

[2]ROTAXANES AS REAGENTS FOR [3]ROTAXANE SYTHESIS

A thesis presented to the faculty of the Graduate School of
Western Carolina University in partial fulfillment of the
requirements for the degree of Master of Science.

By

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TABLE OF CONTENTS

	Page
List of Figures	iv
List of Schemes	v
Abstract	vi
Chapter 1: Introduction	7
Chapter 2: Results and Discussion.....	16
Chapter 3: Experimental	29
Conclusion	47
References	48
Appendices.....	50

LIST OF FIGURES

Figure	Page
1. Rotaxane system containing molecular and cartoon representations of rotaxanes.	8
2. Shuttling and pirouetting of a rotaxane.....	9
3. Bent and relaxed states of the [3]rotaxane bonded to an Au plate.....	10
4. Molecular structure of the [3]rotaxane bonded to gold plate.....	11
5. Molecular structure of guest/host [3]rotaxane	11
6. [3]Rotaxane with rings shuttled close together due to Cu (I) coordination ...	12
7. Principle of the Adaptable [3]rotaxane Receptor.....	13
8. Molecular structure of sorting [3]rotaxane	13
9. [2]Rotaxane precursor, 13 , and [3]rotaxane, 14 , synthetic target.....	14
10. Central “building block” for [3]rotaxane.....	20
11. Amide/amide template vs. ester/ester template	22
12. TBDPS hydrolysis on TLC plate	25
13. HNMR of molecule 3	30
14. HNMR of molecule 4	33
15. HNMR of molecule 6	35
16. Enlarged portion of HNR of molecule 6	36
17. HNMR of molecule 7	38
18. HNMR of molecule 9	40
19. Enlarged portion of HNMR of molecule 9	41
20. Enlarged portion of HNMR of molecule 9	42
21. HNMR of molecule 9a	44
22. Enlarged portion of HNMR of molecule 9a	45
23. Enlarged portion of HNMR of molecule 9a	46

LIST OF SCHEMES

Scheme	Page
1. Dimerization of two [2]rotaxanes to form a [3]rotaxane	16
2. Synthesis pathway through molecule 6	17
3. Amide/ester rotaxane thread formation	17
4. Original plan for [2]rotaxane formation	18
5. Glaser coupling to form [3]rotaxane.....	18
6. Overall scheme for the synthesis of a [3]rotaxane.....	19
7. Original plan for amide/amide thread formation	23
8. Hydrolysis of TBDPS group during mesylation.....	23
9. Alternate plan for amide/amide thread formation.....	24
10. [2]rotaxane synthesis	26

ABSTRACT

It was our hope to demonstrate that fairly simple systems such as a [2]rotaxane can itself be used as a reagent to synthesize even larger systems such as a [3]rotaxane. This modular type approach offers several advantages over alternative methods. The [2]rotaxane was designed using a fumaramide template with a bulky diphenyl stopper on one end, and an aromatic core on the other end. The aromatic core contained three unique functional groups in the 1,3,5 position which allowed connection of the fumaramide thread, the tethering of the two [2]rotaxanes to form a single [3]rotaxane, and the removable stopper, *tert*-butyldiphenylsilyl ether. The aromatic core was synthesized from commercially available 5-Hydroxyisophathic acid using a novel and not fully understood selective reduction of only a single methyl ester of the 5-Hydroxyisophathic acid. Unfortunately, the repeated hydrolysis of the *tert*-butyldiphenylsilyl ether stopper prevented the completion of the full synthesis pathway, and the above mentioned modular approach was not able to be tested.

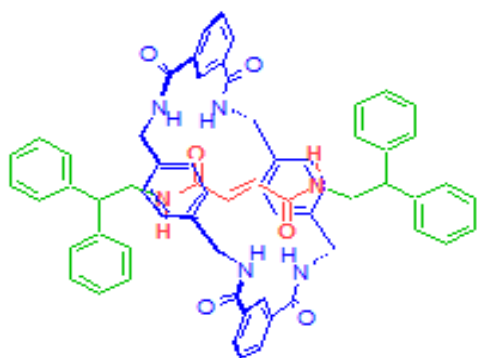
CHAPTER 1: INTRODUCTION

As society and technology has advanced, much work has been done to make machines smaller and thus more efficient.^{1,2} There are two schools of thought on how to achieve this result. The first is the “top-down” approach that states bigger machines will build smaller machines, and in turn those smaller machines will build even smaller ones until molecular or atomic level machines have been obtained. A great amount of success and value has been added to society by this “top-down” approach to nanotechnology. Nanotechnology is defined as research and technology involving devices and machines that are less than 100nm in size. A very notable example of this is the silicon microchip. Intel released microprocessors manufactured on the 90nm scale in early 2004³ and currently offers microprocessors produced using a 32nm scale.⁴

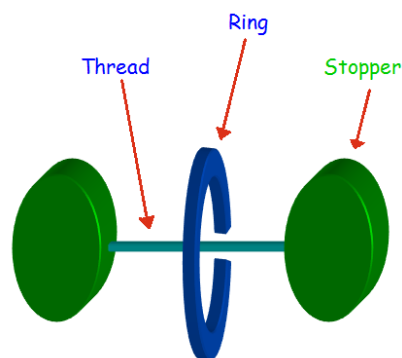
Unfortunately, for the top-down approach, classical mechanics start to break down and quantum mechanical phenomena start to dominate in size scales that have been drastically reduced to the nanometer scale. As a result, Richard Feynman proposed the “bottom up” approach that starts by assembling molecules through chemical reactions to form useful machines much like the inner workings of biological systems. While the value added to our society by the top-down approach significantly outweighs the benefit from the bottom-up approach to date, the biggest future advances are believed to be derived from the bottom-up approach.⁵ The bottom-up approach is providing, or will provide a pathway for technologies such as organic-based transistors^{6,7} for cost-effective spray-on microprocessors, TVs, and even solar panels;⁸ molecular muscles, pumps, and rotors;⁹⁻¹¹ and maybe in the future even “nanobots” that could be used to perform all sorts of work on the microscopic level. To date, no artificial nanobot or nanomachine has been

built. However, much work is currently being done on the pieces to make today's science fiction tomorrow's reality.

One aspect of nanotechnology that has begun to be a building block on which additional technologies are being built which will hopefully make the aforementioned dreams a reality, involves a category of molecules called rotaxanes and catenanes. While the principles and workings of macroscopic machinery such as motors, winches, and pistons are often easy to see and comprehend, molecular machines are not always so easy. However, rotaxanes provide a nice, relatively simple example of a molecular machine. Rotaxanes are mechanically interlocked architectures, which consist of a macrocycle around a thread and large molecular groups (stoppers) at each end that prevent the macrocycle from slipping off the thread. (Figure 1)



Structure of a [2]rotaxane



Cartoon representation of a [2]rotaxane

Figure 1: Rotaxane system containing molecular and cartoon representations of rotaxanes.

One of the main differences between macroscopic machinery and molecular machinery is that macroscopic machinery remains motionless until actuated or perturbed.

This is not the case with molecular machinery. By the very definition, molecular machines are molecules that are subject to the entropic motion at the atomic and molecular level. This can be clearly seen in rotaxanes by the movement of the macrocycle on the thread in two distinct ways. The first component is shuttling or horizontal movement on the thread. The second component is pirouetting or vertical spin. Both components occur simultaneously (Figure 2). The shuttling motion can be controlled by manipulation of the stations on the thread.

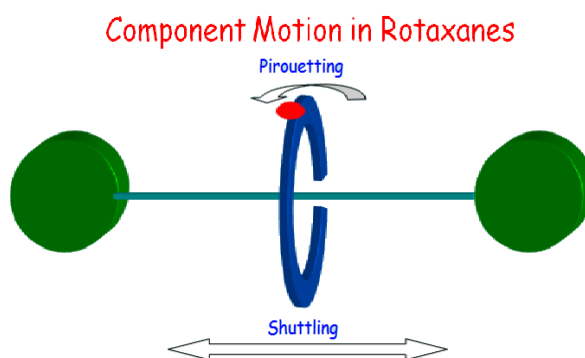


Figure 2: Shuttling and pirouetting of a rotaxane.

With control of the position of the macrocycle on the thread, the rotaxane can act as a molecular switching device or a molecular muscle. By controlling the back and forth motion of the macrocycle on the thread, mechanical energy available for work could theoretically be produced. Indeed, if there were two rings on one thread which moved back and forth in relation to each other, potentials for use would be even greater due to increased motion of each ring relative to each other. Such a rotaxane with two rings and one thread is referred to as a [3]rotaxane.

Several [3]rotaxanes have been previously designed and built for various purposes, one of which was a molecular muscle.¹¹ By attaching a molecular chain to both rings of the [3]rotaxane, and then attaching the opposite end of each molecular chain to a gold film using gold/sulfur bonding techniques, the researchers were able to fabricate the system below (Figure 3, 4). Using electrochemical actuation to switch the ring from one site to the other, the researchers were able to use this [3]rotaxane bonded to a gold surface to bend the surface back and forth at will. They used a laser to detect the deflection of the gold surface. Just the ability to manipulate such a small system is quite astounding. While a practical application for this current system likely does not exist, the potential for such a technology is quite promising. One proposed possibility is to link several [3]rotaxanes together in a string with the hopes of generating macroscopic movement for a particular system; similar to how muscles in a biological system provide macroscopic movement.

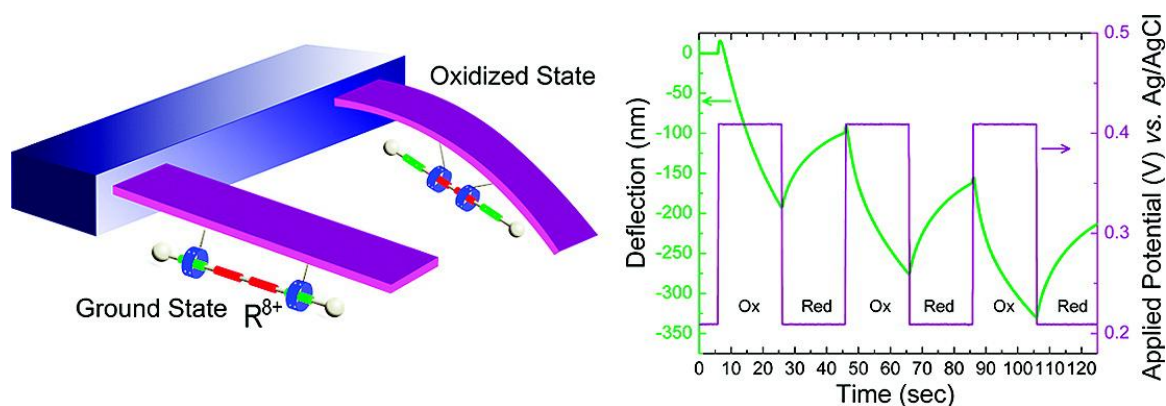


Figure 3: Bent and relaxed states of the [3]rotaxane bonded to an Au plate. Reprinted with permission from ref 11. Copyright 2009 American Chemical Society.

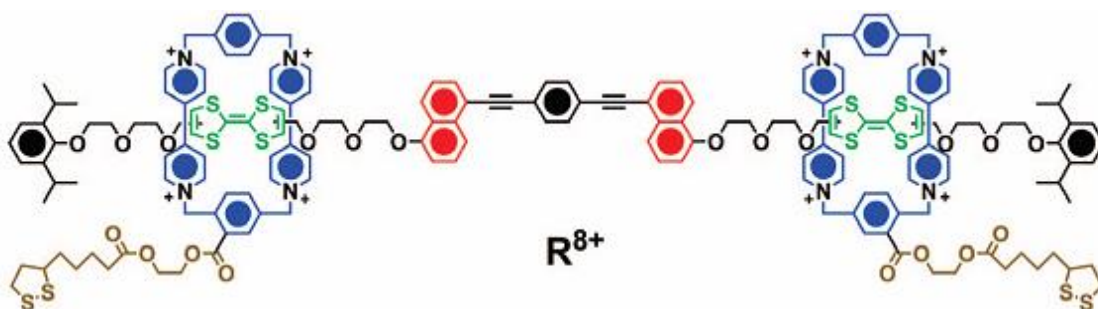


Figure 4: Molecular structure of the [3]rotaxane bonded to gold plate, and relaxed states of the [3]rotaxane bonded to an Au plate. Reprinted with permission from ref 11. Copyright 2009 American Chemical Society.

While molecular muscles are very intriguing, [3]rotaxanes are not limited to this application. Another group synthesized a [3]rotaxane that was functionally similar to Figure 4 in that the rings could move back and forth in relation to each other upon activation (Figure 5,6).

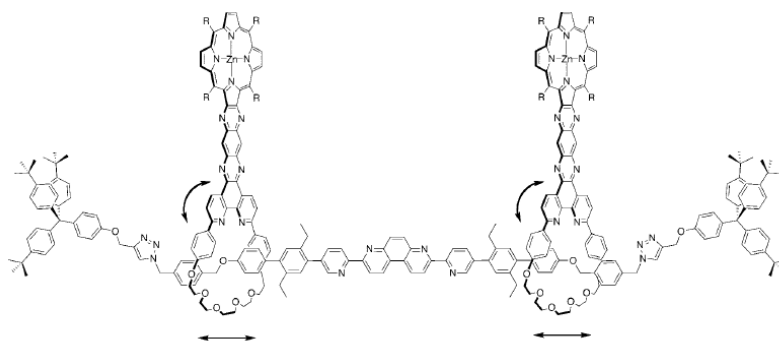


Figure 5: Molecular structure of guest/host [3]rotaxane. Reprinted with permission from ref 12. Copyright 2008 American Chemical Society.

The purpose of the project was to investigate guest/host chemistry; in essence this [3]rotaxane is an instrument used to measure the strengths of different bonding forces under certain circumstances.¹² In this particular [3]rotaxane, the two rings each contain a phenanthroline group which when aligned over the phenanthroline groups on the rotaxane thread, provide a strong coordination effect in the presence of Cu (I) ions.

Without the presence of Cu (I) ions, the rings can freely shuttle away from each other on the thread to the ends of the molecule.

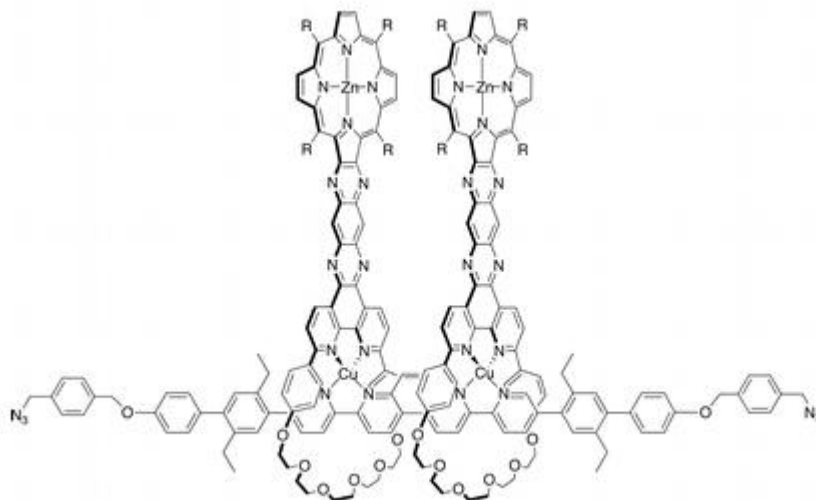


Figure 6: [3]Rotaxane with rings shuttled close together due to Cu (I) coordination. Reprinted with permission from ref 12. Copyright 2008 American Chemical Society.

On the other side of the rings, is a Zn (II) porphyrin designed to coordinate with various organic molecules (Figure 6). When large guest molecules coordinate with the Zn(II) porphyrins, pressure is exerted on the two rings to shuttle away from each other on the thread. Since the Cu(I) coordination of the thread and rings pulls the rings closer towards each another, and the guest molecules push the rings apart, one can compare the strength of the steric strain of the guest molecules relative to the Cu (I)/phenanthroline coordination forces. Larger and larger guest molecules were tested until the steric strain overcame the coordination forces forcing the rings apart. While not quite as stunning as the previous example, it is still remarkable that an instrument can be designed and built on the molecular level.

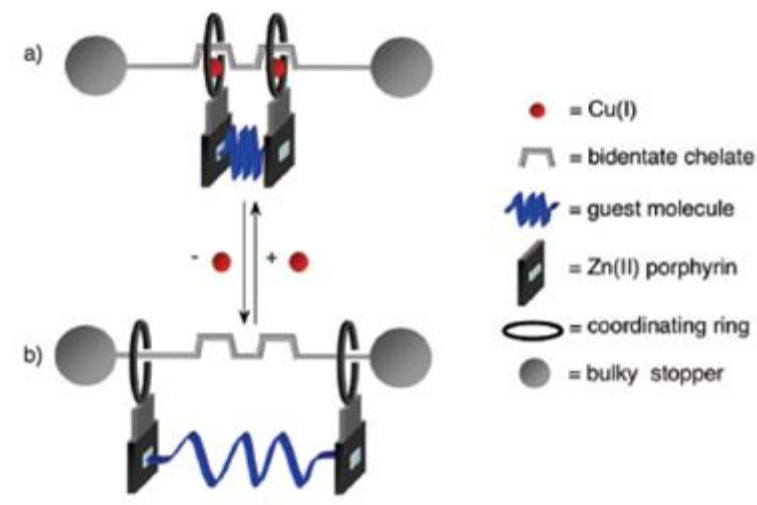


Figure 7: Principle of the Adaptable [3]rotaxane Receptor. Reprinted with permission from ref 12. Copyright 2008 American Chemical Society.

In addition to molecular muscles and instruments, [3]rotaxanes have also been used as molecular sorting devices.¹³ In one case a [3]rotaxane was synthesized to sort two different sizes of crown ethers (Figure 8). The first step was to synthesize the thread or axle with a benzene ring in the middle and only a single stopper on one end. After the axle was made, the crown ether rings were made in solution and assembled themselves around the thread making a pseudo-rotaxane (one that is not fully stoppered on both ends).

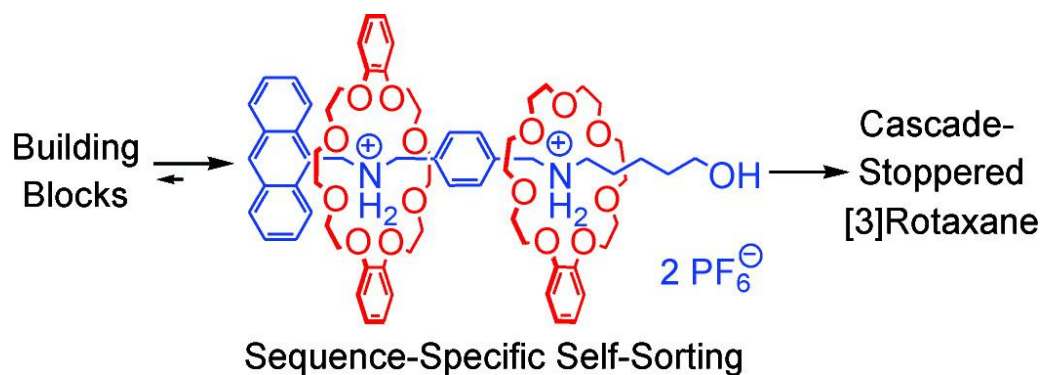


Figure 8: Molecular structure of sorting [3]rotaxane. . Reprinted with permission from ref 13. Copyright 2008 American Chemical Society.

It turns out that only the bigger of the two crown ethers is able to slip over the benzene ring in the center of the thread, so the bigger ring is stationed at the end of rotaxane with the stopper, and the smaller ring is on the unstoppered end of the rotaxane. While the above examples in no way exhaust the development of [3]rotaxanes, they do illustrate some of the most promising work. It is our hope our project will add value and further this field of study.

Of all the [3]rotaxanes that have been made, to our knowledge, none have utilized David Leigh's method of using the fumaryl-based hydrogen-bonding template (thread) plus two, disubstituted acid chlorides and xylylene diamine precursors (macrocycle) rotaxane system. The success of this system for [2]rotaxane formation is well proven and yields of 97% have been reported.¹⁴ Our goal is to synthesize a fumaramide based [2]rotaxane that can easily be dimerized to form a [3]rotaxane (Figure 9).

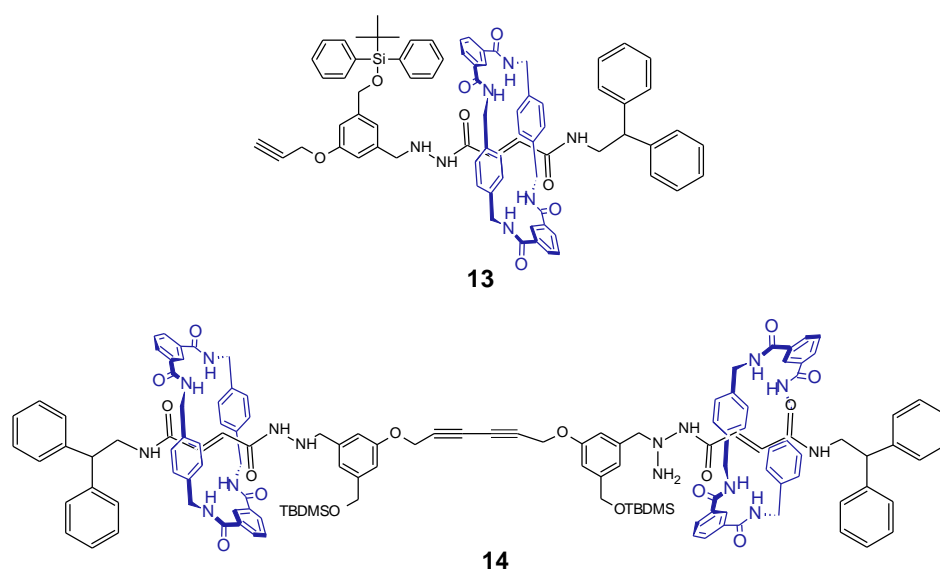
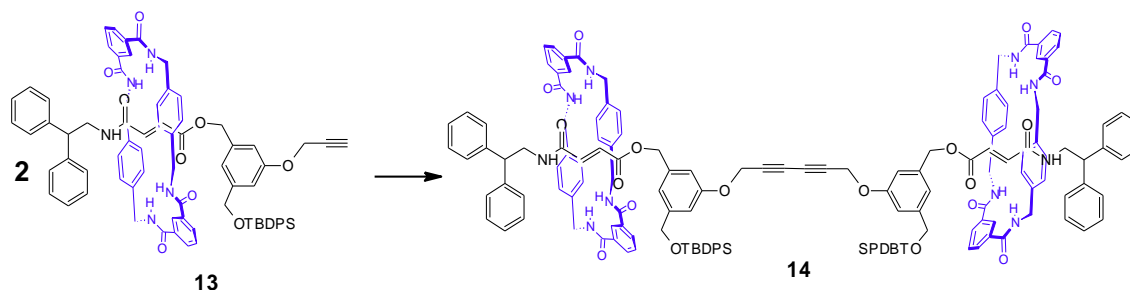


Figure 9: [2]Rotaxane precursor, **13**, and [3]rotaxane, **14**, synthetic target.

In this strategy, two propargyl groups, one from two individual [2]rotaxanes, will be combined to connect the two [2]rotaxanes **13** together to form a [3]rotaxane **14**. It is our hope this project will further the field of rotaxanes and nanotechnology by demonstrating macrocycles themselves can be used as reagents to produce even more complex and thus valuable systems, ultimately adding a better, simpler, more effective tool to the toolbox in order to advance nanotechnology to the next level.

CHAPTER 2: RESULTS AND DISCUSSION

The fundamental goal of this project was to explore and demonstrate how molecular nano-machines built from the ground up can themselves be used as reagents for building more complex and advanced nano-machines or systems of nano-machines. This was to be demonstrated by reacting two [2]rotaxanes (scheme 1, **13**) to join them together to form a single [3]rotaxane (scheme 1, **14**). Unfortunately, multiple roadblocks along the way prevented the project from progressing to this point, and the concept was not able to be tested.

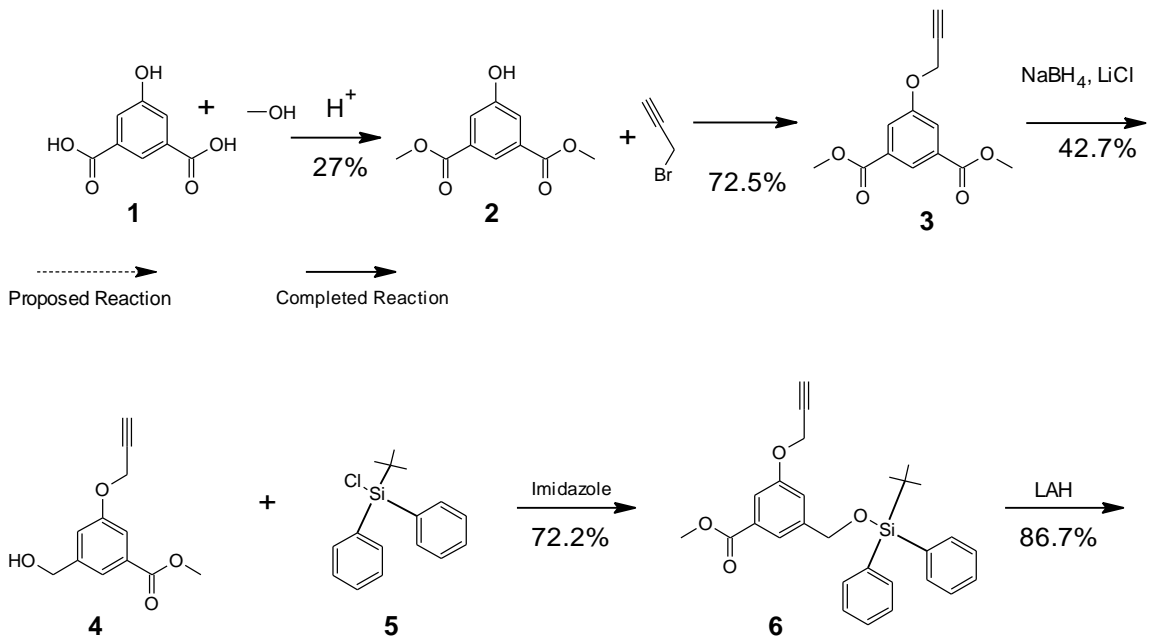


Scheme 1: Dimerization of two [2]rotaxanes to form a [3]rotaxane.

There were several minor problems encountered along the synthesis pathway which is to be expected of any project of this size. There was, however, one major problem with the protecting group TBDPS hydrolyzing which caused substantial frustration and lack of progress. Before specific details of the difficulties of the project are discussed, it seems pertinent to offer an overview of the project.

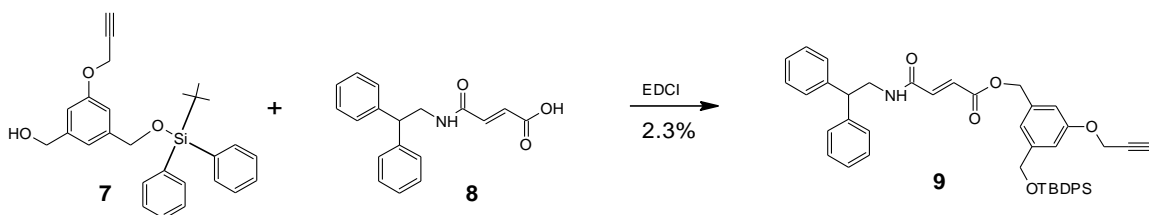
Below is a general step-by-step description of the project plan. The first step in the project is the Fischer esterification of molecule **1** with methanol to yield product **2**. Product **2** is then reacted with propargyl bromide in the presence of K_2CO_4 to yield the

ether product, **3**. The di-ester **3** is then mono-reduced by NaBH₄ to yield **4**.



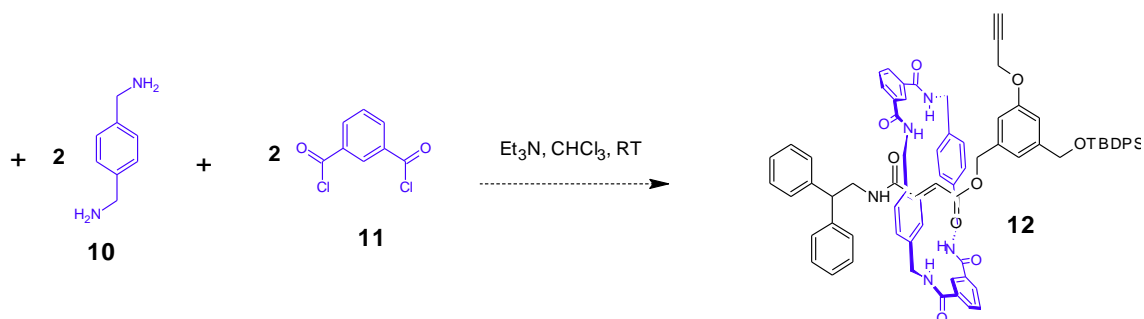
Scheme 2: Synthesis pathway through molecule **6**.

Molecule **4** is then combined with the stopper molecule **5** to produce **6**. The remaining ester group on **6** is then reduced with LAH to yield the alcohol product **7**; NaBH₄ is not sufficiently strong to reduce the monoester. Molecule **7** is then connected with molecule **8** using EDCI coupling to form the rotaxane thread template **9**.



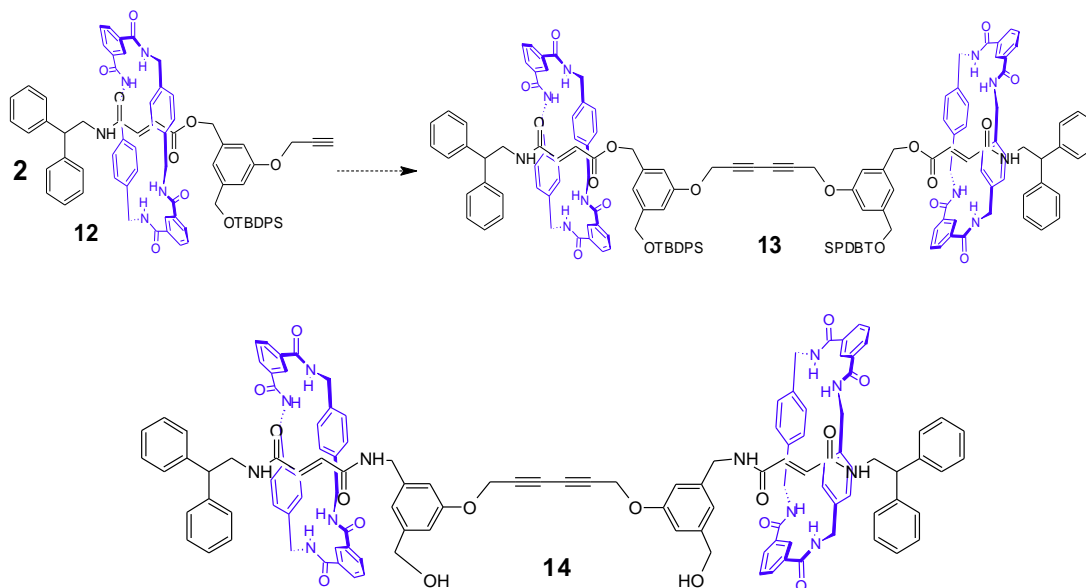
Scheme 3: Amide/ester rotaxane thread formation.

Thread **9** is then reacted with the ring components **10** and **11** to form the [2]rotaxane **12**.



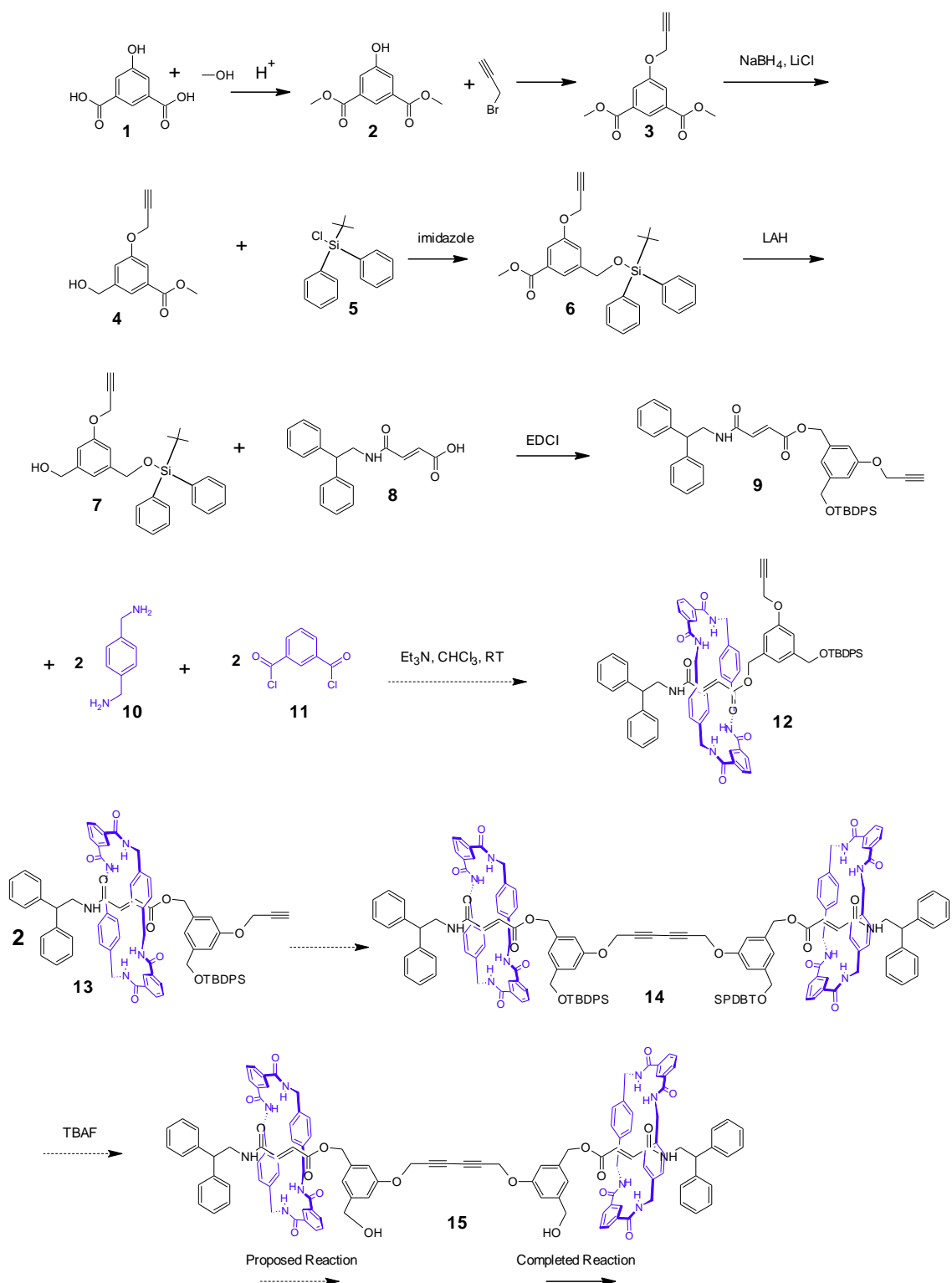
Scheme 4: Original plan for [2]rotaxane formation.

After the [2]rotaxane **12** was formed, it was planned to be dimerized by Glaser coupling of the propargyl groups of each rotaxane to form the [3]rotaxane **13**.



Scheme 5: Glaser coupling to form [3]rotaxane.

Once the [3]rotaxane **13** has been synthesized, removal of the two stopping TBDPS groups using TBAF will generate **14** and allow the two rings to move freely about the rotaxane thread. It was planned to perform NMR experiments on the [2]rotaxane, the stoppered [3]rotaxane and the unstoppered [3]rotaxane to document the properties of these rotaxane systems. Scheme 6 is the overall synthetic scheme presented in its entirety.



Scheme 6: Overall scheme for the synthesis of a [3]rotaxane.

As one can imagine for a project this size, there were several difficulties encountered along the way. Some of these difficulties are the reduction of **3** to **4**, producing the ideal amide/amide thread instead of the amide/ester thread, and finally the hydrolysis of the TBDPS protecting group. As one can see from the above reaction schemes, the core of this project is molecule **7** with a different functional group at each of the 1,3,5 position on the central benzene ring (figure 10).

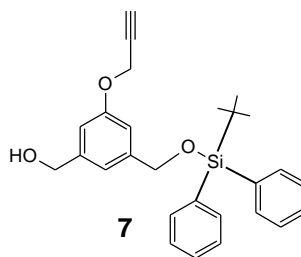


Figure 10: Central “building block” for [3]rotaxane.

The use of an aromatic core provides a very nice template as it is flat and orients the different parts of the eventual rotaxane in space in a convenient, flat, rigid configuration. The main disadvantage is a complex and fairly difficult synthesis pathway. To be fair, any synthesis that depends on three unique sites on a benzene ring to be reacted on with similar chemistry independently will have inherent difficulty. As one can see from the reaction scheme, molecule **7** can be obtained with moderate difficulty by performing five sequential reactions.

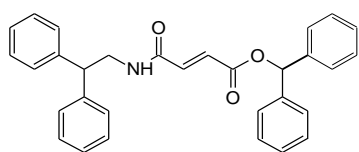
Probably the most troublesome step is reducing the diester molecule **3** to yield the monoester molecule **4**. One of the issues is reactions yields are somewhat low. Yields of 67% have been obtained (1:2 ratio of starting material to product by NMR), but the average is around 50%. In addition, product **4** is the most difficult to purify of all the

molecules from **1** to **7**. Care has to be taken during work-up of the reaction to not lower the pH too far, or heat the reaction mixture too much during removal of excess solvent after neutralizing the NaBH₄ and before extraction. If either of these factors is not taken into account, there is risk of the hydrolyzing the remaining ester group. This phenomenon has been evidenced by tailing of the product spot of molecule **4** when TLC analysis of the reaction mix was performed. When acetic acid was added to the eluting mixture, the tailing was reduced or eliminated indicating the presence of a carboxylic acid. Any product which undergoes hydrolysis is considered waste since both the alcohol and resulting carboxylic acid will react with the diphenyl t-butyl silyl chloride in the subsequent reaction.

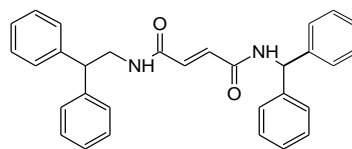
Flash chromatography of **4** has some challenges, but a simple trick eliminates much of the struggle. Separation is complicated by the fact the molecule **4** is more polar than molecule **3** meaning molecule **3** will elute first on the chromatography column. This makes separation and purity of molecule **4** difficult; fortunately, the addition of diphenyl t-butyl silyl chloride in the next reaction is extremely tolerant of molecule **3**. The addition of diphenyl t-butyl silyl chloride to molecule **4** is so tolerant of molecule **3**, it becomes the preferred method of synthesis to not remove un-reacted molecule **3** before synthesis of molecule **6**. After the synthesis of **6**, the reaction product generally contained excess diphenyl t-butyl silyl chloride and other impurities requiring flash chromatography. If pure molecule **4** was used for the synthesis of molecule **6**, flash chromatography using 100% CHCl₂ must be performed to separate molecule **6** from excess TBDPS. Molecule **6** elutes very quickly, but behind leftover diphenyl t-butyl silyl chloride to provide a pure clear oil when solvent is removed. If a mixture of molecule **3**

and molecule **4** was used for the synthesis of molecule **6**, then a volume of hexane equal to the volume of silica gel used should be run prior to eluting with CHCl_2 to ensure adequate separation.

Synthesis of molecule **7** from **6** is fairly straightforward, but requires chromatography with a 3:2 ratio of hexane and diethyl ether as the eluting solvent. While the pathway to synthesize molecule **7** has its difficulties, it is certainly possible. Things start to become more complicated in the next step when it comes to synthesizing the rotaxane thread. Ideally the alcohol group on molecule **7** would be converted to an amine so the center fumaric acid template of the molecule would have two amide groups instead of one amide and one ester (Figure 11).



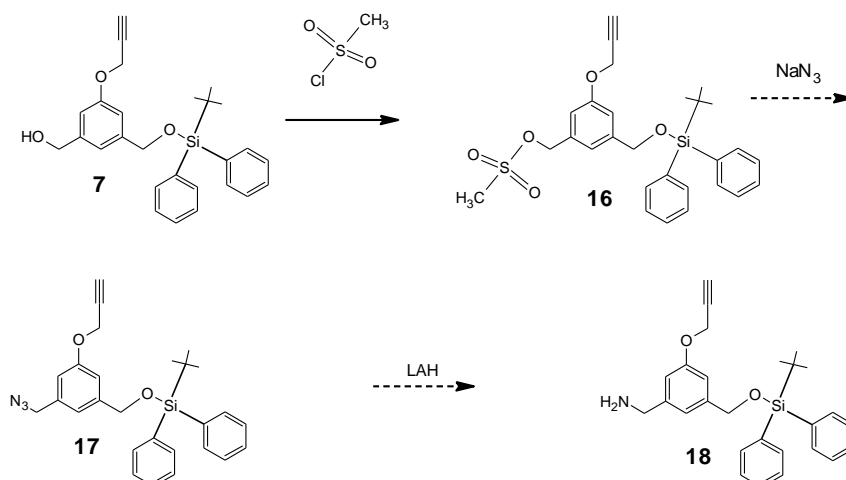
Amide/Ester Rotaxane Thread 35% Yield



Amide/Amide Rotaxane Thread 97% Yield

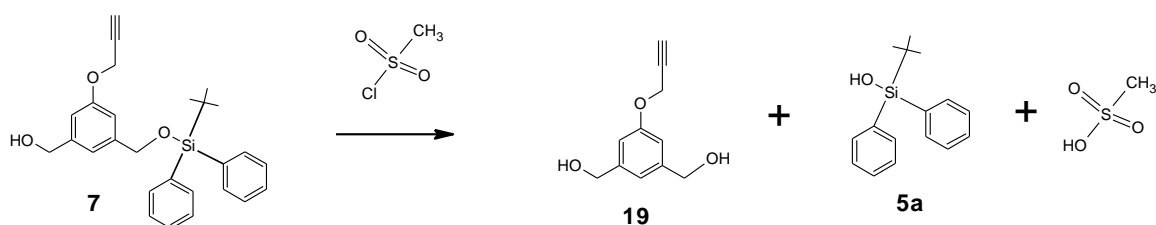
Figure 11: Amide/amide template vs. ester/ester template.

When two amides are present, the maximum reported yield for rotaxane formation is 97%¹⁴; when one amide and one ester are present, the maximum reported yield is 35%¹⁴ (Figure 11). Originally, the alcohol **7** was to be converted to a mesylate group **16** followed by conversion to azide **17**, then finally being reduced to the amine **18** (Scheme 7).



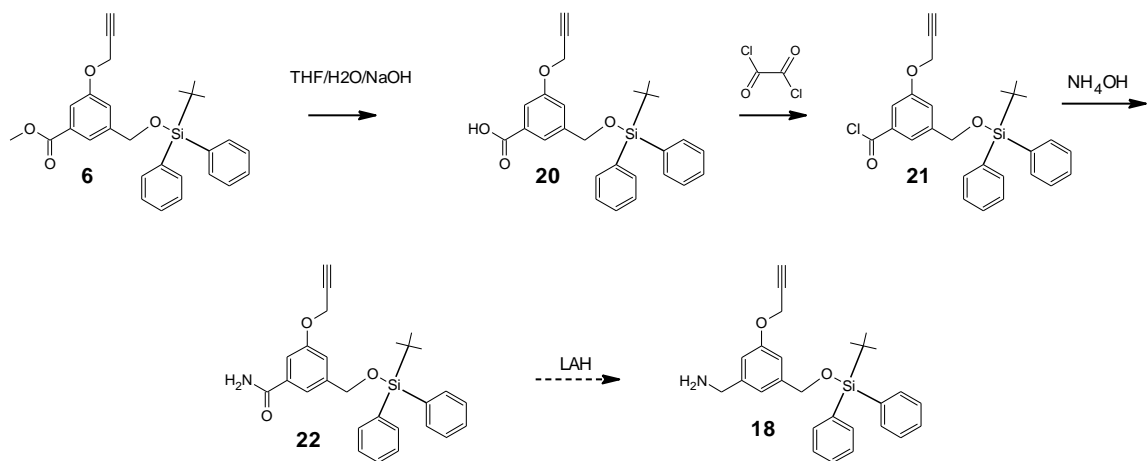
Scheme 7: Original plan for amide/amide thread formation.

This plan was abandoned when the mesylation reaction resulted in cleaving the TBDPS group **5a** resulting in the symmetrical diol product **19** (scheme 8). There is no easy method to recover the symmetrical diol which means more product has to be synthesized from step one.



Scheme 8: Hydrolysis of TBDPS group during mesylation.

An additional proposed route to synthesize an amide/amide rotaxane thread (figure 10) is outlined in scheme 9. When this route was attempted, the TBDPS group hydrolyzed in a manner similar to that shown in scheme 8. As a result, it was decided to proceed with the synthesis of the less desirable, but still viable ester/amide thread.



Scheme 9: Alternate plan for amide/amide thread formation.

The synthesis of the thread molecule **9**, (scheme 6) via EDCI coupling proved to be challenging. One factor is the reaction only proceeds to about 50% completion. The real problem came from the instability of the TBDPS protecting group. During flash column of one thread synthesis (molecule **9**) too small of a column provided insufficient separation and had the result of nearly all of the fractions collected contained mixtures. However, one fraction contained just enough thread to obtain NMR data. A subsequent column was performed, but copious amounts of TBDPS alcohol were collected in the eluting tubes indicating hydrolysis of the TBDPS group had occurred; neither product nor starting material was able to be recovered.

When TLC analysis was performed on samples which contained the TBDPS group, it was a regular occurrence to see a small spot at the very top of the plate which was identified as TBDPS alcohol; normally, one would assume it was leftover starting material. However, this phenomenon mainly occurred during analysis **after** a column was performed in an effort to determine which fractions to combine (figure 12).

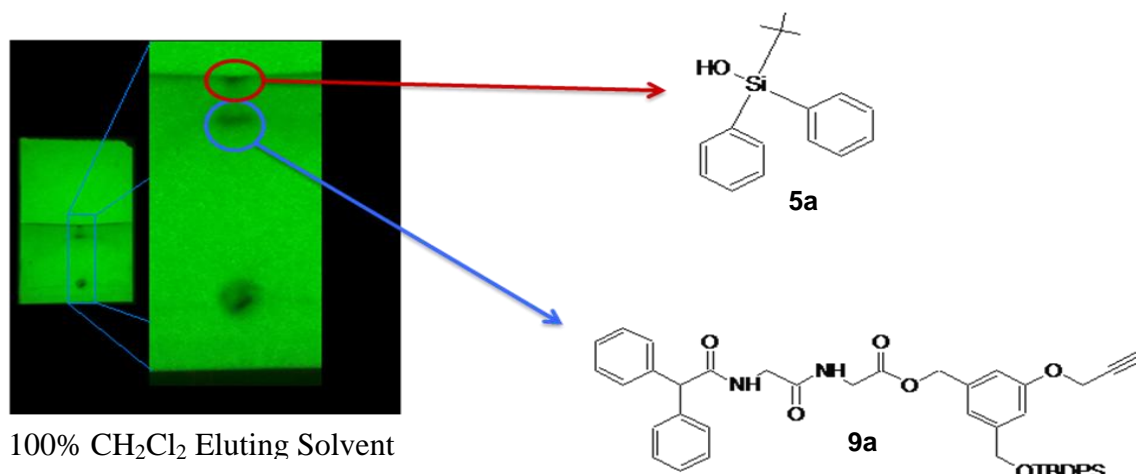


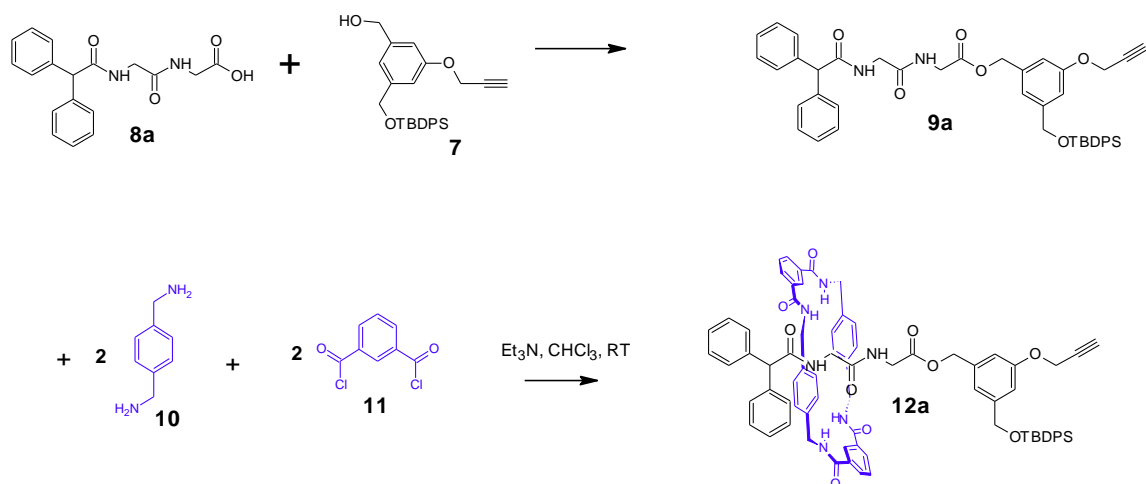
Figure 12: TBDPS hydrolysis on TLC plate.

Any TBDPS alcohol present would have eluted off the column almost instantly (and was often detected in the first few fractions). The only logical conclusion is the TBDPS group was hydrolyzing on the TLC plates/silica gel. While previous rotaxane projects successfully used the TBDPS protecting group, it is quite likely hydrolysis of the TBDPS protecting group was the biggest frustration and hindrance to the completion of the project. More product was rendered useless when the TBDPS group hydrolyzed at various stages of the project than any other cause.

The exact reason(s) for hydrolysis of the TBDPS group are not known. Other rotaxane syntheses have been successfully performed with TBDPS. It is strongly suspected the other two functional groups on the central benzene ring create enough of an electron withdrawal on the aromatic ring to create a partial positive on the benzyl carbon connected to the TBDPS ether. If this were true, it would seem the TBDPS ether would be easily cleaved in basic environments. However, **6** does not decompose during the reduction with LAH. This could be due to the lack of water available for hydrolysis since

any moisture present would quickly react with the LAH. Another potential solution would be to have another carbon atom or two between the benzene ring and the TBDPS ether to isolate any electron withdrawing effects. Other potential solutions to the problem include making sure solvents are dry, and using solvents that are less likely to be wet. The addition of MeOH to CH₂Cl₂ is probably a poor choice in comparison to other options such as diethyl ether. Also, since the TBDPS group seems to be fairly stable except for interactions with silica gel, it would be wise to design the project so the TBDPS group would be bound to the molecule at the very end of the synthesis pathway in an effort to minimize the number of times molecules containing TBDPS were in contact with a column. If an appropriate solution for the TBDPS hydrolysis could be found, the project should be able to be completed.

When all of previously synthesized thread precursor, molecule **8** (scheme 6), was consumed, reactions with a different glycine based tread precursor were attempted (Scheme 10).



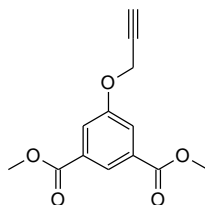
Scheme 10: [2]rotaxane synthesis

TLC analysis demonstrated 100% diethyl ether was an excellent eluting solvent to purify the glycine thread **9a**; the method provided an excellent separation via flash chromatography. The thread was then reacted in a baffled 500ml RFB with ring precursors **10** and **11** added at 8ml/hour via syringe pumps for about 5 hours to create a pseudo high dilution condition for molecules **10** and **11**. This setup is performed to limit side reactions such as polymerization and catenane formation. After the reaction ran it was purified via flash chromatography. A TLC was performed on every fraction collected during the separation, and the thread was present in the early fractions, followed by no material for several fractions, then several fractions with only a single spot on the TLC plate with the same RF value which was presumed to be the rotaxane.

After the fractions were combined, analytical data was collected. NMR analysis was performed and was inconclusive as to whether rotaxane formation had occurred or not. Mass spectrometry was then performed and failed to produce a mass peak equal to the mass of the rotaxane above the baseline. After a couple of hours of trying to interpret the mass spectra for possible pieces or fragments, no correlation between likely decomposition products and peaks in the mass spectrum could be identified. As a final measure, the sample was run through the LC before injection into the mass spectrometer to ensure only a single fraction was present in the solution. The only major peak detected was at 219 m/z. When a simple fumaric based rotaxane and thread were direct injected as references, a clear strong peak was present at the mass of the molecules and/or the mass plus sodium. While positive identification was able to be achieved for the two rotaxane threads synthesized, this was not the case for the final rotaxane. HNMR analysis was inconclusive at best and ESI-MS failed to provide a parent peak equal to the

mass of the molecule. As a result, it was concluded rotaxane formation did not occur and decomposition of the thread potentially occurred as well. At this point, nearly all of the starting material had been consumed. If further attempts were to be made, more material would have had to be synthesized from the beginning. Considering the multiple instances of hydrolysis of the TBDPS group on the rotaxane thread, it seemed doubtful a [3]rotaxane could be synthesized before the TBDPS group hydrolyzed, and the ring and thread dissociated. This combined with the fact the ideal amide/amide thread was not able to be easily synthesized using the current synthetic pathway, it was determined the best approach would be to incorporate the lessons learned from this project into a new, redesigned synthetic pathway.

CHAPTER 3: EXPERIMENTAL

Synthesis of molecule **3**

Previously synthesized dimethyl 5-hydroxyisophthalate (5g, 23.79mmol) and acetone (80 ml) were placed in a 250ml RBF. Next, K_2CO_3 (2g) was placed in a microwave oven for approximately for 2-3 minutes and then added to the 250ml RBF. Propargyl Bromide (5ml, 80% in toluene) was then added to the 250ml RBF slowly via syringe. Finally, the reaction mixture was refluxed under an argon atmosphere for five hours. The reaction was stopped by cooling it down to room temperature, and then placing $CHCl_3$ (75ml) and H_2O (75ml) into the RBF and stirring for approximately 30 minutes. Next, the reaction mixture was transferred to a separatory funnel, and the $CHCl_3$ layer was saved and subsequently extracted 3 times with NaOH (50ml, 2M), 3 times with H_2O (50ml) and three times with saturated NaCl solution (50ml). Finally, the $CHCl_3$ was dried with a scoop of Na_2SO_4 , filtered, rotovaped, and placed on the vacuum pump for a couple of hours. The final solid (g, 75.02% yield) was analyzed via 1H NMR (300 MHz, $CDCl_3$) 8.32 (m, 1H), 7.83 (d, $J=1.1$ Hz, 2H), 4.78 (d, $J=2.20$, 2H), 3.97 (s, 6H), 2.53 (m, 1H).

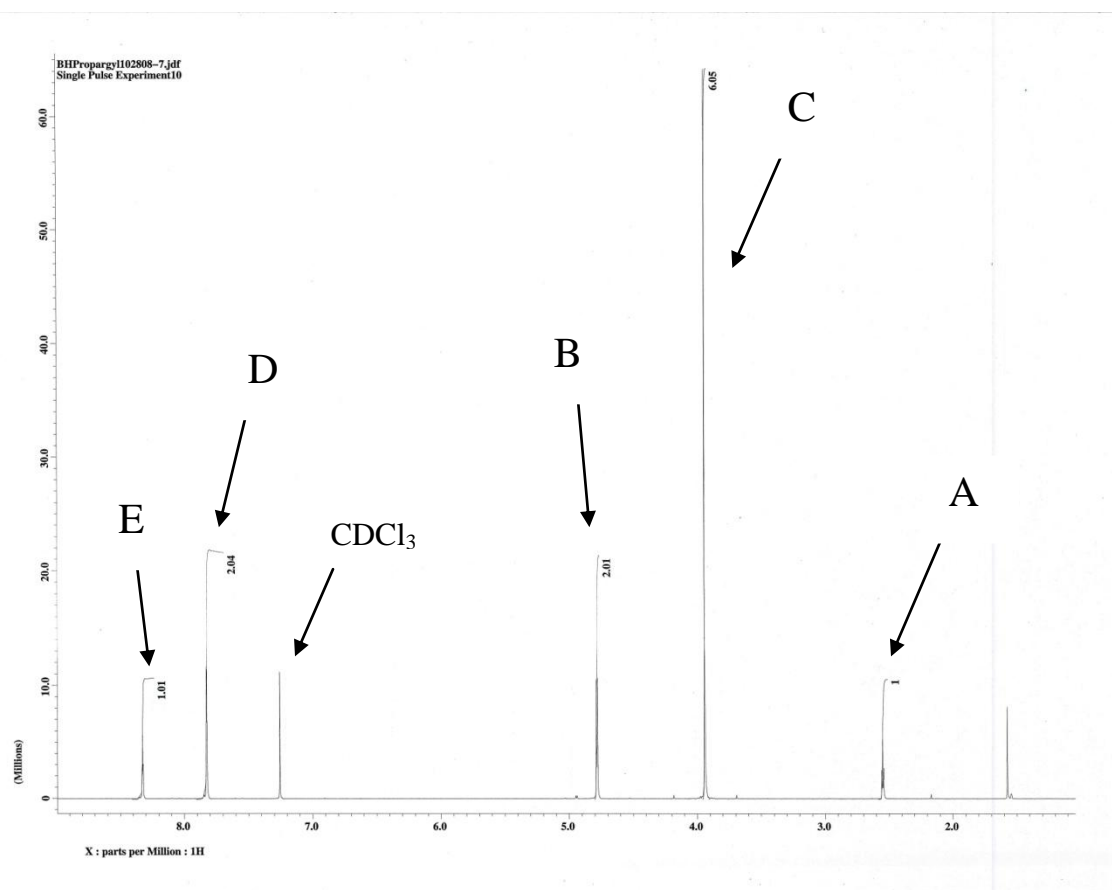
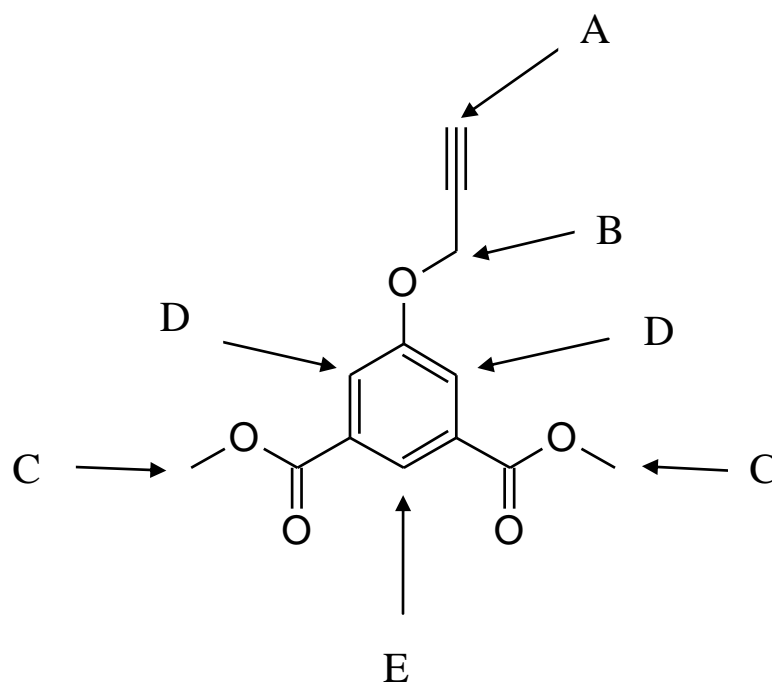
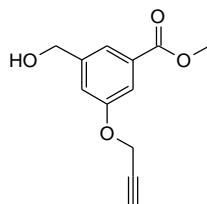


Figure 13: ¹H NMR of molecule 3

Synthesis of molecule 4



Previously synthesized molecule **3** (3.32g, 11.07mmol, 1 eq) and THF (100 ml) were placed in a 250ml RBF. Next, LiCl (1.86g, 44.38mmol, 4eq) was microwaved for 2 minutes to remove moisture and combined with NaBH₄ (1.67g, 44.288mmol, 4 eq) and then added to the 250ml RBF. Finally, methanol (120ml) was added to the reaction mixture stepwise while stirring with a magnetic stir bar (15ml initial addition, followed by 20ml 5 minutes later, and slow addition of the remainder 5 minutes after that.) to minimize the risk of boil-over due to released hydrogen gas. The reaction was then left stirring under an argon atmosphere overnight. The reaction was stopped by cooling it down to -10 C with an ice/acetone/rock salt bath. The pH was then adjusted to 2-4 by adding 1M HCl while stirring. Next, the reaction mixture was placed on a rotary evaporator (with limited heat and time to prevent hydrolysis of the remaining ester), and excess methanol and THF was removed to aid in extraction. The contents were then transferred to a separatory funnel, and extracted 3 times with 100ml CH₂Cl₂. The CH₂Cl₂ extractions were combined and extracted with 40ml of saturated NaHCO₃ and NaCl respectively. Finally, the CH₂Cl₂ solution was dried with a scoop of Na₂SO₄, filtered, rotovaped, and placed on the vacuum pump for a couple of hours. The final solid contained a mix of product and starting material and was purified using flash chromatography with CH₂Cl₂ gradually shifting to CH₂Cl₂ with 3% MeOH as the eluting solvent. The final solid (1.29g, 42.7% yield) was analyzed via ¹H NMR (300 MHz,

CDCl₃) 7.62 (s, 1H), 7.50 (m, 1H), 7.17 (m, 1H), 4.71 (m, 4H), 3.88 (s, 3H), 2.53 (m, 1H).

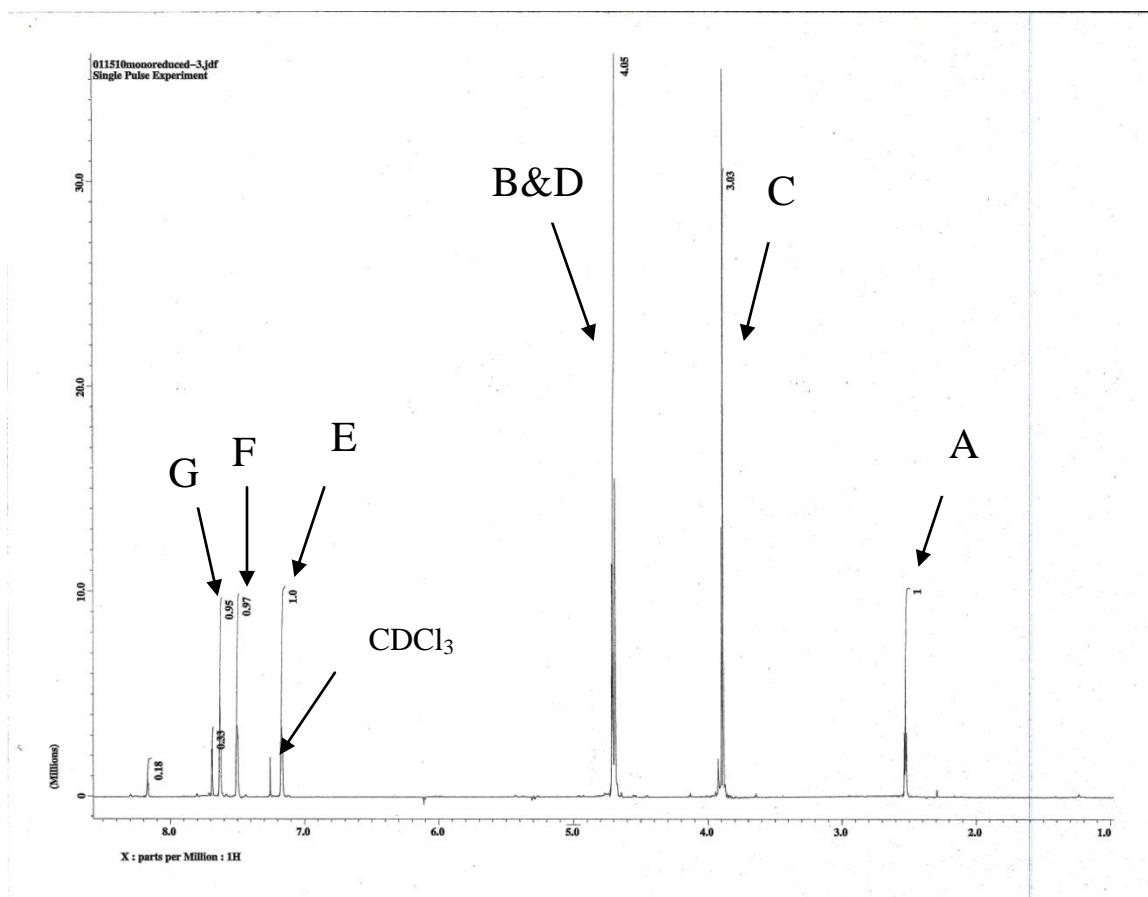
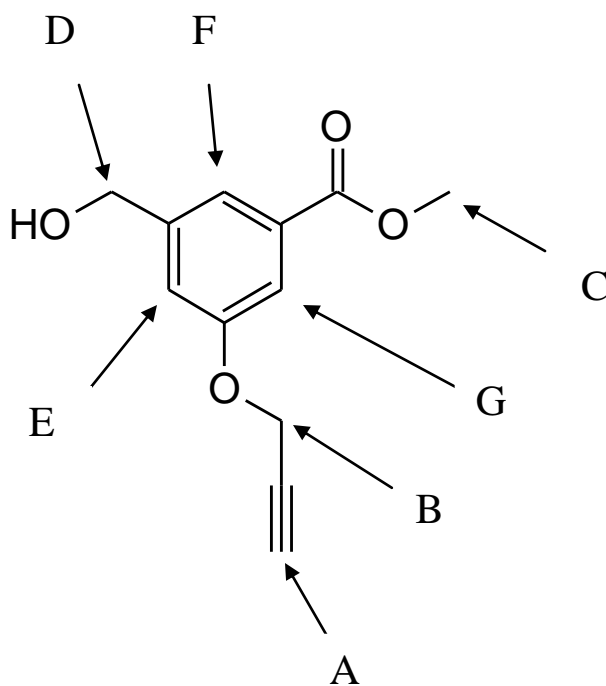
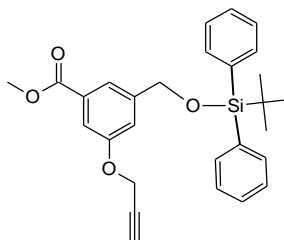


Figure 14: ¹H NMR of molecule 4

Synthesis of molecule **6**

Previously synthesized molecule **4** (1.29g, 4.74mmol, 1 eq), CH_2Cl_2 (50ml) and t-butyl-diphenyl-silyl chloride (1.29ml, 4.97mmol, 1.05 eq) were placed in a 100ml RBF. Next, Imidazole (0.645g, 9.47mmol 2eq) was added to the reaction mix along with a magnetic stir bar and left overnight with an Ar atmosphere. The reaction was stopped by transferring the reaction mix to a separatory funnel with an additional 50ml CH_2Cl_2 and extracting 5 times with 100ml H_2O , 2 times with 75ml saturated NaCl solution. Finally, the CH_2Cl_2 solution was dried with a scoop of Na_2SO_4 , filtered, rotovaped, and placed on the vacuum pump for a couple of hours. The final solid contained a mix of product and starting material and was purified using flash chromatography with CH_2Cl_2 as the eluting solvent and achieved a very clean separation. The final solid (1.47g, 72.23% yield) was analyzed via $^1\text{H NMR}$ (300 MHz, CDCl_3) 7.70-7.67 (m, 4H), 7.58 (s, 1H), 7.51 (m, 1H), 7.46-7.34 (m, 6H) 7.29 (m, 1H), 4.77 (s, 2H), 4.73 (m, 2H), 3.89 (s, 3H), 2.53 (m, 1H) 1.11 (s, 9H).

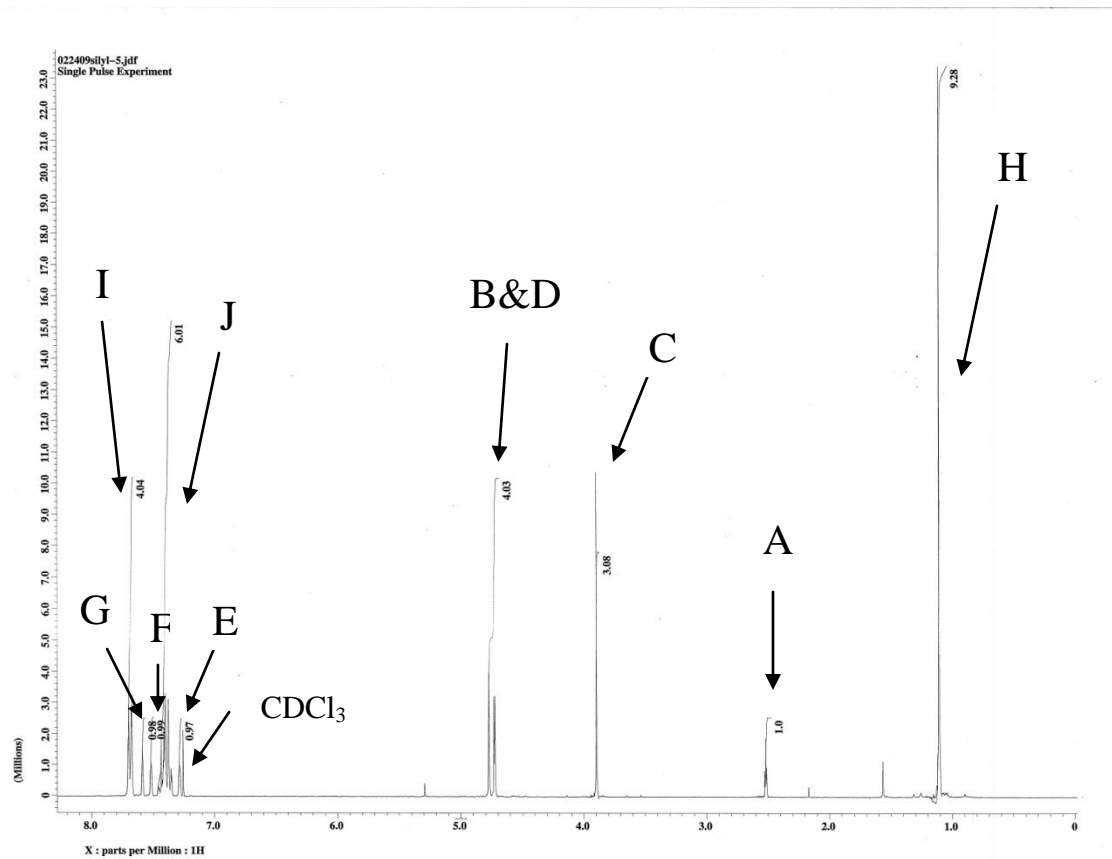
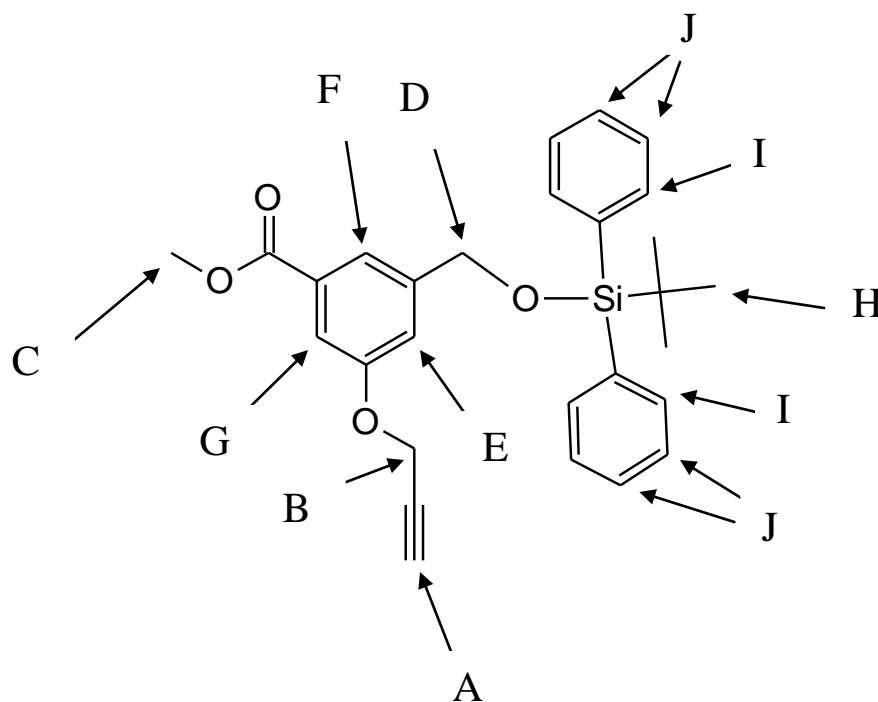


Figure 15: ¹H NMR of molecule 6

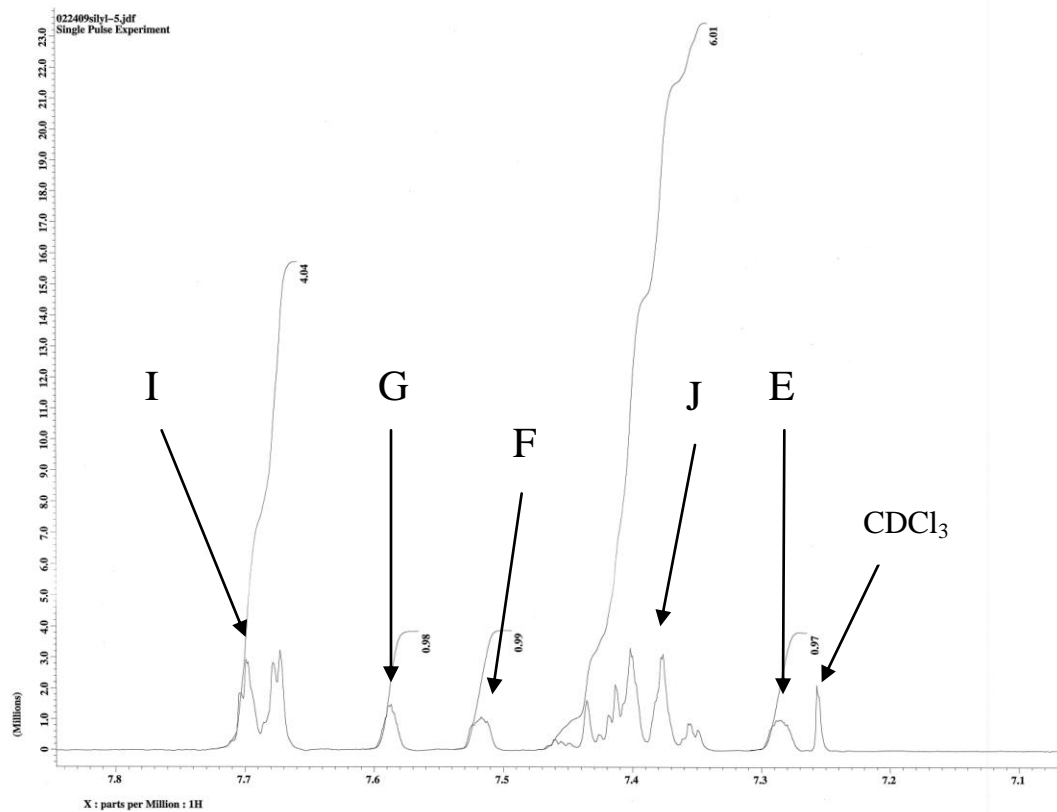
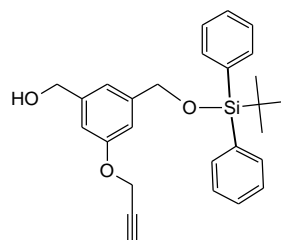


Figure 16: Enlarged portion of HNR of molecule **6**

Synthesis of molecule **7**

Previously synthesized **6** (3.85g, 8.40mmol, 1 eq), THF (200ml) and LAH (1.27g, 33.59mmol, 4 eq) were placed in a 500ml RBF. The reaction was then left stirring under an argon atmosphere overnight. The reaction was stopped by cooling it down to -10 C with an ice/acetone/rock salt bath. The pH was then adjusted to 2-4 by adding 1M HCl, then approximately 100ml of H₂O while stirring. Next, the reaction mixture was placed on a rotary evaporator (with limited heat and time to prevent hydrolysis of the silyl group), and excess THF was removed to aid in extraction. The contents were then transferred to a separatory funnel, and extracted 4 times with 100ml CH₂Cl₂. The CH₂Cl₂ extractions were combined and extracted with 75ml of saturated NaHCO₃ and NaCl respectively. The final solid contained a mix of product, the intermediate aldehyde, and starting material and was purified using flash chromatography with a 3:2 mix of Hexane and DEE as the eluting solvent and achieved a very clean separation. The final solid (3.13g, 86.68% yield) was analyzed via ¹H NMR (300 MHz, CDCl₃) 7.71-7.69 (m, 4H), 7.46-7.35 (m, 6H) 7.01 (s, 1H), 6.89 (s, 2H), 4.76 (s, 2H), 4.69 (m, 2H), 4.64 (s, 2H), 2.50 (m, 1H) 1.11 (s, 9H).

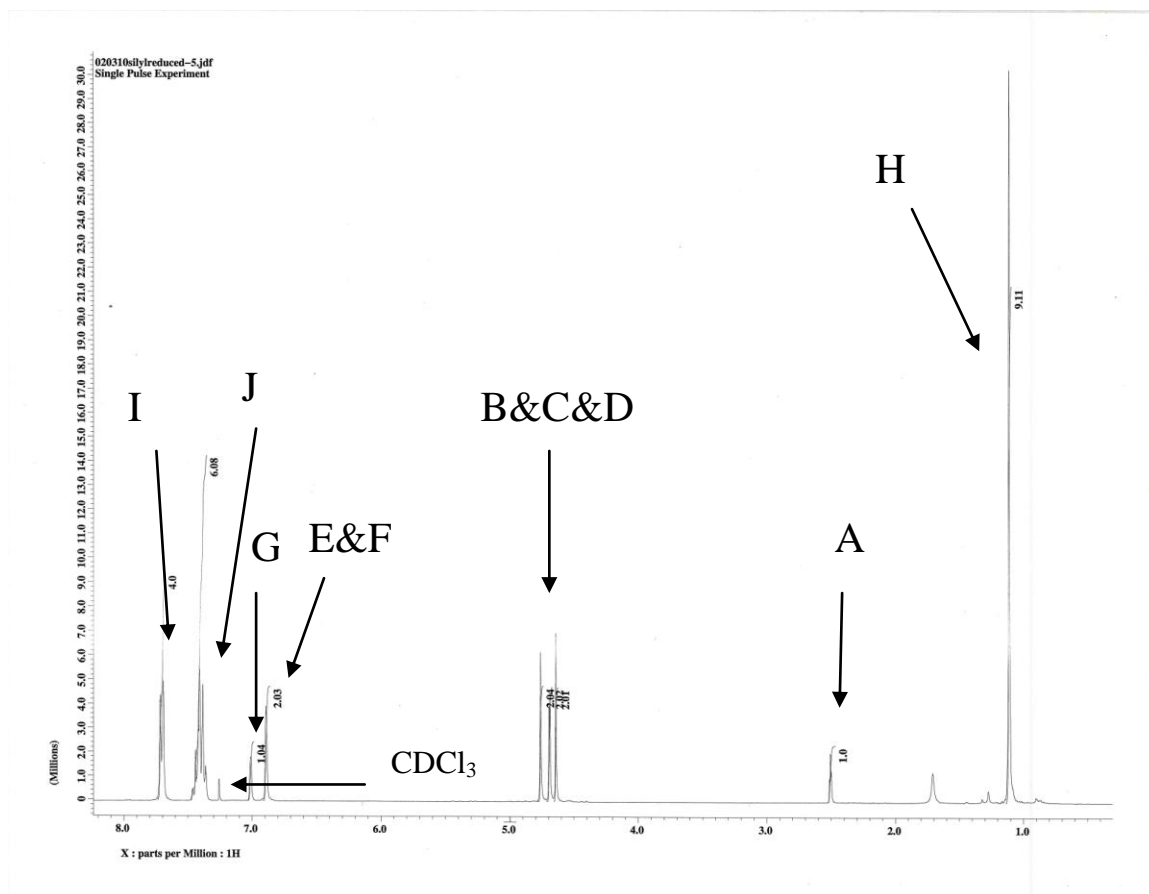
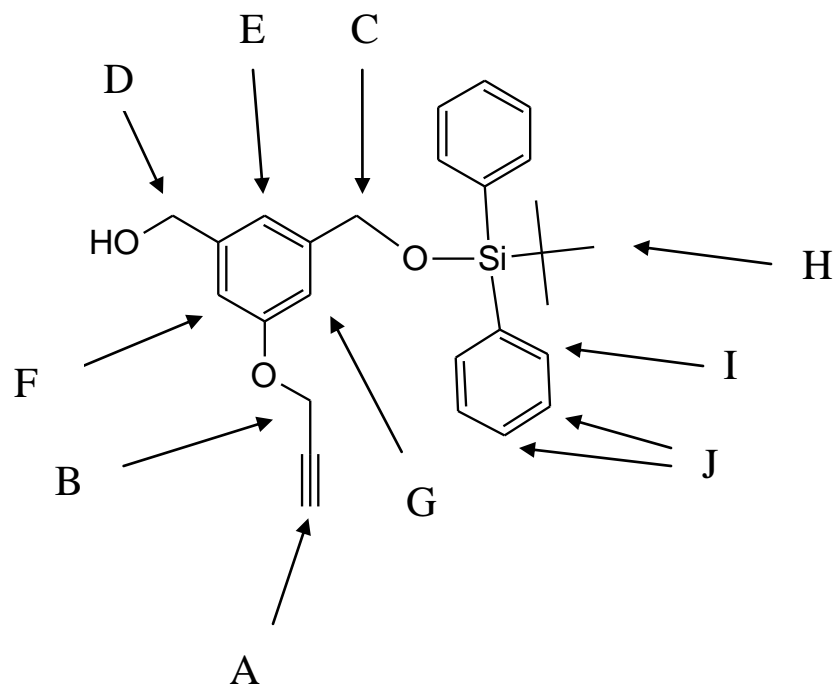
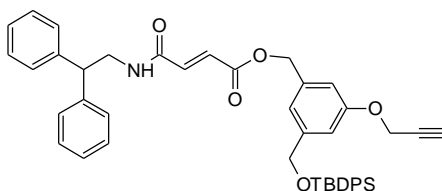


Figure 17: ¹H NMR of molecule 7

Synthesis of Fumeric Thread:



Previously synthesized **7** (0.50g, 1.16mmol, 1 eq), **8** (397.8mg, 1.22mmol, 1.05eq), EDCI (333.58mg, 1.74mmol, 1.5eq), DMAP (400.27mg 2.09mmol, 1.8eq), CH₂Cl₂ (75ml), and a magnetic stir bar were placed in a 250ml RBF that was submersed in an ice bath. The reaction was then left stirring under an argon atmosphere as the reaction mixture warmed to room temperature overnight. Progress of the reaction was checked the next day by TLC, and a significant amount of starting material was present so the 250ml RBF was chilled again and another round of equal mass of EDCI and DMAP was added and ran overnight. On the third day, the reaction was stopped by transferring the mix to a separatory funnel and extracting 4 times with 1M 100ml HCl, 1 time with 100ml saturated NaHCO₃ and NaCl respectively. The final solid contained a mix of product and starting material and was purified using flash chromatography with CH₂Cl₂ with 4% MeOH. Only a single fraction was collected that contained product without starting material, which had a mass of 15mg for a 2.3% yield. The thread was analyzed via ¹H NMR (300 MHz, CDCl₃) 7.75-7.69 (m, 4H), 7.46-7.35 (m, 6H) 7.33-7.26 (m, 11H), 7.25-7.19 (m, 3H), 7.07-7.03 (s, 1H), 6.91-6.72 (m, 4H), 5.92-5.75 (s, 1H), 5.28 (s, 0.5H), 5.15 (s, 2H), 4.76 (s, 2H), 4.69 (m, 2H), 4.21 (m, 1H), 3.95 (m, 2H), 2.50 (m, 1H). 1.11 (s, 9H).

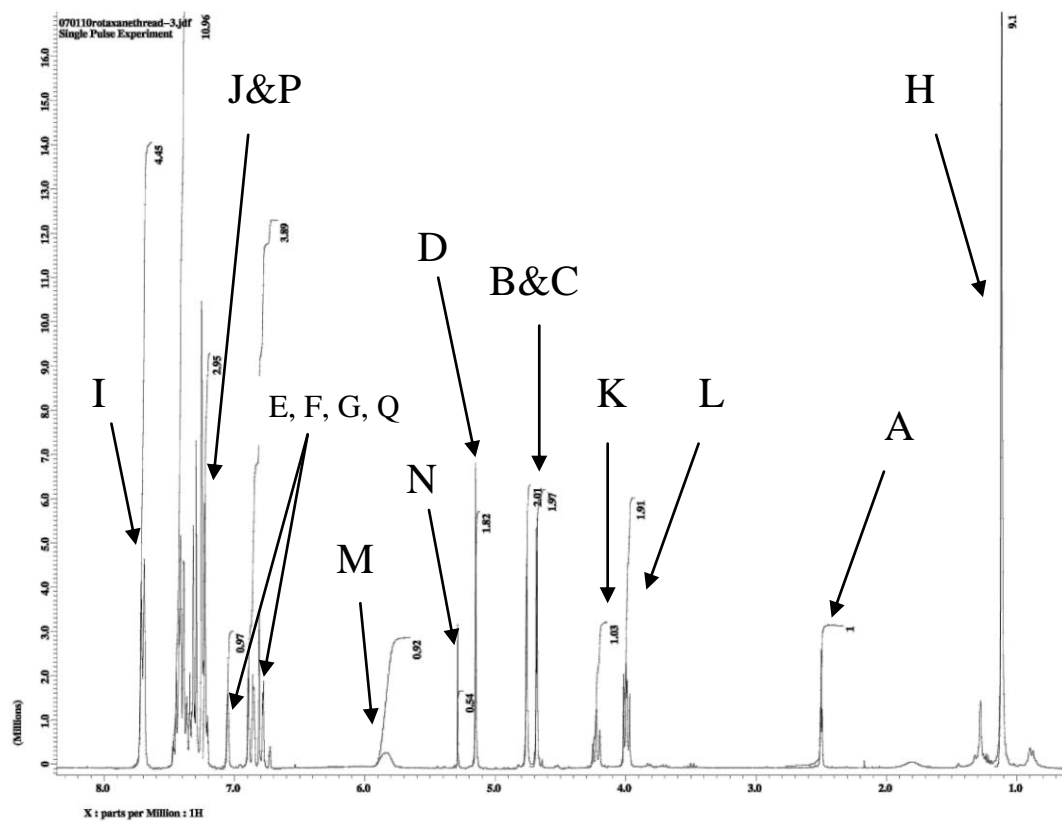
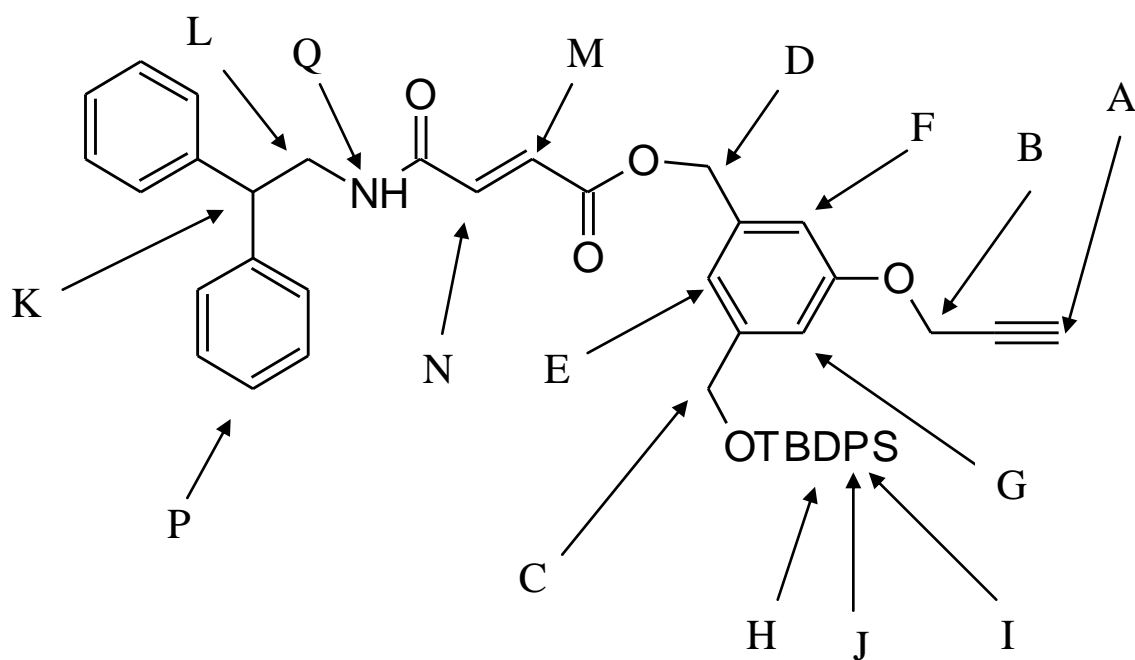


Figure 18: ¹H NMR of molecule 9

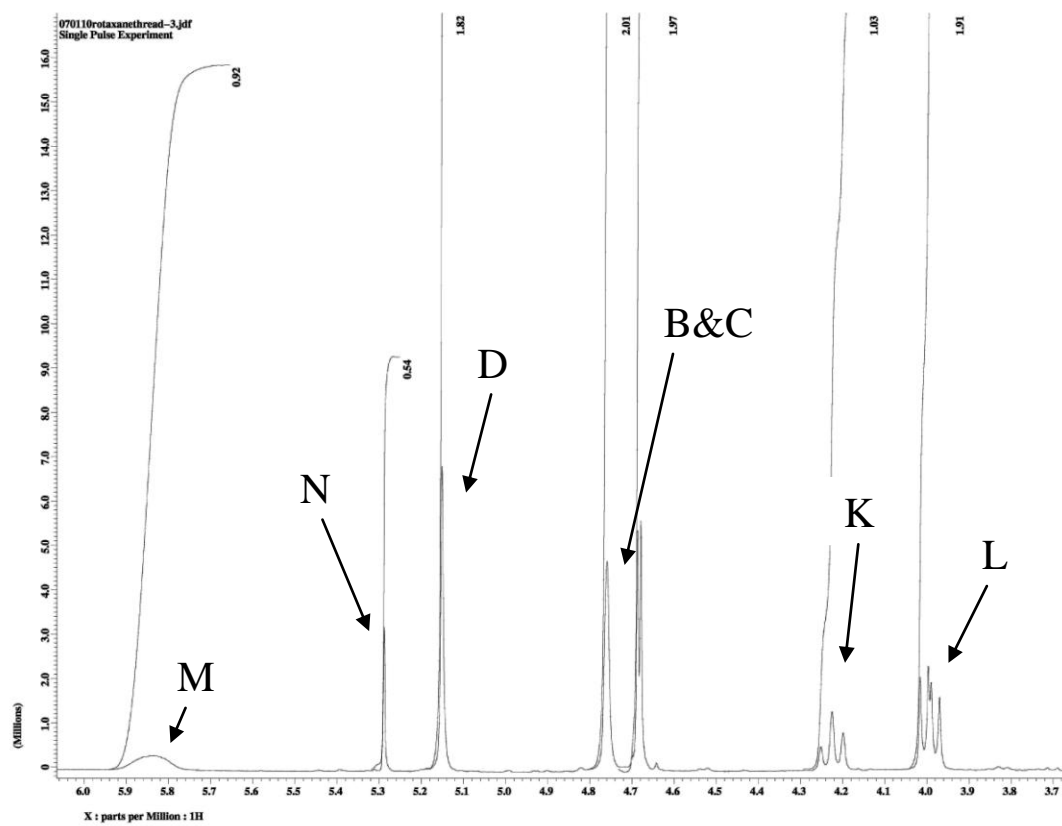


Figure 19: Enlarged portion of ^1H NMR of molecule **9**

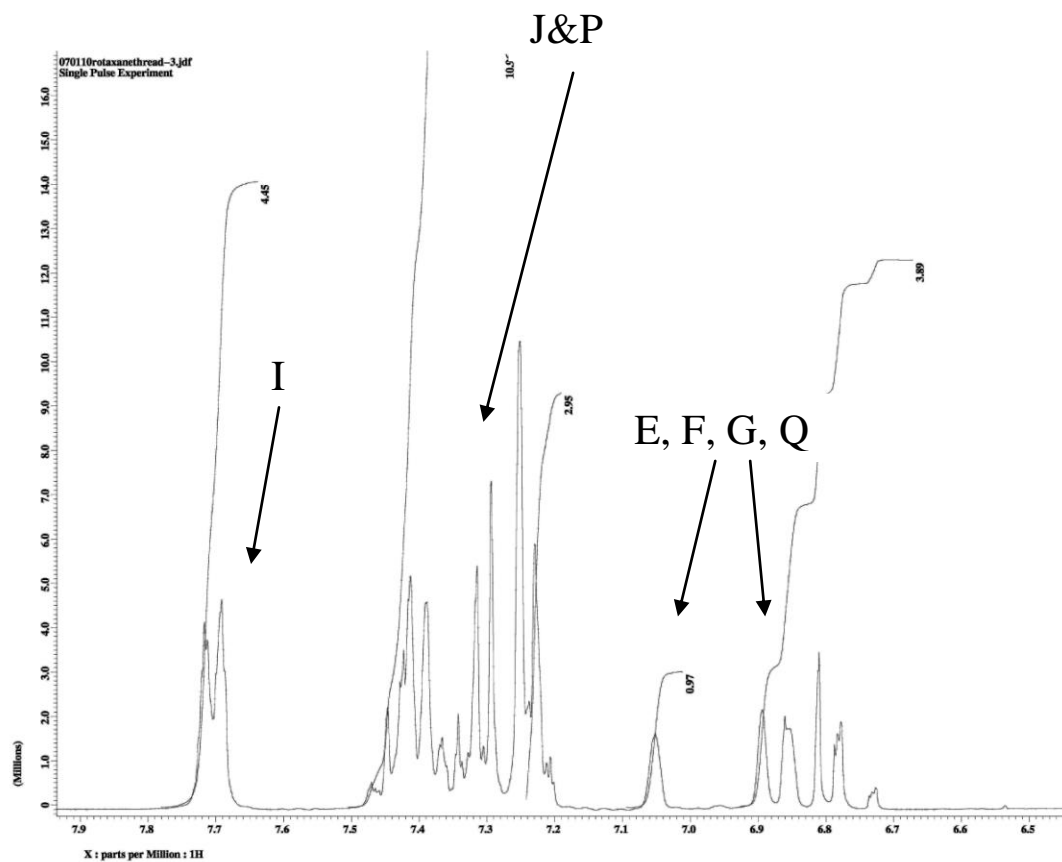
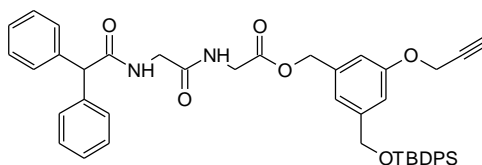


Figure 20: Enlarged portion of HNMR of molecule **9**

Synthesis of Gly-Gly Thread:



Previously synthesized **7** (0.50g, 1.16mmol, 1 eq), Gly-Gly acid thread precursor, **8a** (397.8mg, 1.22mmol, 1.05eq), EDCI (333.58mg, 1.74mmol, 1.5eq), DMAP (400.27mg 2.09mmol, 1.8eq), CH₂Cl₂ (75ml), and a magnetic stir bar were placed in a 250ml RBF that was submersed in an ice bath. The reaction was then left stirring under an argon atmosphere as the reaction mixture warmed to room temperature overnight. The reaction was stopped by transferring the mix to a separatory funnel and extracting 4 times with 1M 100ml HCl, 1 time with 100ml saturated NaHCO₃ and NaCl respectively. The final solid contained a mix of product, and starting material and was purified using flash chromatography with 100% anhydrous diethyl ether. An excellent separation was achieved resulting in 196mg of solid and a 23% final yield. ¹H NMR (300 MHz, CDCl₃) 7.75-7.69 (m, 4H), 7.46-7.35 (m, 6H) 7.33-7.26 (m, 2H), 7.25-7.19 (m, 3H), 7.09-7.06 (s, 1H), 6.98-6.92 (m, 1H), 6.89-6.85 (m, 2H), 5.12-5.09 (s, 2H), 4.99 (s, 0.5H), 4.78 (s, 2H), 4.68 (m, 2H), 4.00 (m, 2H), 3.91 (m, 2H), 2.50 (m, 1H). 1.11 (s, 9H).

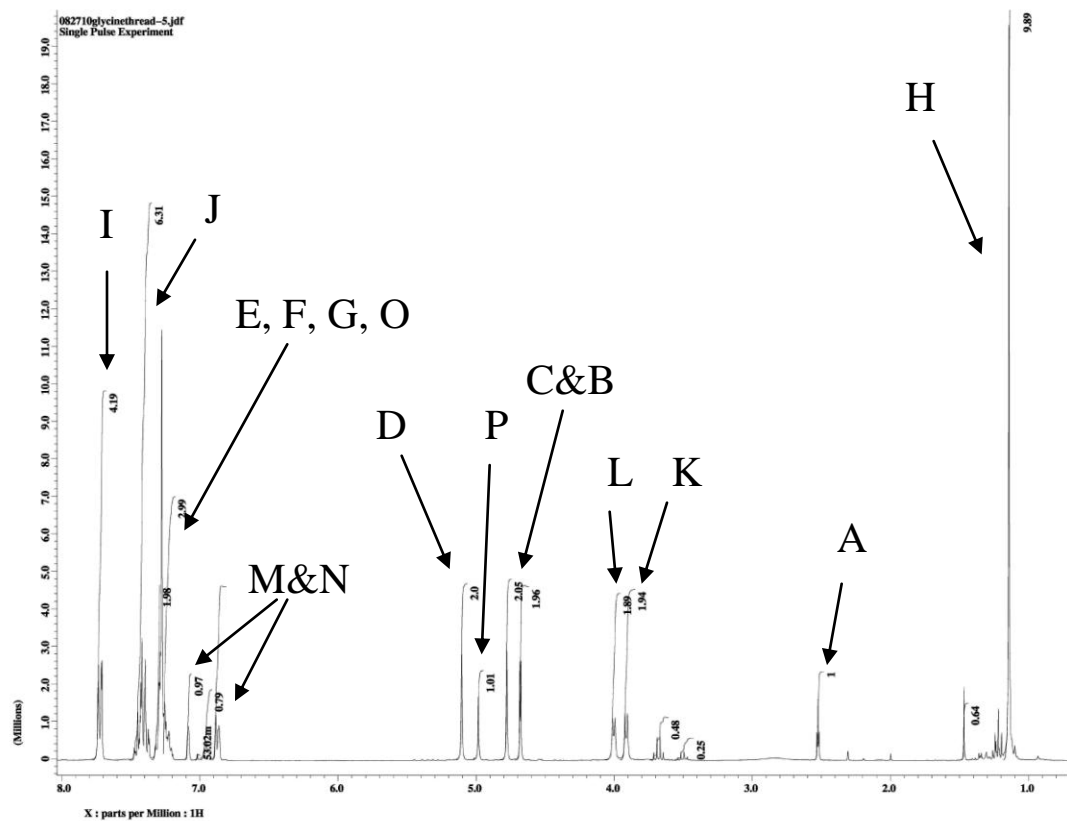
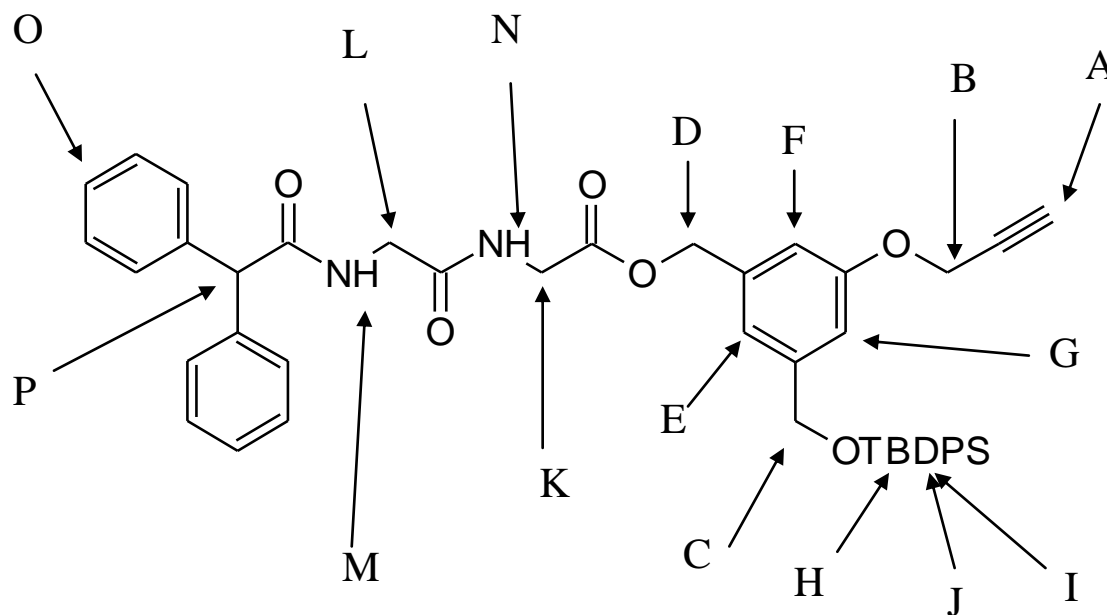


Figure 21: HNMR of molecule 9a

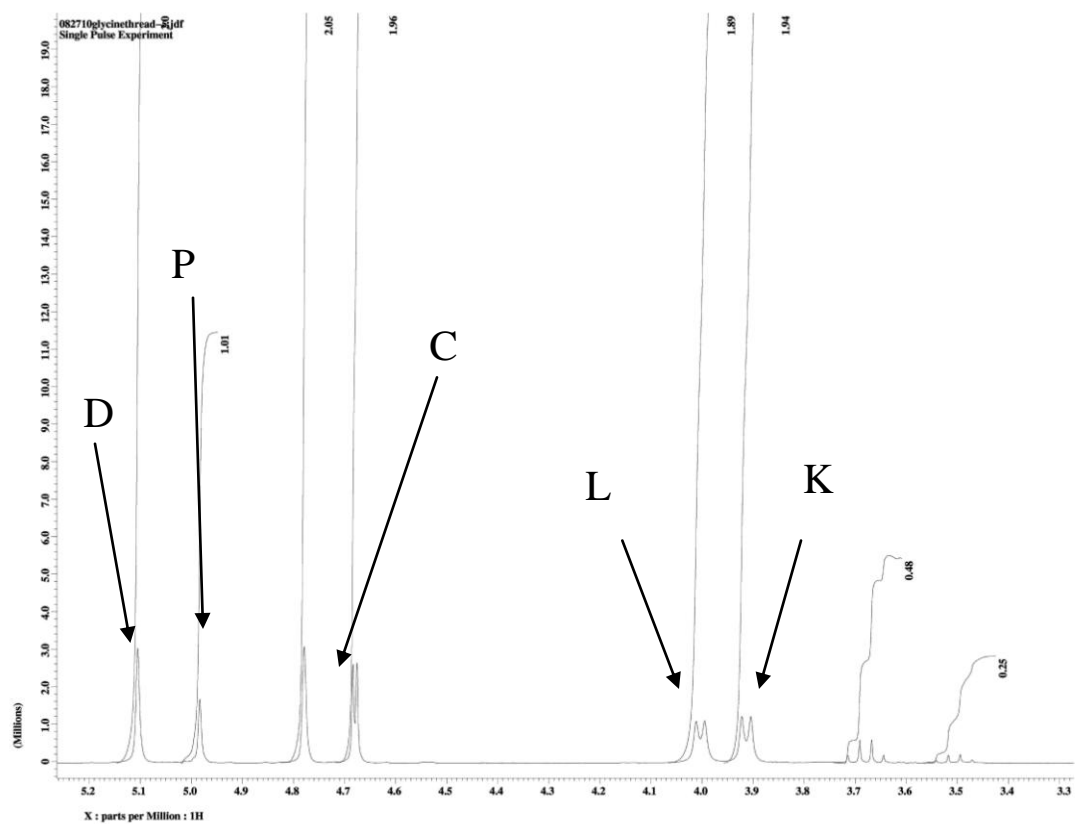


Figure 22: Enlarged portion of ^1H NMR of molecule **9a**

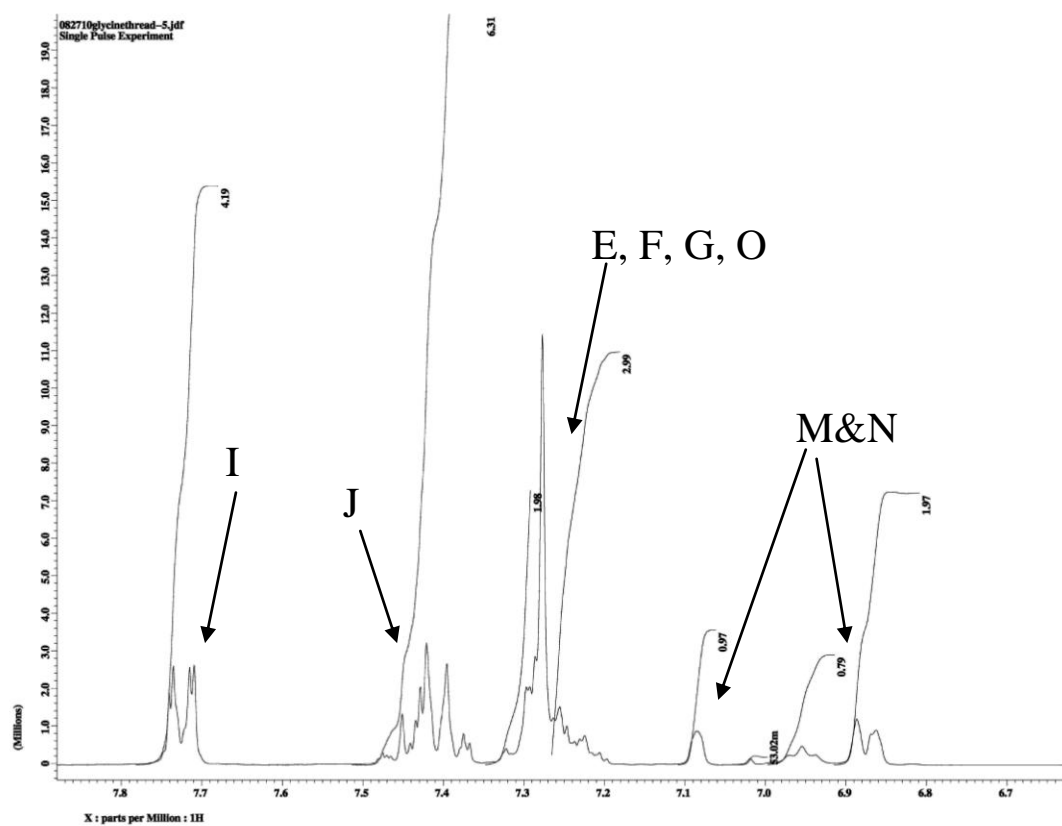


Figure 23: Enlarged portion of ^1H NMR of molecule **9a**

CONCLUSION

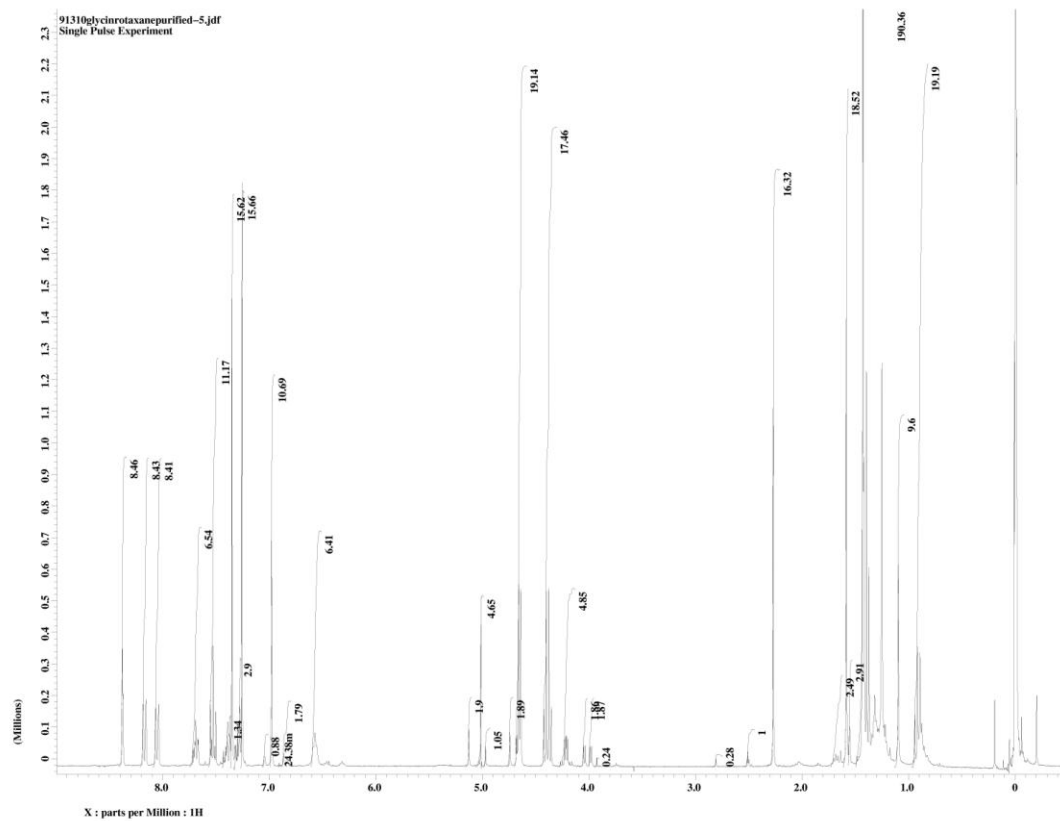
While the project goals were not achieved, several successes were still realized. Methods for several new compounds have been developed and other existing methods have been improved upon. In addition, several lessons can be learned from the difficulties experienced through the course of this project which can be applied to future projects. While the TBDPS protecting group is a powerful asset to organic chemistry, it does have its limitations as demonstrated by this project. However, the realization of TBDPS limitations can be applied to the design of future projects to ensure efficient trouble-free synthetic pathways. While the project goal of synthesizing more complex nanomachines from simpler systems was not able to be tested, nothing was learned in this project that would suggest the original goal is not possible.

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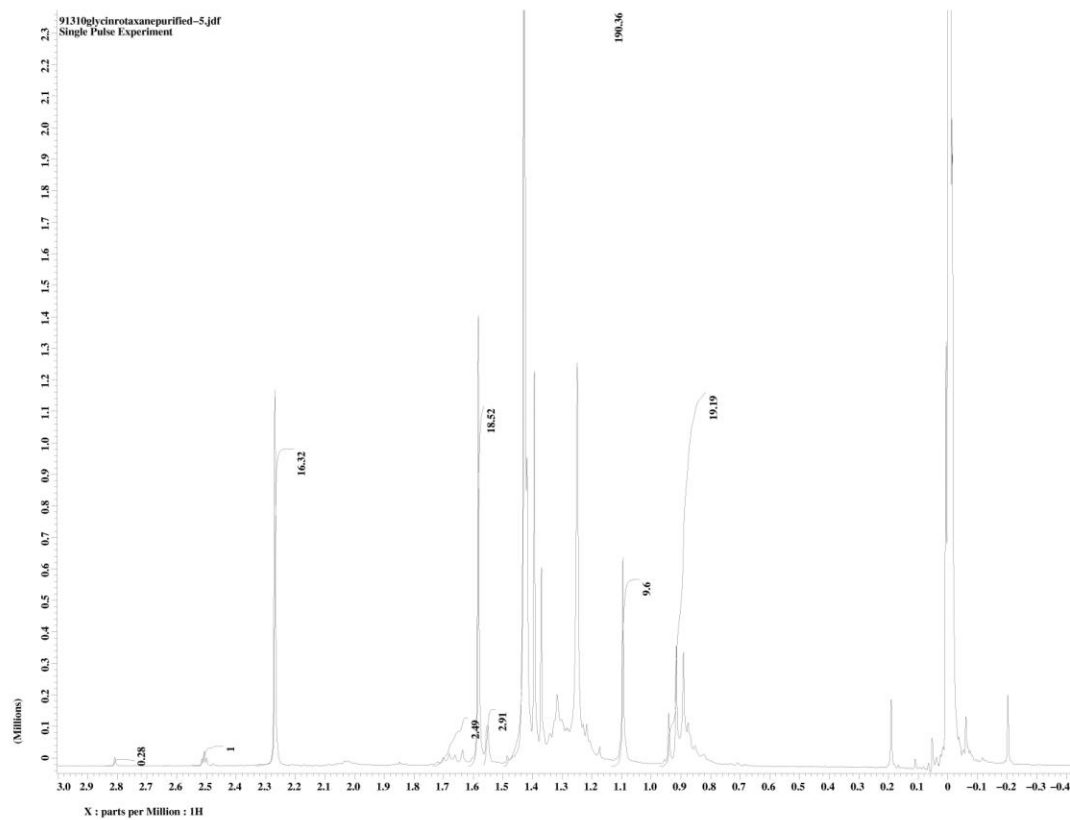
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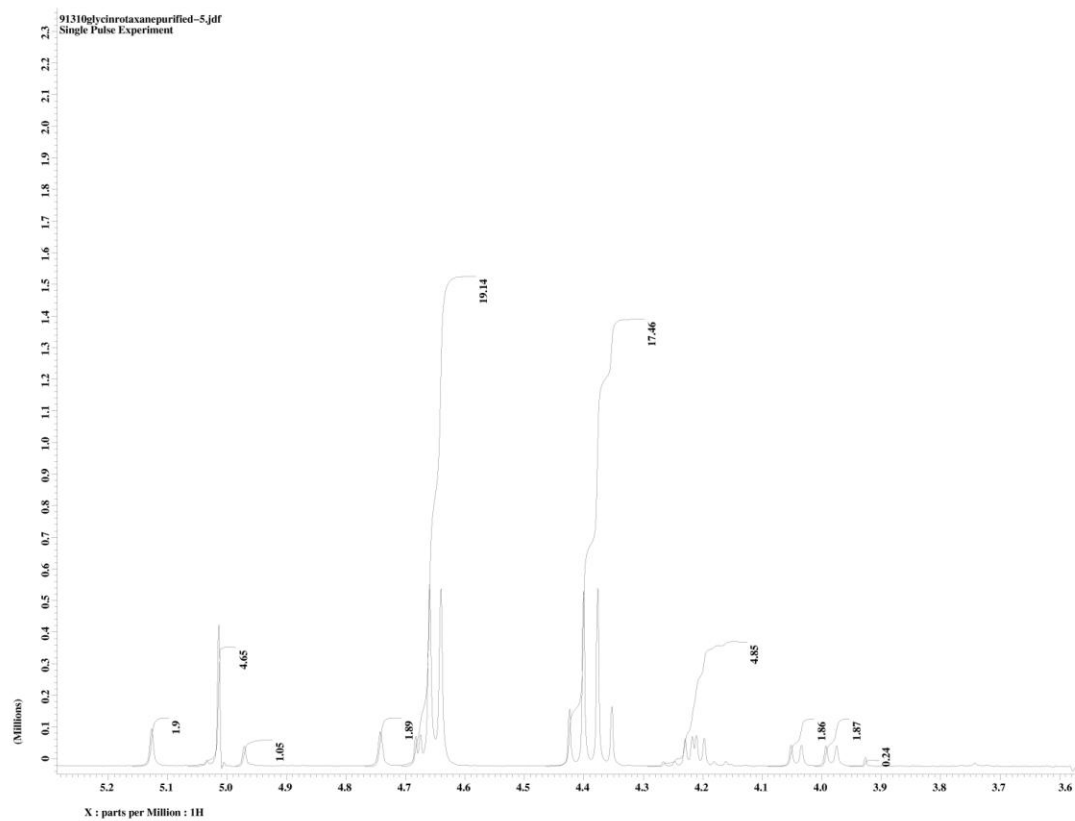
APPENDICES



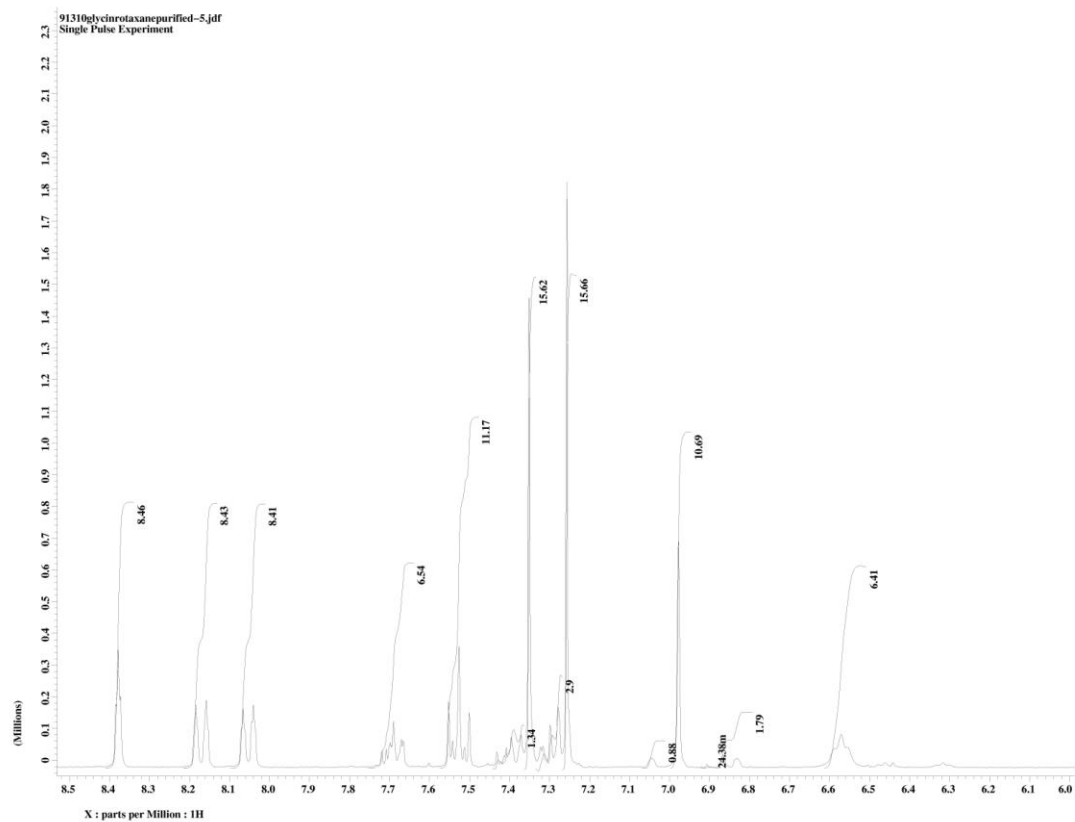
Appendix 1: HNMR of presumed gly-gly rotaxane (molecule 12a)



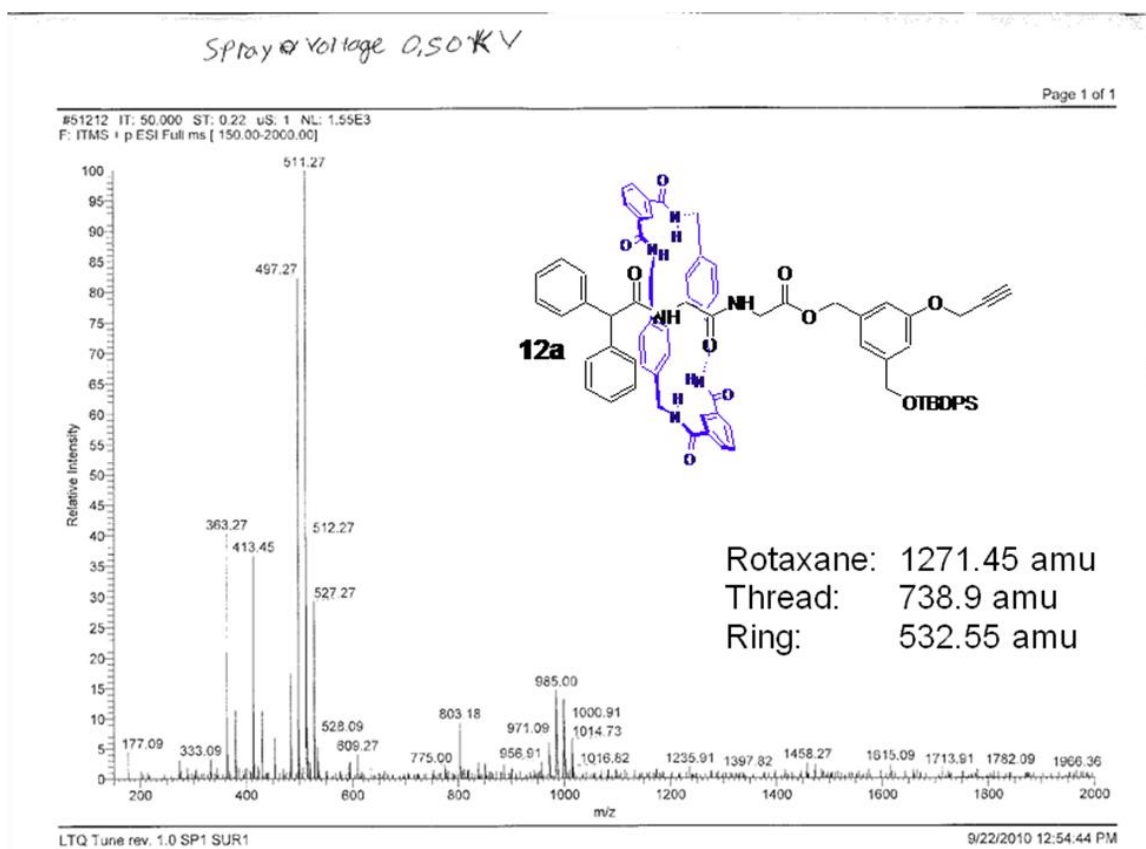
Appendix 2: Enlarged portion of appendix 1



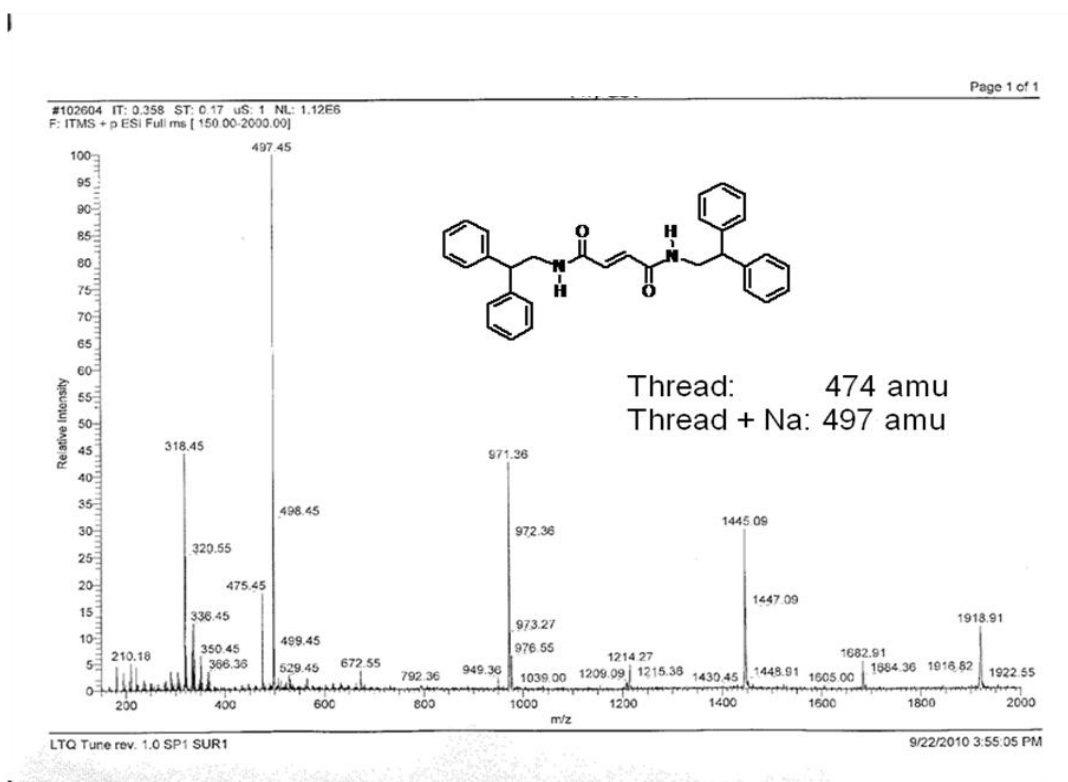
Appendix 3: Another enlarged portion of appendix 1



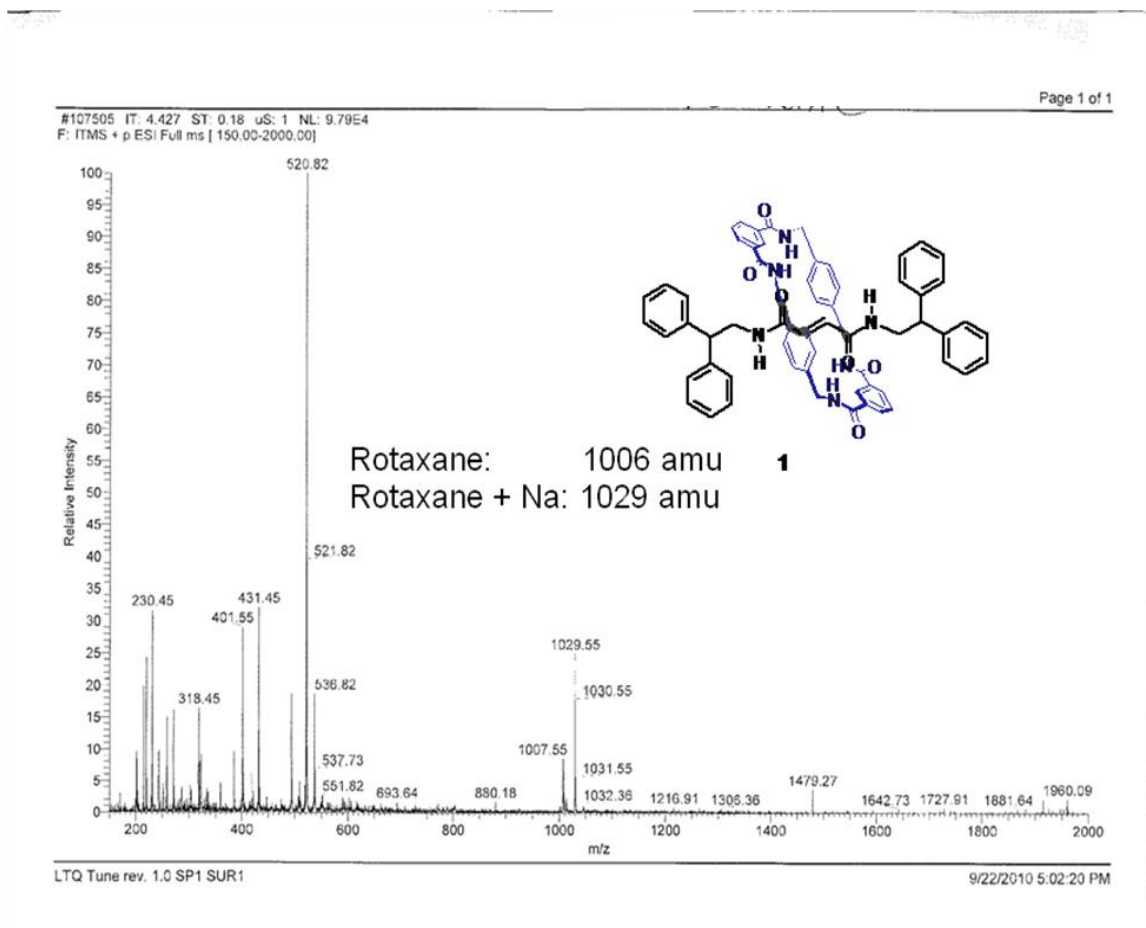
Appendix 4: Final enlarged portion of appendix 1



Appendix 5: ESI-MS of molecule 12a



Appendix 6: Reference ESI-MS of a simple fumaramide rotaxane thread



Appendix 7: Reference ESI-MS of a simple fumaramide rotaxane