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Synthesis of an Aza-Cope Rearrangement - Mannich Cyclization Precursor from L-proline

Patricia T. Sinawe

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Patricia T. Sinawe

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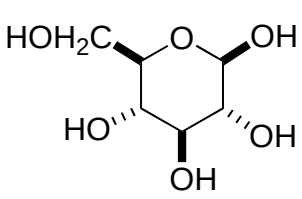
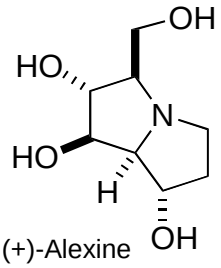
INTRODUCTION

Sugar mimics, molecules that look and act like real sugars **1**, are common compounds found in nature that have many potential biological applications (**Figure 1**) [1]. One property of these molecules is their enzyme inhibiting abilities within the human body in order to prevent the metabolism of certain sugars. These sugar mimics can potentially make good treatments for diseases such as diabetes, cancer, and viral infections [1].



Glucose
(sugar)

1



(+)-Alexine
(sugar mimic)

2

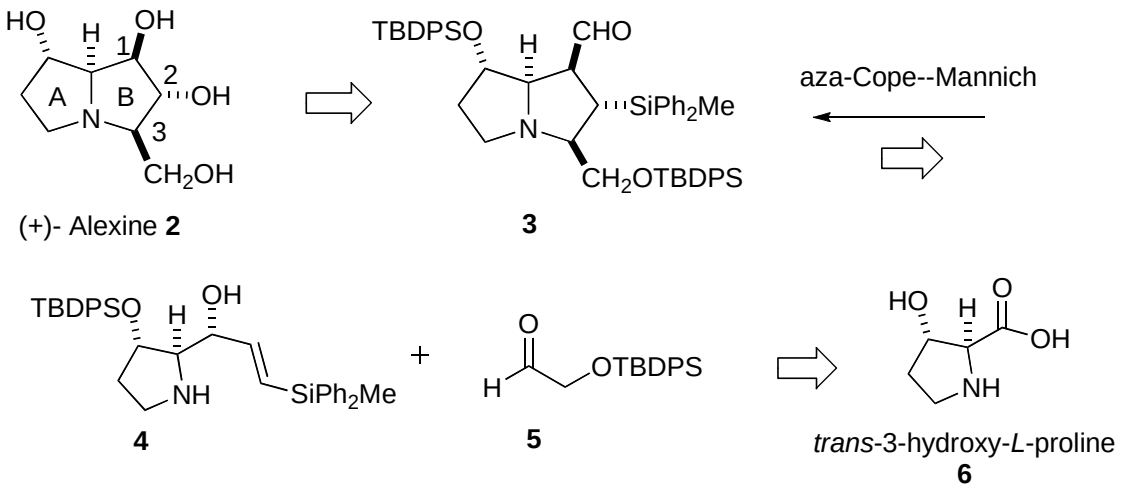
Figure 1

Within the human body, there exists a set of enzymes called alpha glycosidases that reside on the lumen of the small intestine. These enzymes metabolize complex, disaccaride sugars like sucrose, into simpler, monosaccarides such as glucose and fructose. This process increases blood glucose levels. It is for this reason that pyrrolizidine alkaloids such as (+)-alexine **2** (**Figure 1**) are of interest for their ability to inhibit glycosidases [2]. Since glycosidases are sugar-metabolizing enzymes, (+)-alexine's inhibiting activities will serve as a control mechanism of this metabolic pathway [2].

In this research project, the class of sugar mimics that we are attempting to synthesize is known as pyrrolizidine alkaloids. Pyrrolizidine alkaloids are bicyclic five-membered ring structures with containing a nitrogen atom. In particular, the sugar mimic that was the target of this work was (+)-alexine **2** (**Scheme 1**) [3]. We anticipated accomplishing the synthesis of this molecule by using the aza-Cope rearrangement-Mannich cyclization, a cascade reaction that can form and break multiple bonds within a single step [4,5]. We reasoned that this would be a very useful and efficient method in producing multi-ringed structures and would allow us to synthesize our desired sugar mimic, (+)-alexine **2**. We anticipated that the sugar mimic produced may be used as a potential drug treatment for persons with type II diabetes in order to prevent the metabolism of complex sugars [1].

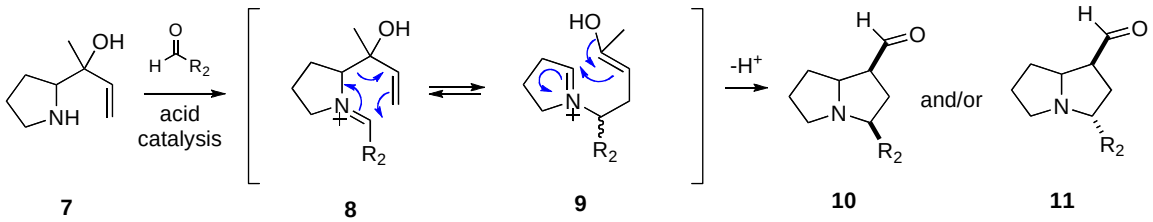
No one has performed an aza-Cope Mannich reaction that has resulted in the formation of pyrrolizidine alkaloids. Therefore the second goal of this project was to expand the methodology of the aza-Cope Mannich cyclization reaction.

The retro synthetic plan (**Scheme 1**) below outlines how the synthesis of the sugar mimic, (+)-alexine, was approached. First, using commercially available *trans*-3-hydroxy-*L*-proline **6,** aza-Cope Mannich presursor **4** could be prepared by reduction and vinyl silane addition. Next, aza-Cope Mannich reaction of amino alcohol **4** with aldehyde **5** should result in the formation of pyrrolizidine **3**, which could be oxidized and deprotected to give (+)-alexine **2**.



Scheme 1

The aza-Cope rearrangement-Mannich cyclization begins with the formation of an iminium cation intermediate **8** (**Scheme 2**), which undergoes rearrangement to give enol **9**. It then quickly cyclizes into the pyrrolizidines **10, 11**, which have the same pyrrolizidine backbone as (+)-alexine **2**.



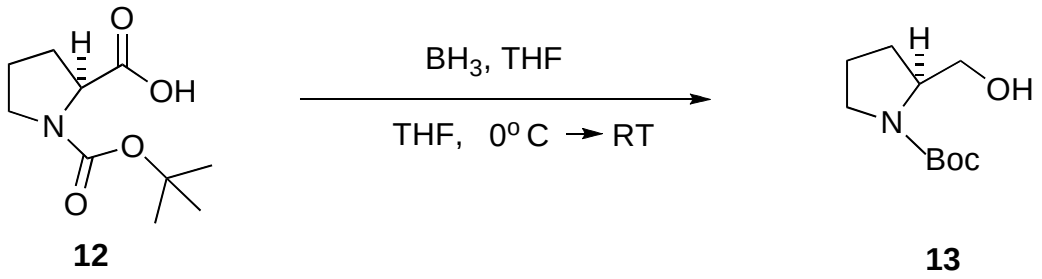
Scheme 2

In addition to providing a quick route to (+)-alexine [6], we planned to use microwave heating to accelerate the aza-Cope Mannich reaction. This work would be the first example of a microwave-assisted aza-Cope Mannich reaction. To optimize the reaction conditions, we anticipated altering variables such as temperature, pressure, and microwave power used. By eliminating the use of conventional heating methods, we

would increase the efficiency and rapid production of the desired product [6]. Our hypothesis was that a microwave-accelerated aza-Cope-Mannich reaction time could reduce reaction times from days to minutes [6,7]. Also, we hoped this could prevent side products from forming and could result in higher yields of the desired product.

RESULTS AND DISCUSSION

Instead of beginning with *trans*-hydroxy-*L*-proline, as is needed for (+)-alexine, we decided to begin work on a simpler, yet similar model system. The first step was a reduction of a protected form of proline **12**. This transformation involves reducing the carboxylic acid **12** to alcohol **13** (**Scheme 3**) [8].

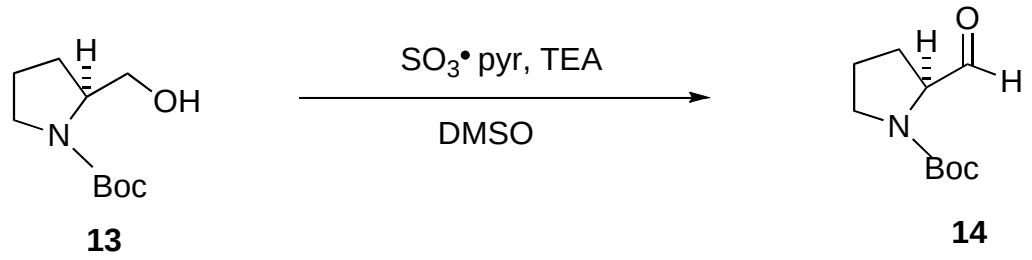


12 **13**

Scheme 3

This reaction showed an 85.6% yield in the production of the alcohol **13**, whose structure was confirmed by the ^{1}H NMR analysis.

The second step was an oxidation of the alcohol **13** to the corresponding aldehyde **14** (**Scheme 4**) [8].

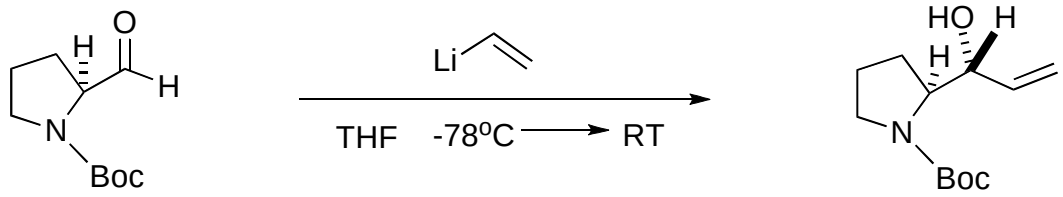


13 **14**

Scheme 4

This reaction showed a 68.4% yield of the aldehyde.

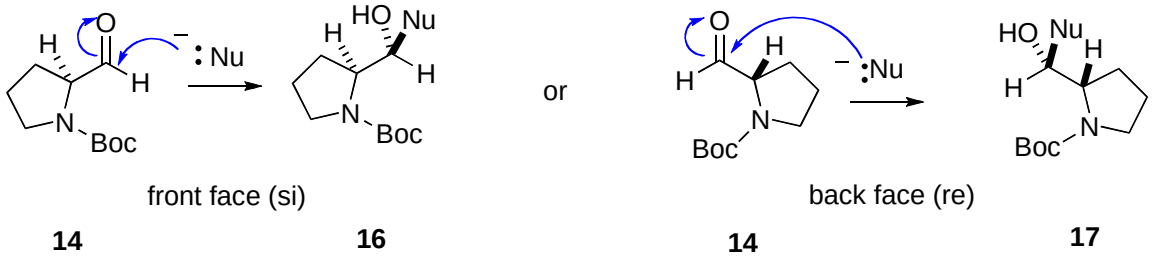
Following this reaction, the third step was a vinyl lithium addition [9] to the aldehyde **14** (**Scheme 5**), which produced alcohol **15** in 47% yield.



14 **15**

Scheme 5

We were aware that, depending on which face of the aldehyde was attached by the vinyl lithium nucleophile, two diastereomers could be produced [10-12]. If the nucleophile (-Nu) attacked the aldehyde **14** from the front face, alcohol **16** would be produced (**Scheme 6**). However, if it attacked from the back face, diasteromeric alcohol **18** would be produced.



14 **16** **14** **17**

Scheme 6

Although this scheme shows how different diasteromers could be produced, further models were needed in order to predict which of the diastereomers would be favored as the major product.

Using the Felkin-Anh [11] and Cram chelation [12] models (**Figure 2**), diasteroselectivty of the products **16, 17** was more closely examined [11,12].

In the Felkin-Anh model [11], the nitrogen on the alpha-carbon orients itself at a dihedral 90° angle relative to the carbonyl oxygen. Two possible conformers that have this dehedral angle may exist (**18, 19, Figure 2**). The nucleophile than attacks opposite the C-N bond. In conformer **18,** the attack is blocked by a large R group. Thus attack via conformer **19** is favored.

In the Cram chelation model **20**, the nucleophile's metal cation coordinates to the α-nitrogen and the carbonyl oxygen. The nucleophile then attacks the carbonyl from the less hindered side.

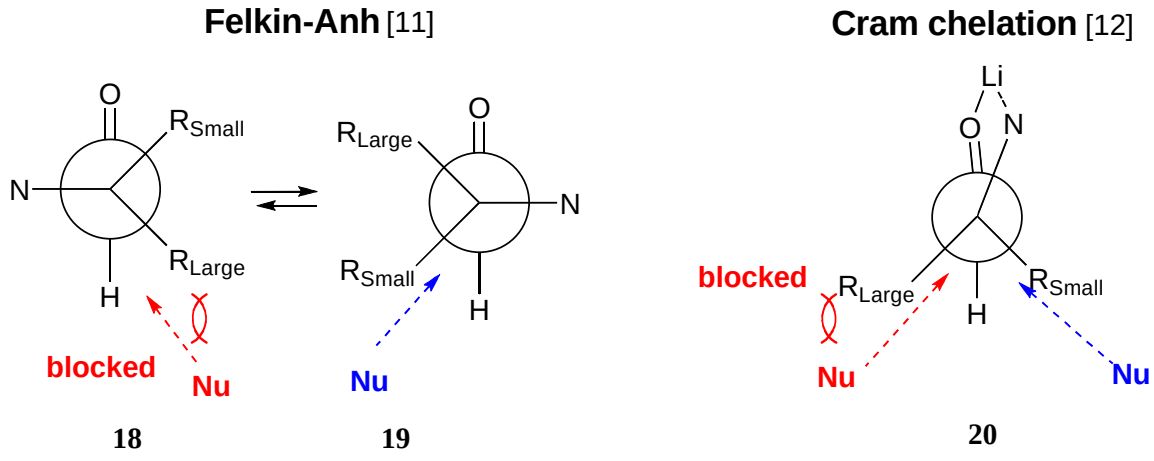
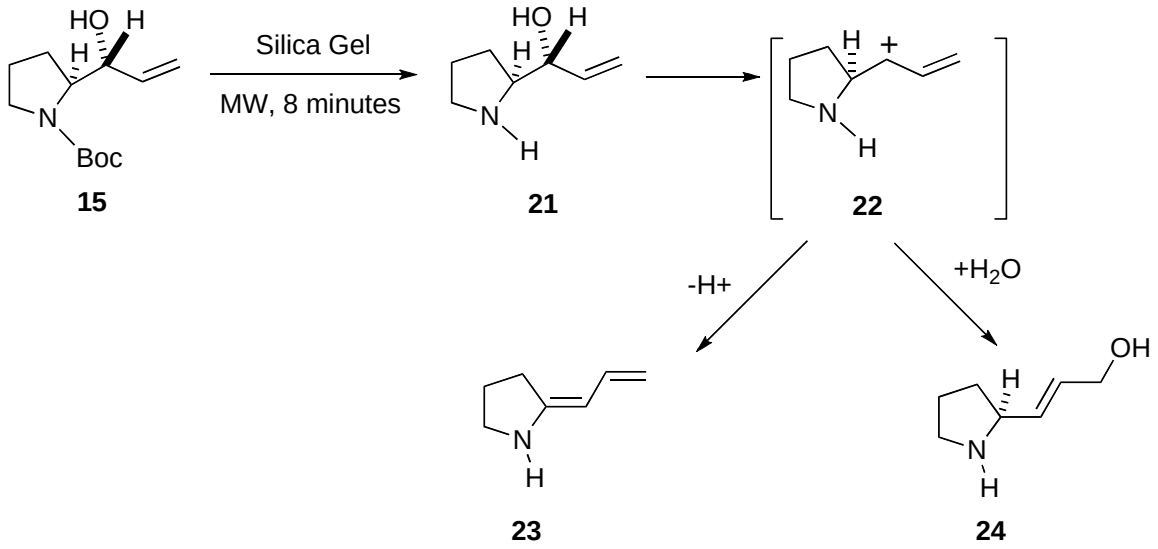


Figure 2

We hypothesized that the diastereomer resulting from the Felkin-Anh model was the major isomer. Overall, the vinyl lithium addition to the carbonyl group was a success, giving a 47.0% yield of the product. We have not yet rigorously determined the stereochemistry of the major isomer.

From here, we had to develop a boc-deprotection method in order to continue on with our synthesis. We anticipated that deprotection would give us the precursor for the aza-Cope Mannich cyclization step.

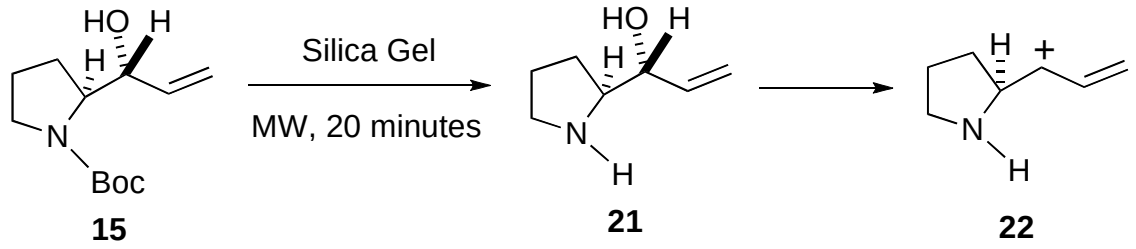
Our first deprotection attempt used a Lewis acid-catalyzed method. We took the product from the vinyl lithium reaction **15** and coated it onto silica gel (a Lewis acid). It was then placed into a microwave for eight minutes (**Scheme 7**) [13].



Scheme 7

No product was isolated, so it was hypothesized that the product **21** may have decomposed or either the starting material or the product may have been adhering to the silica gel. Another possibility is that the reactant could have reacted further to produce an allylic cation **22** (**Scheme 7**)**,** which could deprotonate to form a dienamine **23** or undergo an allylic rearrangement to give an alcohol **24**. Since no product was isolated, it was impossible to determine the final results.

In order to determine if the run time was too short, a second attempt was performed in which the run time of the microwave reaction was extended from eight minutes to twenty minutes (**Scheme 8**) [13].

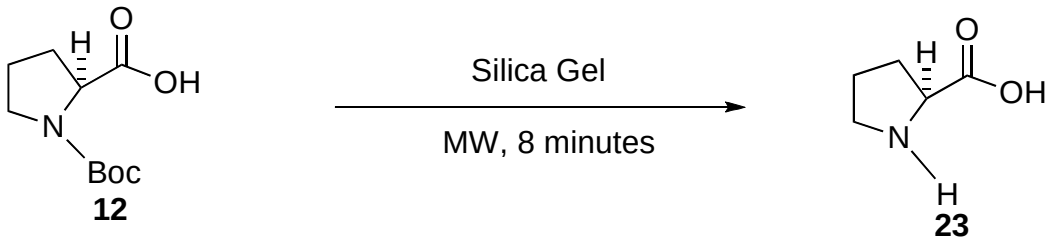


Scheme 8

This reaction showed similar results to the previous experiment; no product was isolated. Thus, reaction time was potentially ruled out as as a reason for the reaction's failure.

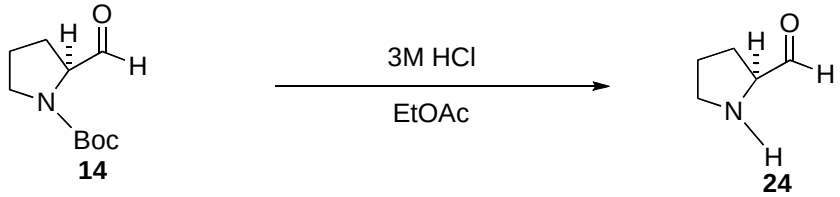
At this point, we decided to confirm the experimental procedure by using a substrate that had been reported to be deprotected by this procedure [13].

This time boc-proline **12** was successfully deprotected, giving L-proline **23** after twenty minutes in the microwave according to ^{1}H NMR analysis [13] (**Scheme 9**). This indicated that our original substrate **15** was in fact the issue. This also showed that the conditions in the microwave were appropriate for the reaction.



Scheme 9

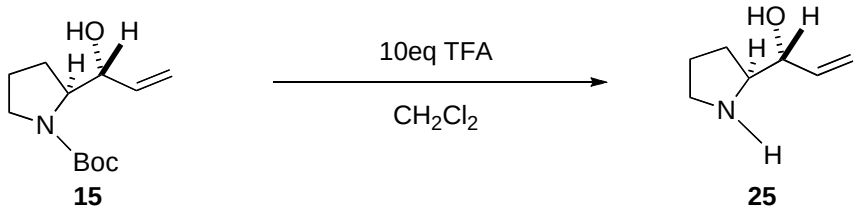
In a fourth attempt at deprotection (**Scheme 10**), we tried an experiment without the microwave, using HCl acid with the protected aldehyde **14** [14].



Scheme 10

The results produced in this experiment were inconclusive due to the amount of solvent still present when the ^{1}H NMR analysis was taken. Because a better deprotection procedure was discovered, this experiment was not repeated.

Returning to the original substrate **15** for deprotection (**Scheme 11**), we attempted another reaction without the microwave using the strong acid trifluoroacetic acid (TFA).

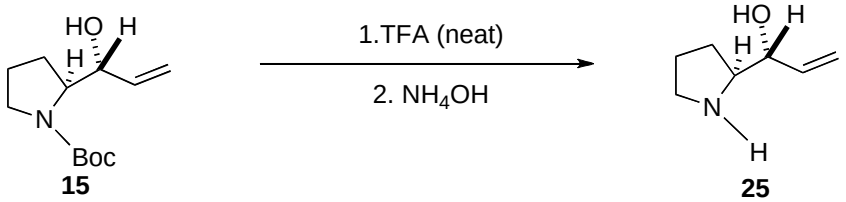


15 **25**

Scheme 11

From the ^{1}H NMR results, decomposition of the starting material **15** had occurred.

Our next attempt at deprotection (**Scheme 12**), showed the most promising results of all the reactions [15]. We treated amino alcohol **15** with trifluoroacetic acid (TFA), and then simply concentrated the reaction mixture and analyzed the results. The ^{1}H NMR showed that the boc group was removed, but lots of TFA remained. A second problem that was encountered was that after the product was stored at room temperature for a day, an unknown side reaction seemed to be occurring, decomposing our product.



15 **25**

Scheme 12

In a second trial (**Scheme 12**), a new evaporating system was used in an effort to get rid of the TFA and see if this was the cause of the side reactions that were occurring in the first trial. The system used was a Kuglrohr evaporator set a temperature of 60 ^{o}C and approximately 5 mm Hg. In running another ^{1}H NMR, it was shown that all of the TFA had evaporated, but once again when the product was stored at room temperature, it decomposed.

In a third trial (**Scheme 12**), a new method was considered to stop decomposition. The product was stored under nitrogen at 0°C. A ^{1}H NMR of product **25** taken a few days later indicated that no decomposition was occurring. Since this deprotection was a success, the next step was purification of the amino allylic alcohol.

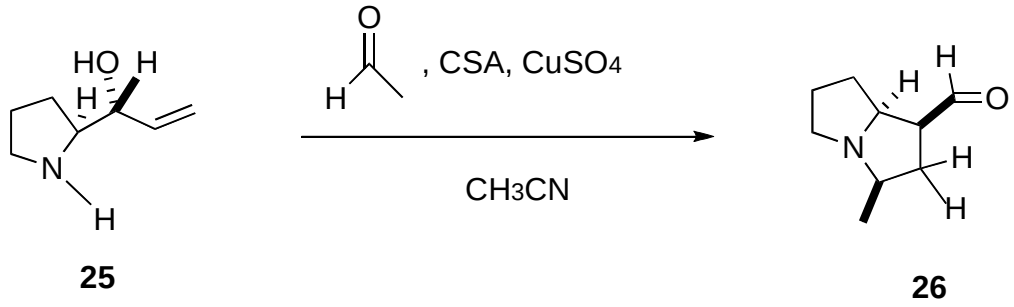
Multiple procedures were performed for purification. First, several solvent systems for column chromatography were screened using TLC. However, no solvent system showed complete separation of the impuritites from the deprotected amine. When column chromatography was attempted, the product adhered to the silica gel, failing to elute with even the most polar solvents.

The next attempt at purification was to mix the product with the charcoal to remove colored impurities. ^{1}H NMR results showed that this purification system was not successful since many impurities still existed within the sample.

A third purification method was performed using an alumina column, which is less Lewis acidic than silica gel. Chloroform-d was used as the solvent. ^{1}H NMR results showed that the all of the impurities were still present, but the product had completely disappeared from this sample. It was then hypothesized that our deprotected amine was clearly adhered the alumina, ironically in what was likely its purified form!

At this point, we attempted to remove the product from the alumina. Acetonitrile was flushed through the column and a ^{1}H NMR was obtained. Once again, no evidence of the desired product was present in the spectrum.

Since purification attempts weren't successful, experiments with the unpurified product were performed. We subjected amino allylic alcohol **25** to aza-Cope Mannich conditions. Allylic alcohol **25** was treated with aldehyde in the presence of acid. Copper sulfate was used as a drying agent in order to remove water produced during the reaction, which should drive the equilibrium toward the product pyrrolizidine **26** (**Scheme 13**).



25 **26**

Scheme 13

All of these trials were performed in a microwave and are summarized on **Table 1**.

Table1: Summary of Microwave-Assisted aza-Cope Mannich Reaction				
Entry	**Purified?**	**Reactants**	**MW Conditions**	**Results**
1	Possibly	Alumina Coated CSA Acetaldehyde Acetonitrile	100psi, 16min 85°C, 200W	No starting material Pure unknown compound isolated
2	No	Same	Same	No starting material Decomposition
3	No	Same	100psi, 16min 90°C, 200W	Complex Mixture
4	Yes	Same	100psi, 16min 90°C, 150W	No starting material Decomposition

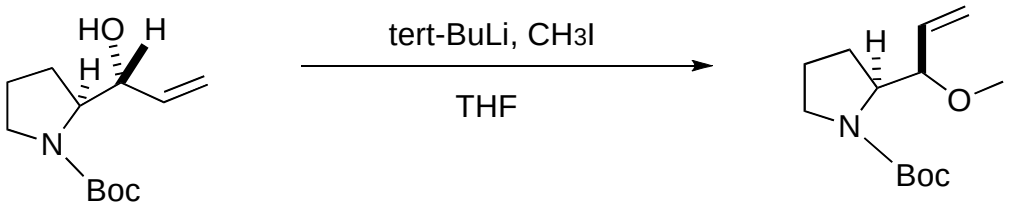
In the first trial, the substrate used was the presumed purified allylic alcohol **25** which was coated on alumina. The purpose of this procedure was to see if the reaction would proceed and in doing so, have the substrates react together, liberate the product from the alumina, and give the pyrrolizidine **26**. However, ^{1}H NMR analysis was inconsistent with pyrrolizidine **26**.

In the second trial, the substrate used was the deprotected amine with impurities. The ^{1}H NMR results were complicated by the presence of too much camphorsulfonic acid (CSA), but showed that starting material was not present. This likely indicated that the product was water soluble and was washing out during the extraction process or that it may have decomposed.

In the third trial, a method of washing out CSA was developed. ^{1}H NMR revealed that CSA was no longer present, but also showed no evidence that the desired reaction had occurred. Once again, the product may have washed out during extraction or other undesired products may have formed leading to a complex mixture. Other problems were that the NMR peaks, including d-chloroform peaks, showed spinning side bands, which suggested a problem with the shimming of the NMR instrument.

A fourth trial was conducted in which the substrate was deprotected and immediately purified to prevent decomposition. Following that reaction, the product was exposed to the aza-Cope-Mannich conditions. This immediate purification step was to help prevent any of the deprotected product from having the chance of decomposing. However, this trial also showed no signs of the starting material and suggested possible decomposition according to the ^{1}H NMR spectrum.

Because of the difficulties with purification and unsuccessful aza-Cope-Mannich reactions using alcohol **15**, we decided to make a derivative that might be easier to purify. In this next series of reactions, the plan was to use the protected amine **15**, protect the alcohol through a methylation step, deprotect the amine, and then attempt purification and/or the aza-Cope-Mannich reactions. The idea behind the methylation step **(Scheme 14**) was to create a less polar and less water soluble ether **27** before proceeding to the deprotection step.



15 **27**

Scheme 14

Table 2 below summarizes the results of the methylation with methyl iodide.

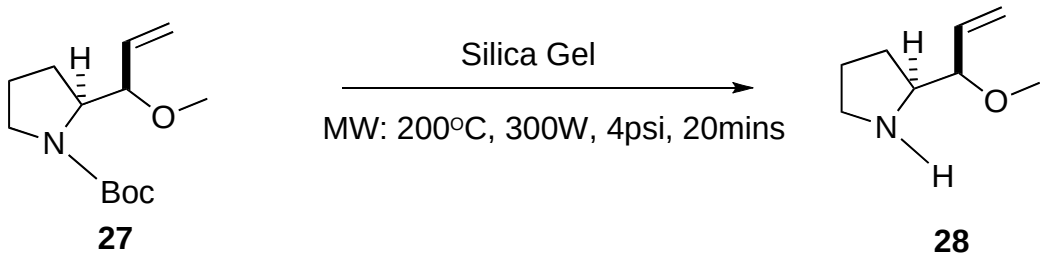
Table 2: Summary of Methylation Formation Reaction		
Trial #	Reactants	Results
1	0.1706mmol SM 1.1eq tert-BuLi 15eq CH_3I	Complex mixture
2	0.1201mmol SM 2.0eq tert-BuLi 30eq CH_3I	Product formed
3	0.769mmol SM 2.0eq tert-BuLi 30eq CH3I	Product formed

In the first trial, the ^{1}H NMR revealed that the methylation was not occurring. In trial 2, issues related to the concentrations of the substrates were explored. Compared to trial 1, concentrations of tert-butyl lithium and methyl iodide were increased. The ^{1}H

NMR showed that the desired product **27** was forming, with a possibility of two diastereomers being created in the process.

The purpose of trial 3 was to scale up the reaction to create more product and develop a purification method. The product **27** was run through a column of 20:80 ethyl acetate: hexane. Most of the impurities were separated from the amine **27,** but the separation of the diastereomers was not successful. The purification resulted in a 25% yield.

Following the methylation experiment, a boc-deprotection was attempted (**Scheme 15**). The new product **27** was subjected to similar microwave and deprotection conditions as previously described (**Scheme 8**).

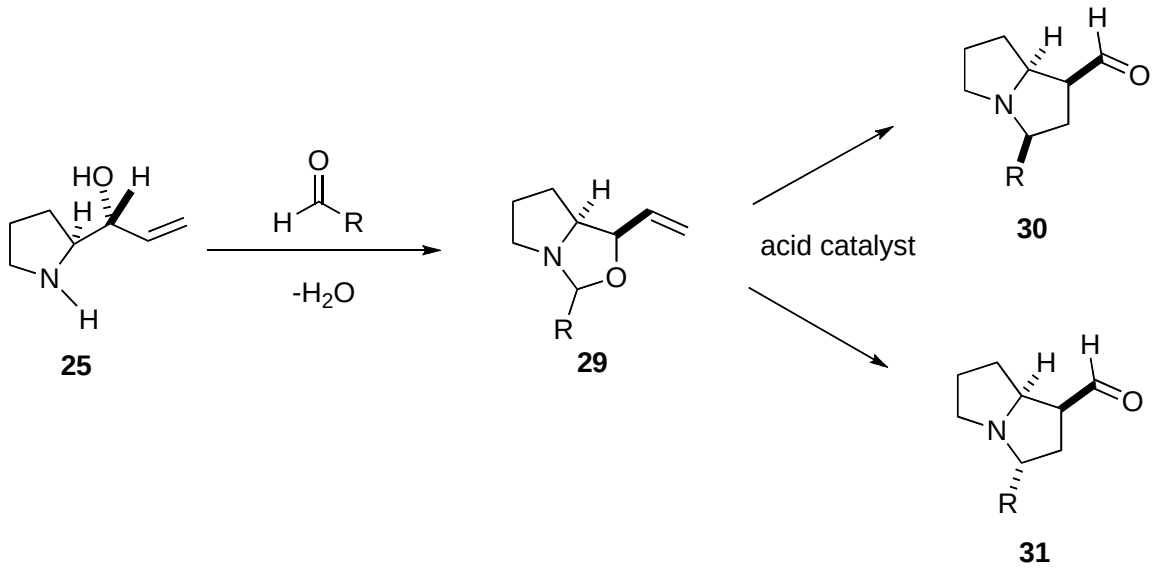


27 **28**

Scheme 15

The ^{1}H NMR showed that no starting material or product was isolated after washing the silica gel with methanol. As was the case previously, the deprotected product may have adhered to the gel.

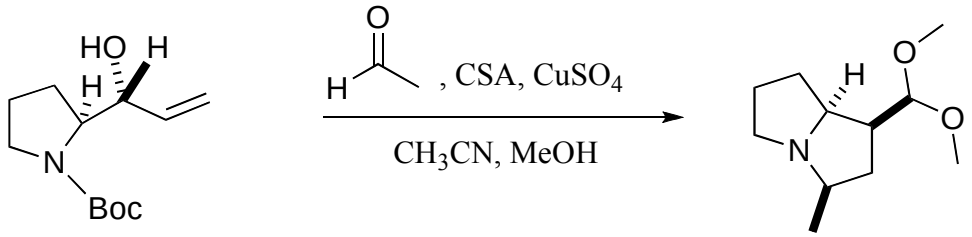
Since the methylation step did not produce the desired results, another strategy was proposed: oxazolidine formation (**Scheme 16**).



Scheme 16

The plan was that if the oxazolidine **29** could be formed from deprotected material **25**, it could then be exposed to the aza-Cope Mannich conditions and should form the pyrrolizidines **30** and/or **31**.

From the reaction scheme outlined above, a sequence of reactions was performed in order to form the pyrrolizidine. In previous reactions, pyrrolizidines **30** or **31** may have been produced but then could have immediately undergone a polymerization reaction [16]. To suppress this, we attempted to form acetal **32** in situ (**Scheme 17**). It was believed that acetal **32** would be stable and isolable [16], unlike pyrrolizidines **30** or **31.** In addition, this reaction is a one-pot reaction in which multiple reactions occur in one microwave tube: an aza-Cope-Mannich reaction followed by an acetal formation.

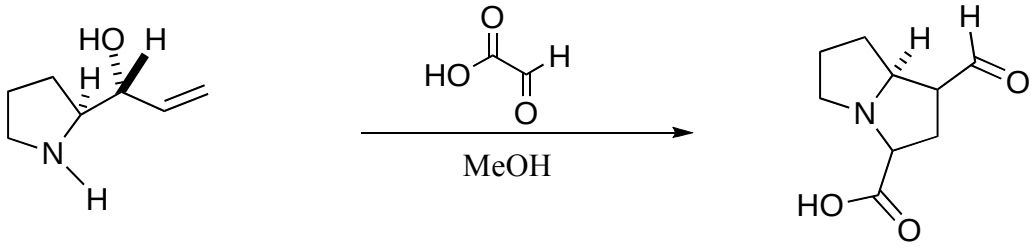


15 **32**

Scheme 17

^{1}H NMR analysis of this reaction showed that an aldol byproduct, crotonaldehyde, was forming. The aldol byproduct was removed by distillation, but no products were present in the sample according to NMR analysis.

Finally, a different approach was pursued in which the acid source and aldehyde are contained on the same molecule. Glyoxylic acid was used as both the acid catalyst and the aldehyde [17]. In this scenario, the resulting pyrrolizidine **33** should contain a carboxylic acid **(Scheme 18).**



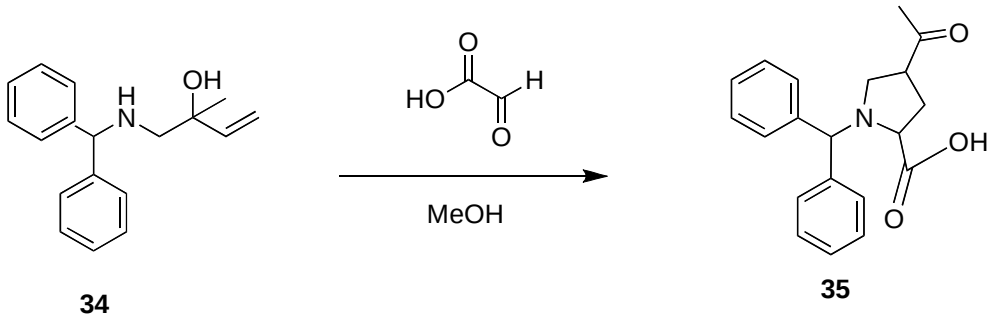
25 **33**

Scheme 18

In this reaction, freshly deprotected material was made and exposed to previously reported conditions [17]. Starting material was stirred with glyoxylic acid in methanol at room temperature for two days and was then washed with ethyl acetate to remove any

starting material and impurities. A dark solid was formed, which was concentrated and dissolved in d_6-DMSO. ^{1}H NMR analysis showed that a complex mixture was formed.

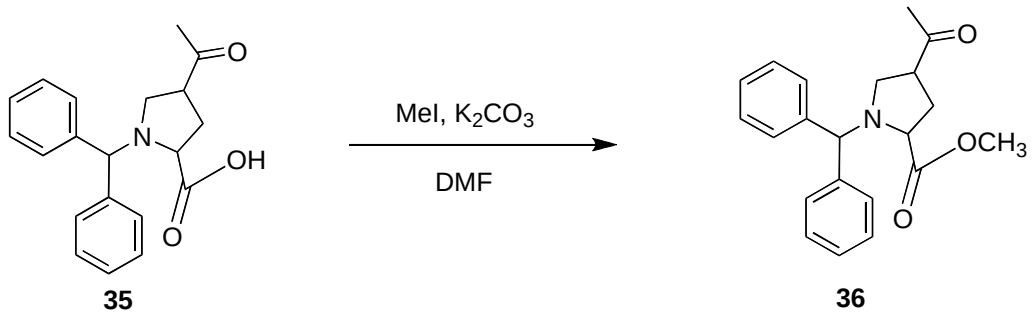
Since the above reaction produced a complex mixture, the next step was to explore model systems in order to see if the glyoxylic acid aza-Cope Mannich reactions would work on a less complex substrate (**Scheme 19**). Thus, the simpler diphenyl protected amino alcohol **34** was used in anticipation of producing pyrrolidine **35 (Scheme 19)**.



34 **35**

Scheme 19

The product **35** was formed. Following the cyclization, methylation of the alcohol **35** was attempted in order to produce the methylated product **36 (Scheme 20).**



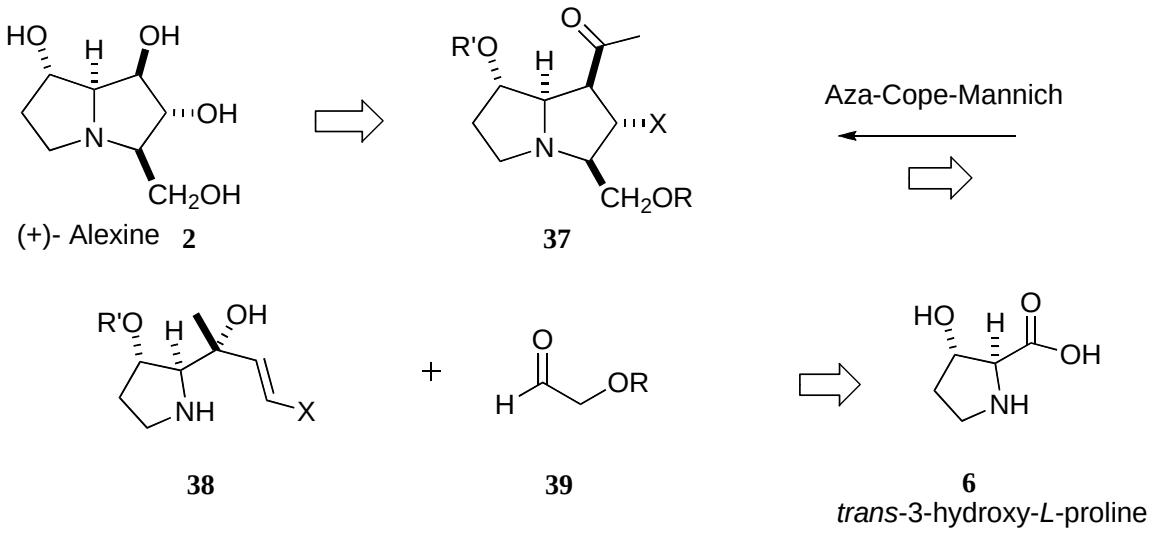
35 **36**

Scheme 20

The purpose of this step was to create a less polar and less water soluble product **36** for easier purification methods. However, ^{1}H NMR analysis indicated that a complex mixture was formed.

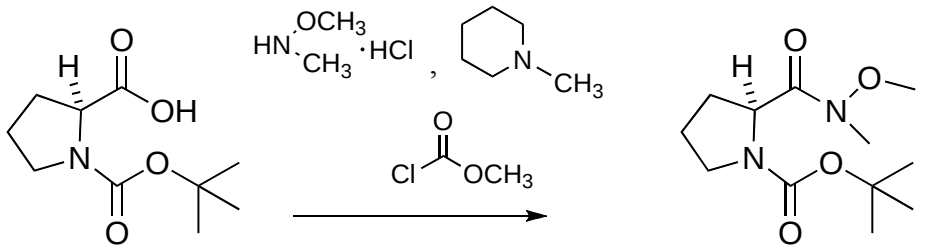
This phase of this project contained many difficulties such as the stability of the aza-Cope Mannich precursor, difficulty of purifying the aza-Cope Mannich precursor, and success of the aza-Cope Mannich reaction itself. Thus we modified our initial plan to address these issues.

The modified retrosynthetic plan (**Scheme 21**) shows a slight difference in how we planned to synthesize (+)-alexine **2**. With the installation of an additional methyl group on the substrate **38,** we predicted that we could expose this new starting material to the same series of reactions leading up to the formation of the pyrrolizidine alkaloid **37** via the aza-Cope Mannich reaction. We believed that this would help with the purification of the free amine as well as make the resulting pyrrolizidine more stable.



Scheme 21

The first experiment attempted (**Scheme 22**) involved the formation of the Weinreb amide from the boc protected proline **12** [18].

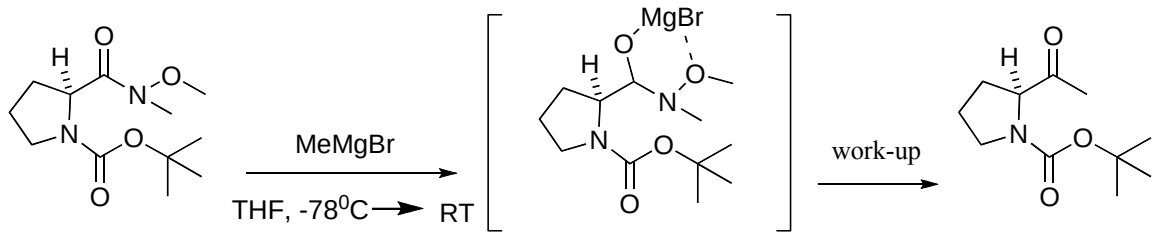


12 **40**

Scheme 22

The purpose of the Weinreb amide was to create a product that would inhibit successive additions of methyl groups during methyl magnesium bromide addition. This overaddition is typically seen with a methyl ester leaving group as opposed to the stable Weinreb amide **40**. This stable product allows only one methyl group to add to the carbonyl group without forming a tertiary alcohol. The Weinreb amide was produced in 69% yield and was used without purification.

After the Weinreb amide was attached onto the boc-protected proline, the next step was to form the required methyl ketone via methyl magnesium bromide addition (**Scheme 23**) [19].

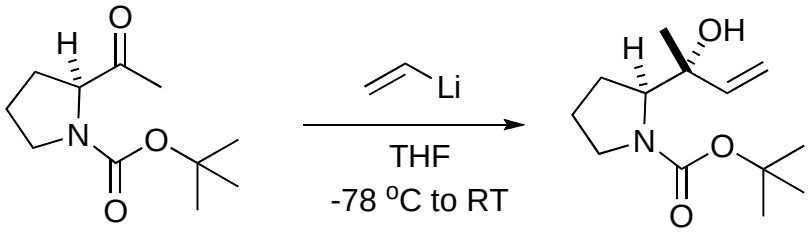


40 **41** **42**

Scheme 23

The methyl group successfully added onto the starting material **40** and to produce methyl ketone **42**. The tetrahedral intermediate **41** formed during this reaction demonstrated the stability associated with the Weinreb amide intermediate. It was extracted with bicarbonate solution to cause the collapse of the intermediate and the formation of the desired methyl ketone **42.** This product was purified by flash chromatography to give a 65% yield.

Following this reaction, vinyl lithium was to be added to the ketone **42** in order to produce a tertiary alcohol **43** (**Scheme 24**) [20].

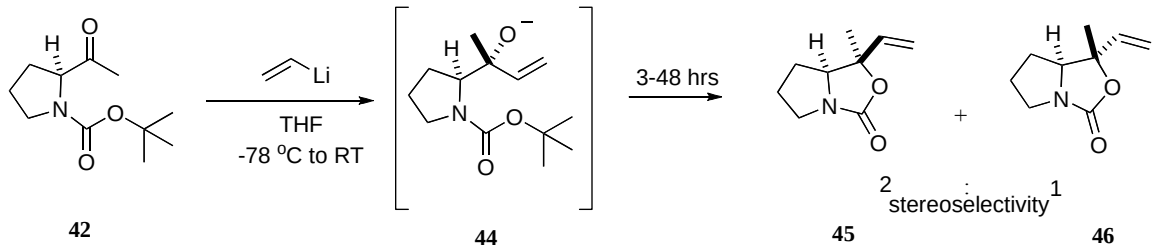


42 **43**

Scheme 24

This reaction proved to be successful and was purified using column chromatography. The stereoselectivity of the alcohol **43** was assumed to be the same as shown in the previous vinyl lithium expriment (**Scheme 5**). The assumption was that the addition follows the Felkin-Anh model where the amine oriented 90° from the carbonyl and the nucleophile attacks from the opposite face (**Scheme 7**) [20].

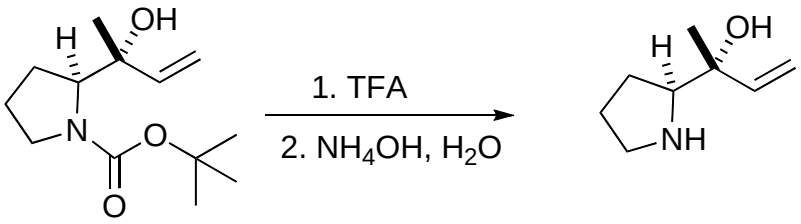
However, when the reaction was repeated, it was found that when the reaction mixture stirred longer than 3 hours, two diastereomers of oxazolidinone **45, 46** were formed from the tertiary alcohol intermediate **44 (Scheme 25)**.



42 **44** **45** **46**

Scheme 25

After the two vinyl lithium reactions, there were two kinds of products that had formed. The first was the protected allylic alcohol **43** and the second was the mixture of oxazolidines **45** and **46**. From this, two routes would be taken in order to get to the desired free amine (**Schemes 26 and 27**).

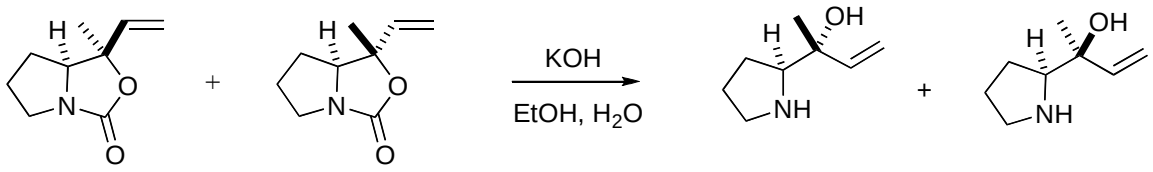


43 **47**

Scheme 26

Allylic alcohol **43** was subjected to deprotection **(Scheme 26).** This reaction was successful and had an 80% crude yield. A 2:1 mix of stereoisomers was not evident until deprotection. A purification attempt was made using silica gel, eluting with 1% triethylamine in methanol to see if our predictions were correct in regards to the stability of the deprotected tertiary alcohol **47** as compared to the secondary alcohol **25 (Scheme 12)**. According to ^{1}H NMR analysis, both the major and minor products were isolated from this procedure, but the overall yield was only 1.5% after purification.

Since there was successful deprotection of the allylic alcohol **43**, the oxazolidinones **45** and **46** were hydrolyzed in order to produce the deprotected allylic alcohols **48** and **49** as well. Following literature procedure [21], the oxazolidines **45** and **46** were treated with potassium hydroxide, ethanol, and water, and stirred at 75°C for seven days **(Scheme 27).**

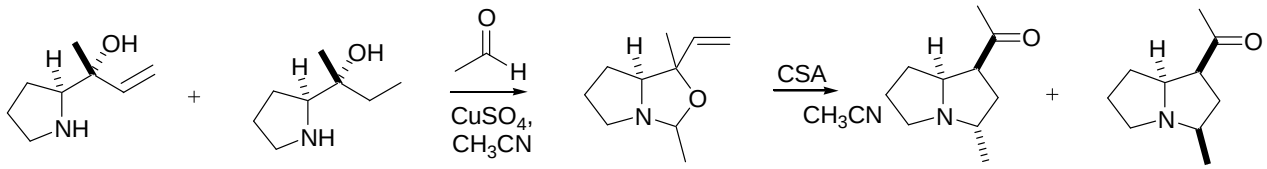


45 **46** **48** **49**

Scheme 27

This reaction was a success, yielding 37% of the allylic alcohol stereoisomers **48** and **49.**

After obtaining amines **48** and **49,** two methods of the aza-Cope rearrangement Mannich cyclization reaction were attempted. The aza-Cope Mannich reaction can be carried out as a one-step or a two-step sequence. In the in the two-step sequence, oxazolidine **50** is formed in the first step (**Scheme 28**). In the second step, oxazolidine **50** can be treated with an acid such as CSA, which should result in the aza-Cope Mannich reaction to produce pyrrolidines **51** and **52** (**Scheme 28**).



48 **49** **50** **51** **52**

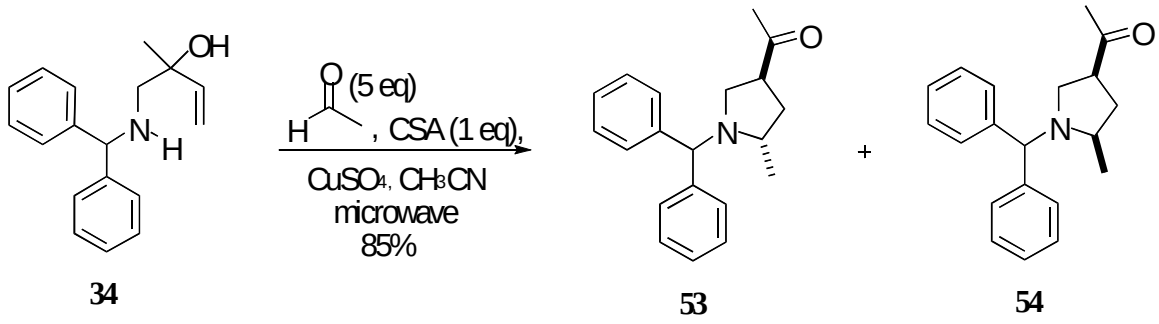
Scheme 28

The microwave conditions for this experiment are summarized on **Table 3**, but the reaction proved to be unsuccessful during both trials.

Table 3:Reaction Conditions For Oxazolidine Formation

Entry #	Purified ?	Reactants	MW Conditions	Results
1	Yes	1 eq Acetaldehyde Acetonitrile	30psi, 16min 90°C, 200W	Complex Mixture
2	No	50eq Acetaldehyde Acetonitrile	Same	Complex Mixture

During the first trial, only one equivalent of acetaldehyde was used. This was believed to be the main source of the problem and thus a second trial was conducted where the equivalents of acetaldehyde were increased to 50. Since neither one of these reactions worked, the single-step method was attempted. In addition to adding the acid, a modification was made to the amount of acetaldehyde that was to be added. Research conducted by others in our lab [22] demonstrated that, in model systems, the aza-Cope Mannich reaction can work with only 5 equivalents of acetaldehyde. This model system uses a diphenyl amino alcohol **34**, which is treated with 5 equivalents of acetaldehyde and CSA, and undergoes aza-Cope Mannich reaction **(Scheme 29)**.

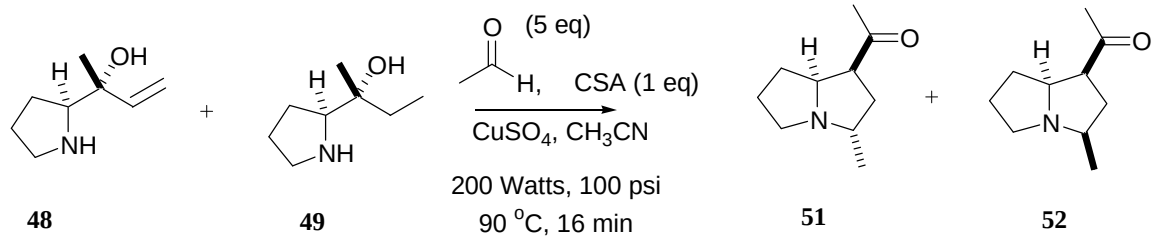


34 **53** **54**

Scheme 29

This reaction showed a 90% conversion to the pyrrolidines **51** and **52** with a mixture of stereoisomers being 4.5:1 favoring the *trans* isomer **51.** The conditions used in this reaction were applied to our own reaction in hopes that we would get the same results.

Once again the deprotected allylic alcohols **48, 49** were exposed to the same reactants, but with the addition of the acid catalyst CSA and microwave conditions listed below (**Scheme 30**). Unfortunately pyrrolizidines **51** and **52** were not formed. Instead, a complex mixture was observed by ^{1}H NMR analysis.



48 **49** **51** **52**

complex mixture - no product isolated

Scheme 30

The first deprotection attempts seemed to have brought us one step closer to the cyclization step. However, multiple problems have occurred in purification of the desired

free amine **25**. Since these direct methods seemed to have failed, methylation of the alcohol, oxazolidine formation, and production of glyoxylic salts were alternative procedures attempted in order to get more stable compounds and create a precursor molecule to make (+)-alexine. However, more recently, the more stable tertiary alcohols **48** or **49** showed promising results for the deprotection step. The aza-Cope-Mannich rearrangement has proven to be difficult and more data will need to be gathered before the synthesis of (+)-alexine becomes a reality.

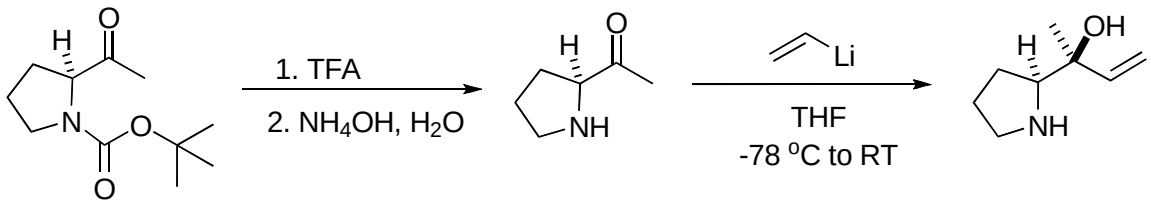
FUTURE RESEARCH PLANS

Producing the deprotected allylic alcohol has been accomplished, but attempting the aza-Cope Mannich cyclization has proven to be difficult. Further modifications will need to be made to the microwave reactions in order to obtain optimum conditions for the cyclization reactions. These include varying the amount of aldehyde, considering different temperatures, power, and pressures for the aza-Cope Mannich reaction and determining whether the sequence should be divided into two steps or performed in a single step.

Since the above modifications can be made directly to improve the cyclization of the deprotected allylic alcohol, other indirect methods are proposed to improve experimentation conducted this far in hopes that these small changes can help greatly when it comes to the cyclization reactions. One possibility is to use column chromatography to separate the oxazolidinone isomers **45, 46** (**Scheme 25**) to determine the most reactive diastereomer in the aza-Cope Mannich reaction.

A second method proposed is using an alternate route for forming the deprotected allylic alcohol **47** where deprotection of the methyl ketone **42** would occur first followed

by the vinyl lithium addition **(Scheme 31)**. This route would prevent the formation of oxazolidinone and thus allow us to synthesize the desired free amine **47** in fewer steps.



42 **55** **47**

Scheme 31

Finally, since there was success with the hydrolysis reaction of the oxazolidinone, this reaction could be subjected to microwave conditions. This reaction had to be stirred for many days at a high temperature, which makes it an ideal candidate for microwave assistance. This would help in making products faster while avoiding the deprotection step with trifluoracetic acid.

If these proposed experiments are conducted, many questions will be answered that could help lead us to the formation of the pyrrolizidine alkaloids.

EXPERIMENTAL

Preparation of vinyl lithium product **(Scheme 5)**: A 25 mL round bottom flask was evacuated with a stir bar inside. While on the vacuum line, 10 mL of THF was transferred into the flask and then a nitrogen line was attached. The flask was then placed into a -78°C bath for 15 minutes. Using a disposable syringe, 0.052 mL (0.281 mmol) of tetravinyl tin was measured into the flask. Using a glass syringe, 0.703mL

(1.124 mmol) of nBuLi was placed into the flask and the reaction stirred for 1 hour at room temperature. Some THF was added into the starting material **14** and then the solution was transferred via cannula into the reaction, which had been cooled to -78°C. This stirred overnight at room temperature. The reaction was then subjected to aqueous extraction using ethyl acetate, dried, and concentrated. Finally, the crude reaction mixture was purified using silica gel column with 20:80 ethyl acetate: hexanes. An ^{1}H NMR was run on the product, indicating that the carbonyl addition **15** was a success.

Preventing the decomposition of the deprotected material **25**. This procedure was an effort to prevent decomposition. The material produced from the deprotection experiment (**Scheme 12**) was first evacuated for five minutes and then it was back filled with nitrogen, an inert gas. The septum was then tightly sealed and placed in a -80 ^{o}C freezer. The ^{1}H NMR of this sample showed no decomposition or any other side reactions to have been occurring whether the sample stayed in the freezer for the 2 hours or 2 weeks. The amino alcohol was only taken out of the freezer when it was ready to be used in a future experiment.

Methylation of boc-protected starting material. First, 27.3 mg (0.1201 mmol) of boc-protected starting material **15** was placed into a 50 mL round bottom flask along with a stir bar. It was tightly sealed and evacuated, and then back-filled with nitrogen. Next, 2.5 mL of THF was transferred to the flask and chilled at 0°C. Then 0.15 ml (0.2402 mmol) of tert-butyllithium was added in and the reaction was stirred for 5 minutes. Finally, 0.23 mL (3.603 mmol) of methyl iodide was added and the ice bath was removed. This stirred for 1 day. The reaction mixture was then extracted with bicarbonate solution using ethyl ether, dried over magnesium sulfate, and concentrated. A ^{1}H NMR

was obtained. The results showed the methylation had occurred and that there were two diastereomers present in the mixture.

Methyl magnesium bromide addition **(Scheme 23).** 7.841 g (30.4 mmol) of starting material **40** was placed into a round bottom flask with a stir bar. The flask was then evacuated and back-filled with nitrogen. Next, 100ml of THF was canulated into the flask, and the solution was cooled to -78^{O}C. This stirred for 10 minutes. Next, 66 mL (91.06 mmol) of methyl magnesium bromide was added into the mixture and the reaction stirred for 24 hours at room temperature. The reaction mixture was then extracted with sodium bicarbonate solution using ethyl acetate, dried over magnesium sulfate, and concentrated to give methyl ketone **42**.

Vinyl Lithium Addition to Methyl Ketone **(Scheme 24).** THF (15 mL) was distilled and placed into a 100mL round bottom flask that had been evacuated and back-filled with nitrogen. 0.40 mL of tetravinyltin (2.20 mmol) was then added. This was cooled to -78^{O}C and 6.1 mL (9.68 mmol) of n-butyl lithium was added and was stirred for 5 minutes. The acetone bath was then removed and the mixture stirred for 1 hour at room temperature. In another round bottom flask, 0.938 g (4.40 mmol) of starting material **42** was dissolved in 15 mL of THF. The solution was then cooled to -78°C and the vinyl lithium mixture was canulated in for the carbonyl addition. This was stirred for exactly 24 hours at room temperature. (note: When this reaction stirred for 48-72 hours, oxazolidinones **45**, **46** were formed, resulting in the loss of the boc group.) The reaction was then quenched with sodium bicarbonate and then extracted three times with ethyl acetate. The product **43** was dried over magnesium sulfate and concentrated.

Deprotection of the tertiary alcohol **(Scheme 26).** Tertiary alcohol **43** (0.494 g, 2.31 mmol) was dissolved in 2.2 mL TFA and stirred under nitrogen for 1 hour. The TFA was then evaporated under reduced pressure. Four drops of water were added into the material. Using pH paper, ammonium hydroxide was added dropwise until pH paper indicated that the solution was neutral. The solution was then extracted three times with dichloromethane, dried over magnesium sulfate, and concentrated to give free amine **47**.

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