2005

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SYNTHESIS OF PYRROLIDINES AND PYRROLIZIDINES USING THE AZA-COPE REARRANGEMENT MANNICH CYCLIZATION UNDER MICROWAVE CONDITIONS

By

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A Senior Thesis Submitted to the

Eastern Michigan University

Honors Program

in Partial Fulfillment of the Requirements for Graduation

with Honors in Chemistry

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Honors Director (Dr. Heather Holmes)

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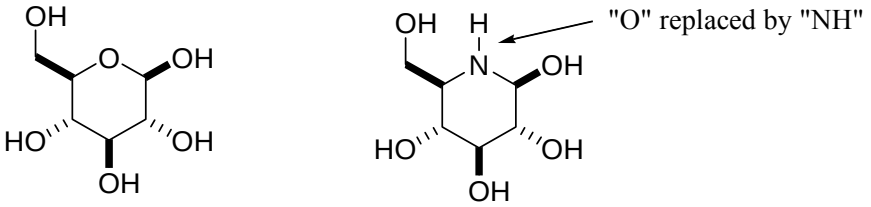
INTRODUCTION

Sugar mimics are molecules that are structurally similar to sugars and thus exhibit many of the same chemical behaviors **(Figure 1)** [1]. In humans, carbohydrates from the diet are metabolized by glycosidases. Once broken down into monosaccharides, they can be taken up through the intestinal wall. Since the sugar mimics are structurally similar to the natural sugar substrates of glycosidases, they can actively bind to the active site of glycosidases. They can therefore directly or indirectly inhibit these glycosidases by reducing the activity of that enzyme by not allowing it to metabolize sugars. Inhibition of glycosidases that break down polysaccharides in the intestine could allow for regulation of carbohydrate absorption. This could be very useful for diabetics in controlling rising blood glucose levels after a meal. At the same time, the sugar mimics themselves are not metabolized. Therefore, the inhibitive behavior of sugar mimics can be potentially very useful for the treatment of diseases like diabetes [1].



glucose
(a sugar)

1

nojirimycin
(a sugar mimic)

2

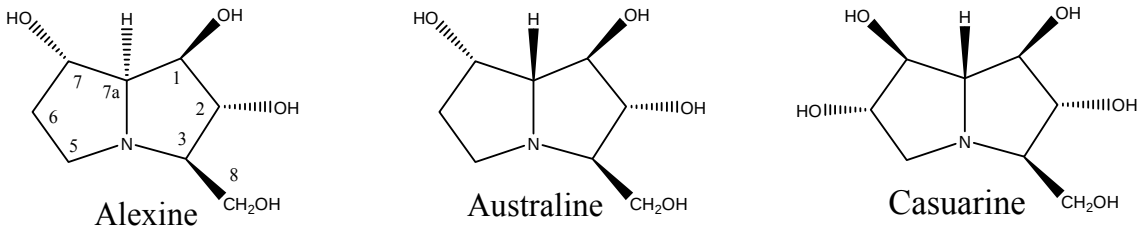
Figure 1

Glycosidases also are involved in post-translational processing of glycoproteins. These glycoproteins have significant biological impacts because they allow for specifity in cell-cell adhesion, differentiation, recognition, regulation, alteration of protein receptors, among other activities [1]. If the sugar mimic molecules can inhibit

glycosidase activity, they can have a profound effect on the cell by altering such areas as synthesis, transport, and secretion. This can have an effect on the metastasis of tumor cells which use carbohydrate residues on the cell surface to spread [1].

The two structural classes of naturally occurring sugar mimics which we are synthesizing are pyrrolidines and pyrrolizidines. Naturally occurring pyrrolidine sugar mimics have been isolated from various plant and microorganism sources, such as in the leaves of the legume *Derris elliptica,* the seeds of *Angylocalyx pynaertii,* the fruits of *Angylocalyx boutiqueanus,* as well as the leaves and roots of *Morus* spp, the leaves of the bluebell *Hyacinthoides non-scripta,* and the bulbs of the hyacinths *Hyacinthus orientalis and Scilla campanulata*. A pyrrolidine which has strong α-glucosidase inhibition in yeasts was isolated from the culture broth of the *Nectria ludica* fungus [1].

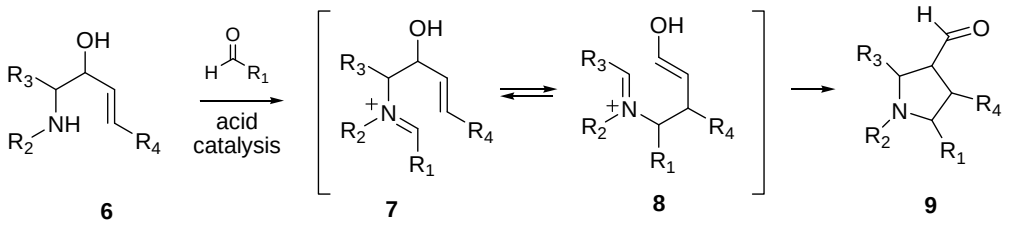
Pyrrolizidines are molecules with two five-membered rings joined by a common nitrogen. Pyrrolizidines with a methylene hydroxy substitution occurring at C-3 have been isolated and shown to act as sugar mimics[1]. Alexine **3 (Figure 2)** was isolated from the legume *Alexa leiopetala* [2]. Another naturally-occurring pyrrolizidine sugar mimic compound is australine **4 (Figure 2)** which was isolated from the seeds of a plant called *Castanospernum australe* [3]. Casuarine **5 (Figure 2)** is a naturally occurring sugar mimic pyrrolizidine molecule that exists in the bark of *Casuarina equisetifolia* which is used in a treatment of breast cancer in Western Samoa [4]. Many pyrrolizidine sugar mimic molecules have already been in use as natural remedies against various ailments [1]. Pyrrolizidine sugar mimic molecules have also been isolated from the leaves of the Indian tree *Eugenia jambolana* whose leaves, fruits, and seeds are used in the treatment of diabetes and bacterial infections.



3 **4** **5**

Figure 2

We are synthesizing certain pyrrolizidine alkaloid sugar mimics [1] such as alexine **3 (Figure 2)** using the aza-Cope rearrangement Mannich (ACM) cyclization reaction, which is a tandem reaction sequence that synthesizes five-membered nitrogen heterocycles such as pyrrolidines. This reaction occurs through a 3,3-sigmatropic rearrangement **(7→8**, **Scheme 1)** which is then followed by a Mannich cyclization (**8→9**, **Scheme 1**) [5]. This reaction is very efficient in the synthesis of pyrrolidines because it can break and form several bonds in a single step.



6 **7** **8** **9**

Scheme 1

The stereochemistry involved in the reaction is also easily controlled. The iminium cation geometry controls diastereoselectivity as can be seen in **Figure 3.** If the R group attached to the nitrogen is small, there is more steric strain between the methyl group and the H group on the other side of the nitrogen if the methyl is axial than between the R group and the methyl if the methyl is in its equatorial position. Thus if the R group is small, the cis conformation is favored. However, if the R group is large, there is more steric strain between the methyl and the R group if the methyl is equatorial than if

the methyl is in its axial conformation. Therefore, the trans conformation is favored when the R group is large. This predictable stereocontrol makes the ACM very useful in synthetic chemistry.

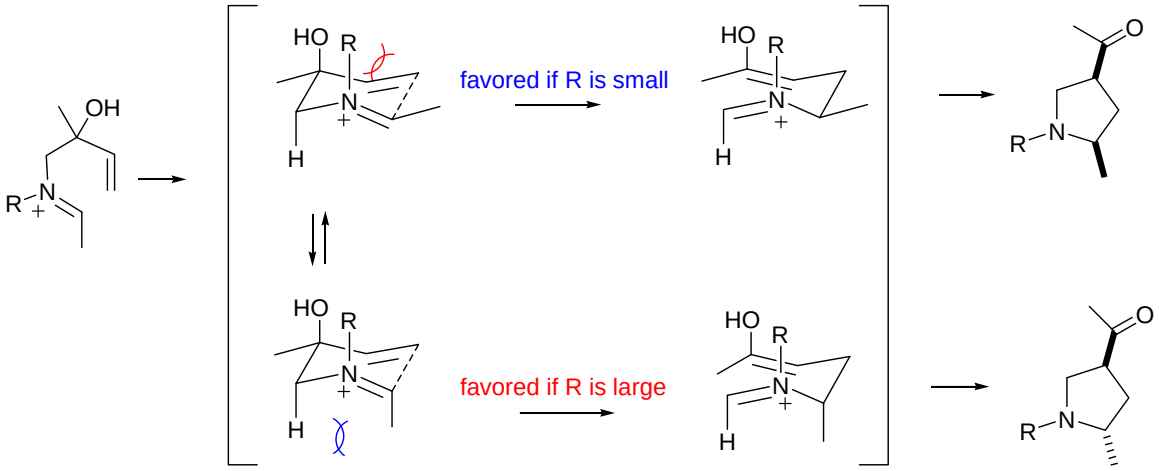


Figure 3

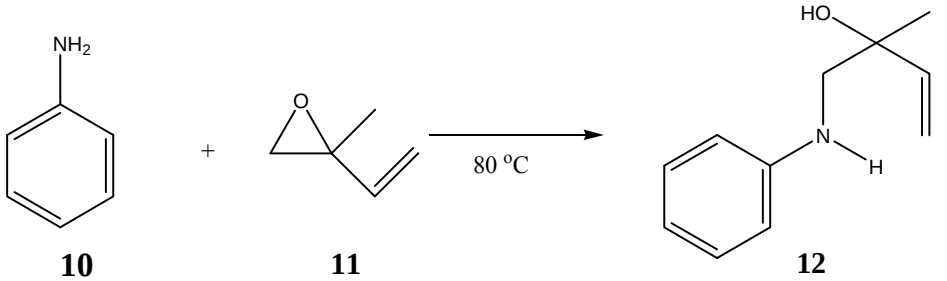
However, a significant drawback of this reaction is the reaction times of up to several days that are often required [5]. With the goal of reducing reaction times, we have attempted to synthesize a number of pyrrolidines and pyrrolizidines using the aza-Cope rearrangement Mannich cyclization reaction with the aid of a microwave reaction oven. This project is the first to use the microwave with this reaction. The goal of using the microwave is to reduce the length of the reaction time of the aza-Cope rearrangement Mannich cyclization reaction. A reduction in reaction times would make this reaction far more useful for other synthetic organic applications. It is known that running a reaction in a microwave significantly reduced reaction times, oftentimes from days to minutes [6].

There are successful examples of a microwave being used to speed up iminium cation condensation reactions [7]. From this we know that the first step in our tandem sequence (**6**→**7**, **Scheme 1**), can be successfully performed in the microwave. There are no sources of literature, however, that give an example of a microwave-assisted aza-

Cope—Mannich reaction. We therefore decided to apply the microwave aza-Cope Mannich-cyclization to the synthesis of pyrrolizidine alkaloids such as alexine **3**.

PLAN

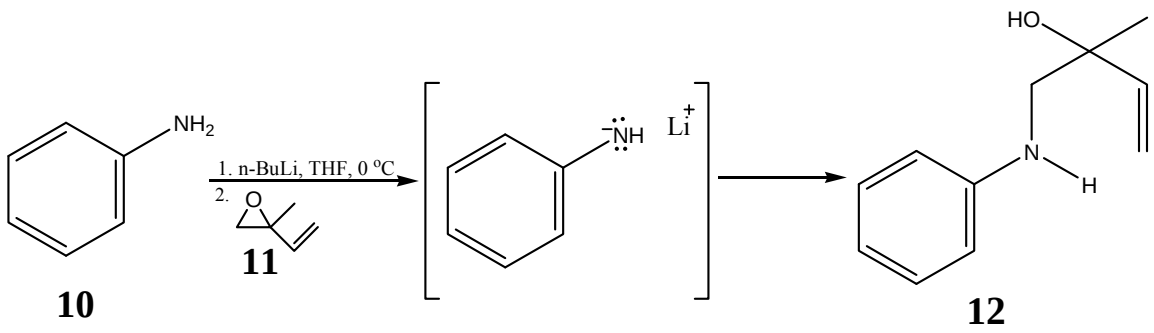
The first step in testing out the aza-Cope rearrangement Mannich cyclization reaction under microwave conditions was to choose materials and conditions that had already been proven to work under standard conditions. Our goal was the synthesis of several amino alcohols such as **12 (Scheme 2)** to use as precursors for the aza-Cope rearrangement Mannich cyclization reaction [8, 9]. The first attempt for the synthesis was the ring-opening reaction of 2-methyl-2-vinyloxirane **11** with aniline **10 (Scheme 2)**. However, the aniline was not a good enough nucleophile due to the delocalization of charge throughout its benzene ring.



10 **11** **12**

Scheme 2

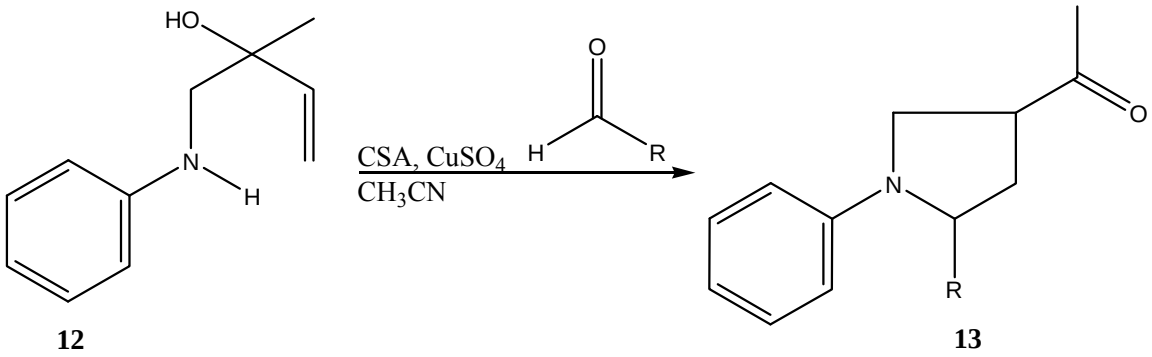
The reaction of aniline and 2-methyl-2-vinyloxirane **11** was again performed. However, n-butyl lithium (nBuLi) was added to the reaction in order to deprotonate the aniline to make it a better nucleophile **(Scheme 3)**.



Scheme 3

The reaction showed a 37.9% yield for production of amino alcohol **12**. The structure of the product was confirmed by a ^{1}H NMR analysis. The same reaction was performed again to create more product with which to use as starting material for the aza-Cope rearrangement Mannich cyclization reaction. This replication of the reaction gave a 69.5% yield and the structure of the product was confirmed by means of a ^{1}H NMR analysis which also showed a small amount of the minor regioisomer. Flash chromatography yielded two isomers as determined by ^{1}H NMR analysis.

The next step was to use the 2-methyl-1-(phenylamino)-3-buten-2-ol **12** from the S_N2 ring opening reaction as the starting material for the microwave-assisted aza-Cope rearrangement Mannich cyclization reaction. We hoped that the amino alcohol **12** would react with an aldehyde under acidic conditions to produce the pyrrolidine **13 (Scheme 4)**. A very similar reaction that used formaldehyde instead of acetaldehyde had previously worked using conventional heating, although the reaction time was 1.5 hours at 110°C with a 66% yield [8]. The goal was to test this reaction under microwave conditions to determine its effectiveness for increasing the rate of reaction.

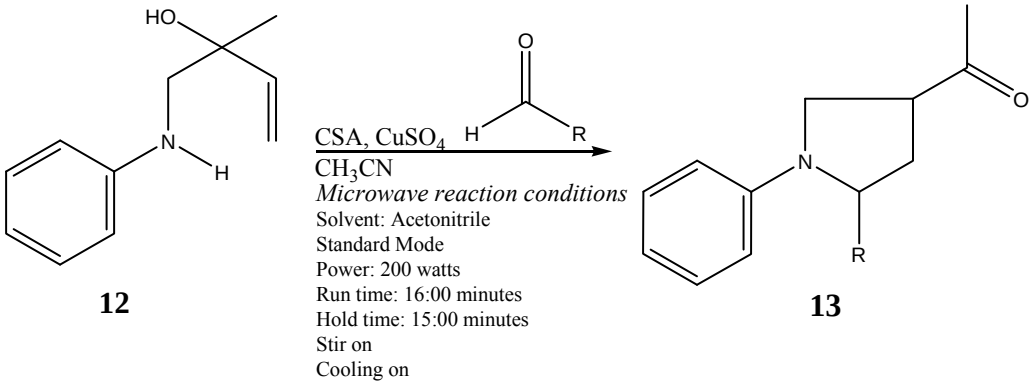


12 **13**

Scheme 4

After the reactants were combined in run 1, the reaction was placed in a microwave; however, the microwave did not run its full length time of a half an hour; however, it was undetermined when exactly the reaction had stopped. A proton NMR revealed no product. The experiment was therefore adjusted to test different variables in the reaction to determine where the product was lost. A ^{1}H NMR of the starting material was run to determine whether or not it had decomposed; it was revealed to be intact. The reaction parameters and results are found in Table I.

Table I



12 **13**

Entry (page #)	Eq. Aldehyde	Eq. CSA	Microwave conditions
1 (39)	102 acetaldehyde	2	100 psi, 85˚C

Result: HNMR revealed no peaks for product. Only solvent peaks present. Microwave aborted the reaction at an unknown time before its set completion time so unsure how far the reaction was allowed to progress. Product may be water soluble and lost in workup.

2 (47)	107 acetaldehyde	2.1	100 psi, 85˚C

Result: HNMR revealed no product or starting material. Peaks present were from solvent.

3 (53)	no aldehyde used	4.2	100 psi, 85˚C

Result: HNMR revealed that the peaks for this reaction were different from that of the starting material, indicating that the starting material decomposes under reaction conditions.

4 (61)	no aldehyde used	no CSA used	no microwave reaction

Result: The starting material was tested to determine if it was water soluble and lost in the workup. HNMR revealed that the starting material was intact. Extra peaks were due to solvents.

5 (65)	no aldehyde used	.44	100 psi, 85˚C

Result: Realized that calculations for CSA equivalency were incorrect and conditions may have been too acidic. CSA was adjusted from 2 to 0.5 equivalents. The HNMR spectrum however only revealed a large acetone peak; no peaks were present for the starting material.

6 (129)	10 propionaldehyde	2.3	150 psi, 90˚C

Result: ^{1}H NMR was overpowered with aldol side product. Benzyl peaks could not be visibly seen and there appeared to be some starting material left but neither could not be seen due to the large aldol peaks.

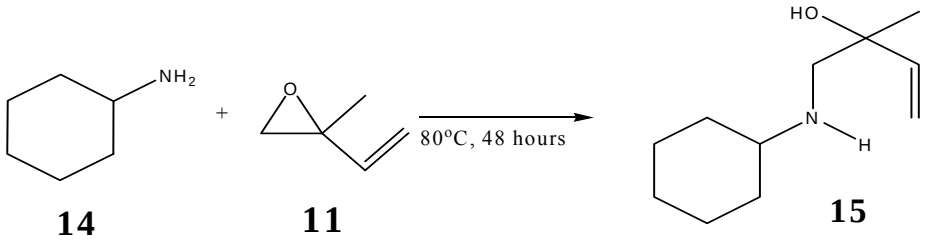
7 (135)	10 propionaldehyde	2.3	150 psi, 90˚C

Result: Flash chromatography was used to separate the complex mixture into three fractions. ^{1}H NMR revealed complex structures including a possible continuing aldol side reaction. No product was revealed.

8 (143)	1 acetaldehyde	2.3	150 psi, 90˚C

Result: ^{1}H NMR revealed no aldol side products. Product unknown.

We then decided to try a different amino alcohol for our studies of the aza-Cope rearrangement Mannich cyclization reaction. We synthesized amino alcohol **15 (Scheme 5)** by the ring-opening reaction of 2-methyl-2-vinyloxirane **11** using cyclohexylamine **14** with heating **(Scheme 5)**.



14 **11** **15**

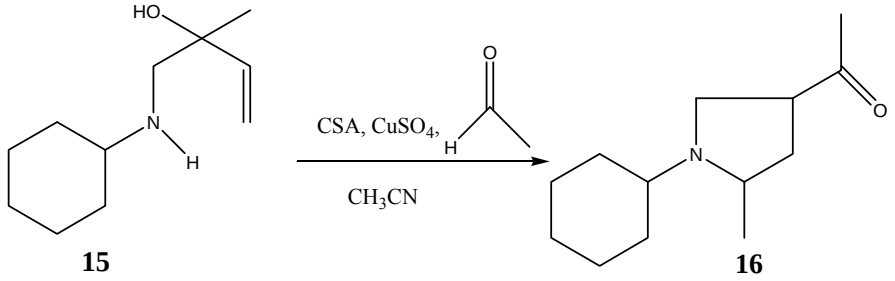
Scheme 5

The cyclohexylamine starting material was distilled using a short column distillation apparatus. However, after reaction and distillation of excess starting material using Kugelrohr distillation, only 4.24 % yield of product was recovered. It is possible that the epoxide could have evaporated during the reaction so that full reaction did not occur.

The reaction of cyclohexylamine and 2-methyl-2-vinyloxirane was again performed beginning with distillation of cyclohexylamine. After the reaction stirred at 80˚C for five days, the excess cyclohexylamine was again removed using Kugelrohr distillation. The product was confirmed by ^{1}H NMR and resulted in 59.3% yield. The product was purified via flash chromatography.

Amino alcohol **15** was used as starting material for the aza-Cope rearrangement Mannich cyclization reaction. 100 equivalents of acetaldehyde were used as the aldehyde source for the starting material to react with under acidic conditions to produce

pyrrolidine **16 (Scheme 6).** It should be noted that under conventional heating the reaction time was 24 hours at 80°C with a 95% yield [8].

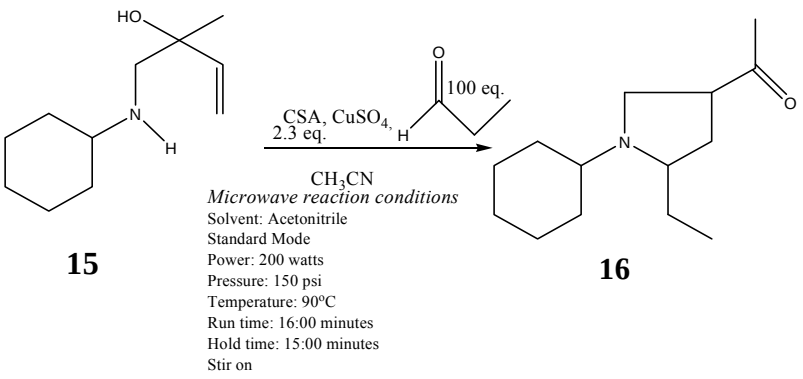


15 **16**

Scheme 6

After the reactants were combined, the reaction was placed in a microwave under the reaction conditions stated in Table I with the exception of the pressure and cooling. The pressure was set at 30 psi and the cooling was turned off. A ^{1}H NMR analysis revealed only starting material. The reaction was then repeated several times, substituting propionaldehyde for acetaldehyde and varying microwave reaction conditions **(Table II)**.

Table II



Entry (page #)	Microwave Cooling	Workup
1 (97)	Off	Ethyl Acetate

Results: The peaks in the proton NMR spectrum were not caused by the desired product.

2 (103)	On	Dichloromethane

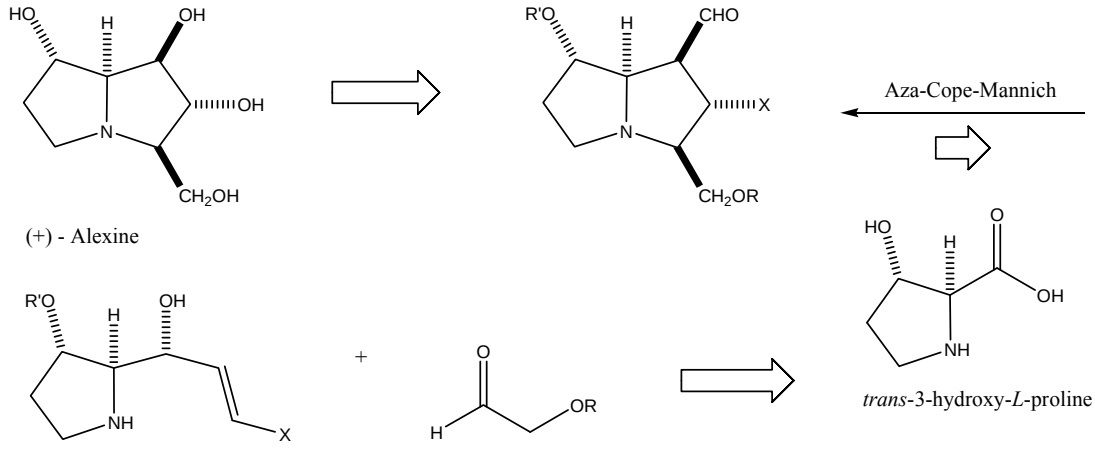
Results: Proton NMR revealed no starting material. Product underwent purification via flash chromatography. Only a single isomer was seen through proton NMR spectra. ^{13}C NMR revealed doubling of peaks, revealing product consists of a mixture of isomers.

3 (113)	On	Dichloromethane

Results: Product was purified using flash chromatography. Fractions 4-8 contained aldol byproduct. Proton NMR spectra of fractions 12-14, 15-18, and 19-24 did not reveal different isomers. However, reproducibility of reaction to obtain product was verified.

With the knowledge of the success of the microwave oven in shortening reaction times, we decided to apply the microwave aza-Cope rearrangement Mannich cyclization reaction conditions to a more complex system of starting materials that had not already been proven by previous experimentation to work under standard or microwave aza-Cope rearrangement Mannich cyclization reaction conditions. This more complex system would enable us to synthesize sugar mimic structures as seen through the retrosynthetic analysis of alexine **3 (Scheme 7)** which shows that alexine can be synthesized from a pyrrolidine amino acid, proline, which has a trans hydroxyl substituent. The

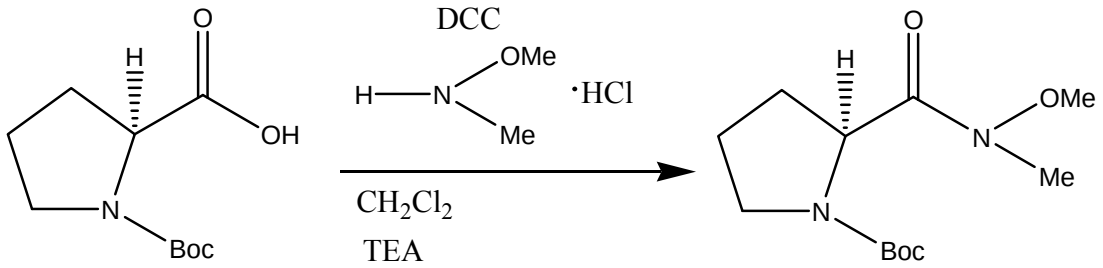
retrosynthetic analysis **(Scheme 7)** also illustrates that stereocenters can be installed at three places in one of the pyrrolidine rings of alexine through the tandem aza-Cope-Mannich reaction.



Scheme 7

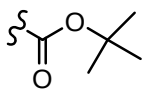
For the purposes of testing the aza-Cope-Mannich reaction in this system, we began our synthesis using N-Boc proline **17** rather than trans-3-hydroxyl proline as the starting material for the formation of Weinreb amide **18 (Scheme 8)**. N-Boc proline **17** is formed from L-Proline, one of the naturally occurring common amino acids, which then has a t-butyl-carbamate (Boc) group which acts as a protecting group for the nitrogen. N-Boc proline is additionally attractive as an initial starting material due to its affordability.

The Weinreb amide **18** was isolated by dissolving the reaction mixture in acetone and filtering out the solid precipitate, keeping only the filtrate. The filtrate was concentrated using a rotary evaporator and a ^{1}H NMR spectrum was taken.



N-Boc proline
17

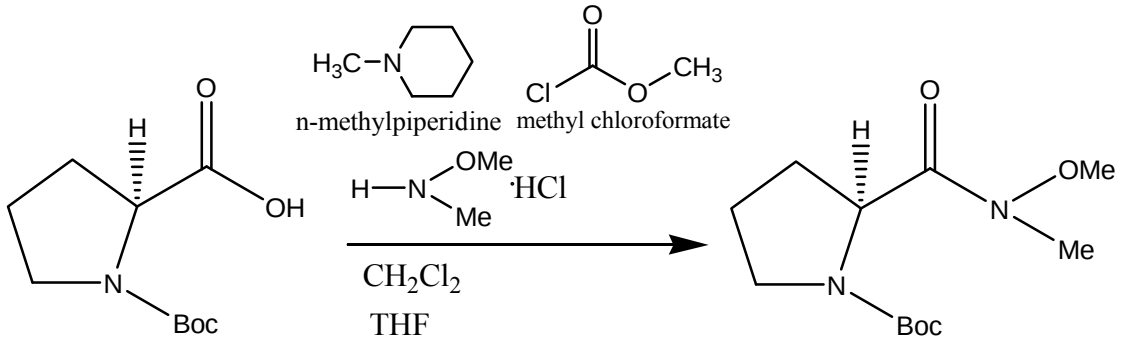
Weinreb amide
18



Boc

Scheme 8

A disadvantage of the previous procedure for preparing the Weinreb amide **(Scheme 8)** is DCC byproducts which create impurities in the product so that it must be purified, thus elongating the synthesis. To avoid DCC bydproducts, we chose another method of Weinreb amide synthesis [10] that uses N-methyl piperidine and methyl chloroformate as reagents **(Scheme 9).**



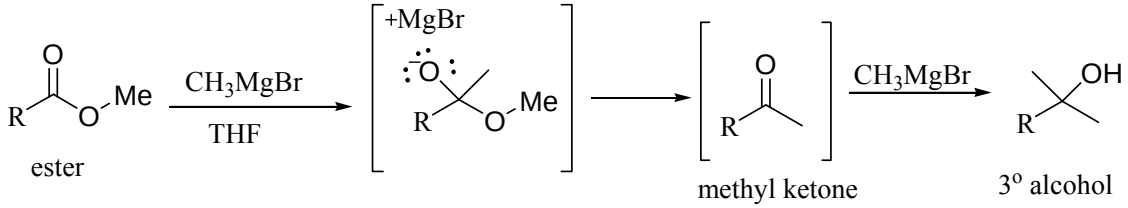
N-Boc proline
17

Weinreb amide
18

Scheme 9

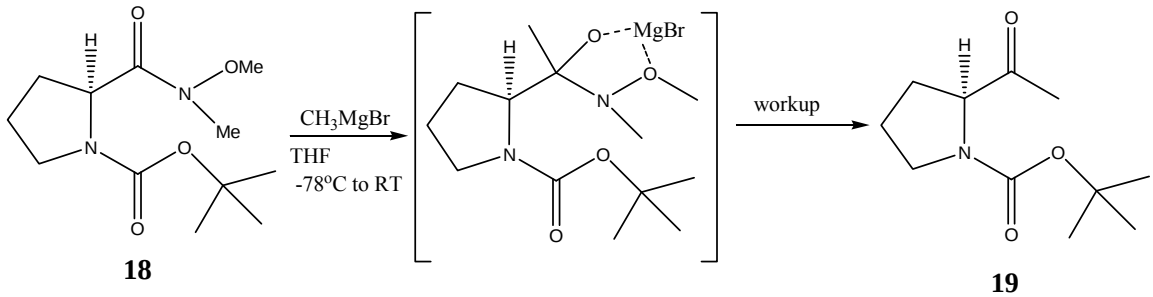
We chose to synthesize the Weinreb amide **18** instead of directly adding the Grignard reagent to N-Boc proline **17** or an ester of **17** because direct addition of a Grignard reagent to a carboxylic acid, like that found on N-Boc proline **17,** results in no

reaction. On the other hand, addition to an ester would result in overaddition to give a tertiary alcohol **(Scheme 10)** because the intermediate methyl ketone that is formed is more reactive than the ester starting material.



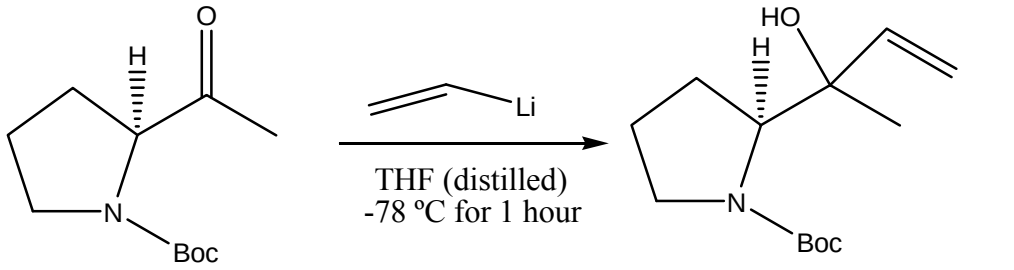
Scheme 10

However, this problem of overaddition is overcome with the formation of the Weinreb amide **18 (Schemes 8 and 9)** because the N-methoxy oxygen and the newly formed alkoxide are stabilized by the positively charged magnesium bromide of the Grignard reagent, making a less reactive intermediate and preventing overaddition. When quenched with water, the MgBr-stabilized intermediate forms the methyl ketone **19 (Scheme 11).** The addition of methyl MgBr to the Weinreb amide **18** was the next step performed **(Scheme 11)**. We used 6 equivalents of Grignard reagent in this reaction, which is excessive; however, we wanted to insure that there was enough Grignard to run the reaction to completion. Optimization of Grignard equivalents would make this step of the synthesis more cost-effective.



Scheme 11

The next step in the reaction sequence was a vinyl lithium addition to the methyl ketone **19** which yielded a ca. 2:1 mix of stereoisomers **20 (Scheme 12)**.

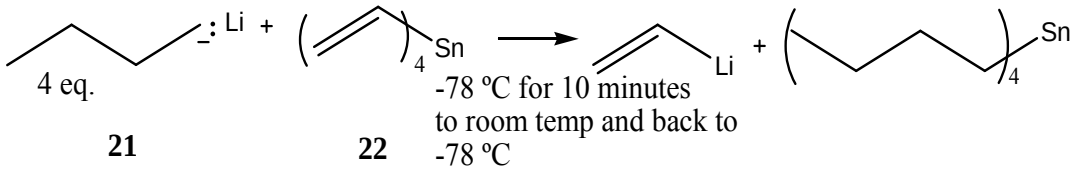


19

ca. 2:1 mix of stereoisomers
20

Scheme 12

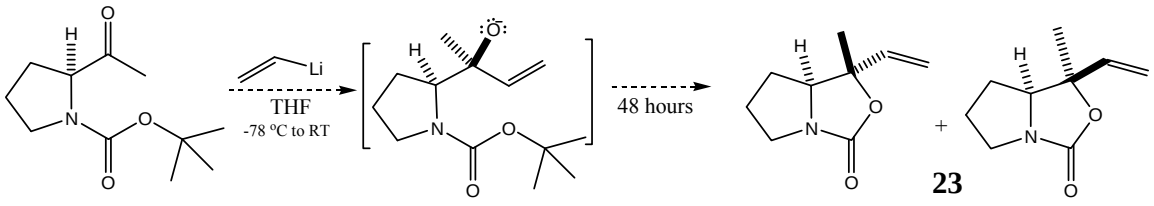
The vinyl lithium was formed from n-butyl lithium (in hexanes) **21** and tetravinyl tin **22 (Scheme 13)**.



21 **22**

Scheme 13

Oxazolidinone formation can occur during the vinyl lithium addition to the methyl ketone **19** if the oxygen from the ketone does not get fully protonated, making that oxygen very reactive. Cyclization to oxazolidinone **23** could readily occur **(Scheme 14)**.



19

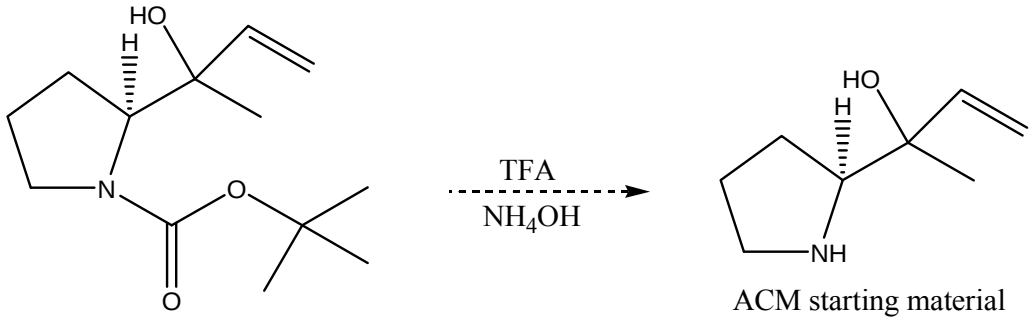
23

2 : 1
stereoselectivity

Scheme 14

The final step in the formation of the ACM starting material **24** was a Boc-

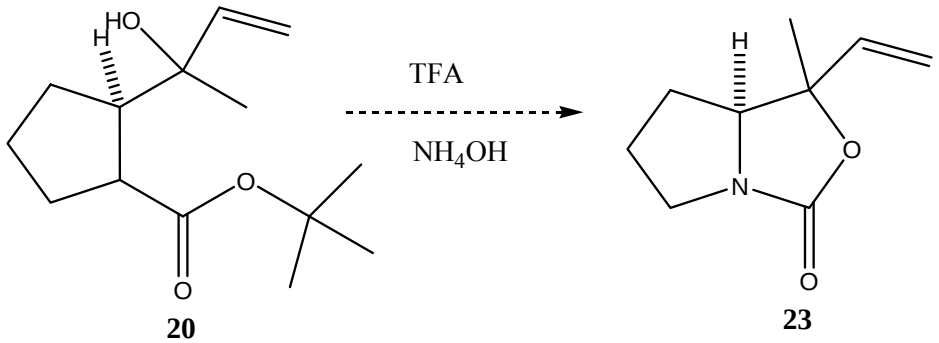
deprotection of the tertiary amino alcohol **20** formed by vinyl addition to methyl ketone **19 (Scheme 15)**.



20 ACM starting material **24**

Scheme 15

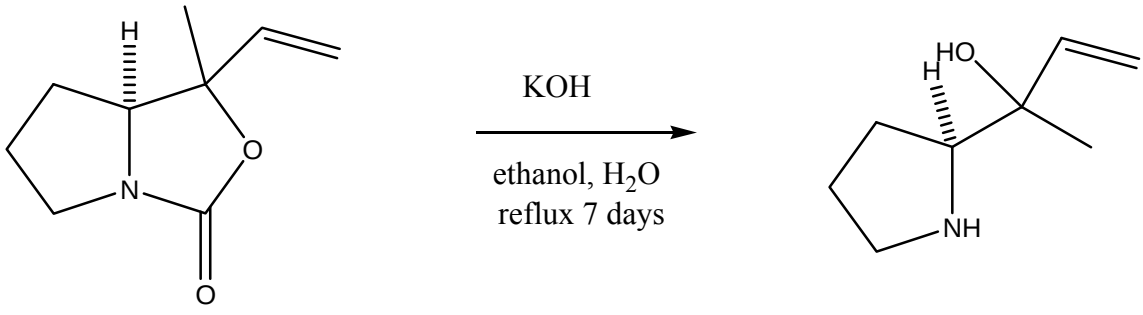
During the first attempt at this final step to the ACM precursor **24**, the deprotected product was contaminated while distilling off excess trifluoroacetic acid (TFA) **(Scheme 15)**. The desired product could not be purified. Upon analysis by ^{1}HNMR it was discovered that when the deprotection was again attempted, the formation of oxazolidinone **23 (Scheme 16)** and not the desired product had occurred. Thus oxazolidinone formation could occur under acidic or basic conditions.



20 **23**

Scheme 16

To recover the desired amino alcohol **24** we used a potassium hydroxide solution to hydrolyze oxazolidinone **23 (Scheme 17)**. The hydrolysis resulted in a 2:1 mixture of stereoisomers.



23 **24**

Scheme 17

The ACM precursor however had a high rate of decomposition and decomposed before any microwave reaction of the aza-Cope cyclization-Mannich rearrangement reaction could be performed. Deprotection earlier in the synthesis sequence may be a solution to avoiding oxazolidinone compound formation. However, one advantage of the oxazolidinone route is that the stereoisomers can be separated before being subjected to the aza-Cope cyclization-Mannich rearrangement.

EXPERIMENTAL

2-Methyl-1-(phenylamino)-3-buten-2-ol (12) A solution of aniline (0.74 g, 8.0 mmol) and dry THF (10 mL) was treated with n-BuLi (8.0 mmol, 5.0 mL of a 1.6 M in hexane) at 0°C. 2-methyl-2vinyloxirane (4.0 mmol, .40 mL) was added at 0°C and the resulting solution was left at 0°C for an hour. The residue was partitioned between hexane-ethyl acetate (19:1, 15 mL) and brine (30 mL), the aqueous layer was extracted with hexane-ethyl acetate (19:1, 4 x 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. Excess aniline was removed by Kugelrohr distillation (66-70°C). The material was purified by flash chromatography (silica gel, 4:1 hexane-ethyl acetate). A separation of two products was obtained over a range of 70 fractions. The fractions were concentrated using a rotary evaporator. Proton NMR spectra revealed isomers and determined that the desired product, 2-methyl-1-(phenylamino)-3-buten-2-ol **12**, had been eluted within the first 50 fractions.

(**15)** 2-methyl-2vinyloxirane (17 mmol, 1.70 mL) was added to a solution of freshly distilled cyclohexylamine (70 mmol, 8.0 mL), and was stirred at 80 °C for five days. Excess cyclohexylamine was removed using Kugelrohr distillation. The material was purified by flash chromatography (silica gel, 4:1 methanol-methylene chloride). A separation of two products was obtained over a range of 12 fractions. The fractions were concentrated using a rotary evaporator. Proton NMR spectra revealed the desired product, **15**, had been eluted within the 12 fractions.

Weinreb amide old method (18) A solution of CH_2Cl_2 (25 mL), N-Boc proline (0.9930g, 4.61mmol), N,O-dimethylhydroxylamine HCl (0.6972 g, 7.15 mmol), and DCC (0.8827g, 6.99 mmol) was made. Triethylamine (2.59 mL) was added to the

solution. It stirred for 24 hours under an N_2 atmosphere and then concentrated. Workup consisted of using acetone to dissolve white solid which was then suction filtered and concentrated. Product then dissolved in ethyl acetate (75 mL) and washed with saturated sodium bicarbonate (3 x 75 mL), dried ($MgSO_4$), and concentrated.

Weinreb amide new method (16) A solution of N,O-dimethylhydroxylamine HCl (0.6798 g, 6.97 mmol) and CH_2Cl_2 (5 mL) stirred in an ice bath. After cooling to 0˚C, N-methylpiperidine (0.85 mL, 6.99 mmol) was added to this solution. A solution of N-Boc proline (1.0190 g, 4.73 mmol), CH_2Cl_2 (30 mL), and freshly distilled THF (8 mL) stirred. After cooling to 0˚C in an ice bath, N-methylpiperidine (0.56 mL, 4.64 mmol) and methyl chloroformate (0.35 mL, 4.55 mmol) were added to this solution. The contents of the flask containing the N,O-dimethylhydroxylamine HCl was then transferred to the flask containing the N-Boc proline starting material. Let stir at room temperature for 30 minutes. The residue was cooled using ice and the organic layer was extracted with 0.2 N HCl (2 x 15 mL) and NaOH solution (2 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated.

Methyl ketone (19) Freshly distilled THF (10 mL) was cannulated into the flask containing the starting material Weinreb amide (0.5300 g, 2.05 mmol) and stirred. Flask was cooled to -78 ºC with a dry ice/acetone bath. Methylmagnesium bromide (6.0 mL, 8.4 mmol) was syringed into flask. Removed dry ice/acetone bath and allowed to reach room temperature, and the reaction stirred for 24-48 hours. The reaction mixture was partitioned between ethyl acetate (15 mL) and brine (30 mL), the aqueous layer was extracted with ethyl acetate (3 x 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated.

Tertiary amino alcohol (20) Freshly distilled THF (10 mL) cannulated into flask containing stirbar to which tetravinyltin (0.13 mL) was added. The solution was cooled to -78°C with a dry ice/acetone bath and n-butyllithium (1.84 mL) was added. The reaction stirred five minutes at -78°C then the dry ice/acetone bath was removed. The reaction stirred at room temperature for an hour. Freshly distilled THF (10 mL) was cannulated into flask containing starting material, the methyl ketone **19** (0.2856 g, 1.34 mmol). The flask containing vinyl lithium solution was again cooled to -78°C , and the methyl ketone solution was cannulated in. The reaction warmed to room temperature and stirred for 24 hours. Saturated sodium bicarbonate (30 mL) was added to the solution. Aqueous layer was extracted with ethyl acetate (4 x 30 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The material was purified by flash chromatography (silica gel, 9:1 hexane-ethyl acetate). A separation of products was obtained over a range of 26 fractions. The fractions were concentrated using a rotary evaporator. Proton NMR spectra revealed that the desired product, the tertiary amino alcohol **20**, had been eluted in the seventh through nineteenth fractions.

Deprotected ACM precursor (24) A solution of oxazolidinone (3.1117 g, 18.6 mmol), ethanol (32 mL), H_2O (28 mL), and KOH (22.0152 g, 386 mmol) was stirred at reflux (80°C) for 7 days. Proton NMR revealed the desired tertiary amino alcohol product **24**. The solution was concentrated to remove ethanol, extracted with ethyl acetate, dried ($MgSO_4$) and concentrated.

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