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Synthesis and Application of (R)-3-Methylpyrrolidine-3-Carboylic Acid

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Synthesis and Application of (*R*)-3-Methylpyrrolidine-3-Carboylic Acid

by

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Abstract

L-Proline is an amino acid widely used in pharmaceutical and biotechnological research due to its catalytic activity and biological relevance. L-Proline has been recognized and utilized as an organocatalyst, which allows cleaner, more sustainable reactions. However, one issue with L-proline is its low solubility in organic systems, limiting its reactivity and efficiency, especially when considering industrial research. Two reactions that utilize L-Proline are the Michael and Aldol but require 100 mol% of L-Proline and 30 mol% of L-Proline, respectively. This research will focus on the synthesis of an analogue of L-Proline utilizing inexpensive, commercially available reagents. A variety of organic reactions are used to generate the analogue whose structure is adapted for better solubility. The analogue is known to the Masterson research group and involves a multi-step synthesis, so efforts to improve the current synthetic strategy were made to maximize the efficiency of the production for the analogue. The current method has shown to be the most efficient pathway allowing maximum production at each step. Future goals for the project will include using organic reactions, including Aldol and Michael, to analyze the solubility and reactivity of the analogue and compare with studies performed with L-Proline.

Key Terms: Organic Synthesis, Organocatalyst, L-Proline

Dedication

Mom, Dad, Katherine, Kristina, and Sam:

Thank you for always believing in me, even if I don't, and for listening to presentation after presentation to help me be the best I can be. I can face any challenge knowing you all will always be there in any way you can.

Acknowledgements

This thesis would not be possible without the support and guidance of many people, the most influential and important being my thesis advisor Dr. Douglas Masterson. His understanding demeanor and unwavering confidence in me made all the difference in surviving this project. Even when I made mistakes, Dr. Masterson turned them into learning experiences. Thank you. Thank you for seeing something in the shy student that sat in your class two years ago and giving her a chance.

I would like to thank all the past and present members of the Masterson Research Group. I hope the willingness to help each other and see each other succeed will continue to thrive in the lab. Emily and Hari, thanks for answering the hundreds of questions I had and being patient with me.

I would also like to thank the faculty of the Honors College, especially Paula Mathis. Thank you for responding to every last minute (late night) email and being my saving grace. I have enjoyed our conversations and will miss our advisement sessions.

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List of Abbreviations

Abbreviation	Term	Abbreviation	Term
Bn	Benzyl	MeOH	Methanol
Br	Bromide	$MgSO_4$	Magnesium Sulfate
$CHCl_3$	Chloroform	mL	milliliters
CH_2Cl_2	Dichloromethane	mmol	millimoles
CN	Cyanide	mol	moles
CO_2Et	Ethyl Ester	N_2	Nitrogen Gas
CO_2H	Carboxylic Acid	NaBr	Sodium Bromide
DMF	Dimethylformamide	NaH	Sodium Hydride
DMSO	Dimethyl Sulfoxide	N_2H_4	Hydrazine
Et	Ethyl	Ni	Nichel
Et_2O	Diethyl Ether	NO_2	Nitrite
EtOAc	Ethyl Acetate	Pd	Palladium
g	grams/gas	Ph	Phenyl
H_2	Hydrogen Gas	PLE	Pig Liver Esterase
HCl	Hydrochloric Acid	ppm	parts per million
KBr	Potassium Bromide	rt	room temperature
K_2CO_3	Potassium Carbonate	s	solid
L-Pro	L-Proline	S_n2	Substitution
Me	Methyl	TLC	Thin Layer Chromatography

CHAPTER 1: Introduction

A catalyst decreases the activation energy to allow reactions to occur at faster rates. There are numerous reactions that take days or weeks to go to completion; in the presence of a catalyst, these times can be dramatically reduced. Catalysts can be seen in organisms to aid in biological processes or to increase the efficiency of industrial research. There are a variety of catalysts used in chemistry, such as organocatalysts, organometallic catalysts, and enzyme catalysts. However, there are benefits to using specific catalysts for certain reactions.

Organocatalysts have contributed to advancements in sustainable chemistry. The availability of organocatalysts from natural molecules or variations of natural molecules is a major benefit, allowing the production of organocatalysts to be relatively inexpensive. Since the catalysts are chiral, there are different enantiomers of the catalysts that can exist. Enantiomers are chiral molecules with the same molecular composition and are mirror images of each other; however, enantiomers cannot be overlapped perfectly, or are not superimposable. Peoples' feet and hands are examples of chiral objects. Despite being mirror images, a person's hands cannot be overlapped where the thumbs perfectly align facing the same direction.

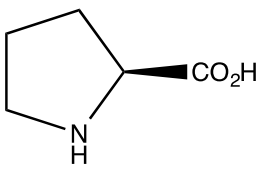
Enzyme catalysts do not readily make both enantiomers. This is desirable because the production of both enantiomers in equal yield, a racemic mixture, is not very useful if one enantiomer cannot be extracted from the other. Also, the amount of product yielded is reduced because starting material is being used to create the second enantiomer. However, the possible applications for enzyme catalysts are lowered because both enantiomers are not simultaneously available. Unlike organometallic catalysis, the

absence of transition metals in organocatalysts prevents the production of hazardous heavy metal waste and allows "cleaner" synthetic reactions.

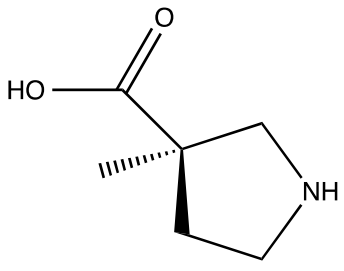
The "cleaner" reactions reduce the amount of heavy metal pollution that can result from using organometallic catalysts. This is very beneficial for pharmaceutical companies because the amount of heavy metals in medications is also reduced. The availability of both enantiomers is very helpful in producing different drugs. Each enantiomer could have different biological properties, which allows a drug to have multiple uses depending on the enantiomer.

One organocatalyst that is widely used in pharmaceutical research is L-Proline. L-Proline can be found in cartilage and helps the preservation of heart muscles. It is used in a variety of chemical reactions, especially the Aldol, Mannich, and Michael reactions because L-Proline is capable of allowing the production of one enantiomer over the other in these reactions, which is known as stereoselectivity. The stereoselectivity of L-Proline makes it a popular catalyst. However, L-Proline is not very soluble in organic solvents. Due to the low solubility, large amounts of the catalyst are then needed for the reactions, which is inefficient. One solution to this problem is to generate analogues of L-Proline that have better solubility.

Figure 1a: Comparison of L-Proline and Analogue



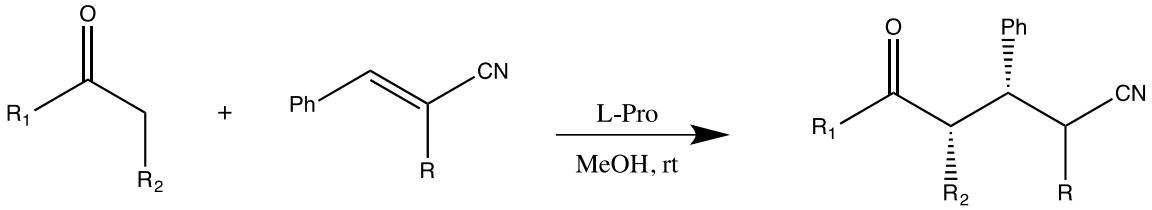
L-Proline



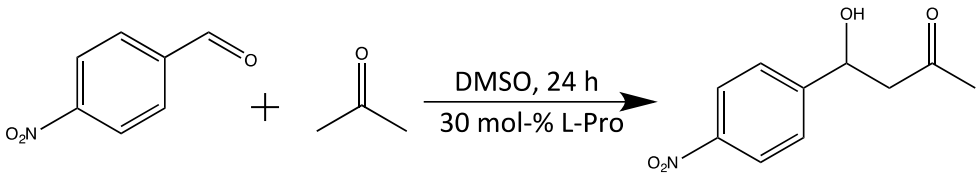
(*R*)-3-Methylpyrrolidine-3-Carboxylic Acid

This research will focus on the application of an analogue of L-Proline, (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid (**Figure 1)**. There are a few structural differences between L-Proline and the analogue. The main difference between the two catalysts is the stereochemistry (L-Proline is *S*, and the analogue is *R*). There is also a methyl group on the chiral carbon, which is expected to improve the solubility. The amine group is farther away from the chiral center, but this is due to the experimental design used to generate the analogue. Specifically, the solubility and reactivity of (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid will be analyzed using different organic reactions, including the Michael and Aldol reactions seen in **Scheme 1a** and **Scheme 2a**.

Scheme 1a: Example of Michael Reaction



Scheme 2a: Example of Aldol Reaction



Once the solubility of the catalyst has been determined, the selectivity of the reaction will be studied by analyzing the enantiomeric excess of the enantiomers. This data will then be compared to L-Proline to determine if (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid is a more efficient catalyst.

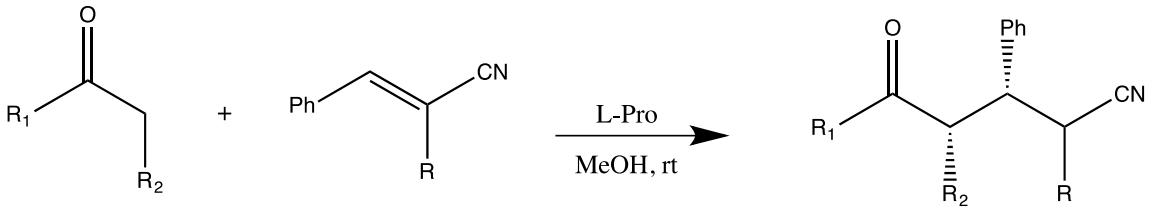
CHAPTER 2: Literature Review

Chiral molecules have major advantages in the pharmaceutical industry. Due to the production of enantiomers, the possibilities for biological applications are increased. Enantiomers have the potential to behave differently due to the spatial arrangement of the functional groups. Because the configurations of two enantiomers are different, the interaction of one enantiomer with a drug can differ from the interaction of the second enantiomer with the same drug. Previously, artificial drugs were not chiral, but the majority of drugs developed from natural sources were chiral[1].

L-Proline is a popular organocatalyst that is naturally abundant in both of its enantiomer forms. Because it exists in nature, proline is an inexpensive chiral molecule. The two functional groups on proline, the carboxylic acid and the amine group (**Figure 1**), allow the catalyst to act as both an acid and a base. This versatility allows proline to participate in a variety of reactions. The key feature to proline is its ability to catalyze reactions to produce stereoselective molecules. If two enantiomers had opposing functionalities but were produced simultaneously in equivalent ratios (racemic mixture), then the reaction would be less efficient if only one functionality was needed. Therefore, stereoselective reactions allow one enantiomer to be produced in excess, maximizing the efficiency of the reaction[2].

The Michael reaction has primarily been studied using enamines with nitro olefins, but enamine catalysis has not been as thoroughly explored. Proline is a starting point for the enamine catalysis using asymmetric Michael reactions (**Scheme 1**). A recent study used proline in DMSO and methanol solvent systems for ketones and nitro-olefins, which can be seen in Scheme 1.

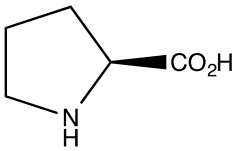
Scheme 1b: Example of Michael Reaction

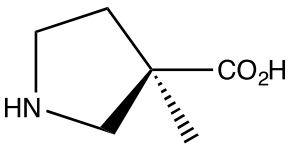


The study produced yields as high as 96%. These reactions did not require harsh conditions such as high/low temperatures, inert atmospheres, or metallic salts. However, the key issues in these experiments were the low enantioselectivities and high reaction times. The highest enantioselective excess reported was 37% when R = CO_2Et (ethyl ester), R_1 = Me (methyl group), and R_2 = Et (ethyl group). This set of conditions also gave the 96% yield. Since this process has not been thoroughly studied, (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid will be used to try and improve the enantioselectivity of the Michael reaction products.[3]

Another issue with L-proline is its solubility in organic solvent systems, although it is very soluble in aqueous systems. The catalyst has been used in Aldol reactions to generate carbon-carbon bonds, but the low solubility of proline in organic systems, 50 mol% of L-Proline in methylene chloride, causes low product yields.[4]

Figure 1b: Comparison of Unsubstituted and Substituted Catalysts





Unsubstituted Catalyst **Substituted Catalyst**

This study also required large amounts of the catalyst to be used, which is not very efficient. One way the study improved the results was by substituting a methyl group on

the chiral carbon on the catalyst, which is seen in **Figure 2**. This improved the solubility in nonpolar organic solvents. The substituted analogue allowed good product yields with increases in enantioselectivity compared to the unsubstituted catalyst. By placing substituents on the analogues of L-proline, it is possible the solubility of the catalyst can be increased in not only the Mannich reaction but other reactions as well, including the Michael reaction (Kazuhiro, et. al). The objectives of my research are to synthesize the analogue (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid of L-Proline and test its catalytic activity in the Michael reaction[5]

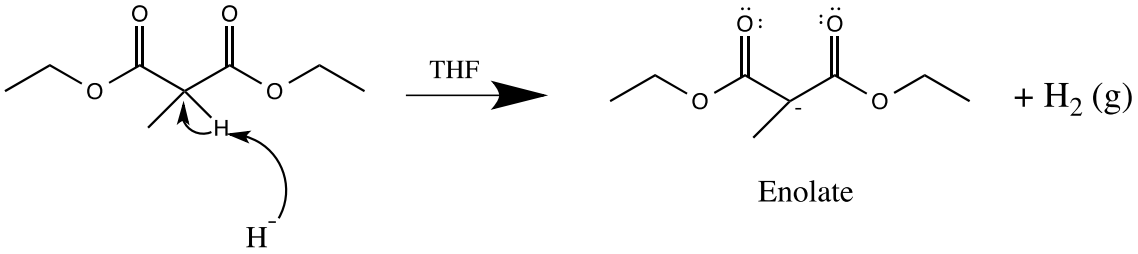
CHAPTER 3: Methodology

Catalyst Production:

Before (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid can be tested in the Michael reaction, the catalyst must be synthesized. The synthetic route developed by the Masterson research group at the University of Southern Mississippi will be used as a reference in making the catalyst, however the main goal in this project was to optimize the reaction conditions to provide the most efficient and inexpensive reaction pathway.

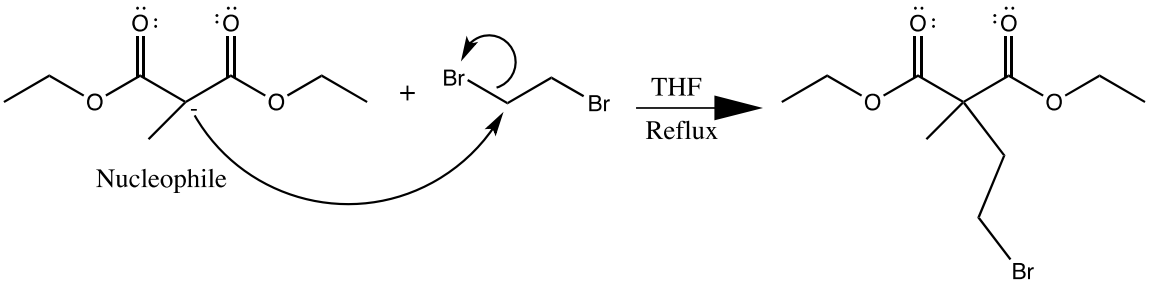
The synthesis begins with diethyl methylmalonate. This malonate is chosen because one of the goals is to have a methyl group substituted on the catalyst. Therefore, substituted diesters have been used for the starting point. This malonate undergoes an S_N2 reaction. In this S_N2 process, the acidic hydrogen between the two ester groups is removed by sodium hydride (NaH) to generate an enolate and hydrogen gas (H_2) seen in **Scheme 2**.

Scheme 3a: Generation of Enolate



The enolate then attacks one of the carbons on the dibromoethane while bromine leaves simultaneously. In this reaction (**Scheme 3**), a 1:2 molar relationship between the nucleophile (enolate) and dibromoethane is usually utilized. However, a purification step is needed to remove excess starting material. Therefore, a 1:1 molar ratio will be used in this research to try and eliminate the purification step. Other reaction conditions including the solvent system and refluxing (addition of heat) will also be manipulated to optimize the reaction.

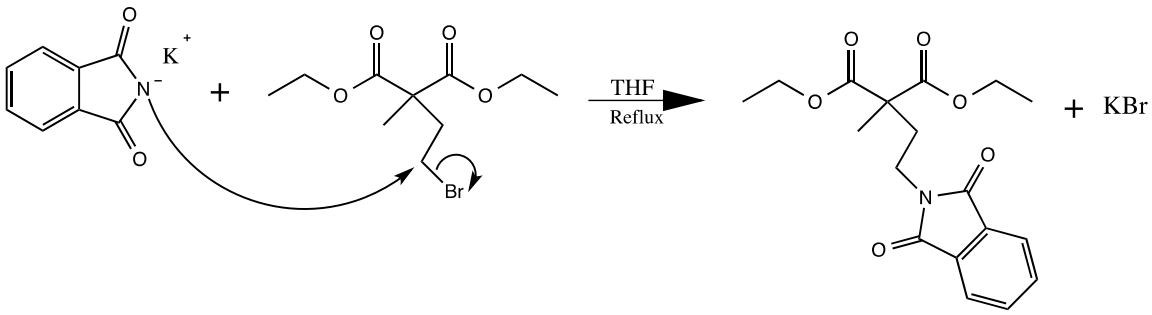
Scheme 3b: Substitution of Diethyl Methylmalonate



Formation of sodium bromide (NaBr) is an indication that the reaction occurred.

The second step of the synthesis is the Gabriel Synthesis (**Scheme 4**), which is also an S_N2 reaction. This takes the previous product to react with potassium phthalimide.

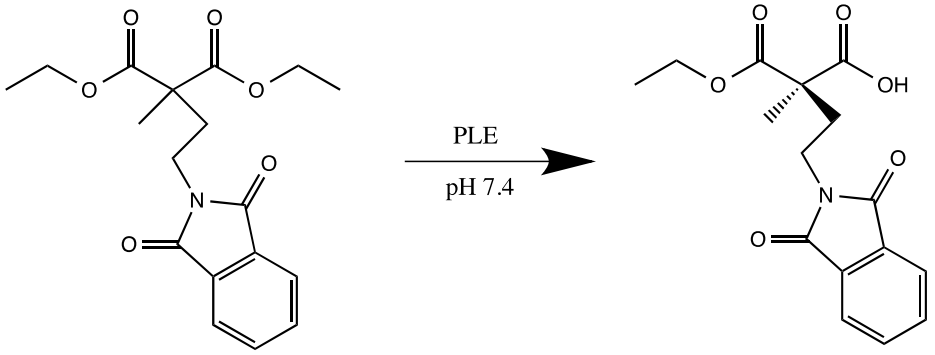
Scheme 4a: Gabriel Synthesis



Again, formation of the salt potassium bromide (KBr) could indicate the reaction occurred, but NMR spectroscopy will be used to confirm the reaction took place. This step introduces the nitrogen necessary for the amine seen in the catalyst.

In the third step the chiral center of the catalyst is formed with the formation of a carboxylic acid from one of the esters. This is a hydrolysis reaction (**Scheme 5**) with Pig Liver Esterase (PLE) in a pH 7.4 buffer.

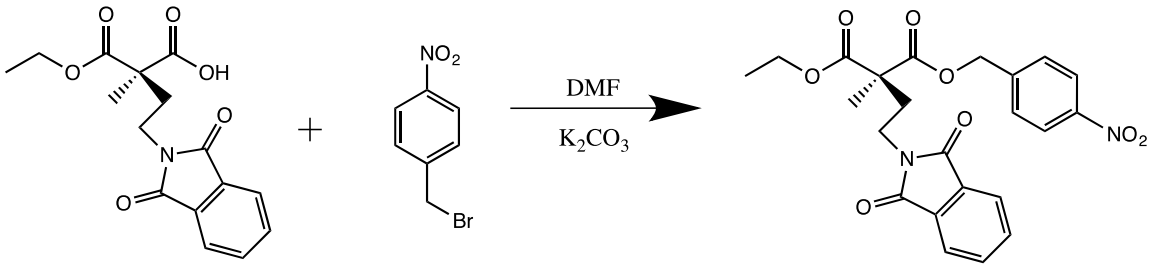
Scheme 5a: PLE Hydrolysis



Once the chiral center is generated, *para*-nitrobenzyl bromide is substituted for the hydrogen on the carboxylic acid. This step will help direct cyclization to form the pyrrolidinone ring. The addition of *para*-nitrobenzyl bromide is also a director for the *S* stereochemistry (**Scheme 6**). This is a novel reaction designed by the Masterson Research

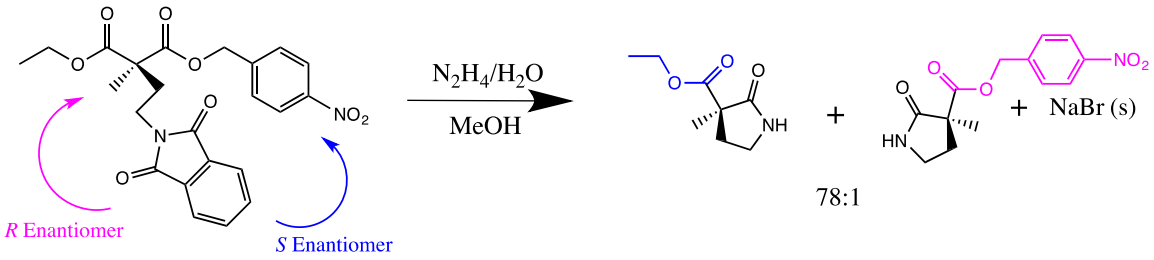
Group. Multiple groups can be substituted on the benzene ring, and these groups will also affect the stereochemistry of the catalyst.

Scheme 6a: Addition of *Para*-Nitrobenzyl Bromide



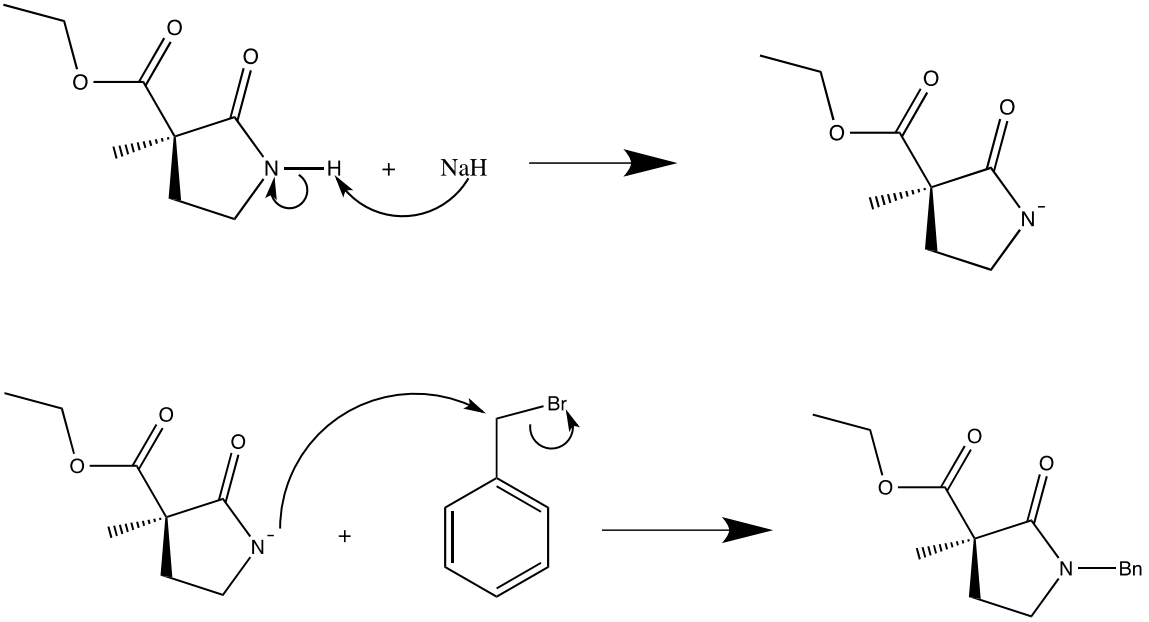
Once the benzene is added, the cyclization step can occur to form the pyrrolidinone ring seen in **Scheme 7**. Depending on how the cyclization occurs, the *R* or *S* enantiomer can be produced. If cyclization occurs on the side with the benzene, the *S* enantiomer is produced (**Scheme 7**). If cyclization occurs on the side with the ester group, the *R* enantiomer is produced (**Scheme 7**). This selective step is novel in the Masterson research lab and a variety of functional groups were used to test selectivity.[67] Using *para*-nitrobenzyl bromide, as seen in **Scheme 7**, allowed a 78:1 molar ratio of *S*:*R*.

Scheme 7a: Selective Cyclization

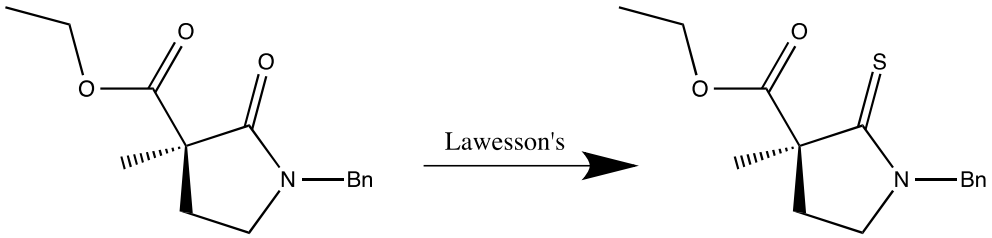


After cyclization, a phenyl group will be added to the compound using benzyl bromide (**Scheme 8**). Again, this is an S_N2 reaction using sodium hydride to generate the nucleophile from starting material.

Scheme 8a: Addition of Benzyl Group to Nitrogen

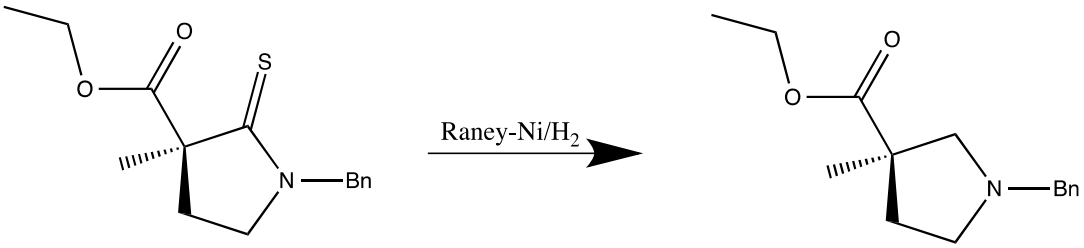


Scheme 9: Formation of Thioketones



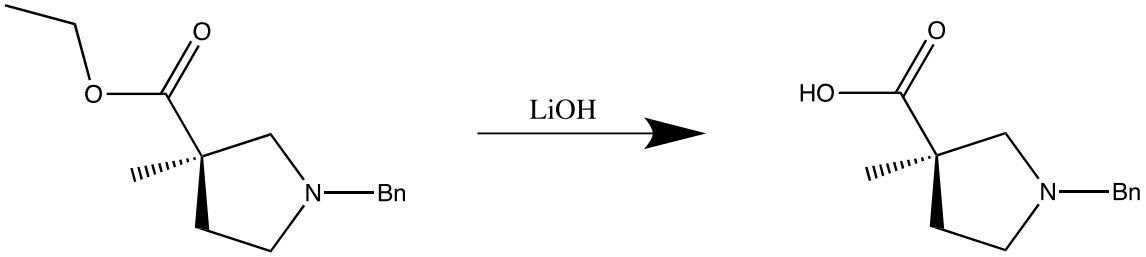
Once the thioketone is formed, it can be removed using Raney-nickel catalyst in **Scheme 10**[8910].

Scheme 10: Removal of Thioketones



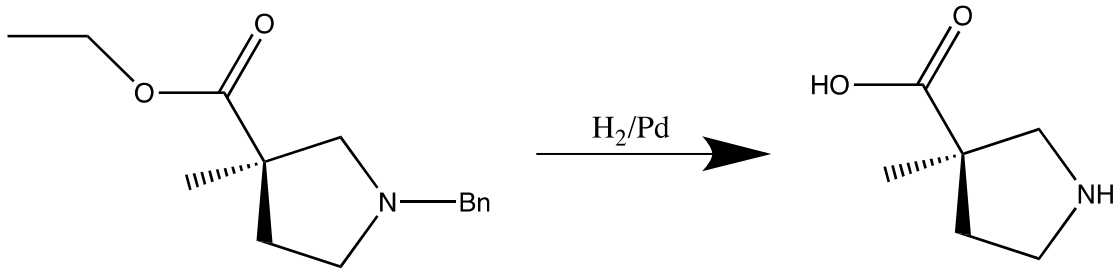
Lithium hydroxide (LiOH) will be used to convert the remaining ester group to a carboxylic acid group, generating the same product from the two reactants (**Scheme 11**).

Scheme 11: Generating Carboxylic Acid



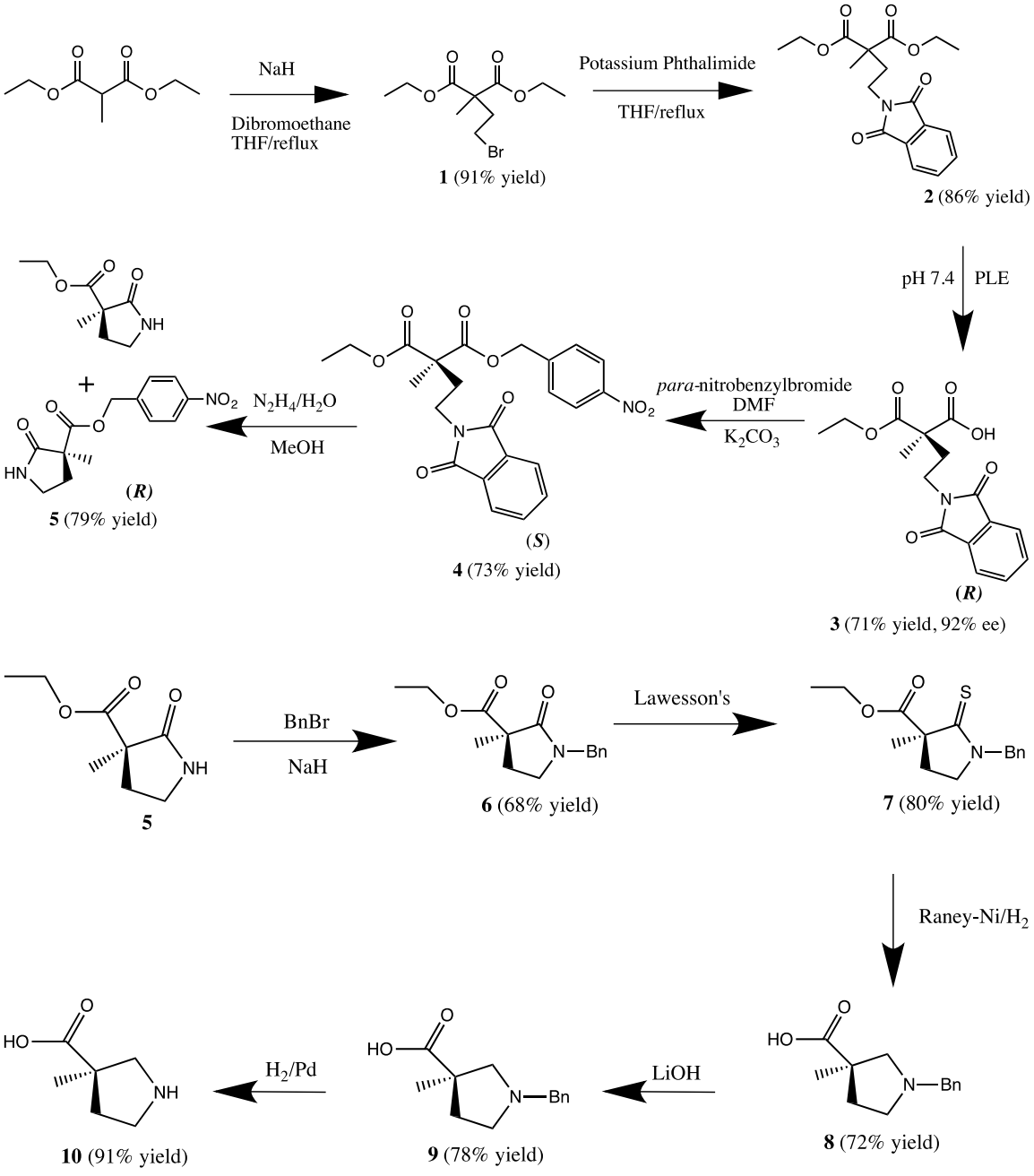
The final step is the removal of the benzene group seen in **Scheme 12**. This will be done using hydrogen and palladium catalyst.

Scheme 12: Formation of Target Catalyst



Once the benzyl group is removed, the synthesis of the catalyst is complete. Because this reaction is known in the Masterson laboratory, optimization of the synthesis will be a potential goal for certain steps. The complete synthetic route is displayed in **Scheme 13**.[11] Once enough of the catalyst is generated, it can be tested in the Michael reaction.

Scheme 13: Complete Synthesis of (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid



Experimental Procedure:

The protocol utilized in this studied was based on the synthetic route developed by Dr. Banerjee and the Masterson Research Group.

General Methods:

"THF, CH_2Cl_2, and DMF were dried by passage through activated alumina. All reagents were used as received unless otherwise stated. Flash chromatography was performed using P-60 silica gel, and TLC analysis was performed using silica precoated TLC plates. Pig liver esterase (PLE) refers to the commercially available crude preparation[12]."

Synthesis of Diethyl 2-(2-Bromoethyl)-2-methylmalonate (1):

Approximately 65 mL of dry THF was added to 2.35 g of NaH (58.5 mmol, 60% suspension in mineral oil) under N_2 atmosphere before being cooled to 0°C. A solution of 10.2 g of diethyl-2-methylmalonate (58.6 mmol) in THF was added over 20 minutes, with stirring at rt. A solution of 10.9 g dibromoethane (58.0 mmol) in THF was added dropwise with stirring under N_2 atmosphere. The reaction mixture refluxed overnight. Half the solvent was evaporated under reduced pressure, and the solution was diluted with a 5% solution of HCl and water. The mixture was washed with $CHCl_3$ (3 X 30 mL), washed with brine, dried over $MgSO_4$, and filtered. The remaining solvent was evaporated under reduced pressure. The resulting yellow liquid was distilled to remove the excess dibromoethane, diethyl-2-methylmalonate, and THF giving 9.0 g (29 mmol, 47%) of **1** as a yellow liquid. ^{1}H NMR corresponded to literature.

Synthesis of Diethyl 2-Methyl-2-[2-(1,3-dioxoisoidndolin-2-yl)ethyl)malonate (2):

Approximately 6.8 g of **1** (22.4 mmol) was placed in a 250 mL sealed tube with 120 mL DMF. A 5.3 g (28.6 mmol) portion of potassium phthalimide was added to the sealed tube. The reaction mixture stirred at 90°C overnight. The reaction mixture was cooled to

rt, diluted with 300 mL of H_2O, and extracted with Et_2O (3 X 200 mL). The combined organic layer was washed with water (10 X 100 mL), washed with brine (2 X 100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure giving the crude product was a white solid. The crude was recrystallized from cold Et_2O giving 1.62 g (4.4 mmol, 23%) of **2** was a white solid. ^{1}H NMR corresponded to literature.

Synthesis of (*R*)-2-(*N*-Ethylphthalimido)-3-ethoxy-2-methyl-3-oxopropanoic Acid (3):

A 6.5 g portion of **2** (17.6 mmol) was add to 610 mL of phosphate buffer (0.1 N, pH 7.4) with stirring. An 89.3 mg portion of pig liver esterase (PLE) (27 units/mg, 90 unites per mmol of the substrate) was added to the buffer. The pH was maintained with an auto buret set to deliver 1 equivalent of 1 N NaOH solution to keep a pH of 7.4. The hydrolysis proceeded overnight. The pH was lowered to 1 with concentrated HCl and extracted three times with 600 mL of Et_2O. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure giving 1.87 g (5.5 mmol, 31%) crude product as yellow viscous oil. ^{1}H NMR corresponded to literature.

Synthesis of (*S*)-1-(4-Nitrobenzyl)-3-ethyl-2-methyl-[2-(1,3-dioxoisoindolin-2yl)ethyl]malonate (4):

A portion of 0.76 g of K_2CO_3 (5.5 mmol) was added to a solution of 1.87 g of **3** (5.5 mmol) in 20 mL of DMF. Approximately 1.1 g (5.1 mmol) of *para*-nitrobenzyl bromide was slowly added to the solution. The reaction stirred overnight under an N_2 atmosphere. The reaction mixture was then diluted with 20 mL of water and washed with Et_2O (3 X 20 mL). The combined organic layer was washed with water (5 X 20 mL), washed with

brine (2 X 20 mL), and dried over $MgSO_4$. The solvent was removed under reduced pressure, and 1.79 g (3.8 mmol, 76%) of **4** was obtained as a white solid. ^{1}H NMR corresponded to literature.

Synthesis of (*R*)-Ethyl 3-Methyl-2-oxopyrrolidine-3-carboxylate (5):

Approximately 400 microliters (4.1 mmol) of 35% hydrazine in water was added to 1.69 g (3.5 mmol) **4** in solution with 24 mL of MeOH. The reaction mixture was refluxed overnight, resulting in the formation of white precipitate. The solution was cooled to rt and filtered. The solvent was removed from the filtrate under reduced pressure to obtain a solid, which was put back into solution with CH_2Cl_2. The solution was washed with H_2O (1 X 100 mL), and the organic layer was dried with $MgSO_4$, filtered, and placed under reduced pressure. The resulting solid was "chromatographed using 30% hexanes/EtOAc" producing 0.2 g (0.8 mmol, 25%) of **5** as pure white solid. ^{1}H NMR corresponded to literature.

Synthesis of (*R*)-Ethyl 1-Benzyl-3-methyl-2-oxopyrrolidine-3-carboxylate (6):

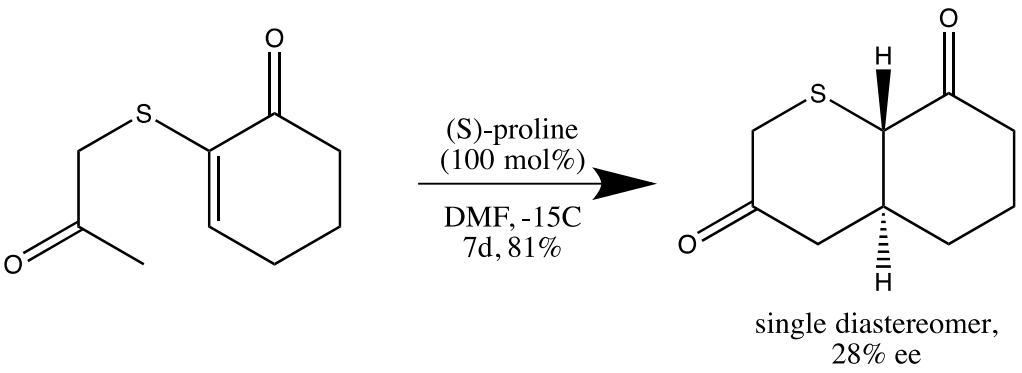
A volume of 2 mL anhydrous THF was added to 0.4 g (1.8 mmol) of **5**. The solution was slowly added to 0.07 g NaH (2.9 mmol) in (volume) of THF at 0°C under a N_2 atmosphere and stirred for 5 minutes. Approximately 0.3 g of BnBr (1.8 mmol) was added dropwise, and the mixture stirred for 10 minutes at °C. The reaction was warmed to rt and continued for 1 hour at rt. Dry DMF 10 mL was added to the reaction and continued stirring for 2 h. The mixture was added to 7 mL of H_2O where the water layer was extracted with Et_2O (3 X 20 mL). The combined organic layer was washed with

water (5 X 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting oil was "chromatographed (gradient, 15-20% EtOAc/hexanes)" allowing 0.14 g (0.5 mmol, 19%) of **6**. ^1H NMR corresponded to literature.

Michael and Aldol Reactions:

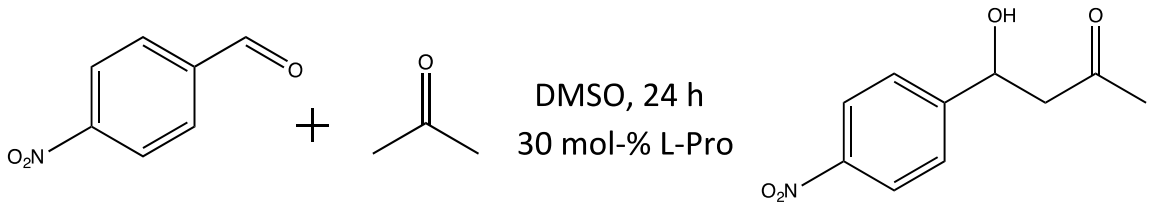
To test the reactivity of the analogue, a series of trials will be conducted for the Michael and Aldol reactions. These will include different solvent systems, protic and aprotic, to see if better enantioselectivity is seen compared to the literature values of L-proline. Potential reactions for the study are displayed in **Schemes 14a-b**, but the analogue will be used in place of (*S*)-proline.

Scheme 14a: Michael Reaction



single diastereomer,
28% ee

Scheme 14b: Aldol Reaction

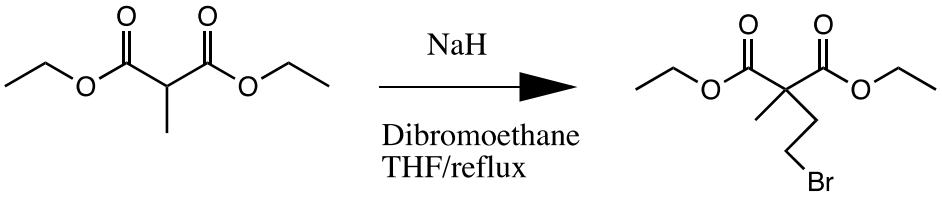


Once each of the reactions has been conducted, the enantioselectivity of each experiment will be compared to the literature values of the (*S*)-proline reactions.

CHAPTER 4: Results

Synthesis of Catalyst

Scheme 3c: Alkylation of Diethyl Methylmalonate



Trial	Molar Ratio of Diethyl Methylmalonate to Dibromoethane	Solvent	Reflux	Amount of Diethyl Methylmalonate Used	Percent Yield
1	1:1	DMF	No	5 mL	51.57
2	1:1	THF	No	10 mL	55.11
3	1:1	THF	Yes	10 mL	10.10
4	1:1	THF	Yes	40.81 g	87.96
5	1:1	THF	Yes	40.80 g	16.57
6	1:1	THF	Yes	20 mL	9.60
7	1:1	THF	Yes	20 g	47.24

Table 1 displays different trials for the alkylation of diethyl methylmalonate using different reaction conditions with yields. The table specifies the solvent used, quantity of diethyl methylmalonate used, and whether or not the solution was refluxed.

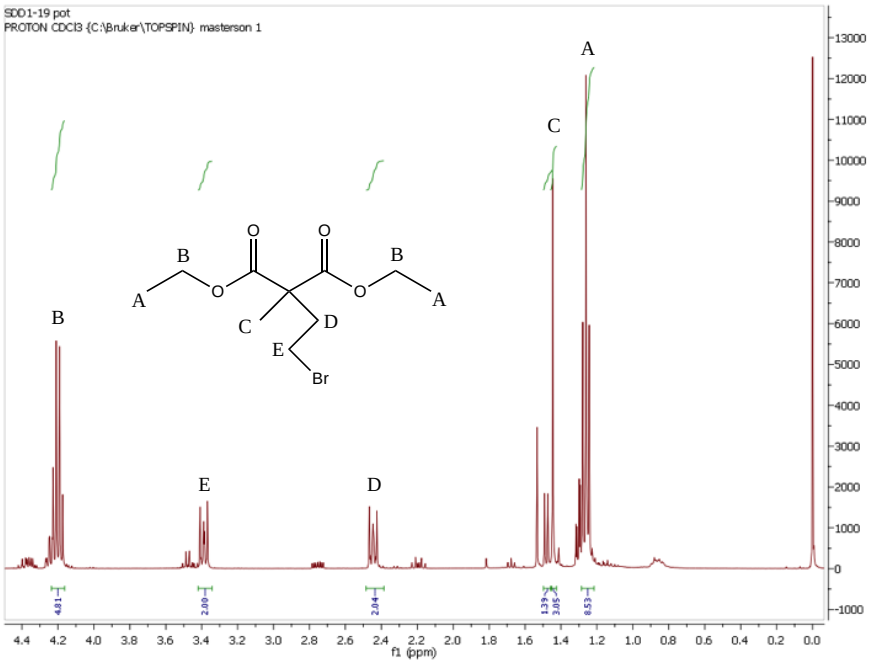
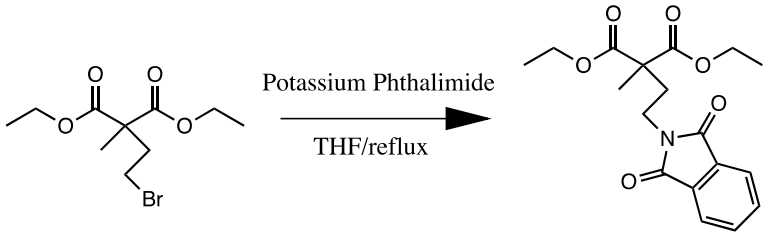


Figure 2 depicts the NMR for the alkylation product. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 4b: Gabriel Synthesis



Trial	Amount of Starting Material Used	Percent Yield
1	10.91 g	9.79
2	6.76 g	22.90
3	16.63 g	36.15

Table 2 shows the amount of starting material used for each trial in the Gabriel Synthesis and the corresponding percent yield.

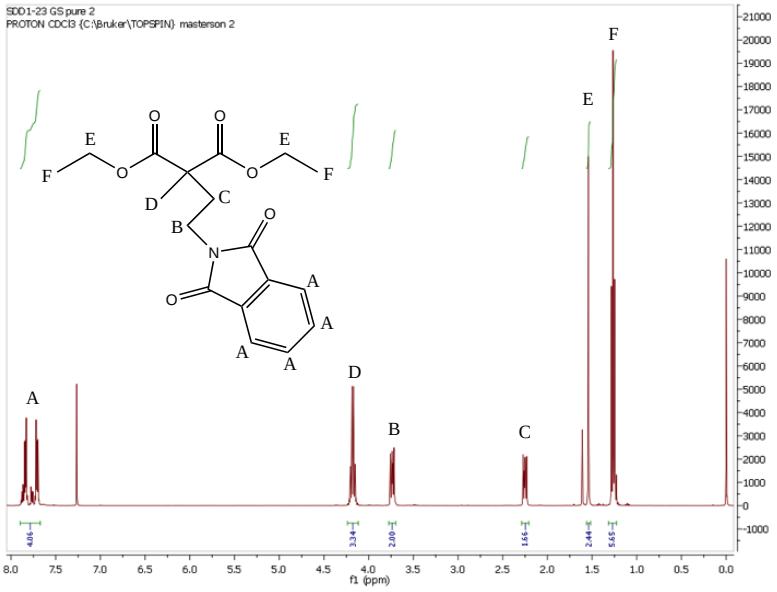
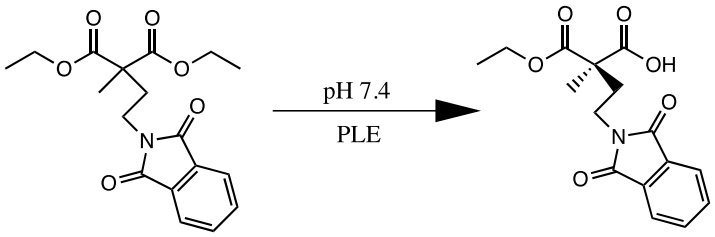


Figure 3 depicts the NMR for the substituted product. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 5b: PLE Hydrolysis



Trial	Amount of Starting Material Used	Percent Yield
1	1.32 g	55.23
2	6.74	21.57
3	6.80 g	24.94
4	6.50 g	31.13

Table 3 shows the amount of starting material used for each trial in the PLE Hydrolysis and the corresponding percent yield.

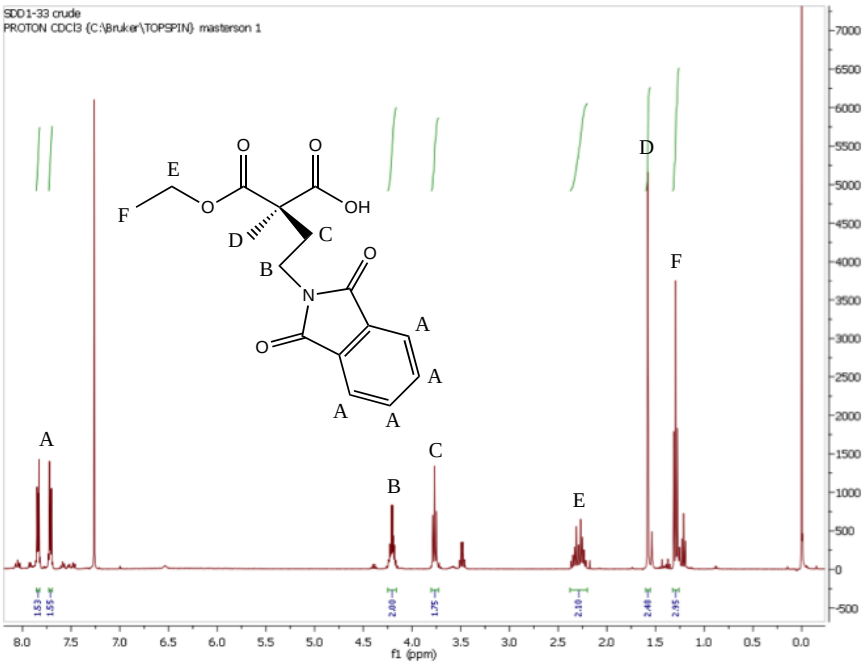
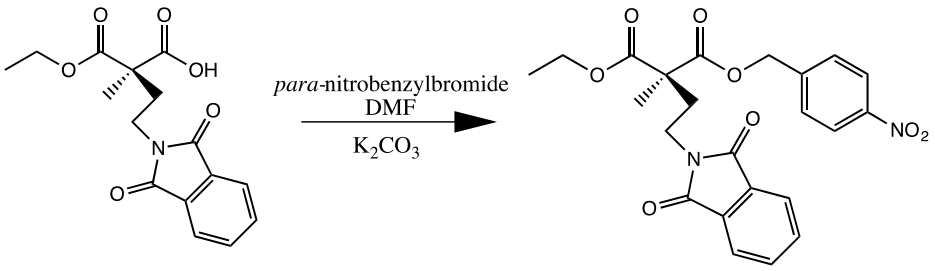


Figure 4 depicts the NMR for the chiral product. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 6b: Substitution of *Para*-Nitrobenzyl Bromide



Trial	Amount of Starting Material Used	Percent Yield
1	2.05 g	38.33
2	1.87 g	76.20

Table 4 shows the amount of starting material used for each trial in the reaction and the corresponding percent yield.

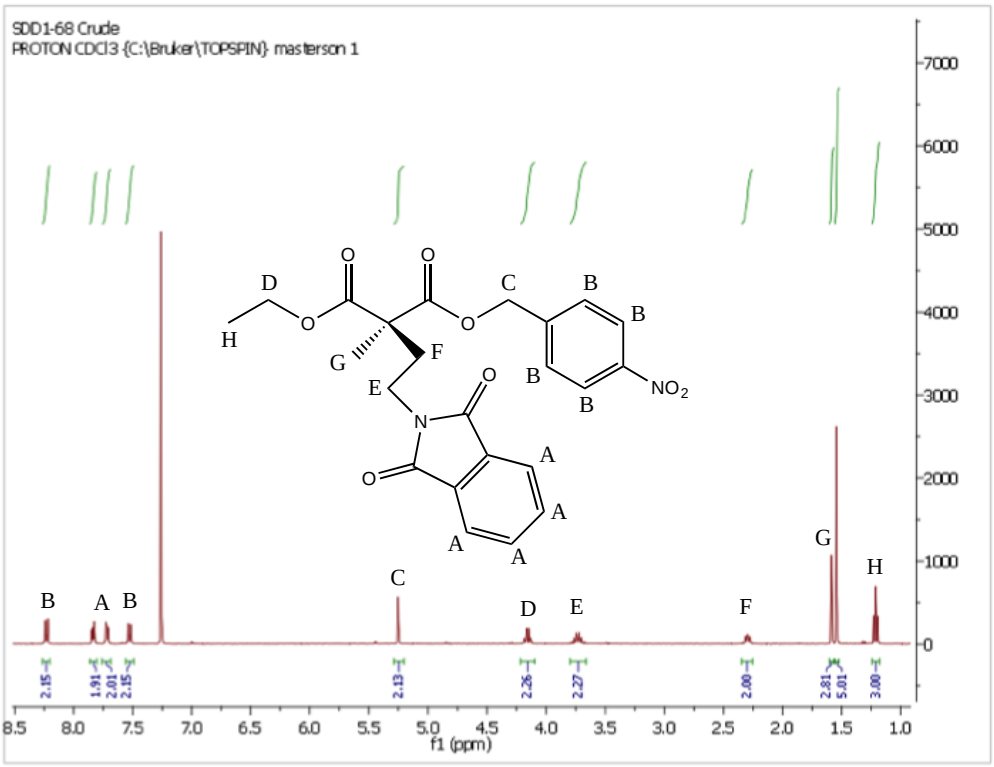
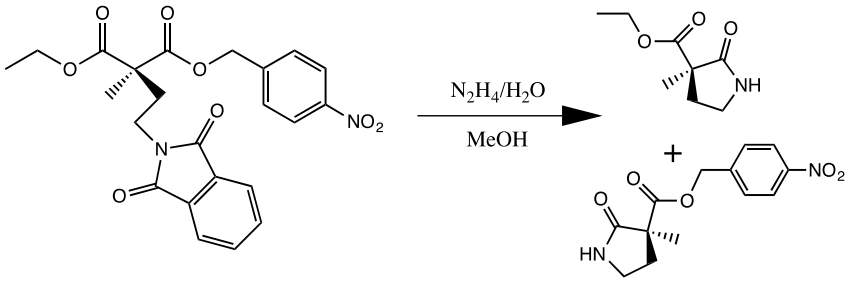


Figure 5 depicts the NMR for the substituted product. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 7b: Selective Cyclization



Trial	Amount of Starting Material Used	Percent Yield
1	1.69 g	38.33

Table 5 shows the amount of starting material used in the cyclization step and the corresponding percent yield.

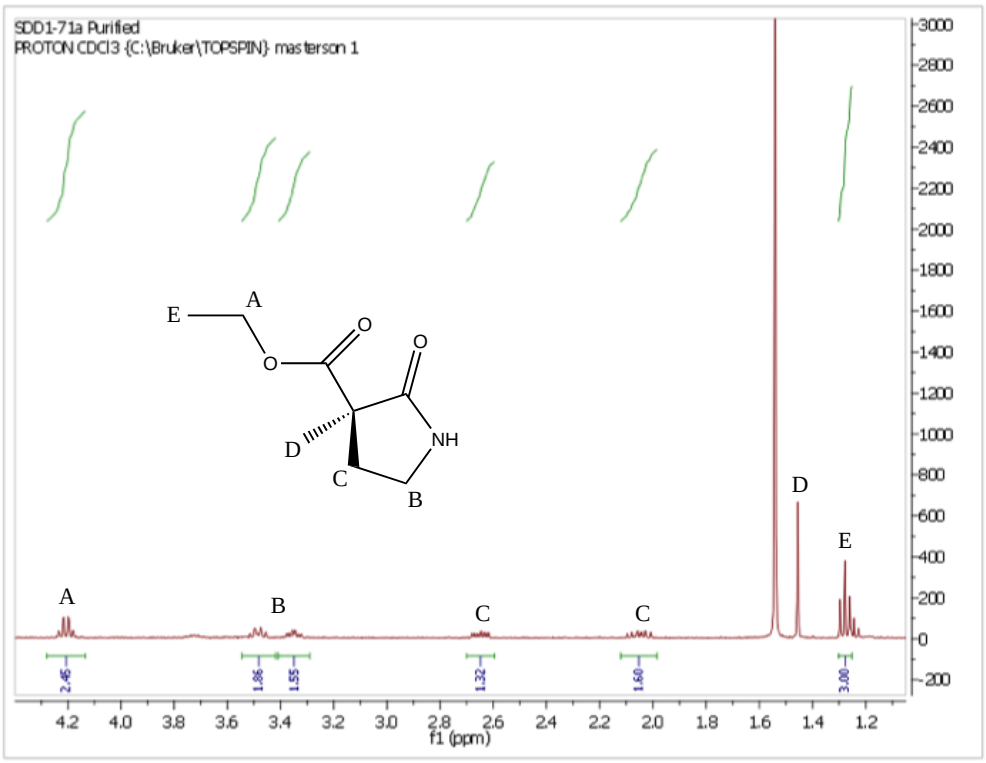
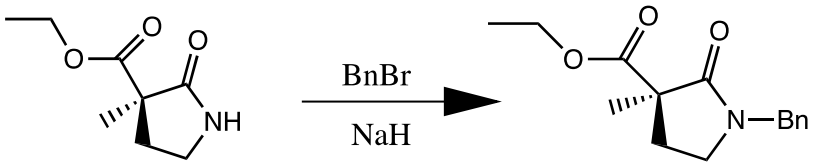


Figure 6 depicts the NMR for the cyclized product. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 8b: Addition of Benzyl Groups



Trial	Amount of Starting Material Used	Percent Yield
1	0.4435 g	27.72

Table 6 shows the amount of starting material used in the addition and the corresponding percent yield.

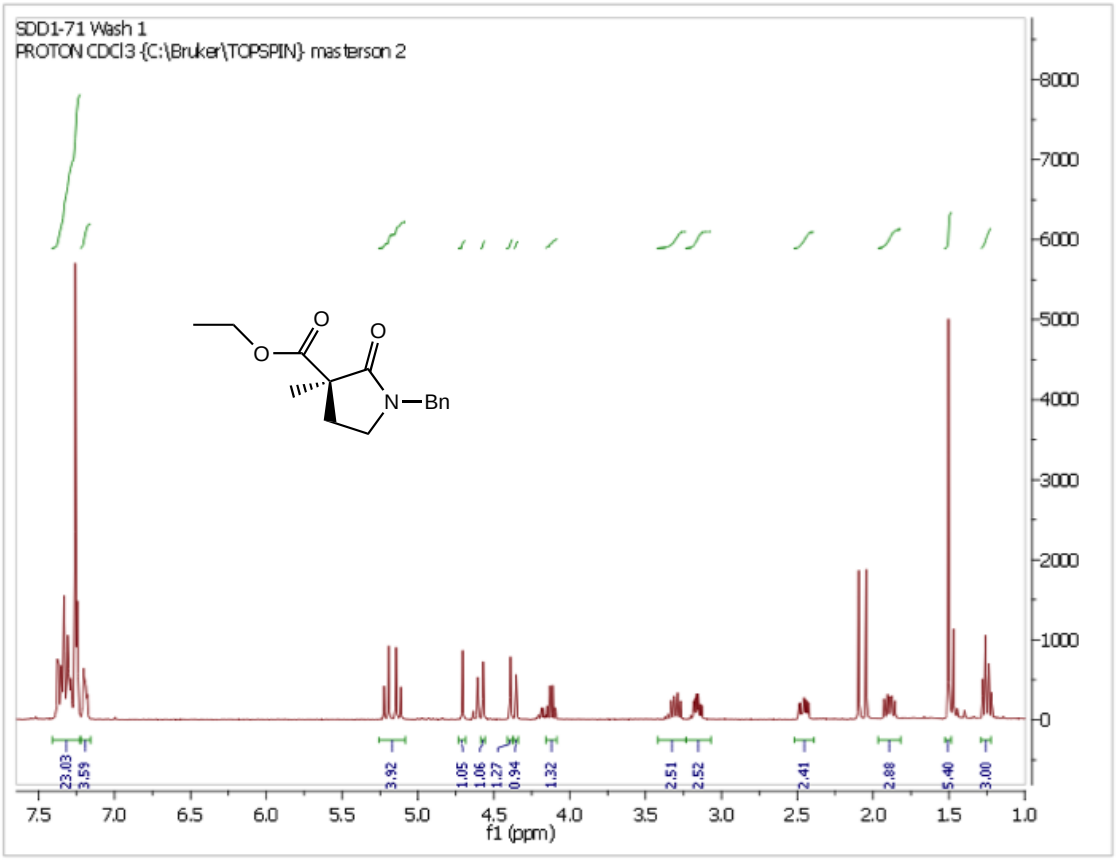
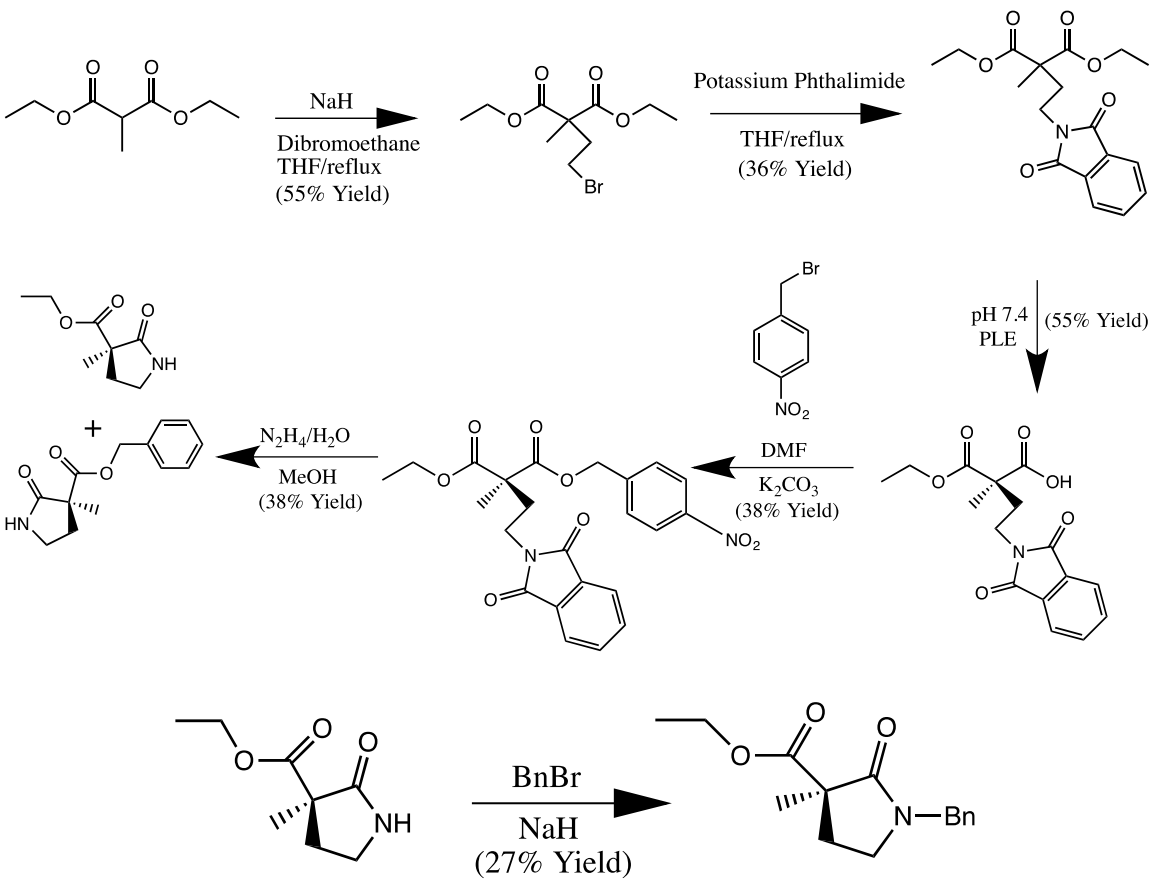


Figure 7 depicts the NMR for the benzyl-substituted products. The peaks and values correspond to Dr. Banerjee's reported spectrum.

Scheme 15: Steps Completed in Synthesis



CHAPTER 5: Discussion

Looking at the individual steps in the synthesis, one can conclude the current synthetic pathway is most optimized for this analogue. When considering the first step, the goal was to reduce the need for purification. The protocol for purification involved distillation, which is a time-consuming process, and the presence of starting material indicated the reaction was not going to completion. Changing the molar ratio of diethyl methylmalonate to dibromoethane to 1:1 was a proposed solution because it would decrease the amount of starting material leftover from the reaction. However, purification was still needed with this molar ratio as seen in the NMR (Figure 3). A peak around 1.5 ppm that integrates to 1.39 signifies the presence of unreacted diethyl methylmalonate.

Also, the reaction yields (**Table 1**) were half the yield reported with the 2:1 molar ratio. Trial 4 has a high percent yield but it is believed to be due to a tear mass error. Changing the solvent system and reflux conditions did not really change this outcome. Another issue with early trials was deciding which reactant was in excess. The procedure said to add the generated enolate to dibromoethane, but errors in technique had the dibromoethane being added to the enolate. This could have affected the rate of the reaction and prohibited the reaction from reaching completion. However, low yields were still being seen when the generated enolate was added to dibromoethane. Therefore, it was decided the current synthetic pathway with the 2:1 molar ratio provided the most optimized and efficient reaction conditions.

Once enough alkylated diester was produced, the next reaction was the Gabriel Synthesis, which replaced the bromide with a phthalimide group. This step does not have an extensive purification process like the previous because the product crystallizes pure out of solution after work up. The first few trials have low yields (**Table 2**), and the NMR (**Figure 3**) is pure for the crude product except for some remaining phthalimide but not enough to cause concern.

The following step was the addition of *para*-nitrobenzyl bromide. Trial 1 showed a low yield but required purification by column. Column purification is very tedious and loss of mass can be an issue, especially if beginning with low mass. Therefore, the low yield could be contributed to having a small scale (2.05 g starting material). Also, this reaction must be stopped after a certain amount of time or the desired product will start reacting again. Therefore, it is possible not all of the *para*-nitrobenzyl bromide was added in the reaction. Trial 2, however, shows improvement in yield with no purification

needed, so technique could also have contributed to the low yield in Trial 1. NMR analysis (**Figure 5)** showed purified material after purification for Trial 1.

The cyclization of the phthalimide group had a low yield (38.33%), but the reported yield was 40%. Therefore, despite the "low" yield, the reaction went very well because it is known to be a low-yielding step. Column purification was also utilized in this step but not much mass loss was seen. After purification, NMR (**Figure 6)** showed purified product. This reaction also had a small scale due to the low yield in the *para*-nitrobenzyl bromide substitution reaction, so lack of material was staring to become a concern when this step produced less than a gram of material.

After cyclization, benzyl groups were added to the amine and ester groups as demonstrated in **Scheme 8**, which actually give two products. NMR analysis confirmed the production of both products (**Figure 7**), which complicates the spectra, but peaks at 2.5 ppm and 3.25 ppm confirm the diasteric hydrogens. As seen in **Scheme 13**, having two products is not a concern because both will lead to the catalyst in the synthetic route. This step also had a low yield, but column purification was also needed after working up the reaction. Therefore, loss of mass could have also resulted from running a column, especially since less than a gram of material was used for starting material.

Limitations

The synthesis of the catalyst (*R*)-3-Methylpyrrolidine-3-Carboxylic Acid was not completed. This was due to a variety of factors relevant to specific steps in the synthesis. Specifically, lack of material prevented the advancement of synthesis, and time had to be taken to build up starting material at various points during the project.

The first step in the synthesis, the alkylation of diethyl methylmalonate, took the longest since attempts at optimization were taken. The original synthetic strategy calls for a 1:2 molar ratio of diethyl methylmalonate to dibromoethane. However, purification was needed in this step due to the presence of starting material. In this project, one of the goals was to manipulate the reaction conditions to minimize the amount of starting material leftover from the reaction. Therefore, a 1:1 molar ratio of diethyl methylmalonate to dibromoethane was suggested as an initial change. Table 1 shows differences in other conditions such as solvent, reflux, and scale size of each optimization trial. The percent yield for each trial was also measured for comparison to the yield of original reaction conditions. Due to the low yields observed, more time was taken to generate enough material to continue the synthesis.

During the PLE hydrolysis step, there were some issues with electrodes of the titrator that influenced the reaction. During the titration, a set amount of base was expected to be added but only half of that amount was being added during Trials 2-3. During calibration of the electrodes, the electrodes were not stabilizing. This limited the production of the chiral product and lowered the yield of this reaction.

For several of the reactions, column chromatography was used for purification. This is a very tedious, time-consuming process. Columns were more relevant towards the end of the synthetic route when material was low, so extra care was given while running columns to insure all products were removed from the columns for maximum yields; however, loss of mass is a possibility when using columns.

CHAPTER 6: Conclusions

This study suggests the established synthetic pathway is the most optimized for the desired analogue (*R*)-3-methylpyrolidine carboxylic acid. The reaction yields above are significantly lower than those reported by the Masterson Research Group, so the focus of the research shifted to completing the synthesis of the analogue instead of optimization. Once the analogue is produced, its solubility and catalytic reactivity will be tested and compared with L-proline's.

Future Research

Future goals of the project include completing the synthesis of the catalyst. Because the last successful step was the addition of *para*-nitrobenzylbromide, the remaining steps include Lawesson's, Raney-Ni, acid/base, and catalytic hydrogenation reactions. Once the catalyst is synthesized, enough must be generated for catalytic studies of Michael and Aldol reactions. The solubility of the catalyst and stereoselectivity of the reactions will be observed and compared to literature data on reactions with L-proline.

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