better yield of methyl ketone **173a**, a reaction was performed using a larger excess of the Grignard reagent. Weinreb amide **171** (3.08 mmol) was treated with 6 eq of $MgBr\text{-}CH_3$ in THF for 24 hrs under the same conditions, producing quantitative crude yield (**Table 14**, entry 3). ^1H NMR analysis revealed complete conversion of starting material to product.

Although we were able to achieve complete conversion of Weinreb amide **171** to methyl ketone **173a** using the Grignard reagent, we investigated different procedures to make

the desired ketone because of reproducibility issues, likely due to the poor quality of the Grignard reagent. Thus, similar reactions were attempted using MeLi. In the initial attempt, 2.5 eq of MeLi was allowed to react with 2.38 mmol of Weinreb amide **171** for 30 minutes at -78 °C, then room temperature for 90 minutes (**Table 14**, entry 4). A crude yield of 33% was obtained and ^{1}H NMR analysis revealed complete conversion of Weinreb amide **171** to methyl ketone **173a**. Increasing the amount of MeLi used in the reaction was considered as a possible way to obtain a better mass recovery of methyl ketone **173a**. To that end, 2.58 mmol of starting material was treated with 4 eq of MeLi in THF for 30 minutes at -78 °C, then raised to room temperature for 60 minutes (**Table 14**, entry 5). A crude yield of 13% was obtained from this reaction and the ^{1}H NMR analysis revealed a complex mixture and trace amounts of methyl ketone **173a**. When the reaction time was increased to 2 hours at room temperature, 3.4 mmol of Weinreb amide **171** and 4 eq of MeLi provided a purified yield of 64% of methyl ketone **173a** (**Table 14**, entry 6). The increase in reaction time showed a significant increase in the amount of methyl ketone **173a** recovered. Unfortunately, these results were not reproducible likely due to the instability of the MeLi reagent. Indeed No-D NMR spectroscopy techniques[29] showed that in three months the amount of MeLi present in the reagent bottle diminished from 1.7 M to too little to be detected.

Butyl lithium was then used as a nucleophile because it was believed that it would be more stable during storage. Also, one possibility for low yields could have been the water solubility of methyl ketone **173a**. Use of a butyl ketone might remedy this potential problem. Weinreb amide **171** (1.69 mmol) was allowed to react with 4 eq of BuLi in THF for 10 minutes at -78 °C, then 2 hours at room temperature (**Table 14**, entry 7). The reaction

resulted in a crude yield of 73%. ^{1}H NMR analysis revealed a complex mixture, but also showed some peaks consistent with product. The reaction was repeated, increasing the reaction time to 40 minutes, and ether was used as the solvent instead of THF (**Table 14**, entry 8). This reaction provided a crude yield of 96% with a ^{1}H NMR spectrum that featured resonances consistent with a butyl ketone. The products were purified by flash chromatography, but yields under 10% were obtained.

Table 14. Methyl and Butyl Additions Data

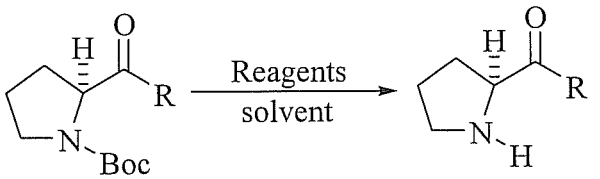
Entry	R-M	Solvent	Conditions	Crude Yield (%)
1	MgBr-CH_3	THF	-78 °C to RT 24 hr	80
2	MgBr-CH_3	THF	-78 °C to RT 24 hr	34[a]
3	MgBr-CH_3	THF	-78 °C to RT 24 hr	quantitative
4	MeLi	THF	-78 °C 30 min, RT 90 min	33
5	MeLi	THF	-78 °C 30 min, RT 60 min	13
6	MeLi	THF	-78 °C 30 min, RT 120 min	64[b]
7	BuLi	THF	-78 °C 10 min, RT 120 min	73
8[c]	BuLi	ether	-78 °C 40 min	96

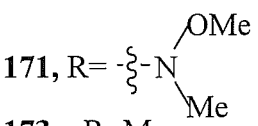
[a] 46% conversion to product was observed.
[b] Purified yield after flash chromatography.
[c] Average mass return of multiple experiments.

C. Boc-Deprotection

After the carbonyl addition to Weinreb amide **171** to provide methyl ketone **173a** or butyl ketone **173b**, the next step en route to the ACM precursor amino alcohol was removal of the Boc protecting group (**Scheme 47**). Several different deprotection procedures were examined.

Scheme 47

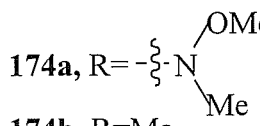




171, R=

173a, R=Me

173b, R=



174a, R=

174b, R=Me

174c, R=

Initially, Boc-deprotection was attempted with a microwave-assisted procedure that used Montmorillonite K 10 clay as an acid catalyst.[30] Weinreb amide **171** (0.71 mmol) was placed into a microwave vessel along with 20% by mass of K 10 clay and ethanol (**Table 15**, entry 1). The reaction was subjected to microwave irradiation at 300 W, 250 °C, and 200 psi for 30 minutes. A 14% mass return was obtained upon completion of this reaction. Unfortunately, the Boc group was still present according to the ^{1}H NMR spectrum. The experiment was repeated using 50% by mass of K 10 clay under the same microwave conditions for 60 minutes (**Table 15**, entry 2). As before, the Boc protecting group did not cleave.

Nudelam developed a mild Boc-deprotection procedure utilizing acetyl chloride in methanol.[30] In accordance with the procedure, Weinreb amide **171** (0.55 mmol) was allowed to react with 3 eq of acetyl chloride in methanol for 2 hours (**Table 15**, entry 3). A 62% mass return was obtained but ^{1}H NMR analysis revealed only starting material. When the reaction time was extended to 3 hours, ^{1}H NMR analysis revealed a more complex mixture, but characteristic Boc group resonances were still present. Next, Weinreb amide **171** (0.86 mmol) and acetyl chloride (3 eq) were allowed to react in methanol at room temperature for

24 hours (**Table 15**, entry 5). This experiment provided a mass return of 63%, which was higher than the previous attempt at 24 hours. However, the Boc group was clearly present in the ^{1}H NMR spectrum. In continued efforts to cleave the Boc-protecting group, two more reactions were performed. In the first reaction, Weinreb amide **171** was allowed to react under the same conditions as before, but for 72 hours (**Table 15**, entry 6). The ^{1}H NMR spectrum revealed the absence of the Boc group. However, although the Boc group had been cleaved, the product did not have the methyl and methoxy peaks characteristic of the Weinreb amide **174a**. A similar reaction run for 48 hrs provided essentially identical results (**Table 15**, entry 7).

Since attempts at deprotecting the Boc-protected Weinreb amide **171** were unsuccessful, deprotecting the methyl and butyl ketones **173a** and **173b** was attempted. The microwave-assisted Montmorillonite K 10 clay-catalyzed procedure was used first. Methyl ketone **173a** (0.71 mmol) was placed into a microwave vessel along with 20% by mass of K 10 clay and ethanol (**Table 15**, entry 8). The reaction was subjected to microwave irradiation at 300 W, 250 °C, and 200 psi for 30 minutes. Once the reaction was complete, an 86% mass return was obtained. When analyzing the ^{1}H NMR spectrum, the distinctive Boc group peak was still present. Another experiment on methyl ketone **173a** was performed using 50% by mass of K 10 clay under the same microwave conditions for 60 minutes (**Table 15**, entry 9). As before, the Boc protecting group did not cleave.

Next, the procedure using acetyl chloride in methanol was employed for deprotection of the ketones.[31] Methyl ketone **173a** was allowed to react with 3 eq of acetyl chloride for 90 minutes at room temperature (**Table 15**, entry 10). A mass return of over 100% was obtained, but the ^{1}H NMR spectrum showed the presence of the Boc group. A similar

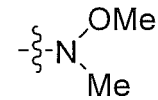
reaction was performed with the reaction time extended to 24 hours (**Table 15**, entry 11). When the reaction was complete, a mass return of 78% was obtained, but the ^{1}H NMR spectrum revealed that the Boc group was still present. This procedure was also attempted using butyl ketone **173b**. The first attempt used 0.78 mmol of the starting material and was treated with 3 eq of the acetyl chloride in methanol for 1 hour (**Table 15**, entry 12). A mass return of 61% was obtained, but according to the ^{1}H NMR spectrum, the Boc group did not cleave. As before, another reaction was performed using a 24-hour reaction time (**Table 15**, entry 13). A mass return of 43% was obtained, but still the Boc group resonance was present in the ^{1}H NMR spectrum.

Deprotection using trifluoroacetic acid (TFA) was then attempted. Butyl ketone **173b** (0.20 mmol) was treated with 0.5 ml of TFA in dichloromethane (**Table 15**, entry 14). The reaction was not complete after 2 hours according to TLC. The mixture was allowed to react for a total of 24 hours, and after this time a mass return of 34% was obtained. Like the previous procedures, the Boc group resonance was still present in the ^{1}H NMR spectrum.

Next, a procedure developed by Frank and Schutkowski was tried.[32] This Boc-deprotection technique was a mild method involving tin tetrachloride ($SnCl_4$). The authors report that Boc-proline can be deprotected using $SnCl_4$ in ethyl acetate at room temperature after only 35 minutes. Thus butyl ketone **173b** (2.90 mmol) was allowed to react with 5 eq of $SnCl_4$ for 35 minutes at room temperature (**Table 15**, entry 15). A mass return of over 100% was obtained, presumably due to the presence of coordinating tin. The ^{1}H NMR spectrum showed no signs of a Boc group being present. The Boc group had successfully cleaved, but the ^{1}H NMR spectrum was difficult to interpret aside from the absence of the

characteristic Boc group resonance. Purification of this product was attempted, but efforts to get a more definitive NMR spectrum were unsuccessful.

Table 15. Boc-Deprotection Data

Entry	R Group	Reagent	Solvent	Conditions	Mass Return (%)	Cleavage
1		K10 (20%)	EtOH	300 W, 250 °C, 200 psi, 30min	14	No
2		K10 (50%)	EtOH	300 W, 250 °C, 200 psi, 60min	NA	No
3		AcCl	MeOH	RT, 2 hr	62	No
4		AcCl	MeOH	RT, 3hr	69	No
5		AcCl	MeOH	RT, 24 hr	63	No
6		AcCl	MeOH	RT, 72 hr	55	Yes
7		AcCl	MeOH	RT, 48 hr	78	Yes
8	Me	K10 (20%)	EtOH	300 W, 250 °C, 200 psi, 30min	86	No
9	Me	K10 (50%)	EtOH	300 W, 250 °C, 200 psi, 60min	NA	No
10	Me	AcCl	MeOH	RT, 90 min	100	No
11	Me	AcCl	MeOH	RT, 24 hr	78	No
12	Bu	AcCl	MeOH	RT, 1 hr	61	No
13[a]	Bu	AcCl	MeOH	RT, 24 hr	43	No
14	Bu	TFA	Ch_2Cl_2	RT, 24 hr	34	No
15	Bu	$SnCl_4$	EtOAC	RT, 35 min	100	Yes

[a]Average mass return of multiple experiments.

D. Summary of the Progress Toward Synthesis of ACM Precursor

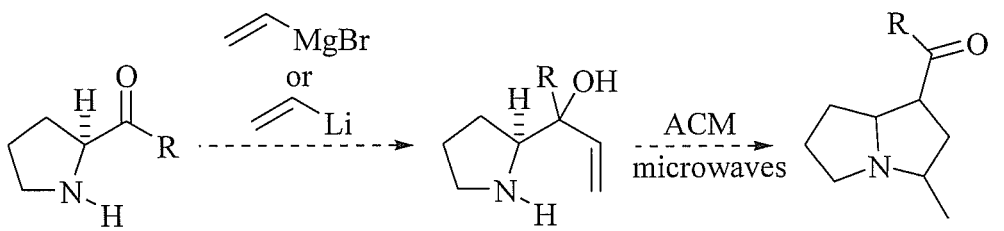
Efforts at synthesizing Weinreb amide **171** were successful. Modifications to the procedure developed by Goel and co-workers have provided Weinreb amide **171** in good yield without the need of purification. Attempts at the carbonyl addition to Weinreb amide **171** have not been as successful. Attempts at synthesis of methyl ketone **173a** resulted in modest mass returns, but purification attempts provided poor yields of the product. Efforts directed toward the synthesis of butyl ketone **173b** resulted in greater mass returns, but after purification even lower yields of butyl ketone **173b** were obtained compared to that of methyl ketone **173a**. Optimizing the reaction conditions to provide methyl ketone **173a**

should be investigated further in the future since it has provided the better results. Thus far the greatest challenge in the multi-step synthesis of the ACM precursor has been removal of the Boc group. Although $SnCl_4$ in EtOAc successfully cleaved the protecting group, purification has been difficult due to the polarity and water solubility of the product.

E. Future Work

The next step in the synthesis of pyrrolizidine **176a** or **177b** by way of the ACM is the vinyl addition to the deprotected methyl or butyl ketone (**Scheme 48**).

Scheme 48

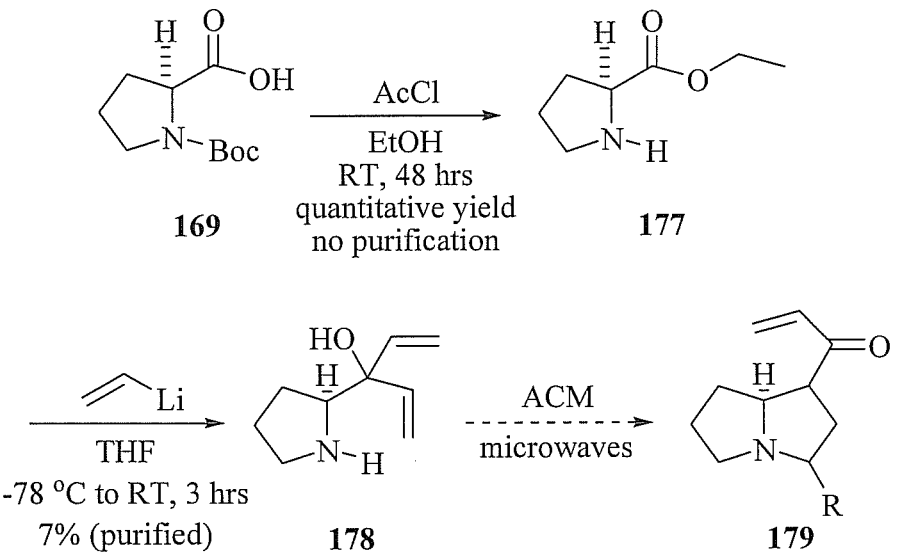


174b, R=Me **175a,** R=Me **176a,** R=Me

174c, R= **175b,** R= **176b,** R=

The vinyl addition could be accomplished using either vinyl magnesium bromide or vinyl lithium. Initial attempts at vinyl additions to butyl ketone **173c** using vinyl lithium have failed but have been successful on another substrate, ester **177** (**Scheme 49**). This reaction provided enough purified product to perform an ACM reaction to synthesize pyrrolizidine **179**. Our initial effort at performing the ACM failed, which leaves us less optimistic that the ACM will work on alcohol **175a** or **175b**. However, related studies are ongoing.

Scheme 49



III. Conclusions

The first microwave-assisted aza-Cope rearrangement—Mannich cyclization to provide acylpyrrolidine diastereomers was successfully developed. In the microwave-assisted ACM, reaction times were drastically reduced compared with those reported for ACM reactions that used conventional heating methods. Although reactions using the free amino alcohol and trityl-protected alcohol were inconclusive, benzyl-protected and benzhydryl-protected reactions provided valuable insight on how the size of the amino protecting group can control diastereoselectivity. In addition, the diastereoselectivity could be significantly increased by lowering the reaction temperature. Although the application of this methodology to the synthesis of pyrrolizidine alkaloids has not been accomplished, the synthesis of key components to the ACM precursor has been successful. Work in this area is ongoing.

Experimental

General Procedure

All commercially available compounds were purchased from Aldrich Chemical Company or Acros and used as received unless otherwise specified. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Purification of compounds by flash chromatography was performed by using silica gel (40-75 μm particle size, 60 Å pore size). TLC analyses were performed on silica gel 60 F_{254} plates (250 μm thickness). Microwave-assisted reactions were performed using a CEM Discover™ reactor. Pressure was monitored using an IntelliVent™ external pressure monitor. Temperature was monitored using an on-board infrared temperature sensor. Microwave reactor vials and caps were purchased from CEM Corporation. All ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz JEOL ECX instrument, and chemical shifts (δ) reported relative to residual solvent peak $CHCl_3$. All NMR spectra were obtained at room temperature. In some cases, mixtures of diastereomers were obtained and were not separated for characterization purposes. Consequently, some spectroscopic data have been reported on a mixture of diastereomers. Where possible, the diastereomeric ratios were measured by integration of ^{1}H NMR spectra.

1-(Benzhydrylamino)-2-methylbut-3-en-2-ol (143)

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar was added MeOH (0.5 mL), diphenylmethylamine **145** (1.31 g, 7.14 mmol), and isoprene monoxide **146** (0.60 g, 7.14 mmol). The vial was sealed with a reusable cap and then placed into the microwave reactor. The reaction was carried out with the following input parameters: temperature: 250 °C; max. pressure: 250 psi; power: 300 W. After 40 min and a brief cooling period, the solution was concentrated in vacuo. Chromatography using hexanes-

EtOAc (85:15) afforded the title compound as a pale yellow liquid (1.356 g, 71%). IR (film): 3453, 1646, 1495 cm^{-1}. ^1H NMR: (400 MHz, $CDCl_3$): δ 7.31 (m, 10H), 5.81 (dd, J = 17.4, 10.5 Hz, 1 H), 5.34 (d, J = 17.4 Hz, 1 H), 5.10 (d, J = 10.5 Hz, 1 H), 4.82 (s, 1 H), 3.43 (br s, NH), 2.64 (d, J = 11.4 Hz, 1 H), 2.50 (d, J = 11.4 Hz, 1 H), 1.72 (br s, OH), 1.21 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 144.0, 143.8, 143.4, 128.7, 128.6, 127.4, 127.3, 127.2 (2 C), 113.5, 72.1, 67.1, 57.0, 25.9. Electrospray HRMS: *m/z* calcd for $C_{18}H_{21}NO$ $[M+Na]^+$: 290.1521; found 290.1510.

1-(1-Benzhydyl-5-ethyl-pyrrolidin-3-yl)-ethanone (155)

To a 10 mL microwave reactor vial equipped with a magnetic stirring bar was added MeCN (0.4 mL), amino alcohol **143** (0.075 g, 0.28 mmol), propionaldehyde (0.081 mL, 1.1 mmol), camphorsulfonic acid (0.065 g, 0.28 mmol), and anhydrous copper sulfate (0.089 g, 0.56 mmol). The vial was sealed with a reusable cap and then placed into the microwave reactor. The reaction was carried out with the following input parameters: temperature: 60 °C; max. pressure: 100 psi; power: 200 W. After 150 min and a brief cooling period, the resulting solution was diluted with ethyl acetate, washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated. Chromatography using hexanes-EtOAc-triethylamine (80:19:1, v/v) afforded the title compound as a pale yellow oil (0.071 g, 82%, 7:1 mixture of stereoisomers). ^1H NMR: (400 MHz, $CDCl_3$): δ 7.25 (m, 10 H), 4.78 (s, 1 H), 3.05 (m, 2 H), 2.80 (septet, J = 4.6 Hz, 1 H), 2.49 (dd, J = 9.2 Hz, 7.8 Hz, 1 H), 2.10 (s, 3 H), 2.09 (m, 1 H), 1.73 (m, 1 H), 1.43 (m, 1 H), 1.19 (m, 1 H), 0.75 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.6, 143.6, 141.5, 128.8, 128.3, 128.2, 128.1, 127.0, 126.9, 70.0, 62.0, 52.3, 49.8, 31.5, 29.0, 25.2, 10.4. Electrospray HRMS calcd for $C_{21}H_{25}NO$ $[M+Na]^+$ 330.1834; found 330.1825.

Boc-L-Proline N-methyl-O-methylcarboxamide (171)

To a 25 mL round-bottom flask equipped with a magnetic stirring bar was added *N,O*-dimethylhydroxylamine hydrochloride (0.90 g, 9.3 mmol), *N*-methylpiperidine (1.16 mL, 9.58 mmol), and CH_2Cl_2 (6.02 mL). The reaction was stirred under nitrogen in an ice-water bath for 1 hour. A clear colorless solution resulted, which was kept cold and used in the following step.

To a 250 mL round-bottom flask equipped with a magnetic stirring bar was added Boc-L-proline **169** (1.00 g, 4.65 mmol), tetrahydrofuran (11.7 mL), and CH_2Cl_2 (45.9 mL). The mixture was stirred under nitrogen in an ice-water bath until the Boc-proline dissolved. *N*-methylpiperidine (0.58 mL, 4.79 mmol) was then added via syringe, and the reaction mixture was allowed to stir for 2 minutes. Methylchloroformate (0.36 mL, 4.65 mmol) was then added via syringe, and the reaction allowed to stir for 2 minutes. The solution of *N,O*-dimethylhydroxylamine, prepared as described earlier, was added via cannula. The ice-water bath was removed and the reaction mixture was stirred at room temperature for 48-72 hours. The solution was again cooled in an ice-water bath and extracted with two 25 mL portions of aqueous 0.2 *N* hydrochloric acid and two 25 mL portions of 0.5 *N* sodium hydroxide, dried over $MgSO_4$, and concentrated to afford the title compound as a pale brown oil (0.76, 63%), which was used without purification. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 4.5 (m, 1H), 3.65 (s, 3H, OMe), 3.4 (m 2H), 3.1 (s, 3H, N-Me), 2.1 (m, 1 H), 1.8 (m, 3H), 1.3 (s, 9H, *t*-Bu).

(*S*)-*tert*-Butyl 2-pentanoylpyrrolidine-1-carboxylate (173b)

To a 100 mL round-bottom flask equipped with a magnetic stirring bar was added Weinreb amide **171** (0.30 g, 1.16 mmol) and anhydrous ether (25 mL). The solution was cooled to -78 °C in a dry ice/acetone bath for 10 minutes under nitrogen. Butyl lithium (2.9

mL, 4.64 mmol) was added and the solution was allowed to stir for 40 minutes at -78 °C. The solution was quenched with saturated $NaHCO_3$, extracted 3 times with 20 mL portions of EtOAc, dried over $MgSO_4$, and concentrated. Chromatography using CH_2Cl_2-hexanes-MeOH (45:48:7, v/v) afforded the title compound as a brown oil (0.0089 g, 7%). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.23 (m, 1 H, minor rotamer), 4.21 (m, 1 H, major rotamer), 3.51 (m, 2H), 2.45 (m, 2 H), 2.15 (m, 1 H), 1.81 (m, 3 H), 1.55 (m, 2 H), 1.40 (s, 9 H, minor rotamer), 1.35 (s, 9 H, major rotamer), 1.36 (m, 2 H), 0.90 (m, 3 H).

(*S*)-Ethyl pyrrolidine-2-carboxylate (177)

To a 100 mL round-bottom flask was equipped with a magnetic stirring bar was added Boc-L-proline **169** (1.00 g, 4.65 mmol) and EtOH (40 mL). The solution was cooled in an ice-water bath while the Boc-proline dissolved. Acetyl chloride (0.99 ml, 13.95 mmol) was then added and the solution was allowed to stir at room temperature for 48 hours. The solution was again cooled in an ice-water bath and NH_3 (7 M in MeOH, 35 mmol) was added. The resulting suspension was concentrated and then filtered through cotton using CH_2Cl_2. Concentration of the resulting solution afforded the title compound as a yellow oil (0.6727 g, 100%), which was used without purification. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 4.40 (m, 1 H), 4.24 (q, J = 7.32 Hz, 3 H), 3.40 (m, 2 H), 2.32 (m, 1 H), 2.01 (m, 3 H), 1.26 (t, J = 7.32 Hz, 3 H).

References

1. Overman, L.E.; Kakimoto, M.-A. *J. Am. Chem. Soc.* **1979**, *101*, 1310.

2. a) Hseuh, P.; Lukowski, M.; Lindsay, H.A.; Milletti, M.C. *THEOCHEM* **2007**, *806*, 223. b) Johnson, B.F.; Marrero, E.L.; Turley, W.A.; Lindsay, H.A. *Synlett* **2007**, *6*, 893.

3. Overman, L.E.; Trenkle, W.C. *Isr. J. Chem.* **1997**, *37*, 23.

4. For reviews of allylic strain directed reactions, see (a) Hoveyda, A.H.; Evans, D.A.; Fu, G.C. *Chem. Rev.* **1993**, *93*, 1307; (b) Hoffman, R.W. *Chem. Rev.* **1989**, *89*, 1841.

5. Overman, L.E.; Kakimoto, M.-A.; Okazaki, M.E.; Meier, G.P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

6. Hayes, B.L. *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing: Matthews, NC, 2002.

7. For books, see: (a) *Microwave Assisted Organic Synthesis*; Tierney, J.P., Lidstrom, P., Eds.; Blackwell: Oxford, 2005; (b) Kappe, O.; Sadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinhiem, 2005 (c) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH:Weinheim, 2006.

8. For reviews, see: (a) Varma, R.S. *Pure Appl. Chem.* **2001**, *73*, 193; (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (c) Lidstrom, P.; Tierney, J.; Wathey, B.; Wesiman, J. *Tetrahedron* **2001**, *57*, 9225; (d) Kuhnert, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1863; (e) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128; (f) Kappe, O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

9. Heerding, D.A.; Hong, C.Y.; Kado, N.; Look, G.C.; Overman, L.E. *J. Org. Chem.* **1993**, *58*, 6947.

10. Johnson, J.H.; Phillipson, D.W.; Kahle, A.D. *J. Antibiotics* **1989**, *XLII*, 1184.

11. Ferkany, J.W.; Zaczek, R.; Coyle, J.T. *Nature* **1982**, *298*, 757.

12. Asano, N.; Nash, R.J.; Molyneux, R.J.; Fleet, G.W.J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

13. Nash, R.J.; Fellows, L.E.; Dring, J.V.; Fleet, G.W.J.; Derome, A.E.; Hamor, T.A.; Scofield, A.M.; Watkin, D.J. *Tetrahedron Lett.* **1988**, *29*, 2487.

14. Cooke, A.; Bennett, J.; McDaid, E. *Tetrahedron Lett.* **2002**, *43*, 903.

15. Doedens, R.J; Meier, G.P.; Overman, L.E. *J. Org. Chem.* **1988**, *53*, 685.

16. Hong, C.Y.; Kado, N.; Overman, L.E. *J. Am. Chem. Soc.* **1993**, *115*, 11028.

17. Overman, L.E.; Mendelson, L.T; Jacobsen, E.J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

18. Deng, W.; Overman, L.E. *J. Am. Chem. Soc.* **1994**, *116*, 11241.

19. Agami, C.; Cases, M.; Couty, C. *J. Org. Chem.* **1994**, *59*, 7937.

20. Knight, S.D.; Overman, L.E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776.

21. Kuhn, C.; Le Gouadec, G.; Skaltsounis, A.L.; Florent, J.-C. *Tetrahedron Lett.* **1995**, *36*, 3137.

22. Sakurai, O.; Horikawa, H.; Iwasaki, T. *J. Chem. Soc., Chem. Commum.* **1995**, *24*, 2527.

23. Brummond, K.M.; Hong, S.-P. *J. Org. Chem.* **2005**, *70*, 907.

24. Buchanan, G.L. *Chem. Soc. Rev.* **1974**, *3*, 41.

25. Desai, H.; D'Souza, B.R.; Foether, D.; Johnson, B.F.; Lindsay, H.A. *Synthesis* **2007**, *6*, 902.

26. Marrero, E.L.; Turley, W. A.; Lindsay, H. A.; 233rd National ACS Meeting, Chicago, IL; March 25-29, 2007, ORGN 214.

27. Christine, C.; Ikhiri, K.; Ahond, A.; Al Mourabit, A.; Poupat, C.; Potier, P. *Tetrahedron* **2000**, *56*, 1837.

28. Goel, O.P.; Krolls, U.; Stier, M.; Kesten, S. *Org. Syn.* **1993**, *8*, 68.

29. Hoye, T.R.; Eklov, B.M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567.

30. Siro, J.G.; Martin, J.; Garcia-Navio, J.L.; Remuninan, M.J.; Vaquero, J.J. *Synlett* **1998**, *2*, 147.

31. Nudelman, A.; Bechor,Y.; Falb,E.; Fischer, B.; Wexler, B.A.; Nudelman, A. *Syn. Comm.* **1998**, *28*, 471.

32. Frank, R.; Schutkowski, M. *Chem. Commun.* **1996**, 2509.