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Progress Towards the Synthesis of a Novel Ethyleneglycol-Thiolated Hydroquinone Molecule for Surface Modification of Gold Nanoparticles

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Progress Towards the Synthesis of a Novel Ethyleneglycol-Thiolated Hydroquinone Molecule
for Surface Modification of Gold Nanoparticles

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A Thesis Submitted in Partial Fulfillment of the Requirement for the Bachelor of Arts Degree
with Honors in Chemistry at Wellesley College

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Abstract:

Gold Nanoparticle (AuNP) self-assembly is becoming more prevalent in modern science. Gold AuNPs have myriad applications in medicine, biosensing and optoelectronics. The Flynn laboratory is currently working on the development of an innovative method to assemble gold nanoparticle populations. This method employs electrochemistry, which minimizes a number of limiting factors, such as pH and solvent constraints, often encountered when biological-based assembly methods are implemented. In order to achieve this goal, a more water-soluble hydroquinone AuNP population must be created. The Carrico-Moniz lab is working towards the synthesis of a novel ethyleneglycol-thiolated hydroquinone molecule that will be used to modify the surface of an AuNP population. The key steps for the proposed synthesis involve a Buchwald hydroxylation reaction, the insertion of several ethylene glycol units as well as the addition of a terminal thiol. This innovative compound will ensure that the nanoparticle population is more soluble in water, achieving the overall goal of assembling gold nanoparticle populations through electrochemical means.

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Introduction:

Breakthroughs and advancements in science and technology have afforded scientists the opportunity to explore objects on the nanoscale. Many scientists now focus their research on objects that are between 1 and 100 nanometers.[1] Nanoscience plays an integral role in various fields including chemistry, physics, biology, medicine, engineering, catalysis, and electronics.[2] Several applications in these fields require the assembly of nanoparticle (NP) populations.[3] One way by which these assemblies are controlled is through self-assembled monolayers (SAMs), as seen in Figure 1.[4]
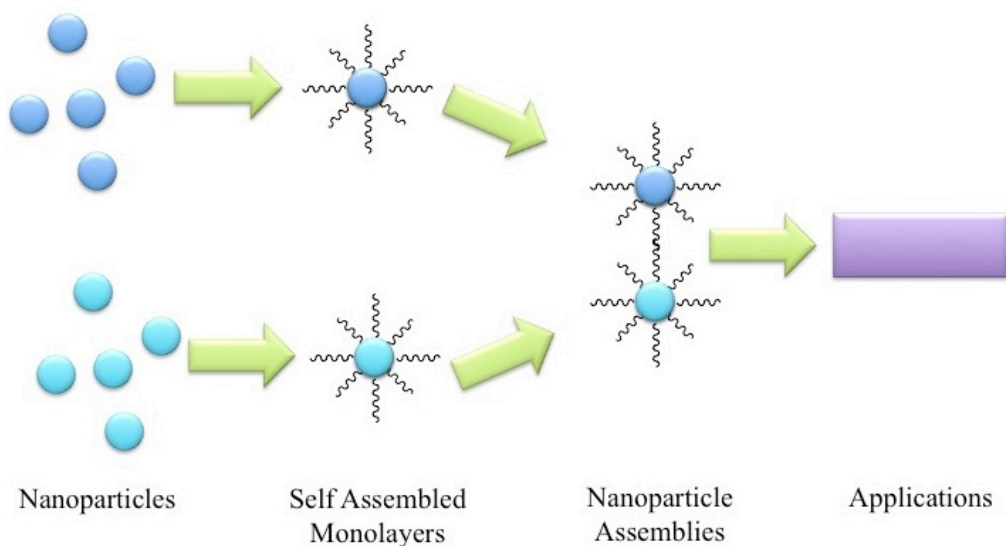

Figure 1. Summary of Nanoparticle Assembly Formation through SAMs

A popular and thoroughly investigated method of SAM formation is the adsorbption of alkanethiols on metal surfaces. The metal surfaces can be planar gold-coated surfaces or gold-coated nanoparticles (AuNPs).[4-6] NPs are often employed as they have several unique chemical, physical, and electronic properties.[7] Also, NPs have the potential to be functionalized by the presence of chemical moieties.[1] The gold coating enhances the unique properties NPs possess. Gold is an inert metal, is able to withstand oxidation under atmospheric pressure, has a strong

natural affinity with sulfur. Additionally, alkanethiols are able to form a dense monolayer on gold surfaces. These qualities make AuNPs the most stable metal NPs.[7-9] Electronic devices, optical devices, sensor components, chemiresistors, medical diagnostic tools, ion detection, and molecular recognition processes can all rely on the nanostructures.[10-16]

Current Self-Assembly Methods:

Current self-assembly methods rely heavily on the use of biomolecules. In one method involving DNA base pair recognition, complementary single strands of DNA are slightly modified to include terminal thiols. This modified DNA strand can be attached to the AuNPs. Modified DNA strands then link together to form a connection between two AuNP populations.[17-18]

Several methods using streptavidin and biotin analogues can also be used to form AuNP assemblies. These assemblies can be formed through the modification of the AuNP by the chemisorption of a biotin analogue and subsequently, streptavidin. Another method by which the assemblies are formed is by linking the streptavidin and the biotin before attaching the AuNPs.[19] This method is favored due to its high specificity and stability.[20]

A third technique involves the use of artificial coiled-coil peptides. This method requires the surface of the AuNP to be functionalized with modified peptides that contain a terminal cysteine residue. The terminal cysteine residue allows for the formation of a gold-sulfur bond between the peptide and the AuNP.[21] Other methods that involve proteins and antibody/antigen biomolecules have also been explored.[22-23] However, these methods, while successful, all rely on biomolecules and biological systems and are limited by certain factors.

Limitations of Current Self-Assembly Methods:

The use of biomolecules to form AuNP assemblies limits the versatility of the linked populations and requires very specific reaction conditions. Often times, because of the biological systems used, there are a number of limiting factors such as pH, ionic strength, solvent systems and temperatures. For example, the method of DNA base pair recognition requires the use of stabilizing ligands as well as aqueous buffers.[18] While these stringent requirements can help control reaction conditions, they also emphasize the limitations of currently known self-assembly methods. [18] These restrictions suggest that future assembly methods developed should aim to work under more universal and less specific conditions.

Development of A Novel Electrochemistry-based Self-Assembly Method:
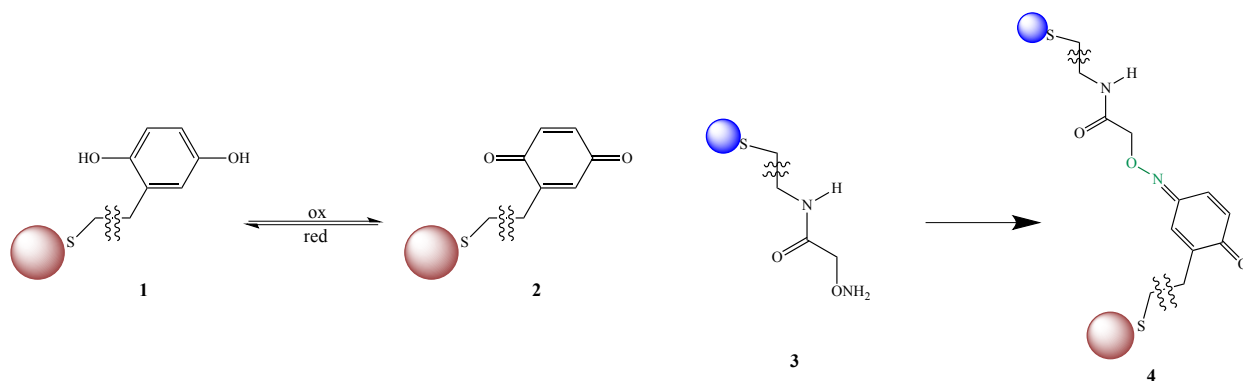
Scheme 1. Electrochemical and Chemical Reactions for the Self-Assembly of
Two Distinct Nanoparticle Populations

Currently, the Flynn laboratory is attempting to develop an electrochemical method to trigger the self-assembly of two distinct AuNP populations (**1** and **2**) to form **3** (Scheme 1). This novel method would minimize the number of factors hindering the versatility of self-assembly methods that rely on biomolecules, including pH, solvent, temperature and ionic strength. As shown in Scheme 1, it is proposed that hydroquinone bearing AuNP population **1** can be

oxidized to its corresponding benzoquinone bearing AuNP population **2**. The benzoquinone

compound **2** will then spontaneously form an oxime linkage, shown in green, with an amino-oxy

bearing AuNP population **3**. This method would allow for two distinct AuNPs to self-assemble,

as represented by compound **4**.

Formation of the Hydroquinone Bearing AuNP Populations:

AuNPs can be functionalized with organic compounds through place exchange reactions.

The AuNPs are stabilized by SPPP, a compound seen in Figure 2. This stabilization occurs

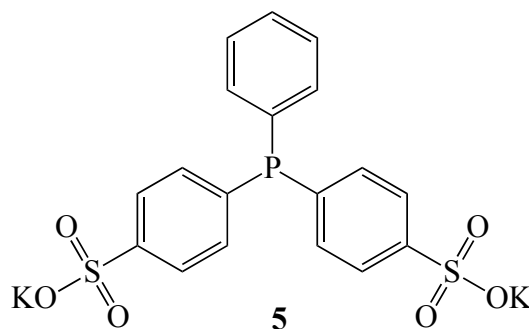because of the negative charge of SPPP, when in solution. This negative charge allows

Figure 2. Molecular structure of bis(p-sulfonatophenyl)phenylphosphine or SPPP (**5**)

compound **5** to attach to the gold surface of the NPs. After the AuNPs are stabilized;

functionalized alkanethiols can be attached to the surface of the NPs through the well-

documented interactions between gold and sulfur.[8, 24] One common method to attach thiols and

gold involves the reduction of $AuCl_4^-$ using sodium borohydride in the presence of the thiol, as

seen in Scheme 2. The strong natural affinity between gold and sulfur can be attributed to their

soft physical characteristics.[8]
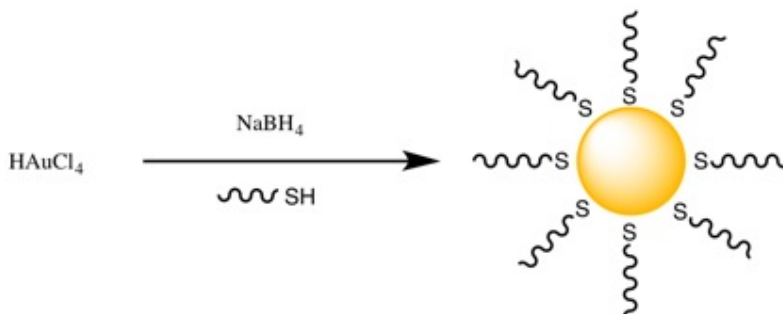
Scheme 2. Functionalization of AuNPs. Adapted From Reference 7

Hydroquinone Bearing AuNP Population:

Previously, commercially available 2-(12-mercaptododecyl)benzene-1,4-diol, **6**, seen in

Figure 3, was used to create the hydroquinone bearing AuNP population **7**, presented in Figure 4.

This compound has several integral components required to achieve the goals of this project.
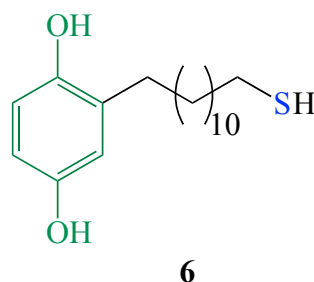

6

Figure 3. Commercially Available 2-(12-mercaptododecyl)benzene-1,4-diol (**6**)

The hydroquinone backbone, shown in green, will be electrochemically converted into

the corresponding benzoquinone. The terminal thiol, shown in blue, allows for the favorable

sulfur-gold interactions to occur. Additionally, the alkane chain spacer between the terminal thiol

and the hydroquinone backbone stabilizes the gold-thiol interaction due to the intermolecular

interactions between adjacent chains. Initial studies conducted by the Flynn laboratory showed

that the AuNP population **7,** shown in Figure 4, is insoluble in common protic, electrochemically unreactive solvents such as ethanol and water.
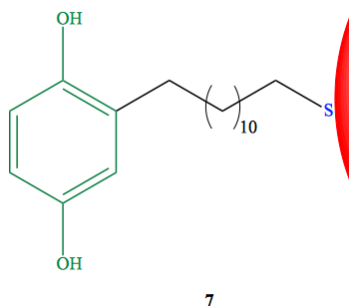

Figure 4. Initial Hydroquinone AuNP Population (**7**) Prepared by the Flynn Laboratory

Design of a Novel Ethyleneglycol-Thiolated Hydroquinone with Enhanced Water Solubility:

Since water has a large potential range for which the electrochemical reactions can occur, water solubility is a desired characteristic of the synthesized AuNP population. Essentially, water is electrochemically unreactive over a wide range of potentials, which helps ensure that the oxidation reaction of the hydroquinone can occur. To counter the water insolubility of AuNP population **7,** a novel compound, **8** was designed to attach to AuNPs. This molecule, presented in Figure 5, incorporates a terminal thiol, shown in blue, and a hydroquinone backbone structure, shown in green. Additionally, a series of ethylene glycol units, highlighted in red, have been added in addition to the alkane chain.

Literature suggests that insertion of several ethylene glycol units will enhance the water solubility of the AuNP population.[25] Ethyleneglycol units enhance water solubility because of their potential to act as hydrogen bond acceptors. Additionally, it is still necessary to still include the alkane chain spacer, despite is hydrophobicity, because of its stabilizing effect.
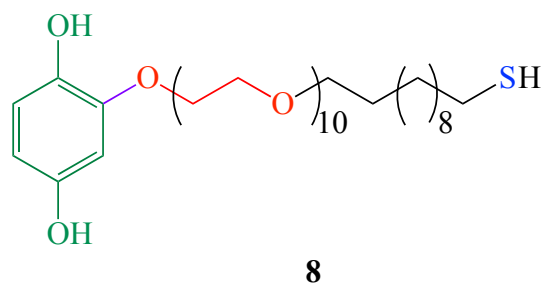
8

Figure 5. Novel Ethyleneglycol-thiolated Hydroquinone Molecule (**8**) with
Improved Water Solubility

The intermolecular interactions between neighboring alkane chains close to the surface of

the AuNP is necessary as it stabilizes the self-assembled monolayer on the NP. Compound **8**,

however, is not commercially available and therefore must be synthesized. Once the Carrico-

Moniz laboratory successfully synthesizes compound **8**, the Flynn laboratory will then attach

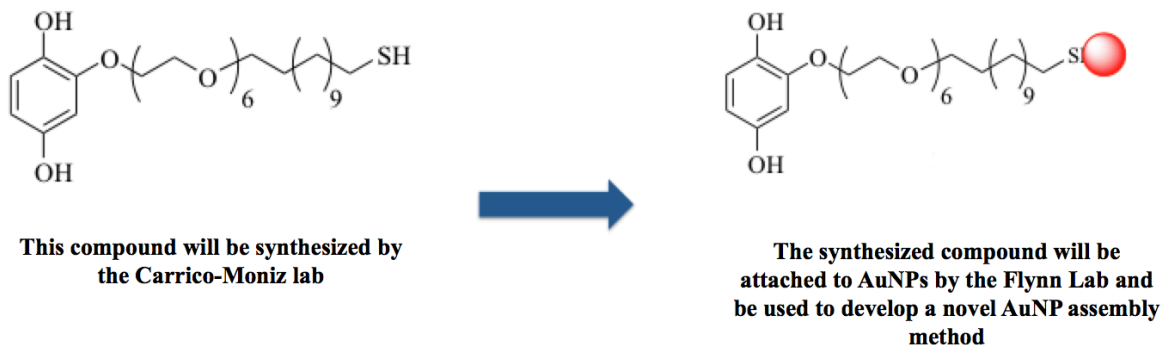alkane thiol **8** to an AuNP population as represented in Figure 6.

This compound will be synthesized by
the Carrico-Moniz lab

The synthesized compound will be
attached to AuNPs by the Flynn Lab and
be used to develop a novel AuNP assembly
method

Figure 6. Summary of the Collaboration between the Carrico-Moniz and Flynn Laboratories

Synthesis of the Novel Ethyleneglycol-Thiolated Hydroquinone Molecule 8:

The Carrico-Moniz laboratory is working towards developing an efficient method to

synthesize **8**. Compound **8** has several structurally intriguing factors that make the proposed

synthetic scheme challenging. First is the incorporation of the two phenols, which compose the hydroquinone backbone, as seen in green in Figure 5. The phenols have the potential to be reactive points on the hydroquinone, which would lead to undesired side products. The terminal thiol, shown in blue in Figure 5, also presents synthetic challenges because of the characteristics of sulfur. Sulfur can be easily oxidized in the presence of oxygen, which makes the thiol components relatively unstable. However, the most intriguing component of compound **8** is the carbon-oxygen bond present on the aromatic ring, shown in purple (Figure 5). There are very few known synthetic methods that allow for the formation of these bonds. Since the desired compound has several structurally complex and intriguing components, a more economical and efficient way to synthesize the desired compound is to test the proposed synthesis on a similar model system.

Design of a Synthetic Model System:

The model system designed for compound **8** is presented in Figure 7. This model system, compound **9**, contains the hydroquinone backbone, seen in green, the terminal thiol, seen in blue, and the aromatic carbon-oxygen bond, seen in purple. The model system in Figure 7, however, does not contain the desired ethylene glycol units incorporated into compound **8** (Figure 5). The insertion of several ethylene-glycol units is expensive and synthetically challenging, so for synthetic trials this model system, compound **9** adequately represents the desired system, compound **8**.
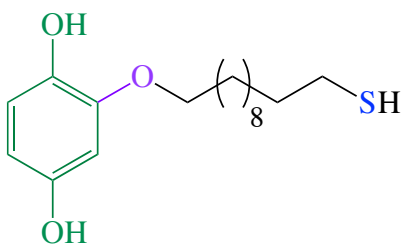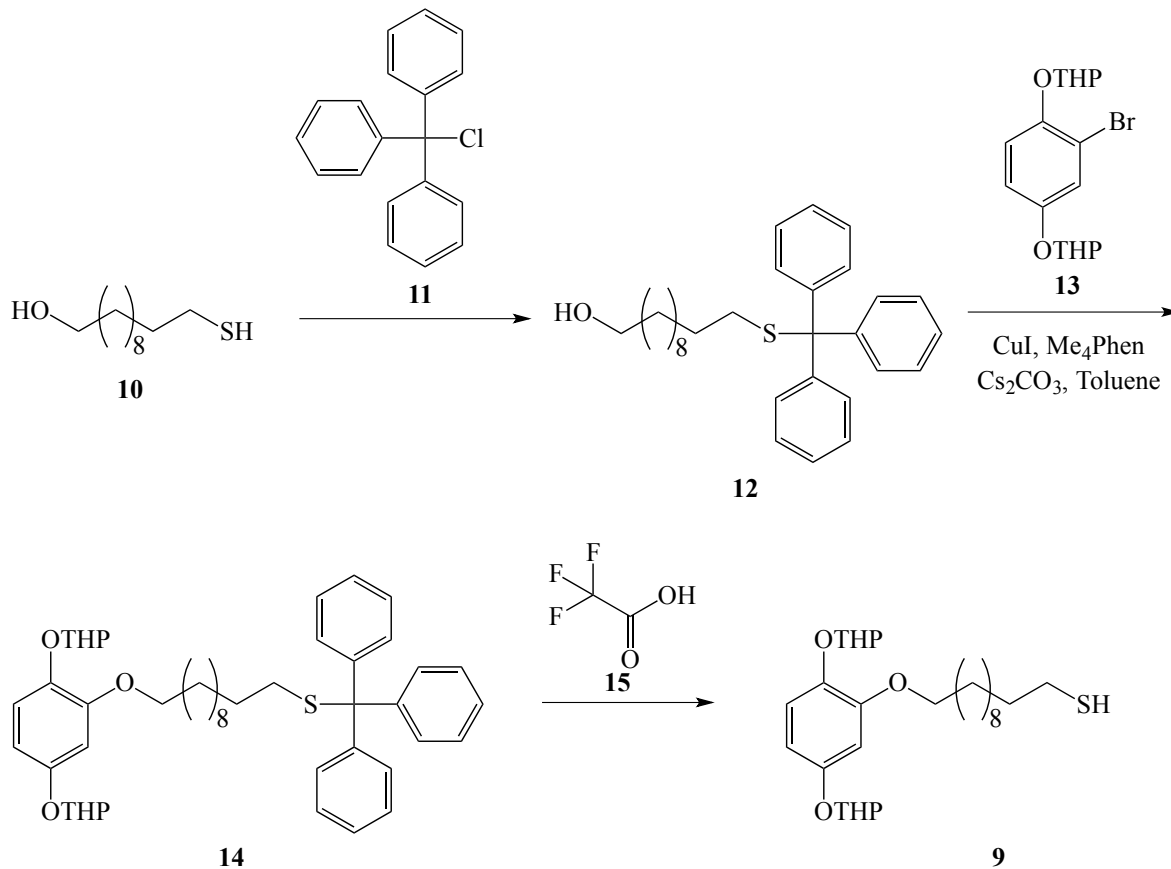
9

Figure 7. First Model System Used for Initial Synthetic Trials

Proposed Synthesis of Model System 9:

Previous studies in the Carrico-Moniz Laboratory were initially focused on synthesizing model system **9**. It was suggested that model system **9** could be synthesized in four steps as shown in Scheme 3 below. A discussion of each step follows.


Scheme 3. The Proposed Synthesis of Compound (**9**)

Step One: Formation of the Protected Thiol Fragment 12

First, the protected thiol fragment **12** is formed, and the thiol-alcohol **10** is protected with trityl chloride, **11**. Literature shows that this protection can be achieved in yields close to 80%.[26] The terminal sulfur must be protected to ensure that the subsequent proposed reactions will occur opposite to the alcohol terminus.

Step Two (A): Protection of Commercially Available Bromohydroquinone 17

It is necessary to protect the hydroquinone backbone to ensure that the bromine is the reactive site of the hydroquinone compound, **13**. The phenols on the aromatic ring of **17** are protected with dihydropyran (DHP) **16**, to form ditetrahydropyranyl ether **13** as presented in Scheme 4.[27]
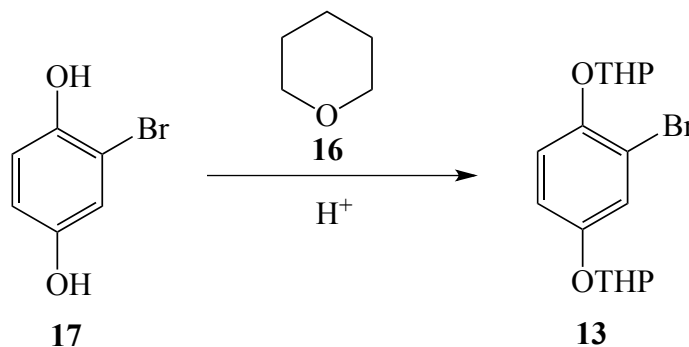

Scheme 4. Protection of Bromohydroquinone (**17**) with DHP (**16**)[27]

Step Two (B): Buchwald Coupling

The coupling of the protected thiol, **12**, and the protected bromohydroquinone, **13**, is considered to be the most challenging step in the synthesis, as it requires the formation of an aromatic carbon-oxygen bond. Previous work done by Buchwald and coworkers shows that the use of ligand **18** favored the production of an *O*-arylated product in a copper-catalyzed arylation

reaction.[28] Buchwald and coworkers made use of Me$_4$Ph, ligand **18**, and its derivatives when they successfully synthesized various forms of **19** (Scheme 5) in high yield from starting materials similar to those shown in Scheme 3.[29]
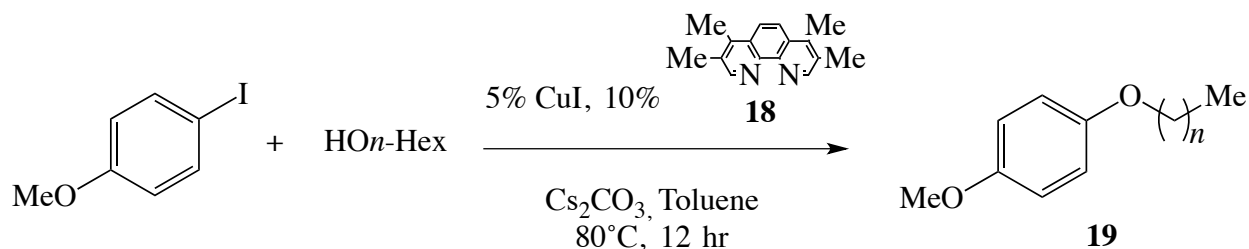

Scheme 5. Copper-Catalyzed Arylation Reaction From Which Reaction Conditions were Adapted (Scheme Adapted from Reference 29)

The work done by Buchwald and coworkers suggests that similar reaction conditions and the use of the Me$_4$Phen ligand, ligand **18**, would lead to the coupling of the two components **12** and **13** to produce the *O*-arylated product, **14**.

Step Three: Deprotection to form The Model System Compound 9

In the final step of the proposed synthesis, both the hydroquinone and the terminal thiol are deprotected. Work done by Mrksich and coworkers in scheme 6, shows that trifluoroacetic acid (TFA), **15**, can be used to remove the trityl-protecting group from **20**. Compound **20** is similar to compound **14** (Scheme 3) as it also contains a phenol, alkane chain and several ethylene glycol units.[27]
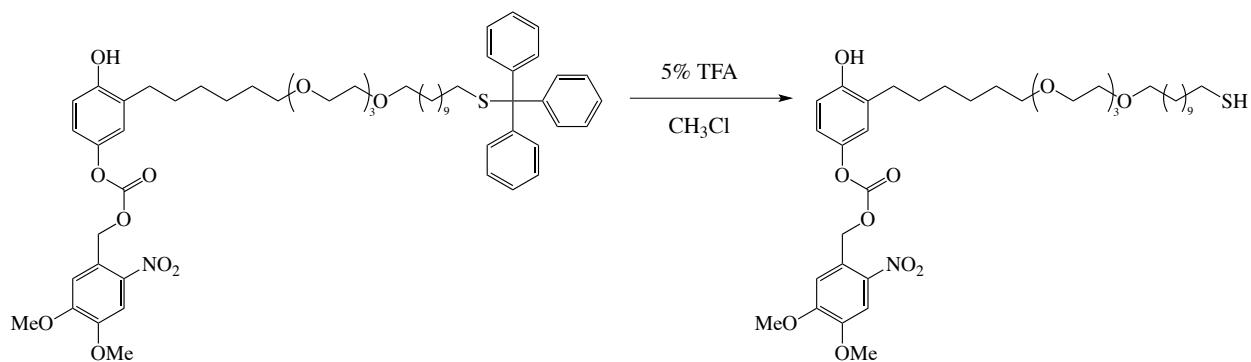
Scheme 6. Reaction Scheme for the Deprotection of a Similar Thiol.
Adapted from Reference 21

The use of DHP, **17**, as the protecting group for the hydroquinone leads to the formation

of an acetal (compound **13**). Acetals can be easily cleaved when in acidic conditions. TFA, **15**, is

a strong acid with a K_a of about 0.5.[30] The acidity of **15** is due to the incorporation of three

fluorine groups and their electron withdrawing properties. It is well known among chemical

literature that compound **15** can easily deprotect the acetal, leading to the deprotection of the

phenols as well as the thiol in one single step and resulting in the desired model system **9**.[31]

Previous Work Towards the Synthesis of Compound 9:

The protected thiol, **12**, and the protected bromohydroquinone, **13**, were successfully

acquired. However, after several trials and studies done by both the Carrico-Moniz and

Buchwald laboratories, it was determined that the sulfur from the terminal thiol poisons the

catalytic system was preventing synthetic intermediate **14** from being obtained. In addition, the

use of DHP, **16**, as the protecting group could also create additional steric hindrance; work done

by Buchwald coworkers suggest that this also limits the success of the copper based catalytic

system.[28-29] As the Buchwald step is critical to achieve the formation of the aromatic carbon-

oxygen bond, it was determined that this synthetic route required modification.

Design of a New Synthetic Model System (21):

Since the presence of the sulfur was hindering the catalytic system, it was decided that the aromatic carbon-oxygen bond should be formed prior to the addition of sulfur component. A new synthetic route was devised (Scheme 7), and the model system was modified. The new model system, shown in Figure 8, is a better representation of the desired system, **8**, displayed in Figure 5. Forming the aromatic carbon-oxygen bond prior to the addition of the sulfur allows for an ethylene glycol unit, shown in red in Figure 8, to be incorporated into model system **21**.
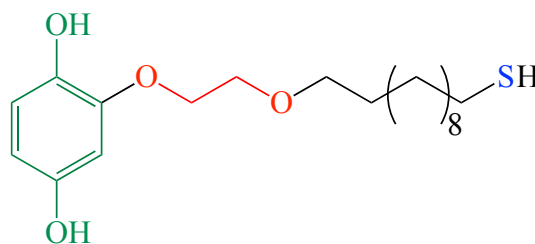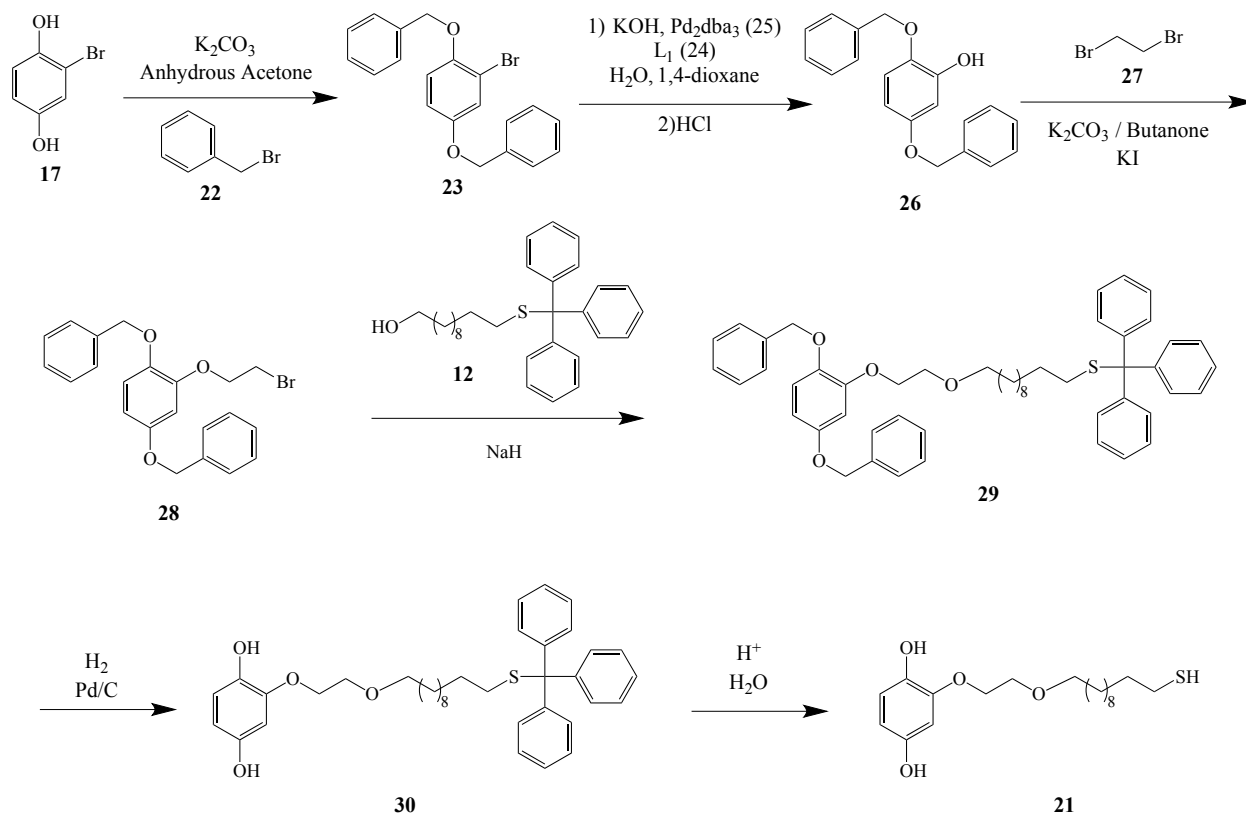

21

Figure 8. Revised Synthetic Model System (**21**)

*Proposed Synthesis of Model System 21*:

Scheme 7 shows the modified synthetic route to obtain the new model system, compound **21**. A discussion of each step follows.

Scheme 7. Revised Synthetic Scheme to Obtain The New Model System (**21**)

Step One: Protection of Bromohydroquinone (17)

First, commercially available bromohydroquinone, **17**, is protected with benzyl bromide, **22**, to form benzyl ether, **23**. As previously discussed, it is necessary to protect the hydroquinone to ensure that the bromine is the reactive center of the compound. Diaz and coworkers achieved the protection of **17** using benzyl bromide, **22**, and potassium carbonate in a high yield of 88%.[32] This protection occurs via a S_N2 mechanism presented in Scheme 8.
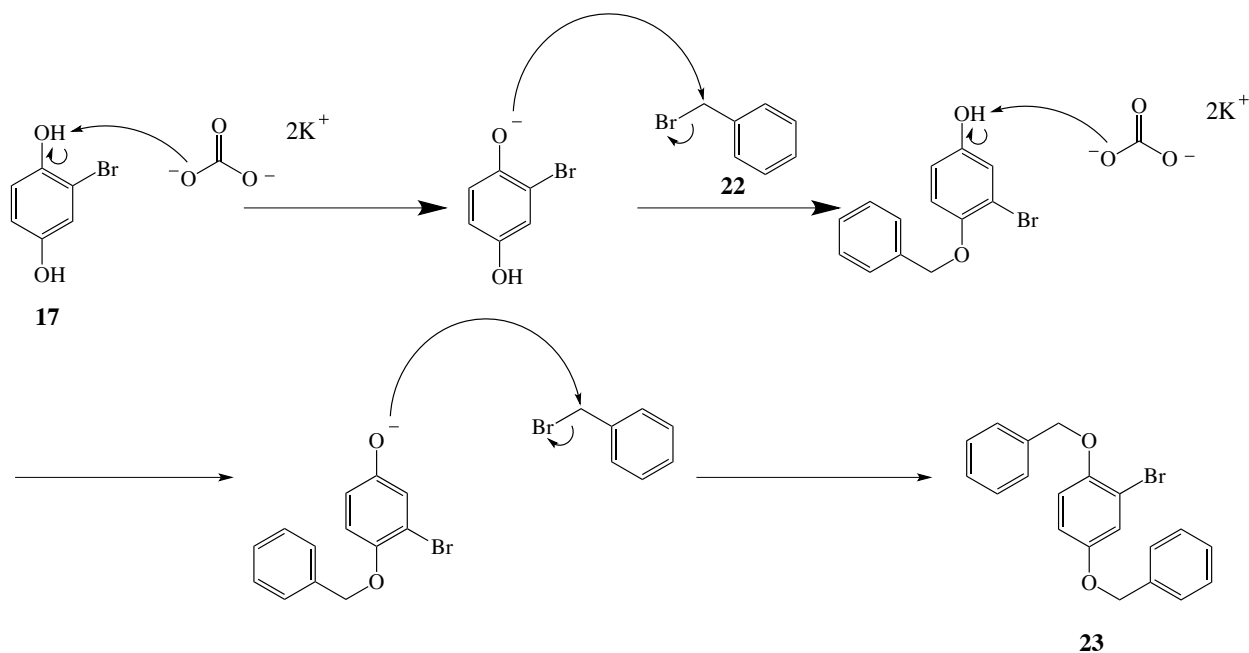
Scheme 8. Mechanism of the Protection of Bromohydroquinone (**17**)

This alternative method of protection was explored for a few reasons. First, the resulting

benzyl ether, **23**, has less steric hindrance than acetal **13**, the hydroquinone protected with DHP,

17. Minimizing steric hindrance helps maximize the efficiency of the catalytic system.

Additionally, acetal **13** can be easily cleaved in the presence of moderate to strong acids.[31, 33-34]

Since several of the subsequent steps in the proposed synthesis of **21**, Scheme 7, require the use

of acidic work up conditions, the THP group could be unintentionally cleaved. The resulting

benzyl ether group from this proposed protection is more robust in acidic conditions. For the

protecting group to be cleaved, the compound must either be in the presence of a very strong acid

such as hydrofluoric acid, or the compound must undergo hydrogenation.[33, 35]

*Step Two: Formation of Phenol **26** via a Buchwald Hydroxylation Reaction*

In the second step of the synthesis, a carbon-oxygen bond is formed on the aromatic ring.

It is proposed that phenol **26** can be formed via a Buchwald hydroxylation reaction.[36] Literature

precedents, represented in Scheme 9, show that the use of Ligand 1, **24,** (Figure 9)**,** and

tris(dibenzylidenacetone)dipalladium(0), **25**, (Figure 10), yields phenols similar to **26**
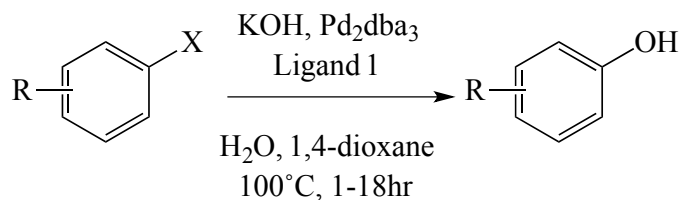
Scheme 9. General Reaction Conditions for the Formation of Phenols from Aryl Halides
Adapted from Reference 36

Scheme 7) from aryl halides with yields ranging from 80 to 99%.[36] From the literature, it can be

inferred that the Buchwald hydroxylation reaction is a palladium-catalyzed oxidative addition
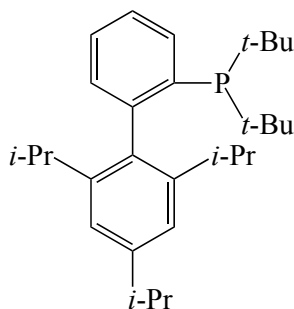
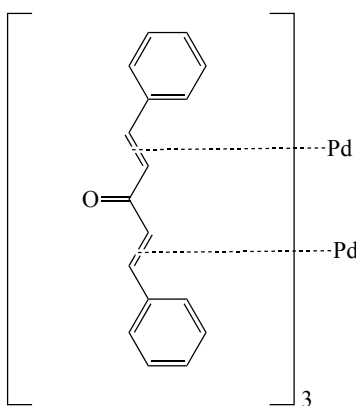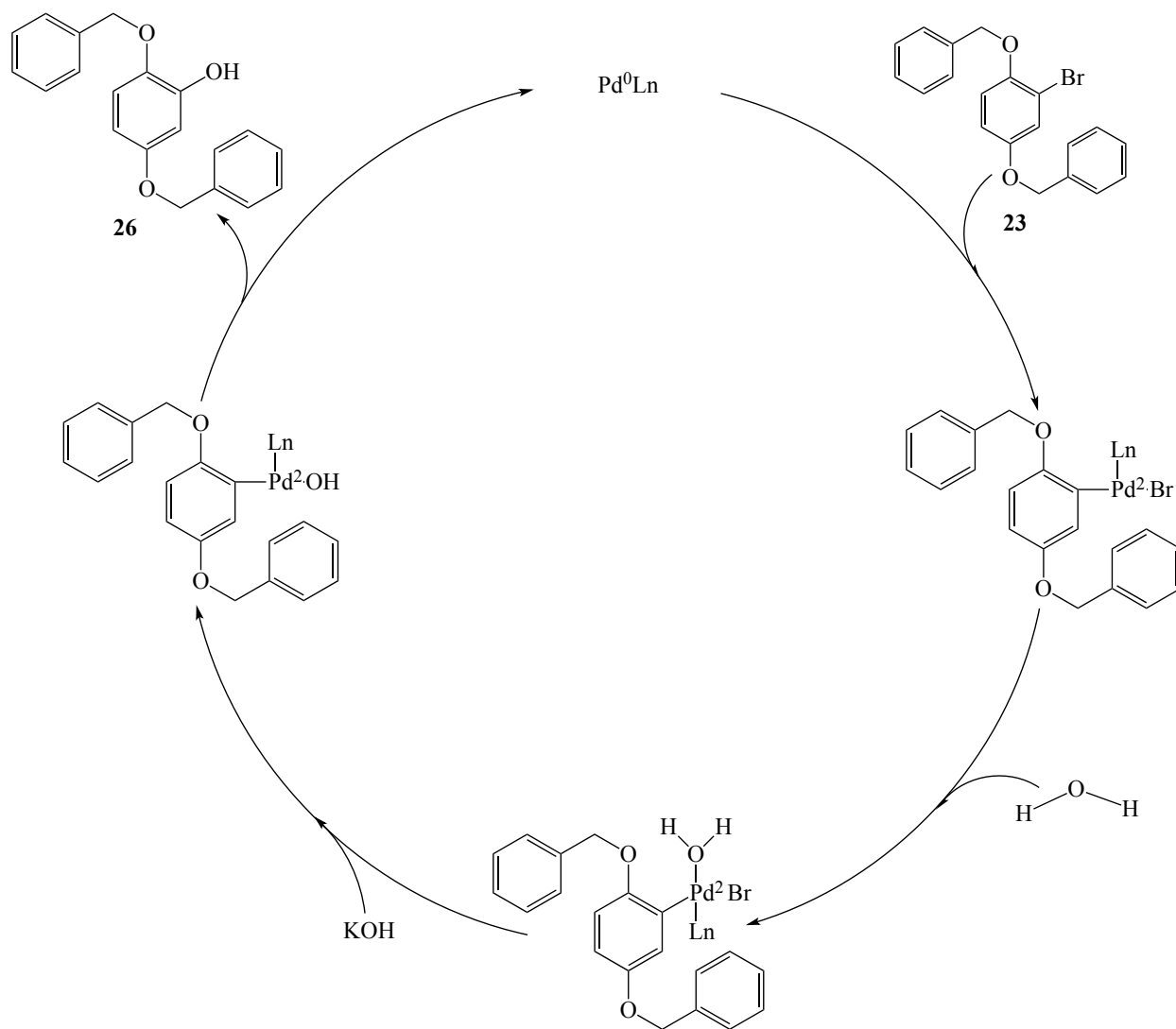reductive elimination reaction, as shown in Scheme 10.[36]


Figure 9. Ligand 1 (**24**)

Figure 10. The Palladium Catalyst, $Pd_2(dba)_3$ (**25**)

Scheme 10. Proposed Mechanism of the Buchwald Hydroxylation Reaction to Yield Phenol **26**

*Step Three: Alkylation to form the Bromoether **26***

In this step, an ether is formed off of the aromatic ring by the reaction of dibromoethane, **27** in the presence of a base. Work by Xingshu and coworkers, presented in Scheme 11, shows that a similar transformation is possible with the use of dibromoethane, **27**, potassium carbonate and potassium iodide.[37]
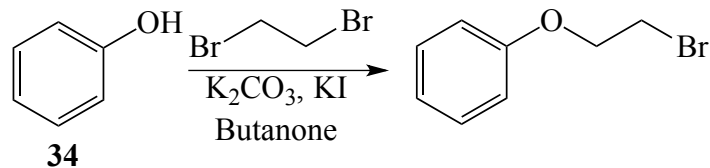
Scheme 11. Formation of Bromoethers from Phenols (Adapted from Reference 36)

Due to the similarities in structure between compound **26** (Scheme 7) and compound **34** (Scheme 11)), the conditions by Xingshu and coworkers were adapted. Their work suggests phenol **26** can undergo a S_N2 reaction with dibromoethane to generate the synthetic intermediate, bromoether **28** as illustrated in Scheme 12.
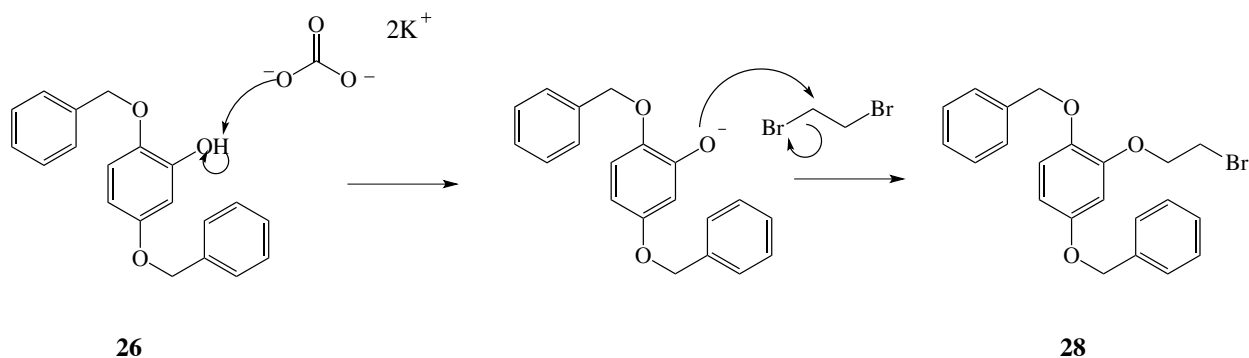
**Scheme 12.** Mechanism of the Formation of Bromoether **28**

*Step Four (A): Formation of the Thiol **12***:

As previously discussed, thiol **10** can be protected by trityl chloride, **11**, to form thiol component **12**.[26] Additional research suggests another viable option to form the protected thiol **12**. Rotello and coworkers successfully synthesized the same desired compound **12** with a high yield of 97%. As presented in Scheme 13, Rotello and coworkers used 11-bromoundecanol, **31**, and triphenylmethanethiol, **32** to form **12**.[38]
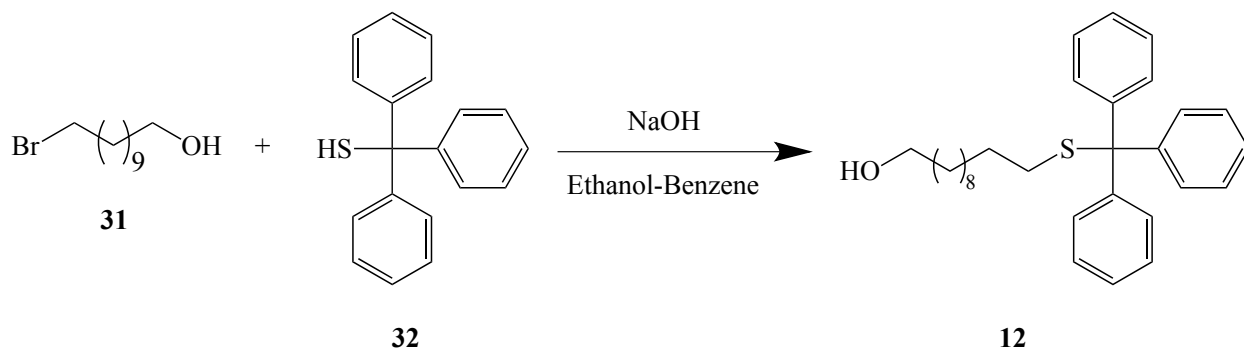
Scheme 13. Alternative Synthesis of Protected Thiol **12** (Adapted from Reference 38)

This reaction also occurs via a nucleophilic substitution reaction. This reaction can occur

via two different mechanisms. In Scheme 14, thiol **32** attacks 11-bromoundecanol, **31**, resulting

in the formation of a sulfonium salt intermediate. The base in solution then deprotonates the

sulfonium salt, leading to the formation of compound **12**.
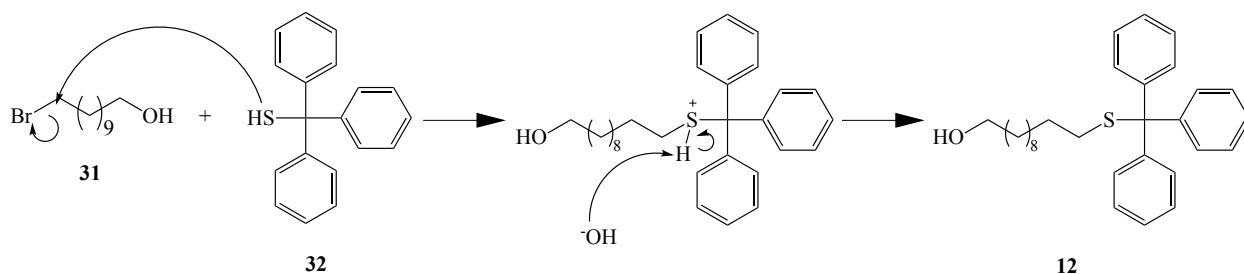
**Scheme 14.** Possible Mechanism for the Formation of Thiol **12**

Alternatively, as shown in Scheme 15, the sulfur anion can act as a nucleophile in a

nucleophilic substitution reaction.
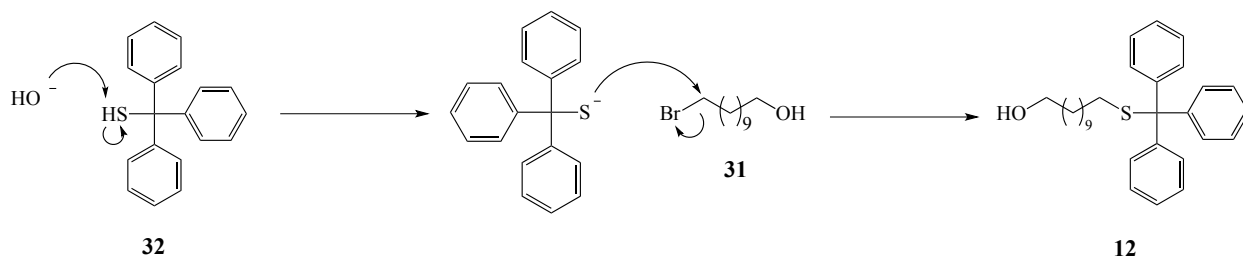
**Scheme 15**. Possible Mechanism for the Formation of Thiol **12**

*Step Four (B): Alkylation Reaction to form Compound **29***

Once bromoether **28** is obtained, it can be coupled to protected thiol **12**. This reaction occurs through an alkylation reaction. Mrksich and coworkers completed a similar reaction shown in Scheme 16.[27] Their reaction conditions were adapted due to the similarities between the compounds in the proposed synthetic scheme (Scheme 7) and the compounds used the work done by Mrksich and coworkers. (Scheme 16)
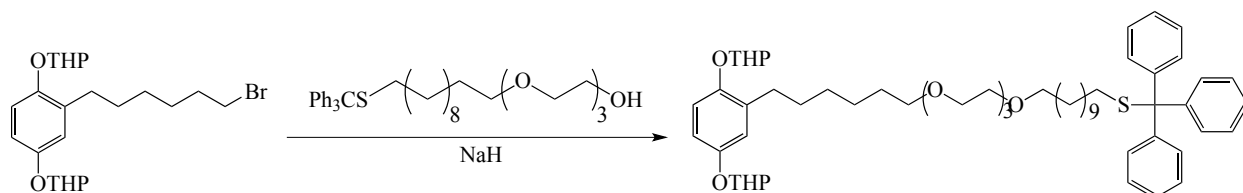
Scheme 16. Work Done by Mrksich and Coworkers Adapted from Reference 27

It is predicted that this reaction will occur via a S_N2 reaction (Scheme 17). As a result of the deprotonation of compound **12,** hydrogen gas (H_2) will be formed in addition to the alkoxide intermediate.
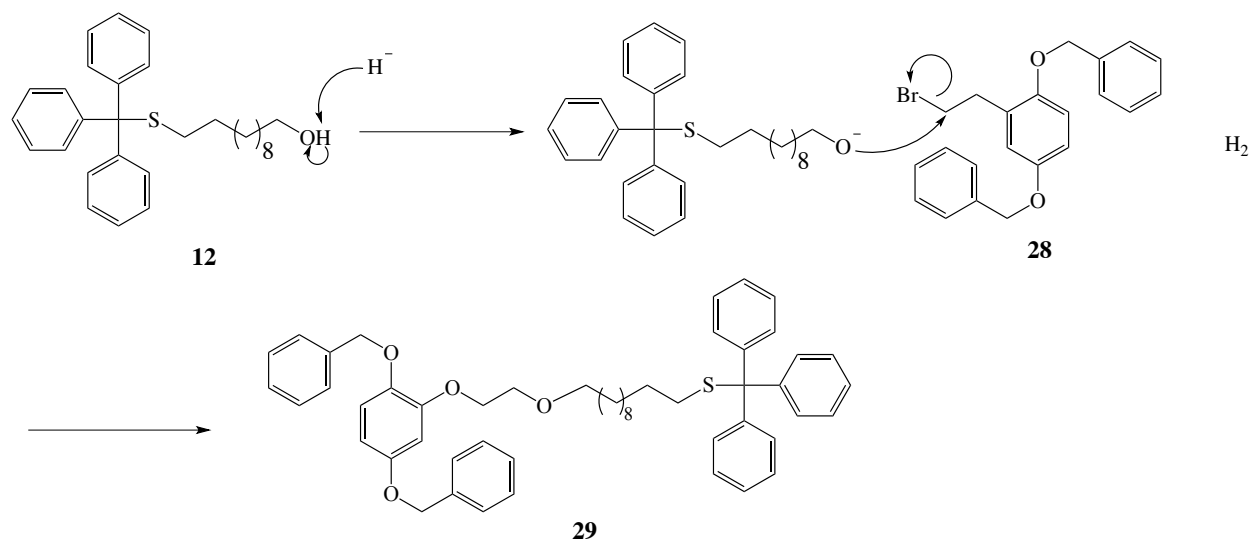
Scheme 17. Proposed Mechanism for the Coupling of Compounds **28** and **12**

Step Five: Deprotection of the Hydroquinone

Compound **29** is deprotected using hydrogen and palladium on activated carbon to afford

the tritylated hydroquinone **30**. This deprotection is a palladium catalyzed hydrogenation

reaction, which occurs via the hydrogenolysis mechanism in Scheme 18.[35] It is important to note

that the deprotection of both phenols may occur simultaneously or in a subsequent manner as

shown; the side product of the reaction is toluene, **33**, shown in Scheme 18.
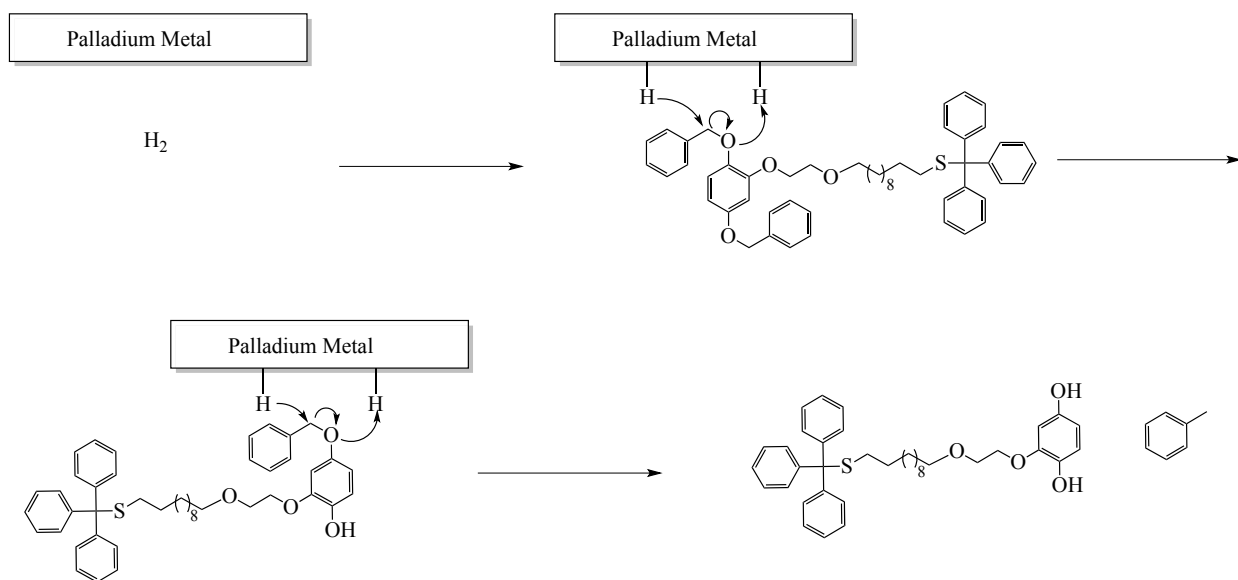
Scheme 18. Mechanism for the Deprotection of the Protected Hydroquinone (**29**)

Step Six: Deprotection of the Thiol

Compound **30** is treated with acid to deprotect the thiol, producing the desired target molecule **21**.[27, 33] The reaction occurs by a S_N2 nucleophilic substitution reaction, as drawn in Scheme 19. The triphenylmethyl carbocation intermediate formed is relatively stable due to resonance from the presence of three conjugated aromatic rings, and it will be quenched during the workup.
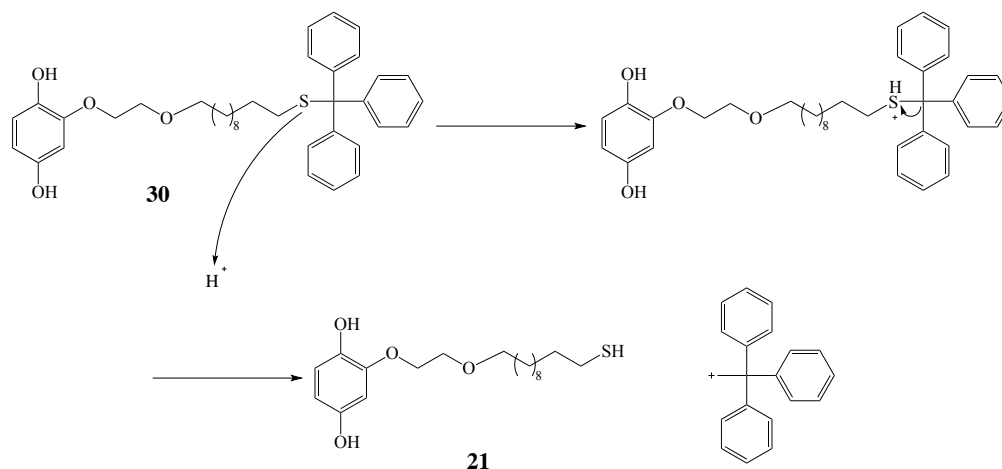
Scheme 19. Mechanism for the Deprotection of Compound **30**

Synthetic Scheme Alterations to form The Desired System 8

The desired real system, compound **8**, can be obtained by modifying the synthetic route to obtain model system **21** (Scheme 7) in a few ways. One method involves modifying the thiol component compound **12.** Thiol **12** is modified in order to include the desired number of ethylene glycol units and generate the ideal protected thiol protected alcohol **34**, shown in Figure 11. Compound **34** would replace compound **12** in Scheme 7.

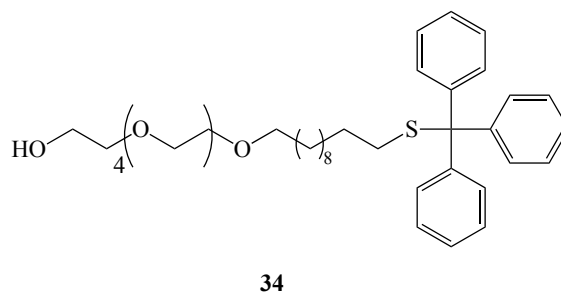**34**

Figure 11. Thiol Protected Alcohol **34** That Will Yield Compound The Desired Compound **8**

The thiol-protected alcohol, compound **34**, can be obtained in two ways. One way is by protecting thiol **35** (Figure 11). This thiol can replace compound **10** in Scheme 3 and be protected with trityl chloride, **11**. This protection reaction would yield thiol-protected alcohol **34**.

However, compound **35** (Figure 12) is extremely expensive and difficult to obtain, and therefore would not be the most practical or economical option.

35
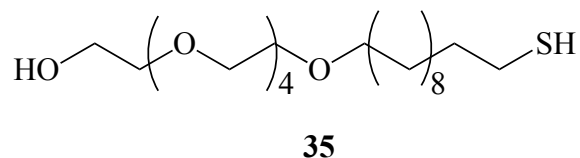
Figure 12. Commercially Available Thiol **35**

Alternatively, a literature review suggested that thiol **34** (Figure 11) could be synthesized. Rotello and coworkers formed a compound very similar to **34**. Their research focused on the formation of compound **36**, drawn in Figure 13.[38]

36

Figure 13. Compound Synthesized by Rotello and Coworkers which contains four Ethylene Glycol Units

The only difference between compounds **34** and **36** is the number of ethylene glycol units. Rotello and coworkers synthesized compound **34** with two additional steps starting with compound **12** as represented in Scheme 20.[38]

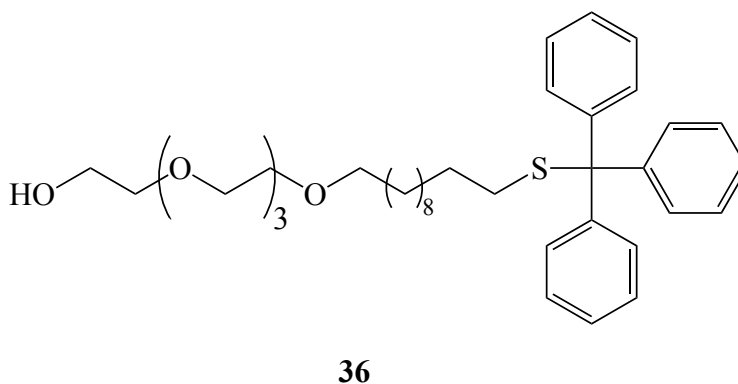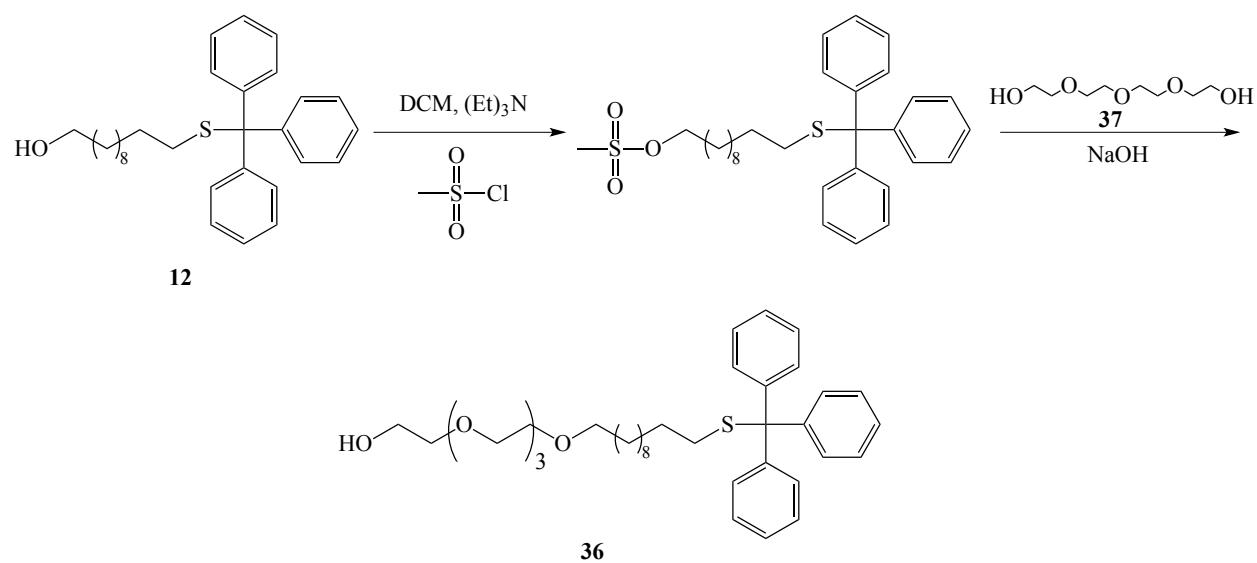**Scheme 20.** Synthesis of Compound **36** from **12** (Adapted from Reference 38)

The work done by Rotello and coworkers (Scheme 20) can be slightly modified to include an additional ethylene glycol unit by using pentaethylene glycol, **38**, instead of tetraethylene glycol, **37**, as noted in Scheme 21. The use of pentaethylene glycol, **38**, should yield the desired protected thiol-alcohol **34** from Figure 11.
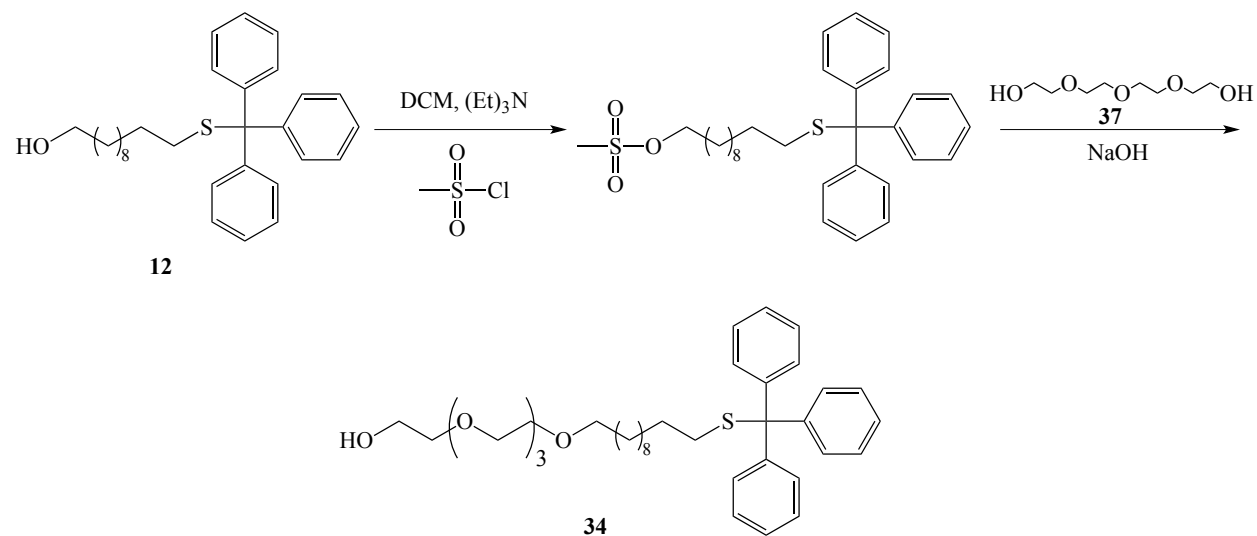
Scheme 21. Modified Synthetic Scheme Based on Work by Rotello and Coworkers to Synthesize **34**

Another less desirable method requires repeating the first alkylation step from the proposed synthesis (Scheme 7), in which the alkylation step to form bromoether **28** is repeated five additional times. The synthetic route presented in Scheme 22 is less desirable as the number of steps included significantly increases, which adds more reactions and potentially decreases the overall yield of the desired product obtained and requires more time. As noted in Scheme 22, the reaction conditions would have to be slightly modified to incorporate the use of a strong base, such as sodium hydride and an acidic work up.

Scheme 22. Modified Synthetic Route to Obtain Compound **8**
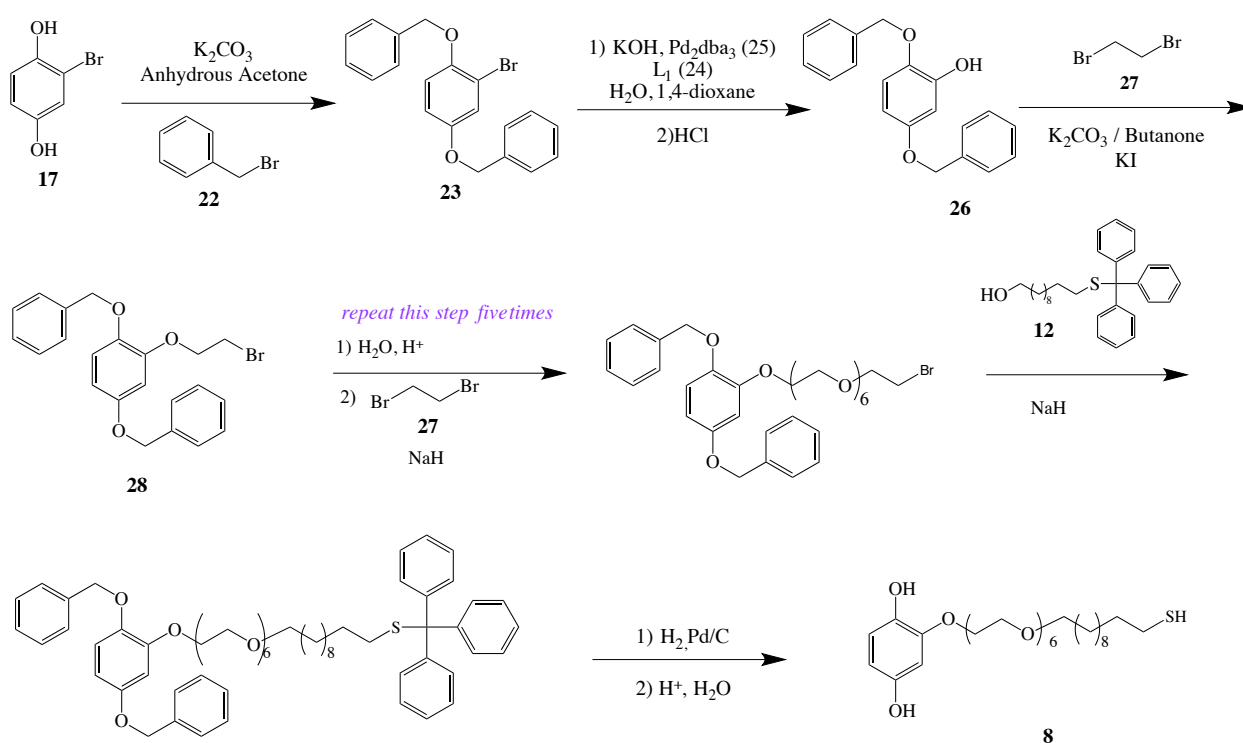
The progress towards the synthesis of the novel ethyleneglycol-thiolated hydroquinone compound **8** will be presented. Current work focuses on synthesizing model system **21** following the synthetic plan presented in Scheme 7.

Results and Discussion:

      The alternative synthetic strategies as well as the optimization of reaction and purification conditions for the synthesis of compound **8** will be presented.

Protection of Bromohydroquinone:

      Initial trials to protect commercially available bromohydroquinone (**17**) commenced based off of work done by Diaz and coworkers.[32] As previously noted, they successfully obtained ((2-bromo-1,4-phenylene)bis(ethane-2,1-diyl))dibenzene, **23**, in a high yield of 88%. In the published procedure bromohydroquinone, **17**, and potassium carbonate were dissolved in anhydrous acetone, and benzyl bromide, **22**, was subsequently added. The reaction was allowed to reflux for 15 hours. Subsequently, the crude was concentrated and treated with *t*-BuOMe and washed with water.[32]

Results:

      Following the procedure published by Diaz and coworkers, initial trials, conducted by Olivia Hulme, showed promising results when slight modifications to the published procedure were made.[39] In the initial trials, the reaction was allowed to reflux for two hours. The reaction was terminated after two hours as thin layer chromatography (TLC) in 5:1 Hex: EtOAc showed no change in the amount of starting material present.

      GCMS, HRMS, ^{1}HNMR and ^{13}CNMR indicated bromohydroquinone (**17**) had been successfully protected with benzyl bromide yielding ((2-bromo-1,4-phenylene)bis(ethane-2,1-diyl))dibenzene (**23**). GCMS showed an m+ peak at 368 as well as a m+2 peak with equal intensity at 370, confirming the presence of Bromine. A 1:1 ratio between the m+ and the m+2

peak is expected because of the isotopic ratio effect. [79]Br and [81]Br are abundant in a 1:1 ratio. This suggests that the bromine-containing compound is equally likely to have [79]Br as it is [81]Br, and the average molecular weight of the compound, 369.25g/mole, is consistent with this.

Additionally, further analysis of the fragmentation suggests that the m/z peak at 290 is representative of **39**, and the m/z peak at 197 is representative of **40** (Figure 14). Additionally, the base peak of 91 is representative of an unsubstituted phenol, **41** (Figure 14). The HRMS spectra also showed the m+ peak at 368 and an m+2 peak at 370.
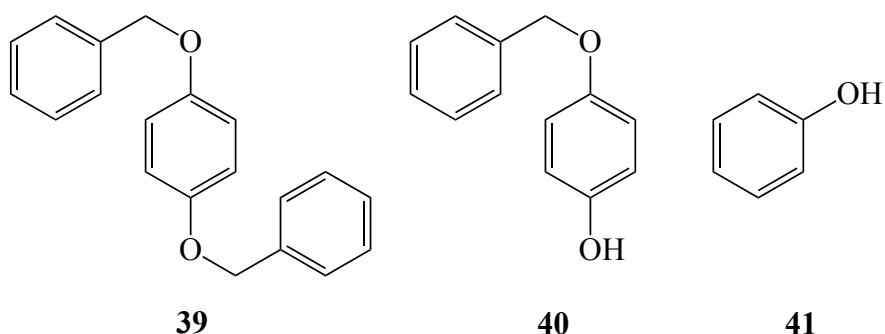

Figure 14. GCMS Fragmentation Analysis

The ^{1}HNMR showed the expected additional aromatic protons from the two additional benzyl groups around 7.5ppm as well as the addition of two methylene peaks at around 5 ppm. Combined these additional peaks are indicative of the addition of two benzyl-protecting groups. The ^{13}CNMR also showed the presence of 16 non-equivalent carbons, which is consistent with the compound's structure.

Two additional protection reactions (trial 1 and trial 2) were run with approximately 1g and 2 g of bromohydroquinone, **17**, respectively. In both trials the reaction was allowed to reflux for a longer period of time. Instead of allowing the reaction to reflux for two hours, the reaction was allowed to run for four and five hours. In both trials, despite starting material being present,

the reactions were quenched, as TLC analysis showed that the intensity of the starting material TLC spot seemed to be constant and that the reaction had stalled.

Isolation of the desired product, **23**, via column chromatography proved to be challenging. An initial purification attempt using 10:1 and 5:1 ratios of hexanes to ethyl acetate afforded the desired product as an impure mixture, and a very small amount of the desired pure product was isolated. An additional column was run using the remaining crude from trial 1. In this second column, the solvent gradient began with a 20:1 mixture of hexanes to ethyl acetate, and additional silica gel was used. Instead of using the conventional 20g silica gel: 1g crude, 22g silica gel: 1g crude was used. These modifications to the column chromatography purification conditions proved to yield the majority of the desired product in its isolated, pure form. (Trial 2)

Trial 3 of the protection reaction, which started with 5g of **17**, suffered from the problems previously encountered. The reaction was allowed to run for five hours and TLC analysis once again suggested that the reaction stalled after approximately four and a half hours. However, the purification of the crude from this reaction was significantly more difficult.

The desired product eluted off of the column with benzyl alcohol **42**, immediately based off of TLC monitoring. The presence of benzyl alcohol **42** in the crude reaction mixture results from the fact that benzyl bromide, **22**, readily converts to **42** in the presence of moisture as presented in Scheme 23.
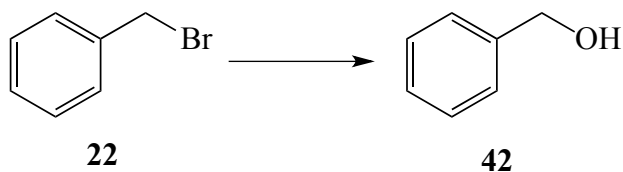
Scheme 23. Formation of Benzyl Alcohol (**42**)

It was subsequently hypothesized that purification of this reaction crude was proving to be difficult because the protected bromohydroquinone **23** is soluble in benzyl alcohol, **42**. Compound **42** is able to elute off the column quickly, dragging the desired product and leading to immediate elution. Upon this discovery, a second column was run on the re-obtained crude from the first column of trial 3. The polarity of the solvent system was further decreased in hopes of slowing down the elution of **23**. Additionally, the amount of silica gel was increased to a ratio of approximate 50g of silica gel: 1g of crude to increase the column length in hopes of maximizing separation.

After 3.4g of the isolated desired product was successfully obtained, the desired protected bromohydroquinone, **23**, in benzyl alcohol was tested. It was found that the protected bromohydroquinone is, in fact, soluble in benzyl alcohol. Since the boiling point of **42** (204.7˚C) is too high to remove by rotatory evaporation, it was determined that a reaction workup, involving an extraction was required to minimize the amount of **42** present in the crude.[40] To determine an appropriate extraction technique and method, literature protection reactions that used benzyl bromide as the protecting group were researched. The respective procedures were examined, and a summary of the different reaction workups is presented in Table 1.

Entry	Reaction Conditions	Reaction Work Up
1[41]	Solvent: DMF Base: Sodium Hydride	Methanol and Brine we added Extract three times with Dichloromethane Organic layer was dried and concentrated
2[32]	Solvent: Acetone Base: Potassium Carbonate	Crude is diluted with *t*-BuOMe Washed with Water Organic layer was dried and concentrated
3[42]	Solvent: Acetonitrile Base: Cesium Carbonate	Crude is diluted with Dichloromethane Washed with 0.2N NaOH and Brine Organic layer was dried and concentrated
4[43]	Solvent: DMF Base: Potassium Carbonate	Washed with ethyl acetate and water Additional extraction with brine Organic Layer was dried and concentrated

5[44]	Solvent: Acetonitrile Base: Potassium Carbonate	Crude is diluted with Sodium Bicarbonate and extracted with Dichloromethane Washed with brine Organic layer is dried and concentrated
6[45]	Solvent: Acetonitrile Base: Potassium Carbonate	Crude is diluted in diethyl ether Washed with water Organic layer is dried and concentrated

Table 1. Summary of Reaction Work Ups from Literature Precedents for Reactions Involving Benzyl Bromide as a Protecting Group

Concurrently, the solubility of benzyl alcohol, **42**, in water, brine and 1M HCl was also tested. 3mL of the respective solvents were tested with 3 drops of commercially available benzyl alcohol. It was concluded that benzyl alcohol is soluble in all three. Based off of the solubility results and the literature research presented in Table 1, a method was devised to separate the desired product from benzyl alcohol, **42**.

To isolate the desired product from the mixture, the crude mixture was first extracted with 1M HCl and ethyl acetate. The organic layer was subsequently isolated and dissolved in water. A precipitate was present, filtered off and washed with water and 1M HCl several times. The remaining solid was the desired product.

Compared to the high yield presented by Diaz and coworkers, the yields obtained in trials 1 through 3 were low. The low yields could potentially be attributed to stopping the reaction prematurely, as TLC shows the reaction stalling after four hours.[32] It appears as if more of the desired product is formed when the reaction time is increased. Additionally, since a reaction workup was not initially included, the presence of excess benzyl alcohol leads to several columns. Despite being careful, it is inevitable that desired product is lost along the way lowering the overall amount of desired product obtained.

Buchwald Hydroxylation:

Conversion of aryl-halides to their corresponding phenols has proven to be a synthetic challenge. Over the past several years, many research groups have investigated methods for the formation of aromatic carbon oxygen bonds. It has been proposed that this conversion requires the use of a palladium catalyst. These methods allow for hydroxide salts, such as potassium hydroxide or sodium hydroxide, to couple with aryl halides.[46] Stephen Buchwald's group published a Palladium catalyzed reaction to form phenols.[36]

The published procedure for the formation of phenols similar to **26** requires charging a pressure tube with the starting material, $Pd_2(dba)_3$, **25**, a commercially available ligand, **24**, KOH and water in 1,4-dioxane and heating the reaction from two hours to overnight. This reaction yields the phenoxide ion, which is readily converted to the desired phenol via neutralization with 1M HCl. The crude mixture is subsequently treated with brine and then purified to obtain the desired product.[36]

Results:

An initial test reaction run by Olivia Hulme suggested that a reaction occurred.[39] This trial was monitored by TLC (9:1 hexanes: ethyl acetate). The reaction was quenched after approximately two hours, as TLC analysis suggested that the reaction stalled. After an initial purification by preparatory thin layer chromatography (9:1 hexanes: ethyl acetate), the band that appeared to be desired product was characterized. The HRMS data presented a 1:1 m/z and m+2 peak at 368-270 indicative of the bromine being present, suggesting that the characterized band was in fact the starting material. Further investigation of a more polar isolated band from a second test reaction (trial 1) suggested that a novel compound had been synthesized.

This novel compound was also isolated from the initial trial run by Olivia Hulme. The HRMS (CI$^+$) of this compound showed an m/z peak at 307. This peak suggested that the desired product had been formed. Similar fragmentation patterns, as those presented in Figure 14, were also observed. However, a more thorough analysis with ^{1}HNMR, ^{13}CNMR as well as FTIR confirmed that the desired product was indeed synthesized.

Initially, the ^{1}HNMR of the isolated desired product was run in acetone d-6. When comparing the ^{1}HNMR of the phenol to that of the protected bromohydroquinone, **23**, the separation between the two-methylene groups (5.2ppm) became more pronounced. The starting material **17** showed the two peaks to be separated initially by 0.8 ppm, and in the ^{1}HNMR of **26** the separation increased.

Additionally, the ^{1}HNMR in acetone showed a new peak at approximately 8ppm. To confirm the hypothesis that this new peak resulted from an exchangeable proton, a ^{1}HNMR was also run in chloroform-d. As indicated in Figure 15, this new peak shifted to approximately 5ppm in the new solvent. The shift in the highlighted peak is indicative of the phenol hydrogen. The peak is shifted downfield in acetone-d6 as a result of the potential for hydrogen bonding to occur in acetone, caused by deshielding which leads to the observed downfield shift for this signal. As there is no potential for hydrogen bonding, when chloroform is used as the solvent, the phenol peak is present farther upfield on the ^{1}HNMR spectra.
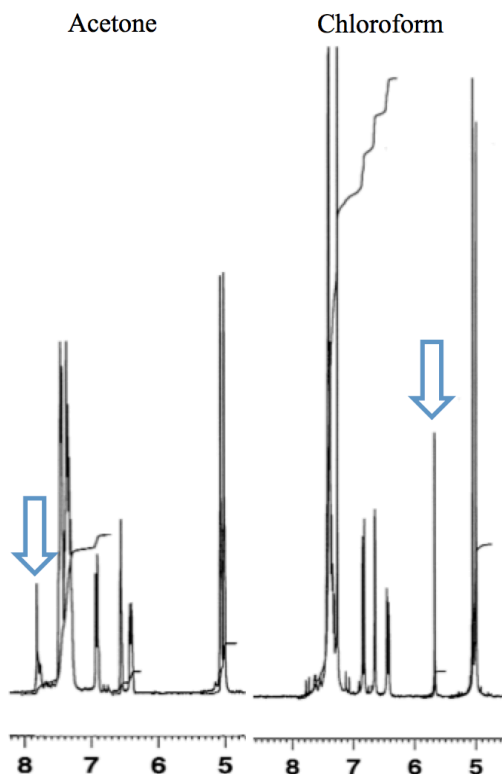
Figure 15. Comparison of the ^{1}HNMR for Compound **26** in COD$_6$ and CDCl$_3$

Additionally, a ^{13}CNMR of compound **23** was obtained, and several notable signals were apparent. For the two-methylene carbons that are part of the protecting group we expect to see a larger difference between the two distinct carbons. The shift is due to the absence of the bromine. Additionally, as expected, the aromatic carbon that is attached to the hydroxyl group is shifted farther downfield.

Finally, FTIR analysis (Figure 16) confirmed that the desired product was obtained. As compound **23** contains an aromatic hydroxyl group, a broad peak in the 3000cm^{-1} region was anticipated. However, the FTIR for **26** showed the presence of a sharp peak at 3532.50cm^{-1}. This sharp peak is indicative of the aromatic phenol seen in **23**. The sharp peak results from the lack of intermolecular hydrogen bonding and the presence of intramolecular bonding, as depicted in red in Figure 17.
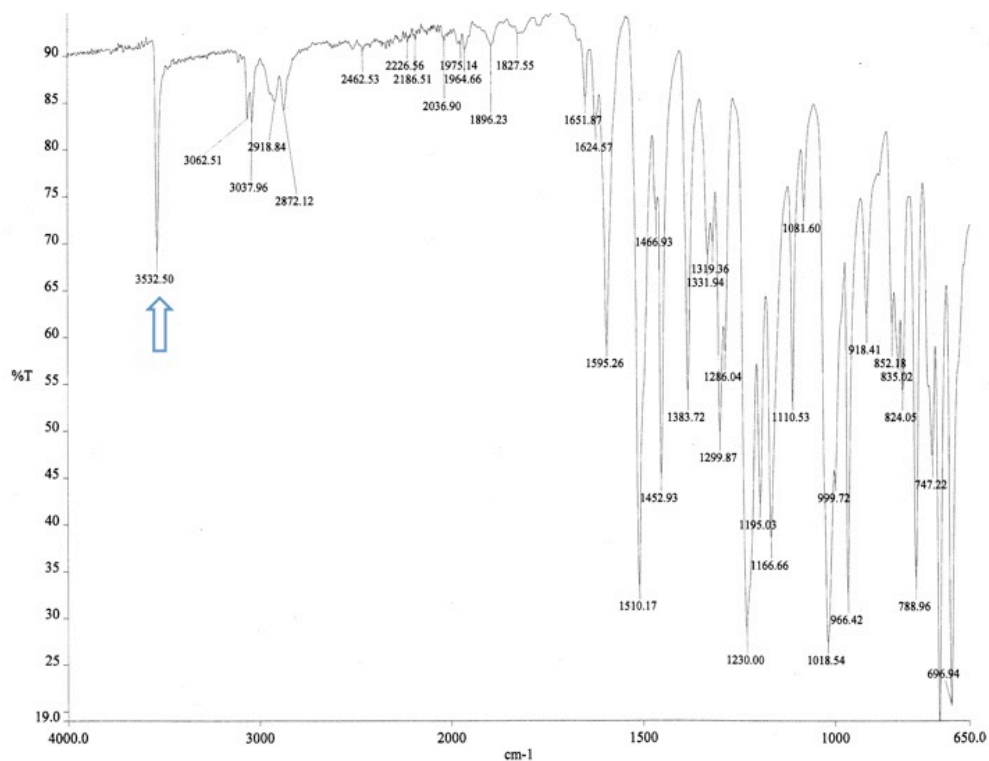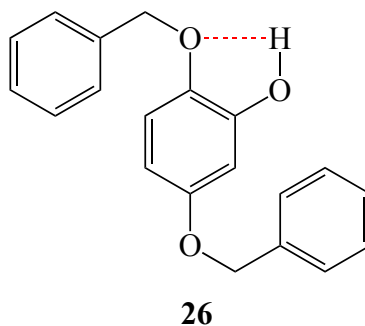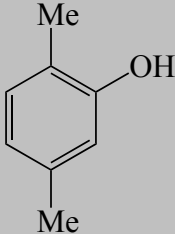
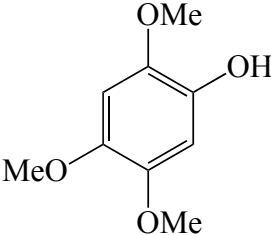**Figure 16.** FTIR of Compound **26**

26
Figure 17. Intramolecular Hydrogen Bonding in Phenol **26**

Although the desired product was isolated, purification proved to be extremely challenging, and often, only a very small amount of the desired product was isolated. When the compound was purified by preparatory thin layer chromatography (9:1 Hex:EtOAc) as in trial 1 and the test reaction run by Olivia Hulme, the desired product was obtained but with a very small impurity.[39] In trials 2-4, various columns were attempted with various hexane: ethyl acetate solvent systems as well as various proportions of silica gel compared to the amount of crude

product to be purified. The desired product was able to be isolated; however, often times, the majority of the desired product was found to have an impurity. In order to optimize the purification and to isolate as much of the desired product as possible, several impure fractions were combined, and a column where the crude material was dry loaded was tested. For this purification attempt, a silica gel: crude ratio of 50g: 1g was also used. The column was run with a step-wise gradient of hexanes: ethyl acetate solvent systems ranging from 40:1 to 15:1. Additionally, smaller fractions were collected to maximize the amount of pure product obtained. However, despite these additional column chromatography purification modifications, no isolated fractions of **26** were obtained.

To determine if purification would present fewer difficulties in the next synthetic step, the subsequent alkylation reaction was conducted with the Buchwald hydroxylation reaction crude mixture. However this reaction did not produce the desired results. Given the difficulties encountered with the previous purification attempts, several solvent systems were screened to find one that could adequately separated the crude mixture. A literature search was completed to survey how similar compounds have been previously purified, and the results have been summarized in Table 2.
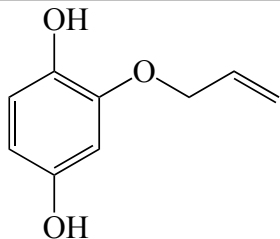
Entry	Compound Purified	Solvent System
1[36]		9:1 Hexanes: Diethyl ether
2[47]		20% EtOAc in hexanes
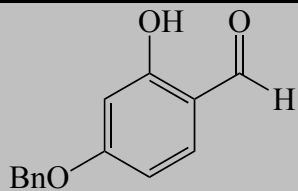
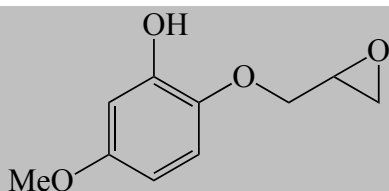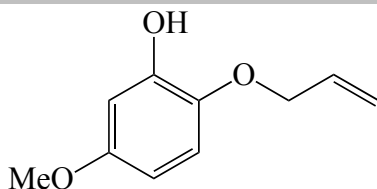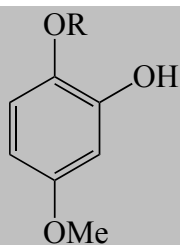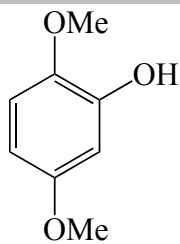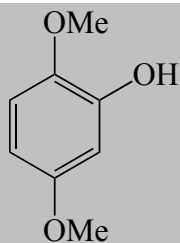|		
3[48]		95:5 Hexanes: Ethyl Acetate 9:1 Hexanes: Ethyl Acetate 8:2 Hexanes: Ethyl Acetate
4[49]		Crude Mixture Carried Through to the Next Step
5[49]		Compound 26 Nelson Journal of Medicinal Chemistry 1979 Volume 22 No 9 1082
6[49]		Distillation
7[49]		Compound 24 Nelson Journal of Medicinal Chemistry 1979 Volume 22 No 9 1082
8[50]		Distillation
9[51]		6:4 Hexanes: Ethyl Acetate
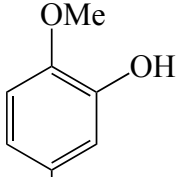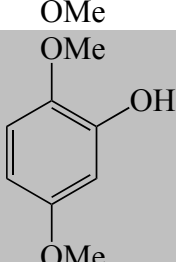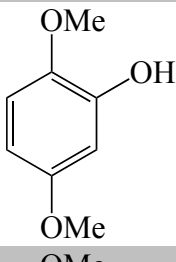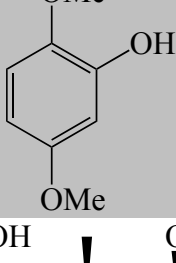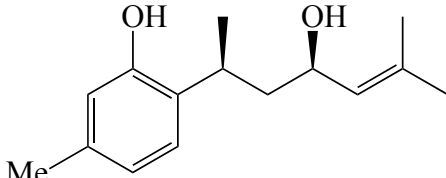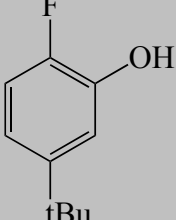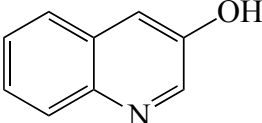
10[52]		Crude Mixture Carried Through to the Next Step
11[53]		2:1 Cyclohexane: Ethyl Acetate
12[54]		7:3 Petroleum Ether: Methyl Tert-Butyl Ether
13[55]		9:1 Petroleum Ether: Diethyl Ether 4:1 Petroleum Ether: Diethyl Ether
14[56]		97:3 Hexanes: Ethyl Acetate
15[57]		20:1 Hexanes: Ethyl Acetate
16[36]		100:1 Chloroform: Methanol

Table 2. Literature Review for Finding an Adequate Solvent System

As previously mentioned, the subsequent reaction was conducted with a crude reaction mixture, and the desired results were not obtained. Because of the number of components that composed the crude mixture, distillation and recrystallization would not be plausible. As a result, the solvent systems used from entries 1, 2, 3, 9, 11, 14, 15, 16 in Table 2 were screened. Before testing the remaining entries, it was determined that cyclohexane: ethyl acetate adequately separated the crude components.

Subsequently, 9:1, 5:1. 3:1, and 2:1 mixtures of cyclohexane and ethyl acetate solutions were tested to see which solvent system afforded the best separation; it was determined that the 5:1 solvent system yielded the best separation. For the subsequent Buchwald Hydroxylation reactions (trial 7), 5:1 cyclohexane: ethyl acetate became the monitoring solvent system.

This new solvent system also proved to successfully isolate compound **26**. In an initial test column, approximately 0.5g of crude (trial 6) was loaded onto a column with about 40g of silica gel. The column was run with 100:0, 9:1, 5:1, 3:1, and 1:1 mixtures of cyclohexane: ethyl acetate. The band for this column was slightly thicker than desired, but generally, the desired product was isolated.

Throughout the various Buchwald hydroxylation trials, the reaction was quenched after different reaction times. While various factors could potentially contribute to the lower yields, such as purification problems, efforts have been made to optimize the amount of starting material that is converted to the desired product. TLC analysis suggests an increased reaction time often leads to a higher conversion of starting material. Additionally, slightly different equivalences of the catalysts and ligand have been employed. As an example, in trial 7, the ratio between the catalyst and the ligand were both increased, which in conjunction with the increased amount of time, lead to higher product conversion as observed by TLC (5:1 cyclohexane: ethyl acetate).

Additionally, for both trials 6 and 7, the solvent: starting material, **23**, ratio was modified in an effort to optimize scale up reactions. In these types of reactions, minor changes can perturb the catalytic system and hinder the production of the desired product. As this reaction is completed in a pressure tube, the reaction vessel can be filled with 6mL of liquid at most, making scale ups of the reaction difficult. In trials 6 and 7, 828mg of starting material, **23**, was dissolved with appropriate amounts of all of the reagents in half as much solvent as proportionally used for trials 1-5 to determine if similar product formation would be observed. This experiment allowed for 800mg scales of the reaction to be run with efficient stirring and with similar results to other previous trials.

Alkylation Reaction to form the Bromoether:

An initial trial of the alkylation reaction to form (((2-(2-bromoethoxy)-1,4-phenylene)bis(oxy))bis(methylene))dibenzene, **28**, commenced based off of a published procedure by Xingshu and coworkers.[37] Their procedure suggested that the desired product could be obtained by dissolving the starting material, potassium carbonate and potassium iodide in butanone. To that solution, dibromoethane was subsequently added and allowed to stir at room temperature for four hours.

Results:

A 75mg initial trial (trial 1) was modeled off of the published procedure. Phenol **26** was mixed with potassium carbonate and potassium iodide and dissolved in dibromoethane. The reaction was monitored with TLC (20:1 hexane: ethyl acetate), which suggested that a reaction was not occurring, so several additional proportions of dibromoethane were added as indicated in

Table 3. After letting the reaction run overnight, no reaction occurred. The starting material, **26**, was still present and was easily recovered by a simple extraction.

Time into Reaction	Additional Amount of Dibromoethne (27)	Evidence of Reaction
3 hours and 30 minutes	30 μL	No
5 hours and 45 minutes	30 μL	No
Overnight	End Reaction	No

Table 3. Summary of Trial 1 of the Alkylation Reaction to form **28**
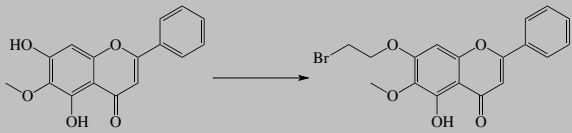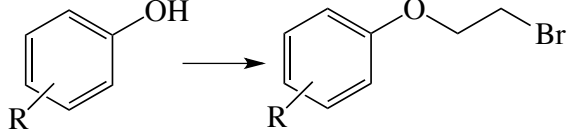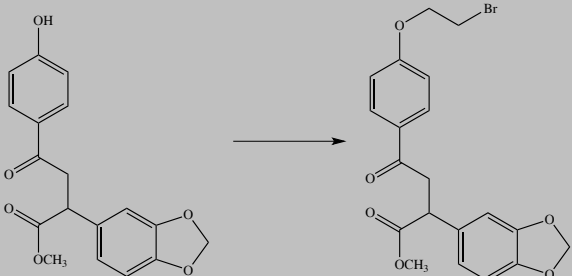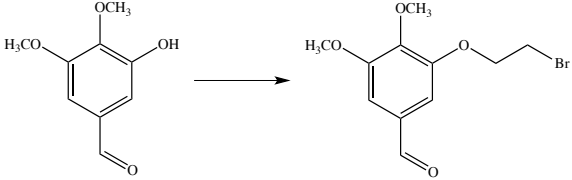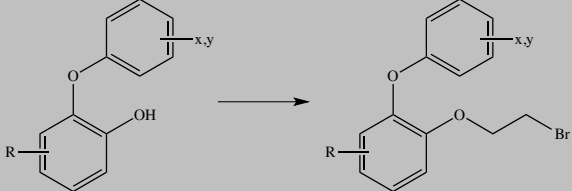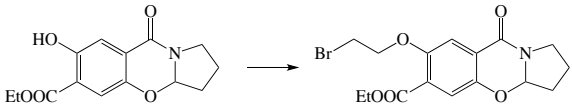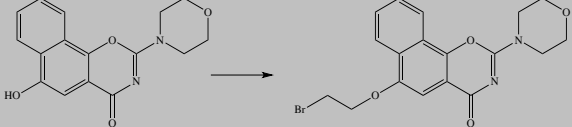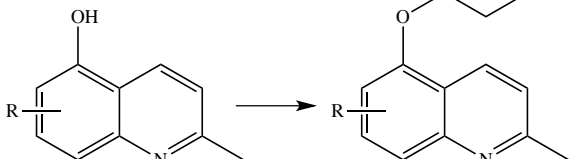
Because dibromoethane can readily be converted to ethylene glycol in the presence of moisture, it was decided that additional precautions would be taken for all future reactions. To
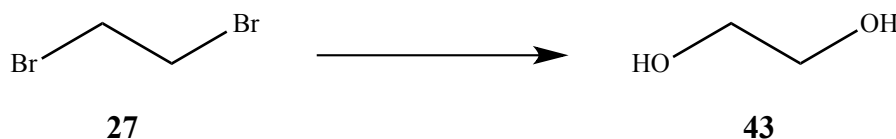
Scheme 1. Conversion of Dibromoethane (**27**) to Ethyleneglycol (**43**)

ensure that very little to no water was present on the starting material, compound **26** was dried three times with toluene and subsequently placed under vacuum to dry for three to five hours. However, since no reaction occurred with the conditions suggested by Huang and coworkers, additional methods of achieving the same transformation were explored by conducting a thorough literature search. The literature search results are summarized in Table 4.

Entry	Presented Reaction in Literature	Reaction Conditions	Reported Yield
1[58]		Dibromoethane, K_2CO_3, Acetone, Reflux for 2 days	10.4 mmol quantitative yield
2[59]		Dibromoethane, K_2CO_3, DMF, 70°C	*Not Available*

	Reaction	Conditions	Yield
3[60]		Dibromoethane, K_2CO_3, Acetone, Reflux, 7-8 hours	*Not Available*
4[61]	R=2,5-Cl	Dibromoethane, NaOH, H_2O, 100˚C, 7 hours	52%
5[62]		Dibromoethane, $CsCO_3$, DMF, 20 hours	64%
6[62]		Dibromoethane, $CsCO_3$, DMF, 3 hours	69%
7[63]		DIAD, Bromoethanol, Ph_3P, THF	68%-92%
8[64]		Dibromoethane, K_2CO_3, Acetone, 110˚C, 4 days	76%
9[65]		Dibromoethane, $CsCO_3$, Acetonitrile, 80˚C, 20 hours	87%
10[66]		Dibromoethane, K_2CO_3, MEK, 85˚C	71%-81%
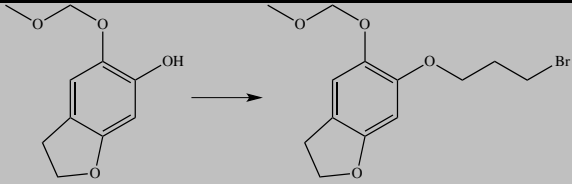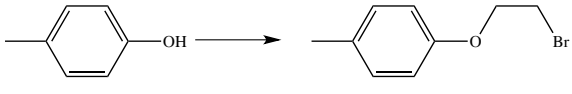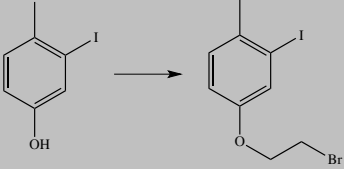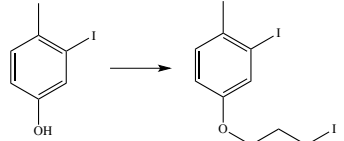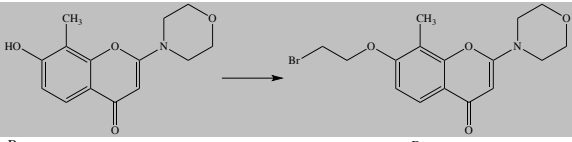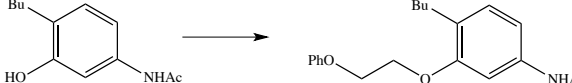
11[67]		Dibromopropane, NaH, DMF	44%
12[68]		Dibromoethane, NaOH/H2O phase transfer catalyst	*Not Available*
13[58]		Dibromoethane, K_2CO3, Acetone, 55˚C, 4 hours	64%
14[58]		Diiodopropane, K_2CO_3, Acetone, 50˚C, 2 days	84%
15[69]		Dibromoethane, Phase Transfer Catalyst	*Not Available*
16[70]		NaH, DMF	71%

Table 4. Literature Search for Similar Alkylation Reactions

After comparing the published procedures and percent yields, it was determined that trial reactions based off of entries 1, 2, 3, 5, 6, 8, 9, 11, 13, and 16 would be tested. In trial 2, reaction conditions similar to those published by Lautnes and coworkers were tested, as presented in entry 1 of table 6.[58] The starting material, **26**, was dissolved in anhydrous acetone and mixed with potassium carbonate and dibromoethane and allowed to reflux. The reaction was monitored with TLC (9:1 Hexane: Ethyl acetate). However, after the first night, it appeared as if no reaction occurred. In order to help drive the reaction forward, as well as compensate for any acetone that evaporated due to the reflux conditions, additional anhydrous acetone and dibromoethane were added. The additional solvent and reagents were added as presented in Table 5.

Time into Reaction	Additional Amount of Dibromoethne (27)	Additional Base (K$_2$CO$_3$)	Additional Solvent (Acetone)	Temperature Change	Evidence of Reaction (TLC)
0 hours	25μL	None	1mL	No Change	No evidence
21.5 hours	30μL	None	None	No Change	Minimal evidence
24 hours	80μL	None	None	55˚C	No Change
25 hours	None	None	None	No Change	Evidence of Reaction
28 hours	None	None	None	None	Evidence of Reaction
46 hours	7.5mL	23.5mg	1mL	None	Evidence of Reaction
70 hours	None	None	None	None	No Change
71.5 hours	2.5mL	None	0.75mL	None	No Change
97.5 hours	None	None	None	None	Reaction Killed

Table 5. Summary of Trial 2 Reaction Conditions

While this method produced the desired product, it was hypothesized that an alternative set of more effective reaction conditions could be determined. In trial 3, reaction conditions used by Euan and coworkers and Manetsch and coworkers were adapted (entries 11 and 16 of Table 4).[67,70] In this trial, phenol **26** was deprotonated by a strong base NaH in DMF. To a solution of dibromoethane in DMF, the phenoxide ion solution was added dropwise. After 7 hours, TLC analysis (20:1 Hexane: Ethyl Acetate) showed no evidence of formation of the desired product.

Next, a new trial was investigated where a smaller mesh K$_2$CO$_3$ was mixed with acetonitrile and the starting material (**26**). Dibromoethane was added and the reaction was refluxed at 80˚C. After 3 hours a new less polar spot was apparent on the TLC plate (20:1 Hexane: Ethyl Acetate). After 7 hours, the reaction was quenched due to the presence of an additional non-polar fluorescent spot. The initial spot was isolated by preparatory thin layer chromatography (20:1 hexanes: ethyl acetate).

Compound **28** was characterized with ^{1}HNMR. Chloroform-d was used as the NMR solvent because of the location of its solvent peaks. As this reaction does not involve the addition of aromatic protons, it is more important to analyze the upfield region of the spectra. Several factors suggested that compound **28** was synthesized.

First, the phenol peak at around 5.8ppm was no longer present. Additionally, the ^{1}HNMR showed the addition of two methylene peaks at 3.6 and 4.3 ppm, each representing two protons. These two peaks are representative of the methylene protons that come from the attachment of the dibromoethane, denoted in green in Figure 18.

28
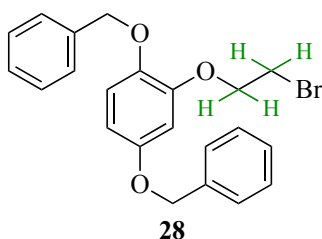
Figure 18. Compound 28 Highlight the New Hydrogens as a Result of the Reaction

In trial 5, Cs_2CO_3 was mixed with acetonitrile and the starting material **26**. Dibromoethane was added and the reaction was refluxed at 70˚C. After 2 hours, the new less polar reaction spot was present. The reaction was quenched after four hours, when the more non-polar impurity was present on the TLC plate (20:1 hexane: ethyl acetate). The crude mixture was purified by preparatory thin layer chromatography (20: 1 hexane: ethyl acetate). Approximately 16mg of the desired product was isolated, and the isolated product was confirmed to be **28** by ^{1}HNMR analysis.

Conditions	Obtain Desired Compound	Percent Yield and Other Notes
K_2CO_3, Butanone, Dibromoethane, KI, overnight	No	Able to recover starting material 0% Yield
K_2CO_3, Acetone, Dibromoethane, four days, 74˚C/ 55˚C	Yes	13% Yield
Smaller Mesh K_2CO_3, Acetonitrile, Dibromoethane, 80˚C	Yes	Starting material present, evidence of dimer formation (5.3mg)
Smaller Mesh $CsCO_3$, acetonitrile, Dibromoethane, 4.5 hours, 70˚C	Yes	Nearly no starting material present (16.6mg)
NaH, DMF, Dibromoethane, 75˚C	No	No Evidence of Desired Product 0% Yield

Table 6. Summary of Methods Tested to Form Bromoether (**28**)

All five different methods test to run the alkylation are summarized in Table 6. In conclusion, it was determined that using Cs_2CO_3 as a base, with acetonitrile as the solvent produced the desired product, **28**, with complete conversion. A more exposed based with a more polar aprotic solvent increases the efficiency and effectiveness of the S_N2 reaction. This reaction is heterogeneous, meaning that the base does not dissolve in the acetone, so a more surface exposed based such as cesium carbonate is beneficial.

After determining appropriate reaction conditions to synthesize compound **28**, optimization of reaction conditions began. As previously noted, the purification of compound **26** was difficult prior to finding the cyclohexane: ethyl acetate solvent system. In trials 6 and 7, crude reaction mixtures from the Buchwald hydroxylation reactions, which contained compound **26,** were used as the starting material.

However, from the purification of trial 6, it was determined purification of this reaction was in fact more arduous than the purification of the Buchwald Hydroxylation reaction due to

presence of numerous components in the crude mixture. In response, a new solvent system was found for the purification and monitoring of the Buchwald Hydroxylation reaction.

In trial 7, a new solvent system for the alkylation reaction to form **28** was implemented. 20:1, 9:1 and 5:1 mixtures of hexanes and ethyl acetate were used to monitor the reaction. It was determined that the 5:1 hexane: ethyl acetate mixture yielded the best separation and showed the presence of a more polar fluorescent impurity at 2 hours and 15 minutes. Due to the presence of this new impurity and a seemingly complete conversion of the starting material to the desired product, the reaction was quenched. However, from this trial, it can be concluded that 2 hours and 15 minutes is insufficient time for the reaction to run as the percent yield from trial 7 was lower than that of trial 5, which was allowed to run for approximately four hours. However, for during trial 5, TLC analysis showed evidence of a relatively non-polar impurity.

Alkylation Reaction to attach the Bromoether and the Thiol Component:

An initial trial to couple the protected thiol **12** and bromoether **28** was conducted based off a procedure published by Mrksich and coworkers.[27] They achieved a similar transformation by deprotonating the thio-alcohol with NaH in DMF. The deprotonation required mixing the thio-alcohol with the base at 0˚C for one hour and then at room temperature for two hours. Subsequently, a solution of a bromide compound in THF was added drop-wise to the alkoxide ion solution. The reaction mixture was allowed to stir at room temperature for 5 hours.

Results:

The first trial was modeled off of the procedure published by Mrksich and coworkers.[27] Thio-alcohol (**12**) was deprotonated by NaH to **12** dissolved in DMF. The solution was allowed

to stir at 0˚C for one hour and then at room temperature for two additional hours. After the time elapsed, a solution of bromoether (**28**) in THF was added drop wise to the alkoxide ion solution. As this was a S$_N$2 reaction, alkoxide ion was to be the limiting reagent; however, excess thiol was added.

The reaction mixture was allowed to stir at room temperature and was monitored by TLC (20:1 hexanes: ethyl acetate). Initial TLC analysis showed that a reaction was occurring. However, TLC analysis also showed that compound **12** had decomposed. The TLC plate had four spots, three of which were consistent with starting materials. The new unmatched spot was less polar than both **12** and **28**. The reaction was allowed to stir for five hours at room temperature. The preparatory TLC plate was consistent with the reaction TLC plates and showed four bands. The first band was representative of the protected thiol fragment, **12**, and the second band was bromoether **28**. The ^{1}HNMR of the third band was inconclusive.

A second trial reaction run by Hong Zhang showed that elimination occurred, as the undesired elimination product, **44**, was isolated in her trial.[71] As the proposed coupling reaction occurs via a S$_N$2 mechanism, E2 is a competitive reaction. The mechanism of the competing reaction is shown in Scheme 25.
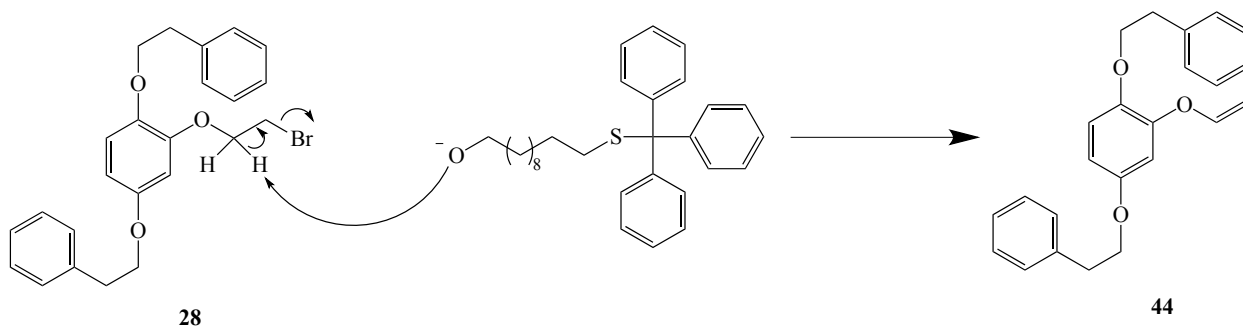
Scheme 25. Mechanism of Competing Elimination Reaction

Several procedural modifications can be employed to minimize the amount of the elimination product produced. First, the reaction should be conducted at 0˚C for the entire time.

Substitution is favored at lower temperatures because as temperature increases entropy becomes a larger factor. The elimination reaction favors entropy, consistent with the fact that more products are obtained when E2 occurs. Additionally, changing the procedure to add the deprotonated thio-alcohol **12** to the bromoether **28** drop wise would also minimize the potential for elimination to occur, as the bromoether would be more concentrated in the reaction mixture.

Formation of the Protected Thiol Component (12):

In 2009 Linh Vu, a previous lab member, successfully synthesized the protected thiol fragment **12** based off of the method proposed by Cuthbertson and coworkers.[26,72] However, the purification of this tritylation reaction proved to be extremely challenging, and the desired product was obtained in low yield. Since then, Rotello and coworkers were able to devise a method that easily allowed for the formation of compound **12** without using triphenylmethane chloride, **11**.[38]

Rotello and coworkers reported that the formation of **12** could be easily achieved by mixing triphenylmethaethiol with 11-bromo-1-undecanol, **31**, in an ethanol/ benzene solution with a solution of NaOH. The reaction was allowed to run overnight, and the desired product was obtained in a high yield of 96%.[38]

Initial results:

A 2g reaction based on the work done by Rotello and coworkers was tested. Both the triphenylmethanethiol, **32**, and the 11-bromo-1-undecanol, **31**, were dissolved in ethanol/benzene solutions, and a solution of KOH was added. The reaction was allowed to run overnight under nitrogen and was monitored by TLC (4:1 hexane: ethyl acetate). The reaction was quenched after

18 hours. TLC suggested that the desired product was obtained; there was a new polar, fluorescent spot.

^{1}HNMR analysis of the isolated fractions showed the presence of the desired product (**12**) as well as the oxidized product (**45**). (Figure 19)
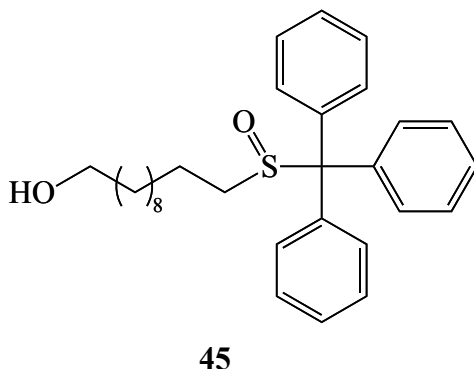

45

Figure 19. Oxidized Thiol Fragment

The overlapping multiplet peaks at around 7.3ppm are representative of the three aromatic 6-membered rings that compose the protecting group. The peak at around 5ppm is indicative of the terminal hydroxyl group. At around 3.5 ppm, the triplet represents the methylene group next to the hydroxyl group at the end. The various peaks at around 1 and 2 ppm are characteristic of the methylene groups that compose the alkane chain. The methylene group adjacent to the sulfur is slightly downfield, closer to 2ppm. The peak at around 3.2 ppm was unexpected and is hypothesized to represent the oxidized thiol fragment (**12**), shown in Figure 19.

Further analysis suggested that the isolated product might have oxidized in the presence of the NMR solvent CDCl$_3$. To test this hypothesis, the isolated desired product was re-purified with preparatory thin layer chromatography (4:1 Hexanes: Ethyl Acetate), and the NMR was run with degassed CDCl$_3$. However, the integration of the peak representing the oxidation did not change, as shown in Figure 20.
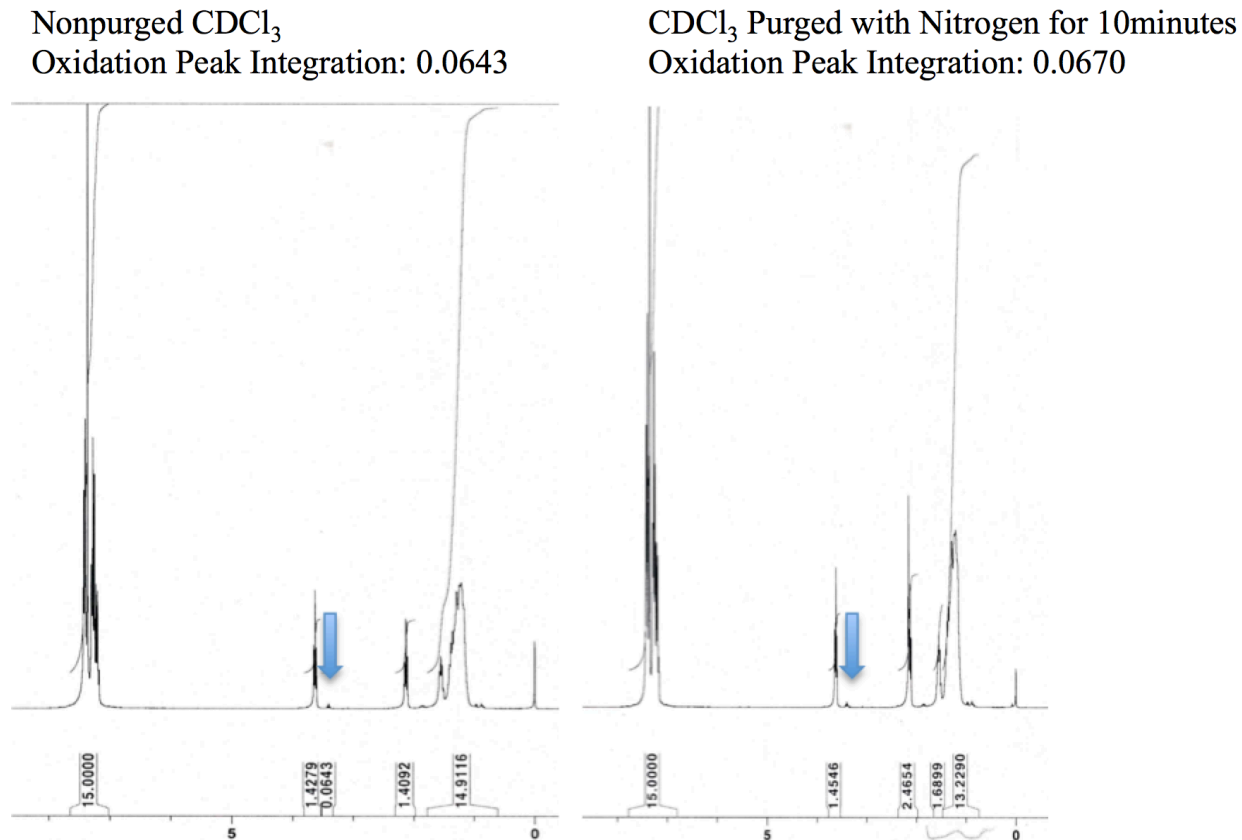
Nonpurged CDCl$_3$
Oxidation Peak Integration: 0.0643

CDCl$_3$ Purged with Nitrogen for 10minutes
Oxidation Peak Integration: 0.0670

Figure 20. HNMR of Thiol Fragment in CDCl$_3$ and Degassed CDCl$_3$

In an attempt to isolate the oxidized product from the desired compound, a preparatory TLC plate was run (4:1 hexanes: ethyl acetate). After this purification, a colorless viscous compound was obtained, matching expectations based off of literature precedents.[38] However, ^{1}HNMR analysis suggested that the oxidized version of the desired product was still present.

In a second trial of this reaction, the reaction was allowed to run for 24 hours and 15 minutes. At the end of the reaction, a very small starting material spot was evident. TLC analysis (4:1 hexanes: ethyl acetate) suggested that the obtained compound was pure. A ^{1}HNMR of the oil was run, and the spectrum suggested that the pure desired product was obtained. However, a very small oxidation peak was still observed.

Additionally, to see if storing the desired product in anhydrous benzene eliminated further oxidation, a small amount of the desired product was stored in anhydrous benzene and a ^{1}HNMR spectrum was obtained the next day (Figure 21). The integration ratio of the oxidation peak did not change; suggesting storing the compound in benzene does not decrease the likelihood of oxidation.
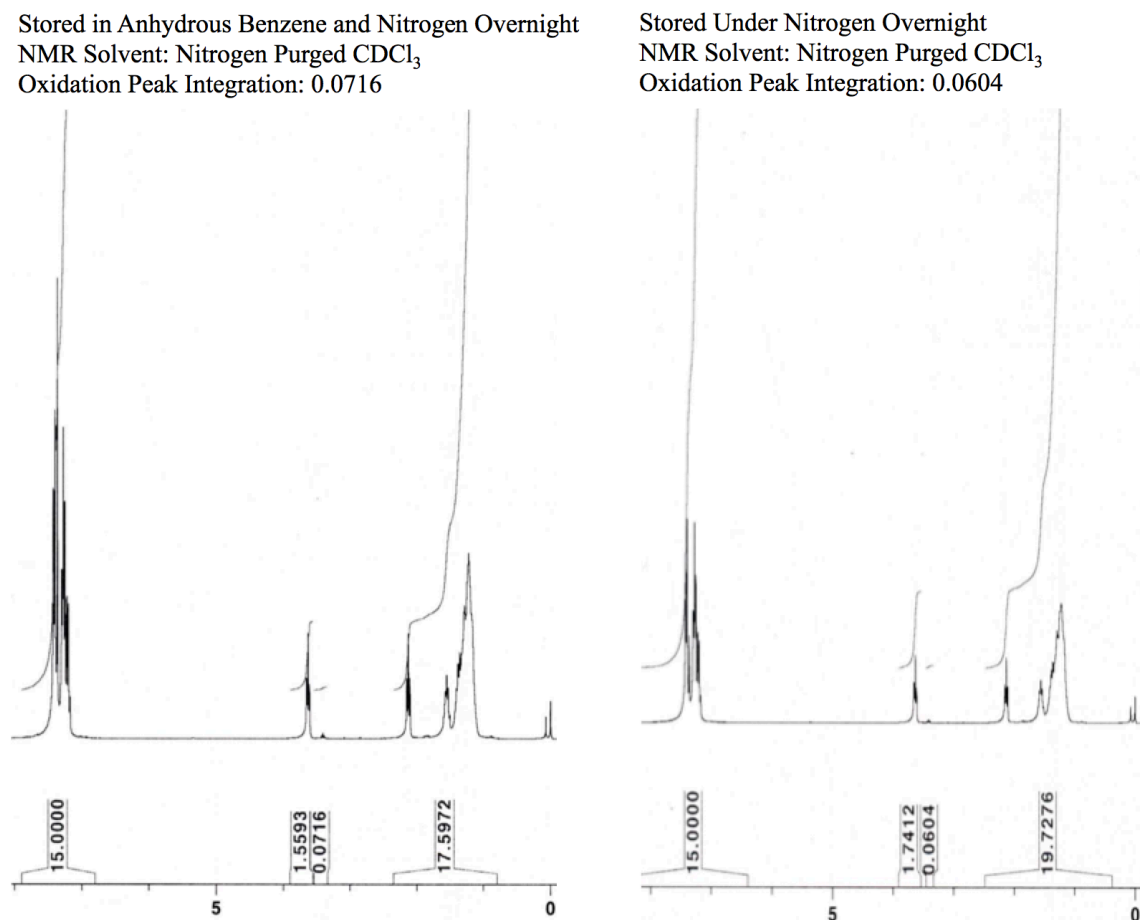
Stored in Anhydrous Benzene and Nitrogen Overnight
NMR Solvent: Nitrogen Purged CDCl$_3$
Oxidation Peak Integration: 0.0716

Stored Under Nitrogen Overnight
NMR Solvent: Nitrogen Purged CDCl$_3$
Oxidation Peak Integration: 0.0604

Figure 21. ^{1}HNMR Comparison of **12** After Being Stored Under Anhydrous Benzene and Nitrogen and Just Nitrogen

It was also of interest to see if compound **12** oxidizes with time. ^{1}HNMR spectra were obtained over the span of a couple of weeks. It was determined that the compound does not appear to oxidize with time. To determine if the compound was oxidizing the integration of the oxidation peak, highlighted by the blue arrow in Figure 22, was monitored. Over the span that

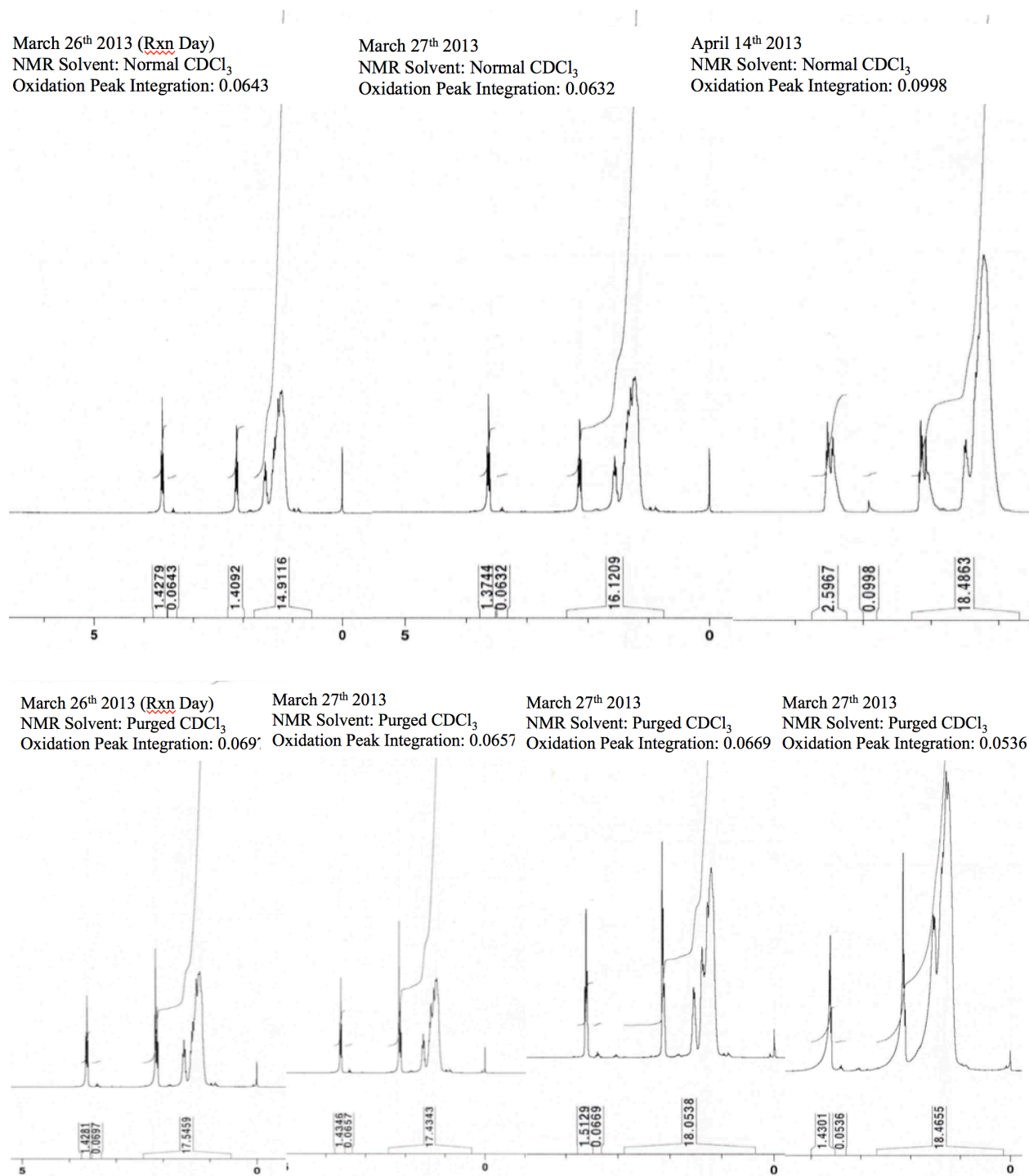the ^{1}HNMR spectra were obtained the integration remained relatively constant.

March 26th 2013 (Rxn Day)
NMR Solvent: Normal CDCl$_3$
Oxidation Peak Integration: 0.0643

March 27th 2013
NMR Solvent: Normal CDCl$_3$
Oxidation Peak Integration: 0.0632

April 14th 2013
NMR Solvent: Normal CDCl$_3$
Oxidation Peak Integration: 0.0998

March 26th 2013 (Rxn Day)
NMR Solvent: Purged CDCl$_3$
Oxidation Peak Integration: 0.0697

March 27th 2013
NMR Solvent: Purged CDCl$_3$
Oxidation Peak Integration: 0.0657

March 27th 2013
NMR Solvent: Purged CDCl$_3$
Oxidation Peak Integration: 0.0669

March 27th 2013
NMR Solvent: Purged CDCl$_3$
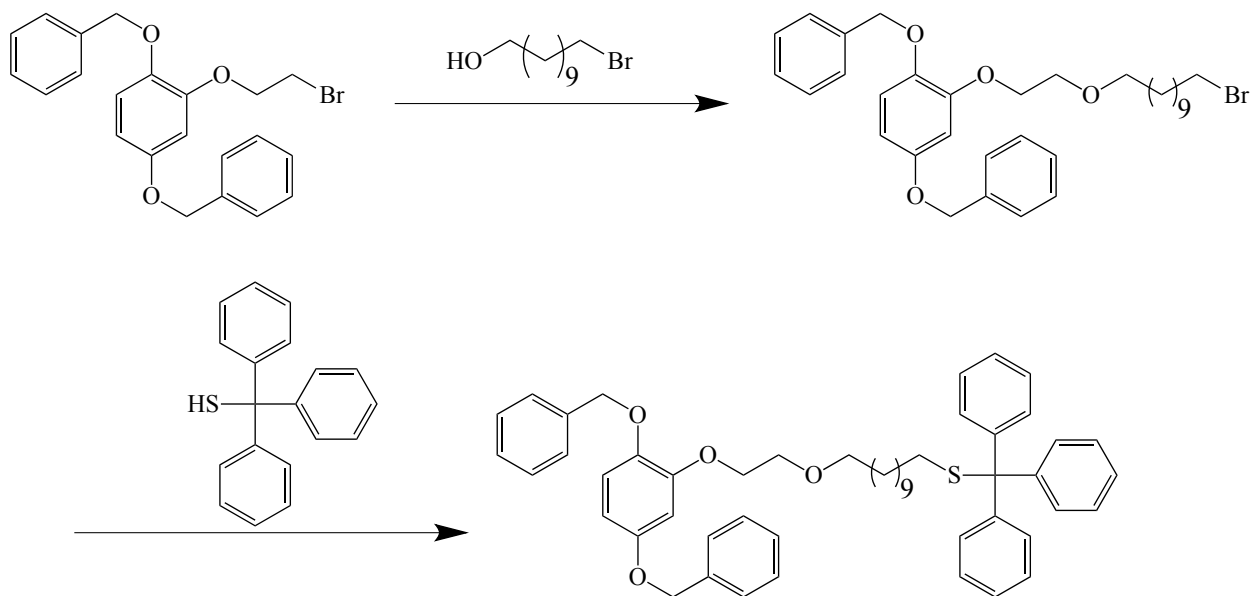Oxidation Peak Integration: 0.0536

Figure 22. ^{1}HNMR of Compound **12** Over Time

Revised Synthetic Approach:

Because the protected thiol fragment **12** appears to oxidize easily to form compound **29**, the synthetic scheme was altered to attach the terminal thiol at a later point in the overall synthesis as presented in Scheme 26.


Scheme 26. Revisions to the Synthetic Plan

In this revised synthetic route, 11-bromo-1-undecanol, **31**, is directly attached to bromoether **28**. Subsequently, the terminal thiol would be attached via the procedure proposed by Rotello and coworkers.[38] The compound would be deprotected as presented in Scheme 7, allowing the sulfur component to be installed later in the synthesis in hopes of minimizing oxidation.

While this synthetic route does have several advantages, various factors could limit the success of this plan. The deprotonated 11-bromo-1-undecanol, **31**, would be able to act as both the electrophile and the nucleophile causing either polymerization or an intramolecular ring

closure as shown in Scheme 27. If this were to occur, several undesired side reaction products would be produced, preventing the production of the desired product.
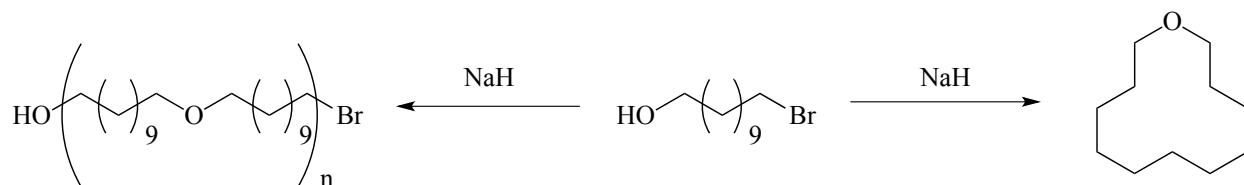
Scheme 27. Polymerization or Intramolecular Ring Closure of **31**

Future Work:

In order to optimize the yield of **23**, the reaction should be allowed to reflux for a longer period of time. Additionally, an extraction method to remove generated benzyl alcohol needs to be implemented prior to purification to maximize the efficiency and effectiveness of the column. The combination of increased reaction time and the extraction should afford the desired product in higher yield.

Further steps towards the optimization of the Buchwald hydroxylation reaction can also be taken. As an example, the reaction time can be increased to determine if the catalytic system stops working after a certain period of time. Additional efforts can also be made to determine the ideal catalyst amounts necessary to maximize complete conversion of the starting material.

The reaction time for the alkylation step to attach dibromoethane to phenol **26** should be optimized while running larger scales of the reaction. Additionally, it would be beneficial to determine how much excess dibromoethane is needed to allow complete conversion of the starting material. As only small-scale trials have been run, a column chromatography purification method should be formulated.

A method to couple compounds **28** and **12** needs to be finalized. It is hypothesized that running the reaction at 0˚C and changing the order of addition would minimize the production of the elimination product **45** and yield the desired compound **29**, but a test trial is required to determine if this is the case.

If the revised synthetic route presented in Scheme 26 is pursued, a new method to form the real system, compound **8**, must be followed. The necessary modifications are proposed in Scheme 29. The revised synthetic plan can be slightly altered to include the additional ethylene glycol units. First, mono-protected penta-ethyleneglycol, **46**, is coupled to bromoether **28** via an

alkylation reaction. It is hypothesized that pentaethylene glycol (**38**) can be monoprotected with

tert-butyldimethylsily chloride (TBDMSCl) based off of a procedure published by Kung, Kung

and Zhuang (Scheme 28).[73] While di-protection is a concern, literature suggests that the desired

product can be obtained in approximately 40% yield.
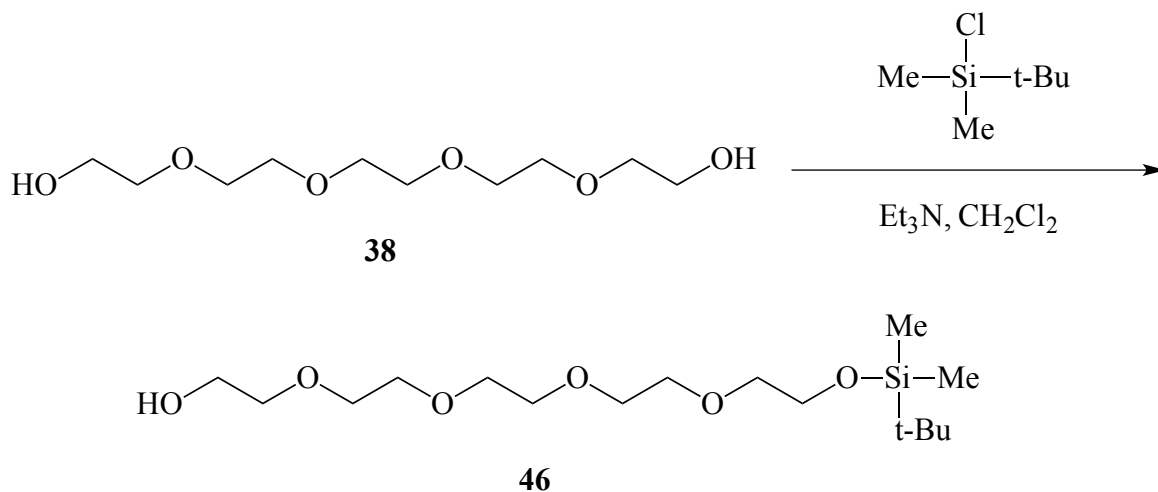
Scheme 28. Synthetic Step to Obtain Monoprotected Ethyleneglycol

The monoprotected pentaethylene glycol, **46**, can be successively coupled to bromoether

28 via an alkylation reaction. The ethylene glycol chain can then be selectively deprotected using

TBAF or other similar reagents.[74-78] 1,11-dibromoundecane, **47**, will then be attached to the

hydroquinone backbone via an alkylation reaction. Finally, the method used to synthesize

compound **12** will be used to form the protected desired product.
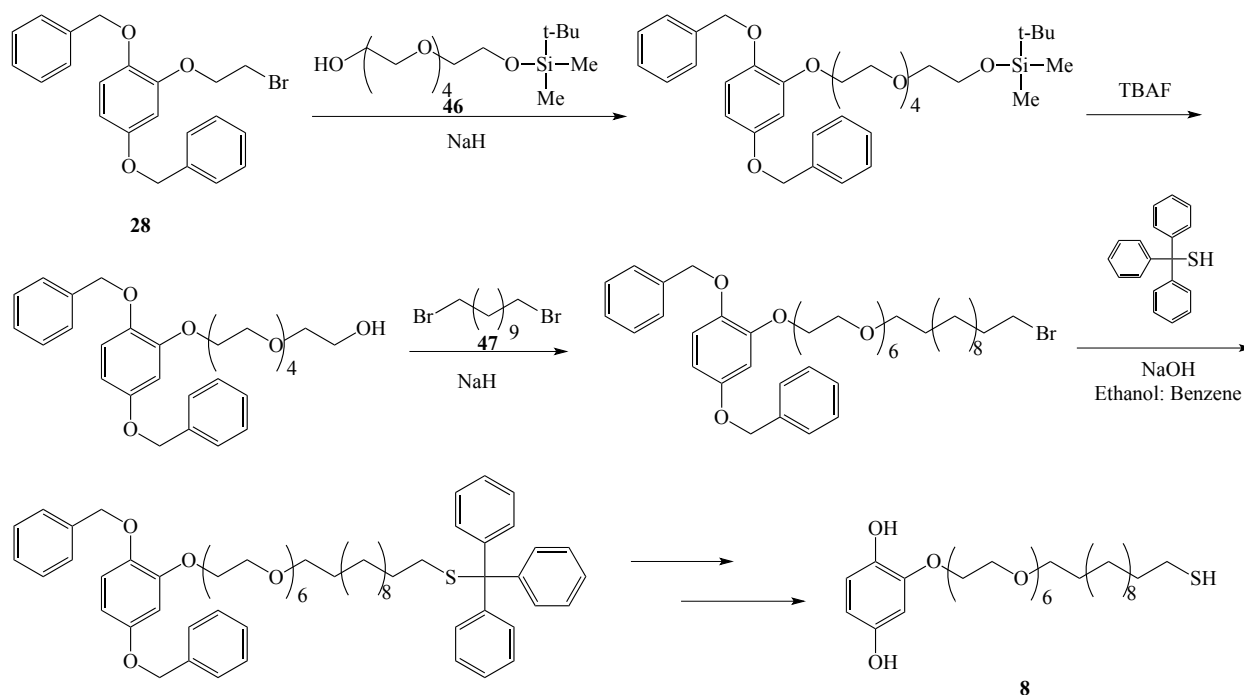
Scheme 29. Revisions to the Synthetic Scheme to Form the Real System

The number of ethylene glycol units required for aqueous solubility of the hydroquinone bearing AuNP population is not known. Once a method of obtaining compound **8** is finalized, optimization of aqueous solubility can commence. Pentaethylene glycol can be replaced with different polyethylene glycol fragments such as tetraethyleneglycol and hexaethyleneglycol in the proposed synthetic schemes. The compounds that can be synthesized are summarized in Table 7, along with compounds that would replace pentaethylene glycol. If the procedure presented in Scheme 7 is used, any of the compounds presented in Table 7 can used as a replacement for tetraethylene glycol in the procedure published by Rotello and co workers as presented in Scheme 21.[38]
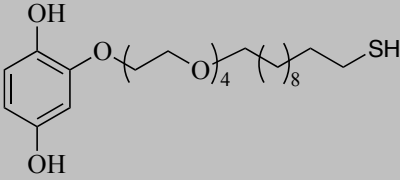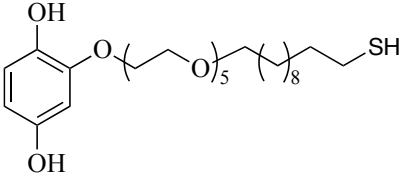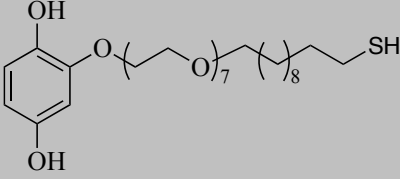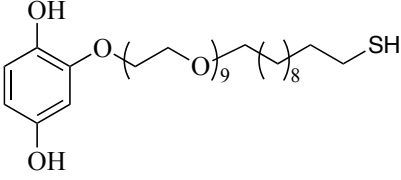
Pentaethylene Glycol Replacement	Proposed Compound to Synthesize
Triethylene glycol	OH / O—(O)$_4$—($_8$)—SH / OH (hydroquinone ring with ether linkage)
Tetraethylene glycol	OH / O—(O)$_5$—($_8$)—SH / OH
Hexaethylene glycol	OH / O—(O)$_7$—($_8$)—SH / OH
Octaethylene glycol	OH / O—(O)$_9$—($_8$)—SH / OH

Table 7. Various Compounds that can be synthesized to test Aqueous Solubility

As purification is often a time consuming step, it is hypothesized that a combination of both the protected desired product as well as the unprotected desired product could be present in the reaction to attach the thiol to the AuNP population. This would eliminate the need to purify the product of the deprotection steps. A combination of the two can be added when the AuNPs are functionalized, as either the protected thiolated compounds will remain on the surface and not attach to the AuNPs. Or alternatively despite the presence of the thiol-protection group the thiol will still spontaneously interact with the Au coating leading to functionalization of the AuNP.

Another possible avenue to explore would involve the electrochemical cleavage of protecting groups. Literature suggests that the benzyl ether protecting groups as well as the, trityl protecting groups can both be removed through electron transfer reactions.[79-81] After optimizing

aqueous solubility explore alternative methods to deprotect the hydroxyl groups, as well as the

terminus thiol should be investigated.

Conclusion:

In conclusion, the protected bromohydroquinone **23** has been successfully obtained. Purification conditions for this reaction have been optimized, and potential methods to increase the yield of the reaction have been considered.

Compound **23** has been successfully converted to its corresponding phenol, **26**, via a Buchwald hydroxylation reaction. Several reaction conditions have been tested, including reaction time, solvent ratios and catalytic proportions. The solvent ratio and catalyst amounts have been optimized, but the ideal reaction time has not yet been determined. Additionally, the purification method to obtain the pure phenol **26** has been determined and optimized.

Several reaction conditions to obtain bromoether **28** have been tested and optimized, and the ideal reaction time has also been determined. The optimized solvent system to monitor the reaction was also found.

Initial trials to couple **28** and **12** have begun. It was found that elimination can occur, and a revised procedural modification is presented in the future work section. While working towards developing a method to couple **28** and **12,** a new method to synthesize **12** has been tested and optimized. This new method affords the desired product without requiring a purification step with almost 100% conversion of the starting material.

Experimental:

General:

All reagents and solvents were purchased from Sigma Aldrich or VWR. Air and moisture sensitive reactions were run in oven-dried glassware, under Nitrogen, and with anhydrous solvents. Thin layer chromatography was performed using silica gel 60, F254 pre coated glass plates purchased from VWR. Pre-coated plates with 1000 microns thick silica gel coating purchased from Analchem were used for purification via preparatory thin layer chromatography. Column chromatography was performed with silica gel 70-230mesh, 60Å purchased from Sigma Aldrich.

A 300MHz Bruker AVANCE ^{TM} spectrometer was used to obtain all Nuclear Magnetic Resonance (NMR) spectra in parts per million (ppm). All NMR solvents were purchased from Cambridge Isotope Inc., with a standard of 0.05% of trimethylsilane (TMS). A PerkinElmer Spectrum One FT-IR Spectrometer with a PerkinElmer Universal ATR Sampling Accessory was used to obtain all Infrared Spectroscopy spectra in wavenumbers (cm^{-1}). A Hewlett Packard 5890 series was used to obtain all Gas Chromatography/ Mass Spectra. The gas spectrometer autosampler was set with the parameters of: 30.0mm column length, 0.250 mm column diameter, 2.5 min solvent delay, 12.5 min total time, 1.0 mL/min flow rate, 40˚C initial oven temperature, 325˚C final oven temperature. The mass detector type 5973 was set with the parameters of: 3.00min solvent delay, 106EM Voltage, in the scan acquisition mode. High-resolution mass spectra (HRMS) were performed in a 70-VSE or OTof Ultima mass spectrometer at the University of Illinois at Urbana-Chapaign Mass Spectrometry Facility.

Synthesis of (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (23):
Trial 1.

Bromohydroquinone (1.0906g, 5.8mmol) and potassium carbonate (1.1531g, 8.3mmol) was

dissolved in absolute acetone (25mL). Benzyl bromide (1.55mL, 13.9mmol) was added to the

solution and the solution was refluxed for four hours. (Monitored by TLC, 5:1 Hex: EtOAc) The

solution was allowed to cool to room temperature. Subsequently, any remaining potassium

carbonate was filtered off and washed with acetone. The remaining reaction mixture was

concentrated at reduced pressure. The crude mixture, a dark orange oil, was purified by column

chromatography over silica gel with a hexane/ ethyl acetate solvent system. (10:1 and 5:1, v/v).

The initial purification was unsuccessful. A second purification over silica gel with a solvent

system of hexane/ ethyl acetate (20:1, 10:1, 5:1; v/v) yielded the desired product as yellow

crystals.

Trial 2.

Bromohydroquinone (2.1826g, 11.5mmol) and potassium carbonate (2.2903g, 16.6mmol) was

dissolved in absolute acetone (50mL). Benzyl bromide (3.32mL, 28mmol) was added to the

solution. The solution was heated to reflux at 74°C for five hours. (Monitored by TLC, 5:1

Hexanes: ethyl acetate) The solution was allowed to cool to room temperature. Subsequently,

any remaining potassium carbonate was filtered off and washed with acetone. The remaining

reaction mixture was concentrated at reduced pressure. The crude mixture, a dark orange oil, was

purified by column chromatography over silica gel with a hexane/ ethyl acetate solvent system.

(20:1, 10:1 and 5:1, v/v). Yellow crystals were obtained.

Trial 3.

Bromohydroquinone (4.8706g, 25.8mmol) and potassium carbonate (5.2779g, 38.2mmol) was

dissolved in absolute acetone (75mL). Benzyl bromide (5.78mL, 48.7mmol) was added to the

solution. The solution was heated to reflux at 74˚C for five hours. (Monitored by TLC, 5:1

hexanes: ethyl acetate) The solution was allowed to cool to room temperature. Subsequently, any

remaining potassium carbonate was filtered off and washed with acetone. The remaining reaction

mixture was concentrated at reduced pressure. The crude mixture, a dark brown oil, was purified

by column chromatography over silica gel with a hexane/ ethyl acetate solvent system. (25:1,

22:1, 20:1, 18:1 v/v). The pure desired product was obtained as solid yellow crystals. (453.7 mg,

21.4%) ^{1}H-NMR COD_6: 5.1 (2H, d), 5.2 (2H, d), 7 (3H, m) 7.5 (10H, m) ^{13}C-NMR COD_6 : δ

71.17, 71.97, 113.08, 115.74, 116.09, 120.66, 128.23, 128.47, 128.65, 128.70, 129.27, 129.30,

138.13, 138.17, 150.39, 154.43 (M+, m/z 368, M+2, m/z 370)

Synthesis of 2,5-bis(benzyloxy)phenol (26):
Trial 1.

A pressure tube was charged with (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene

(92mg, 0.2mmol), finely ground potassium hydroxide (34mg, 0.61mmol), Pd_2dba_3 (7mg, 7.6x10$^-$

^{3}mmol), and Ligand 1 (11mg, 0.025mmol) in 1,4-dioxane (0.25mL), and degassed water

(0.2mL). The pressure tube was evacuated and vented with Nitrogen three times, and then

quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100˚C,

monitored by TLC (9:1 hexanes: ethyl acetate), and allowed to stir for 5 hours. After cooling to

room temperature the solution was neutralized 1M Hydrochloric Acid, and extracted with Ethyl

Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the

crude product; a brown oil. The crude was purified by preparatory thin layer chromatography

(9:1 hexanes: ethyl acetate). The initial purification attempt using hexanes: ethyl acetate was unsuccessful; the impure desired product was re-purified via preparatory thin layer chromatography using the same solvent system. The product as obtained as white solid crystals. (26mg, 34%)

Trial 2.

A pressure tube was charged (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (270.5mg, 0.7mmol), finely ground Potassium Hydroxide (98.9mg, 1.8mmol), Pd_2dba_3 (20.6mg, 2.2×10^{-3}mmol), and Ligand 1 (31.5mg, 0.074mmol) in 1,4-dioxane (2mL), and degassed water (0.6mL). The pressure tube was evacuated and vented with Nitrogen three times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100˚C, monitored by TLC (9:1 Hexanes: ethyl acetate), and allowed to stir for 7 hours. After cooling to room temperature the solution was neutralized with 22 drops of 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the crude product; a brown oil. The crude was purified via column column chromatography over silica gel with a hexane/ ethyl acetate solvent system. (20:1, 15:1,12:1, 10:1 v/v). Initial purification attempts were unsuccessful, so a second purification via column column chromatography over silica gel with a hexane/ ethyl acetate solvent system was attempted. (20:1, 15:1,12:1, 10:1 v/v). A small amount of pure desired product was obtained, however there was still a large amount of impure desired product. A third purification attempt via column chromatography over silica gel with a hexane/ ethyl acetate solvent system was successful. (20:1, 15:1,12:1, 10:1 v/v).

Trial 3.

A pressure tube was charged with ((((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (534.6mg, 1.4mmol), finely ground Potassium Hydroxide (187.3mg, 3.3mmol), Pd_2dba_3 (35.7mg, 3.8×10^{-3}mmol), and Ligand 1 (58.8mg, 0.138mmol) in 1,4-dioxane (4mL), and degassed water (1.2mL). The pressure tube was evacuated and vented with Nitrogen four times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100°C, monitored by TLC (9:1 Hexanes: ethyl acetate), and allowed to stir for **7** hours. After cooling to room temperature the solution was neutralized with 22 drops of 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the crude product; a brown oil. The crude was purified via column chromatography over silica gel with a hexane/ ethyl acetate solvent system. (20:1, 15:1,12:1, 10:1 v/v).

Trial 4.

A pressure tube was charged with ((((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (837.3mg, 2.3mmol), finely ground Potassium Hydroxide (420.2mg, 7.5mmol), Pd_2dba_3 (43.8mg,xmmol), and Ligand 1 (78.4mg, 0.185mmol) in 1,4-dioxane (6mL), and degassed water (1.8mL). The pressure tube was evacuated and vented with Nitrogen four times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100°C, monitored by TLC (9:1 hexanes: ethyl acetate), and allowed to stir for 8 hours. After cooling to room temperature the solution was neutralized with 7 drops of 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the crude product; a brown oil. The crude was purified via column chromatography over

silica gel with a hexane/ ethyl acetate solvent system. (20:1, 15:1,12:1, 10:1 v/v). The pure desired product was obtained as a white solid.

Trial 5.

A pressure tube was charged with (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (47.3mg, 0.13mmol), finely ground Potassium Hydroxide (36mg, 0.64mmol), Pd_2dba_3 (2.7mg,xmmol), and Ligand 1 (5.8mg, 0.014mmol) in 1,4-dioxane (0.5mL), and degassed water (0.1mL). The pressure tube was evacuated and vented with Nitrogen four times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100˚C, monitored by TLC (9:1 Hexanes: ethyl acetate), and allowed to stir for 8 hours. After cooling to room temperature the solution was neutralized with 3 drops of 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the crude product; a brown oil.

*Dry Loading Purification***:**

Various left over crude mixtures (trials 1-5) were mixed together. The compound was dry loaded onto a silica gel column. A column was run with various hexanes: ethyl acetate solvent systems (ranging from 40:1 to 5:1 hexanes: ethyl acetate). While TLC (9:1 hexane: ethyl acetate) initially suggested the isolation of the desired product further analysis showed that no isolated desired product had been obtained.

Trial 6.

A pressure tube was charged with (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (828mg, 2.24mmol), finely ground Potassium Hydroxide (358.8mg, 6.39mmol), Pd_2dba_3 (41.3mg, 0.045mmol), and Ligand 1 (76.4mg, 0.176mmol) in 1,4-dioxane (4mL), and degassed water (1.8mL). The pressure tube was evacuated and vented with Nitrogen four times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100˚C, monitored by TLC (9:1 Hexanes: ethyl acetate), and allowed to stir for 6 hours. After cooling to room temperature the solution was neutralized with 18 drops of 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and concentrated to obtain the crude product, a brown oil. ^{1}H-NMR COD_6: 5.1 (2H, d), 5.2 (2H, d), 7 (3H, m) 7.5 (10H, m) 8(1H, S) ^{1}H-NMR $CDCl_3$: 5.1 (2H, d), 5.2 (2H, d), 7 (3H, m) 7.5 (10H, m) ^{13}C-NMR COD_6 : δ 70.69, 72.19, 104.26, 105.61, 115.53, 128.33, 128.48, 128.59, 128.68, 129.17, 129.22, 138.53, 138.72, 141.82, 148.86, 154.95

Trial 7.

A pressure tube was charged with (((2-bromo-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (876mg, 2.37mmol), finely ground potassium hydroxide (318.8mg, 5.68mmol), Pd_2dba_3 (63.2mg, 0.069mmol), and Ligand 1 (0.110mg, 0.259mmol) in 1,4-dioxane (4mL), and degassed water (1.8mL). The pressure tube was evacuated and vented with Nitrogen three times, and then quickly sealed with a plastic screw cap. The mixture was subsequently heated to 100˚C, monitored by TLC (5:1 cyclohexane: ethyl acetate), and allowed to stir for 12 hours and 15minutes. After cooling to room temperature the solution was neutralized 1M Hydrochloric Acid, and extracted with Ethyl Acetate. The organic layer was dried with magnesium sulfate and

concentrated to obtain the crude product; a brown oil. The crude was purified by preparatory thin layer chromatography (9:1 hexanes: ethyl acetate). The initial purification attempt using hexanes: ethyl acetate was unsuccessful; the impure desired product was re-purified via preparatory thin layer chromatography using the same solvent system. The product as obtained as white solid crystals.

Synthesis of (((2-(2-bromoethoxy)-1,4-phenylene)bis(oxy))bis(methylene))dibenzene: *Trial 1.*

2,5-bis(benzyloxy)phenol (77.3mg, 0.253mmol) was mixed with potassium carbonate (57.8mg, 0.418mmol), potassium iodide (7.1mg, 0.043mmol) and dibromoethane (30μL, 0.346mmol) in butanone (3mL). The solution was stirred at room temperature, under nitrogen, and monitored by TLC. (9:1 Hexanes: ethyl acetate). After three and a half hours additional dibromoethane (15μL, 0.173mmol) was added. After 30 additional minutes there was no evidence of the formation of the desired product so additional dibromoethane was added (30μL, 0.346mmol). The reaction was allowed to run overnight, however there was no evidence of a reaction occurring. Any remaining protected phenol was reobatined via an extraction with water and ethyl acetate.

Trial 2.

2,5-bis(benzyloxy)phenol (25mg, 0.082mmol) was mixed with potassium carbonate (25.4mg, 0.184mmol) in anhydrous acetone (1mL) under nitrogen. Dibromoethane was added (25μL, 0.289mmol) and the reaction was refluxed. The reaction was monitored by thin layer chromatography (9:1 Hex: EtOAc) and additional (1 mL) acetone was added after 3 hours as some evaporated off. The reaction was allowed to run overnight, however there was minimal evidence of a reaction occurring by TLC analysis. Additional dibromoethane was added (30μL,

0.347mmol). Two and a half hours later the temperature was decreased to 55˚C and additional

dibromoethane was added (80μL, 0.924mmol). After about one hour TLC suggested that a

reaction was occurring. The reaction was allowed to run overnight. Subsequently additional

dibromoethane (7.5mL, 86.6mmol), potassium carbonate (23.49mg, 0.17mmol) and acetone

(1mL) were added to the reaction mixture. After letting the reaction run overnight, additional

dibromoethane (2.5mL, 28.9mmol) and acetone (0.75mL) were added. The reaction was allowed

to run overnight, for a forth night. The reaction mixture was allowed to cool to room

temperature. The potassium carbonate was filtered off, and rinsed with dichloromethane. The

crude mixture was extracted with water and dichloromethane, and the organic layer was dried

with magnesium sulfate. The dried organic layer was purified via preparatory thin layer

chromatography. (20:1 Hex: EtOAc). The desired product was obtained as an off white solid.

(4.3mg, 0.010mmol, 13%)

Trial 3.

Sodium hydride, 60% dispersion, (7mg, 0.082mmol) and anhydrous dimethylformamide

(300μL) were mixed under nitrogen. The mixture was cooled to about 5˚C. 2,5-

bis(benzyloxy)phenol (24.5mg, 0.080mmol) was dissolved in dimethylformamide (500μL). This

mixture was added to the sodium hydride solution dropwise over 21 minutes. The reaction was

allowed to stir for thirty minutes. This reaction mixture was added dropwise over thirty minutes

to dibromoethane (70μL, 0.809mmol) in dimethylformamide (450μL). The reaction was heated

to 75˚C and stirred vigorously for approximately four hours. The reaction was monitored by

TLC (20:1 Hexanes: ethyl acetate). After seven hours there was no evidence that the desired

product was formed. Any remaining starting material was re-obtained via an extraction with ethyl acetate.

Trial 4.

2,5-bis(benzyloxy)phenol (25.9mg, 0.085mmol) and potassium carbonate (71.4mg, 0.517mmol) were placed in anhydrous acetonitrile (1.5mL). Dibromoethane (70μL, 0.809mmol) was added and the reaction was refluxed under nitrogen, and monitored by TLC (20:1 hexanes: ethyl acetate). After seven hours the reaction mixture was allowed to cool to room temperature. The acetonitrile was removed, and any remaining potassium carbonate was filtered off and rinsed with dichloromethane. The crude mixture was extracted with dichloromethane and water, and the remaining organic layer was dried with magnesium sulfate. The crude mixture was purified by preparatory thin layer chromatography (20:1 Hexanes: ethyl acetate). The desired product was obtained. (5.3mg, 0.013mmol, 15.1%).

Trial 5.

2,5-bis(benzyloxy)phenol (26.7mg, 0.087mmol) and cesium carbonate (186.8mg, 0.573mmol) were placed in anhydrous acetonitrile (1.5mL). Dibromoethane (70μL, 0.809mmol) was added and the reaction was refluxed under nitrogen, and monitored by TLC (20:1 Hexanes: ethyl acetate). After four hours the reaction mixture was allowed to cool to room temperature. The acetonitrile was removed, and any remaining potassium carbonate was filtered off and rinsed with dichloromethane. The crude mixture was extracted with dichloromethane and water, and the remaining organic layer was dried with magnesium sulfate. The crude mixture was purified by preparatory thin layer chromatography (20:1 Hexanes: ethyl acetate). The desired product was

obtained based off of thin layer chromatography analysis; insufficient amount were obtained for further characterization.

Trial 6.

A crude mixture of 2,5-bis(benzyloxy)phenol (56mg) in 1mL anhydrous acetonitrile and cesium carbonate (0.3697g, 1.13mmol) were placed in anhydrous acetonitrile (4mL). Dibromoethane (200μL, 2.31mmol) was added and the reaction was refluxed under nitrogen, and monitored by TLC (20:1 Hexanes: ethyl acetate). After four hours the reaction mixture was allowed to cool to room temperature. The acetonitrile was removed, and any remaining potassium carbonate was filtered off and rinsed with dichloromethane. The crude mixture was extracted with dichloromethane and water, and the remaining organic layer was dried with magnesium sulfate. The desired product was obtained based off of thin layer chromatography analysis; no purification was attempted.

Trial 7.

A crude mixture of 2,5-bis(benzyloxy)phenol (35.6mg) in 1mL anhydrous acetonitrile and cesium carbonate (521.3mg, 1.6mmol) were placed in anhydrous acetonitrile (4mL). Dibromoethane (200μL, xmmol) was added and the reaction was refluxed under nitrogen, and monitored by TLC (20:1 Hexanes: ethyl acetate). After four hours the reaction mixture was allowed to cool to room temperature. The acetonitrile was removed, and any remaining potassium carbonate was filtered off and rinsed with dichloromethane. The crude mixture was extracted with dichloromethane and water, and the remaining organic layer was dried with

magnesium sulfate. The desired product was obtained based off of thin layer chromatography analysis; insufficient amount were obtained for further characterization.

Trial 8.

2,5-bis(benzyloxy)phenol (52.4mg, 0.171mmol) and cesium carbonate (0.3484mg, 1.07mmol) were placed in anhydrous acetonitrile (6mL). Dibromoethane (70μL, xmmol) was added and the reaction was refluxed under nitrogen, and monitored by TLC (5:1 hexanes: ethyl acetate). After two hours and fifteen minutes the reaction mixture was allowed to cool to room temperature. The acetonitrile was removed, and any remaining potassium carbonate was filtered off and rinsed with dichloromethane. The crude mixture was extracted with dichloromethane and water, and the remaining organic layer was dried with magnesium sulfate. The crude mixture was purified by preparatory thin layer chromatography (5:1 Hexanes: ethyl acetate). The desired product was obtained, and isolated. (0.0199g, 0.048mmol, 28.1%)

*Purification of Crude***:**

Various crude mixtures were mixed together and purified via preparatory thin layer chromatography (9:1 hexanes: ethyl acetate). The desired product was isolated in its pure form as band 2. ^{1}H-NMR CDCl$_3$: 3.5 (2H d) 4.3 (2H d) 5.5 (1H, S) 5.1 (2H, d), 5.2 (2H, d), 7 (3H, m) 7.5 (10H, m)^{13}C-NMR COD$_6$ δ 71.22, 70.13, 70.87, 72.97, 104.51, 107.31, 118.32, 128.46, 128.55, 128.59, 129.13, 129.26, 138.52, 138.97,144.02, 150.73, 155.14

Synthesis of 11-(tritylthio)undecan-1-ol:
Trial 1.

Triphenylmethanethiol (2.0787g, 7.52mmol) is dissolved in 12.5 mL 1:1 ethanol/benzene. A

solution of potassium hydroxide (0.3502g, 6.24mmol) in water (3.75mL) was added to the

triphenylmethanethiol solution. Finally a solution of 11-bromo-1-undecanol (2.18g, 8.68mmol)

in 12.5 mL 1:1 ethanol/benzene was added to the reaction mixture. The reaction mixture was

allowed to stir overnight at room temperature, under nitrogen, and was monitored by TLC (4:1

hexanes: ethyl acetate). Once all the starting material was consumed, the reaction mixture was

poured over saturated sodium bicarbonate and washed three times with brine. The organic layer

was separated, and subsequently washed with brine three times. The organic layer was obtained,

and dried with magnesium sulfate. The remaining solvent was removed and the crude product

was obtained. The crude was purified via column chromatography over silica gel with a hexane/

ethyl acetate solvent system. (9:1, 4:1 and 1:1 v/v) However, not all of the crude was initially

purified. The isolated desired product was further purified by preparatory thin layer

chromatography and the desired product was obtained as a colorless viscous compound, however

^{1}HNMR suggested that a significant amount of the desired product had oxidized.

Trial 2.

Triphenylmethanethiol (0.8341g, 3.01mmol) is dissolved in 6mL of a 1:1 ethanol/benzene. A

solution of potassium hydroxide (0.180g, 3.21mmol) in water (2mL) was added to the

triphenylmethanethiol solution. Finally a solution of 11-bromo-1-undecanol (0.7426g,

2.64mmol) in 6mL of a 1:1 ethanol/benzene was added to the reaction mixture. The reaction

mixture was allowed to stir overnight at room temperature, under nitrogen, and was monitored

by TLC (4:1 hexanes: ethyl acetate). Once all the starting material was consumed, the reaction

mixture was poured over saturated sodium bicarbonate and washed three times with brine. The organic layer was separated, and subsequently washed with brine three times. The organic layer was obtained, and dried with magnesium sulfate. The remaining solvent was removed and the pure desired product was obtained. ^{1}H-NMR CDCl$_3$: δ 1.5 (18H, m) 3.8 (2m), 7.2 (15H, m) ^{13}C-NMR COD$_6$: δ 26.59, 32.40, 33.69, 62.39, 67.02, 127.29, 128.26, 128.53, 129.00, 130.26, 145.91

Synthesis of (4-(2-(2,5-bis(benzyloxy)phenoxy)ethoxy)butyl)(trityl)sulfane: Trial 1.

11-(tritylthio)undecan-1-ol (0.0409g, 0.092mmol) was dissolved in dimethylformide (54 μL), and cooled to 0˚C. A solution of sodium hydride (0.0060g, 0.25mmol) in dimethylformide (54 μL) was added slowly to the 11-(tritylthio)undecan-1-ol solution. The mixture was allowed to stir at 0˚C for one hour and subsequently at room temperature for two additional hours, under Nitrogen. A solution of (((2-(2-bromoethoxy)-1,4-phenylene)bis(oxy))bis(methylene))dibenzene (16mg, 0.039mmol) in thetrahydrofuran was added dropwise. The reaction was allowed to stir at room temperature for 4 hours, under Nitrogen, and was monitored by TLC (20:1 hexanes: ethyl acetate). Once the reaction reached completion; the solution was diluted with ethyl acetate, and subsequently washed with ammonium chloride, and brine three times each. The organic layer was separated, dried with magnesium sulfate and concentrated. The crude mixture was purified by preparatory thin layer chromatography. (20:1 hexanes: ethyl acetate). Insufficient amounts were obtained for complete and thorough analysis.

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NS-1-97-1

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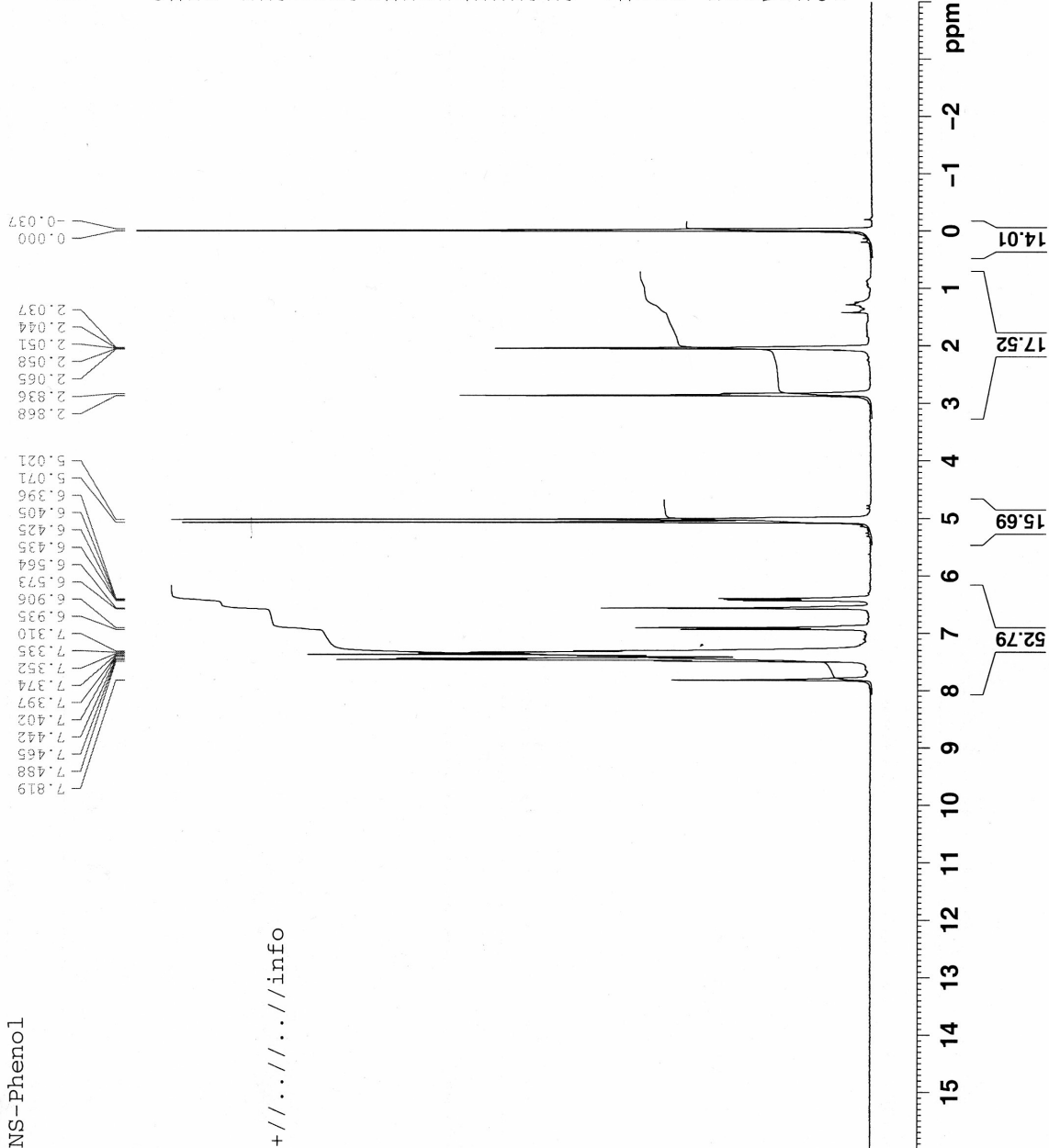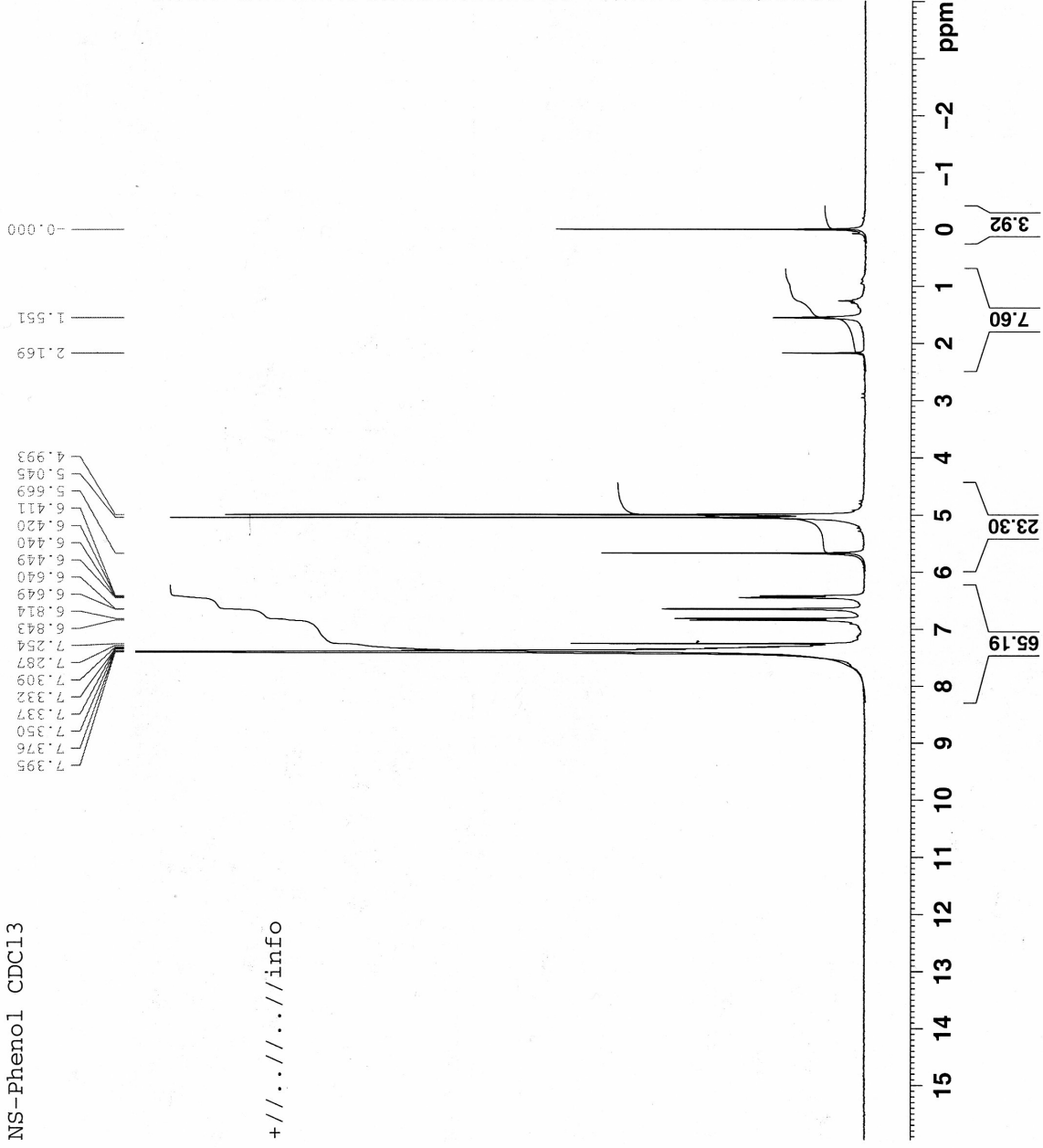

Current Data Parameters
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EXPNO   20
PROCNO   1

F2 - Acquisition Parameters
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INSTRUM   spect
PROBHD   5 mm BBO BB-1H
PULPROG   zg30
TD   32768
SOLVENT   Acetone
NS   16
DS   0
SWH   5995.204 Hz
FIDRES   0.182959 Hz
AQ   2.7329011 sec
RG   456.1
DW   83.400 usec
DE   6.00 usec
TE   295.2 K
D1   2.00000000 sec
TD0   1

======= CHANNEL f1 =======
NUC1   1H
P1   9.00 usec
PL1   -1.00 dB
SFO1   300.1318008 MHz

F2 - Processing parameters
SI   16384
SF   300.1300032 MHz
WDW   EM
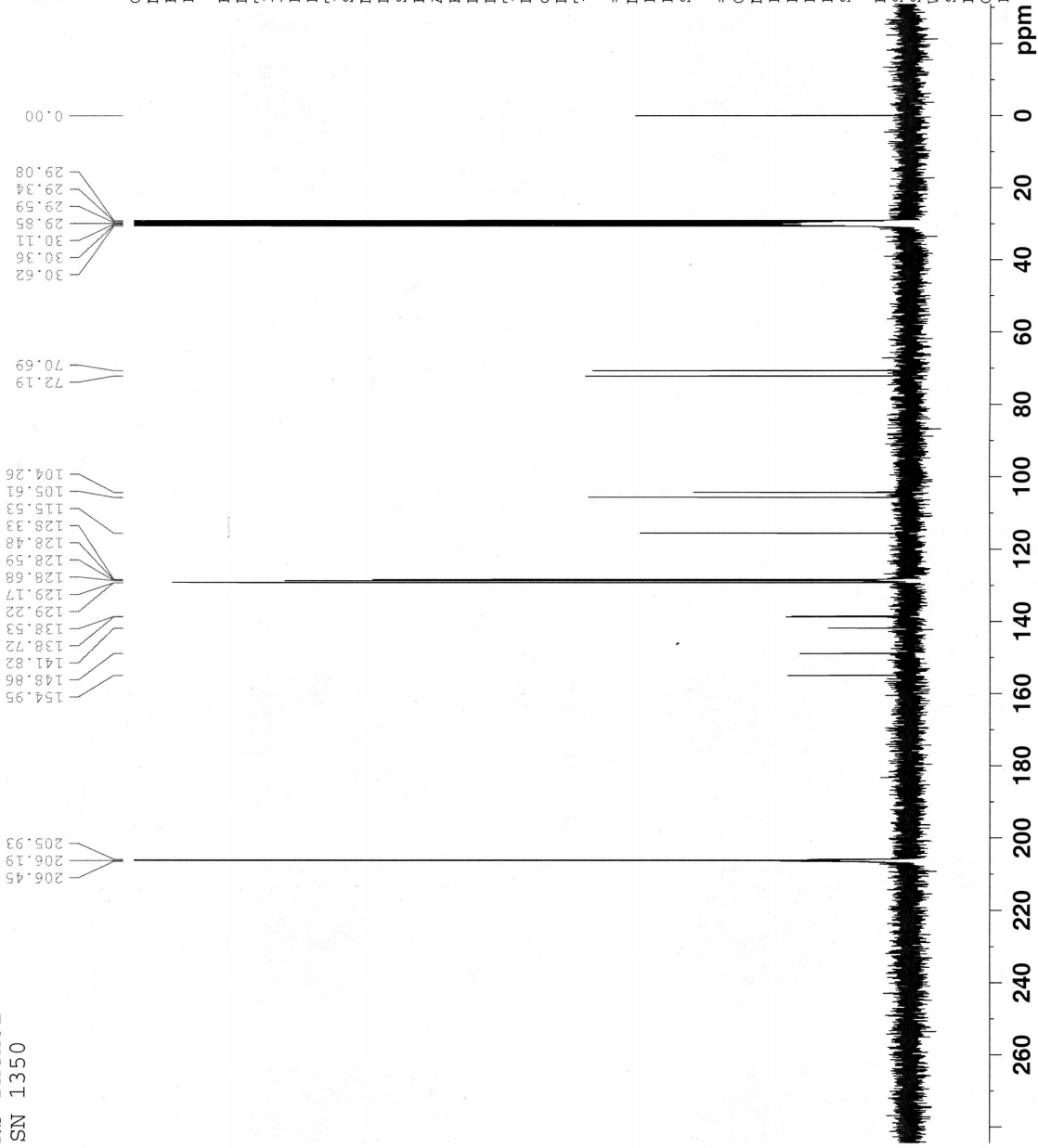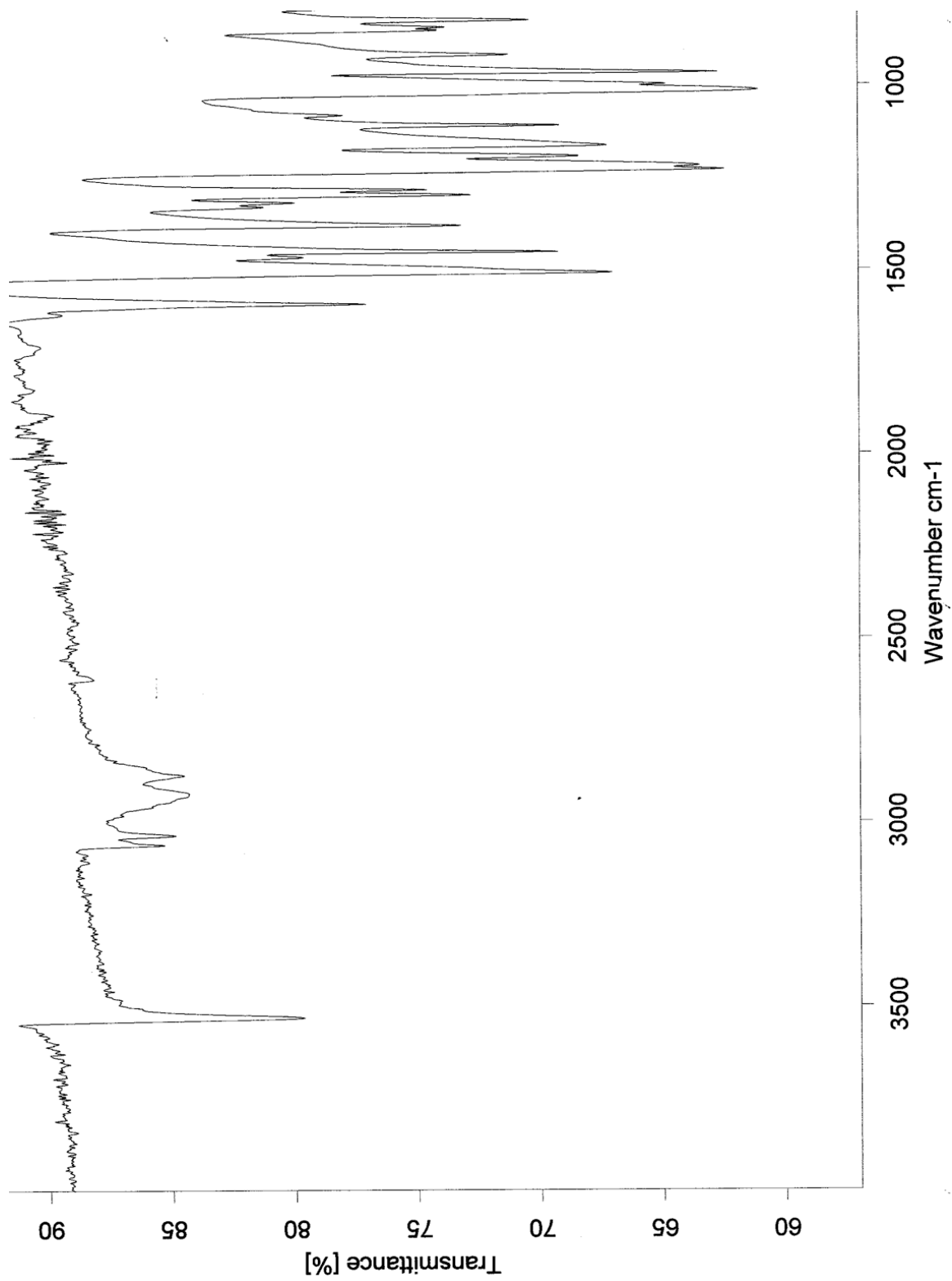SSB   0
LB   1.00 Hz
GB   0
PC   1.00

0.000

2.053

File   : D:\1\KAC\IGOA24.D
Operator : OH
Acquired : 28 Mar 2012 18:36   using AcqMethod DCMLOW
Instrument :   Instrumen
Sample Name: Band 2 Pure check
Misc Info :
Vial Number: 37

Abundance   TIC: IGOA24.D

Abundance   Scan 2039 (13.733 min): IGOA24.D

87

Scan: 5
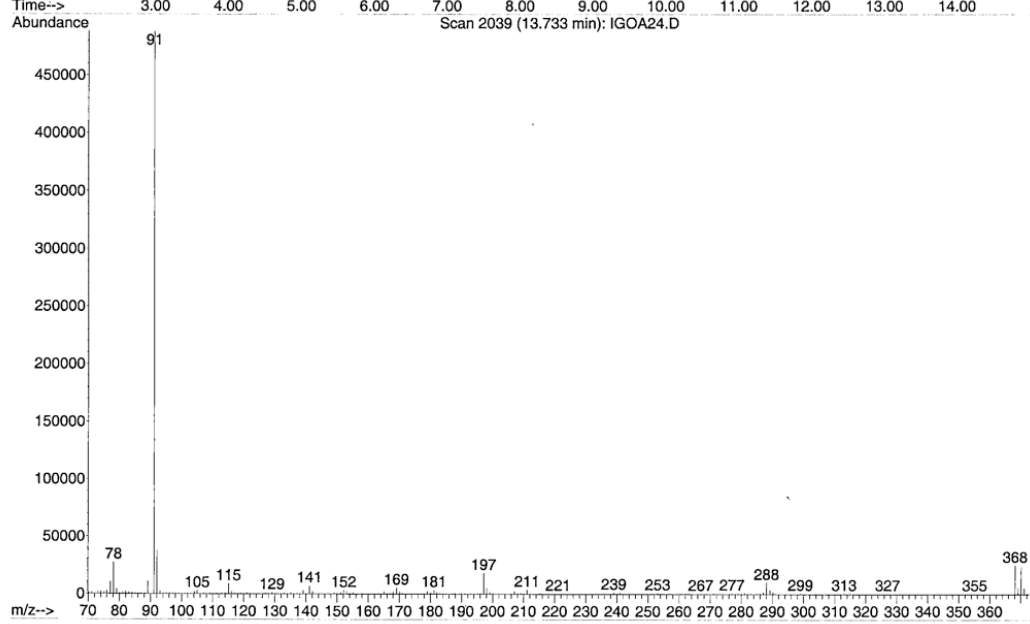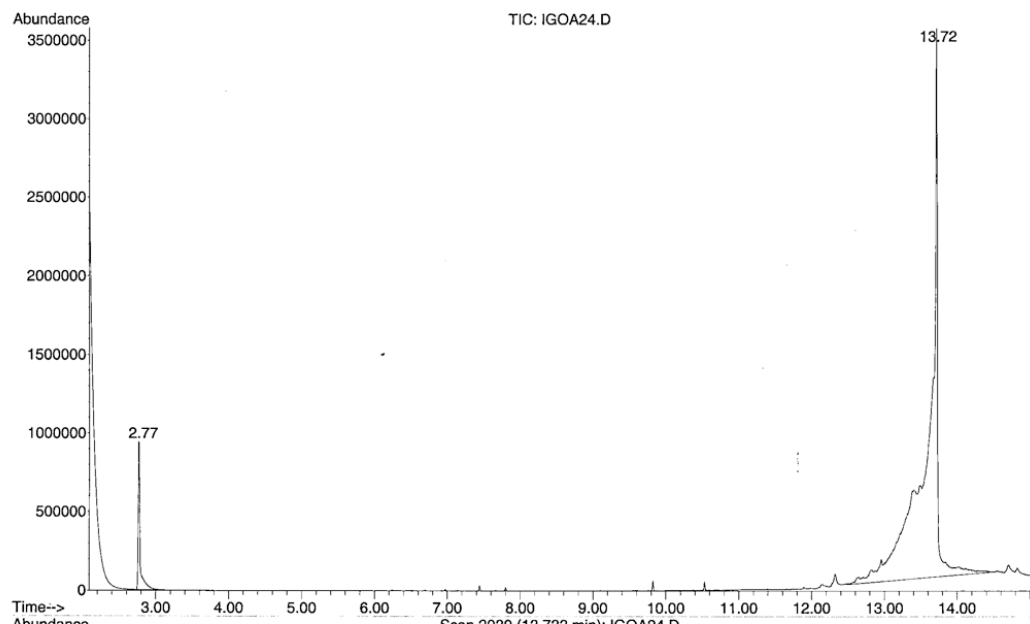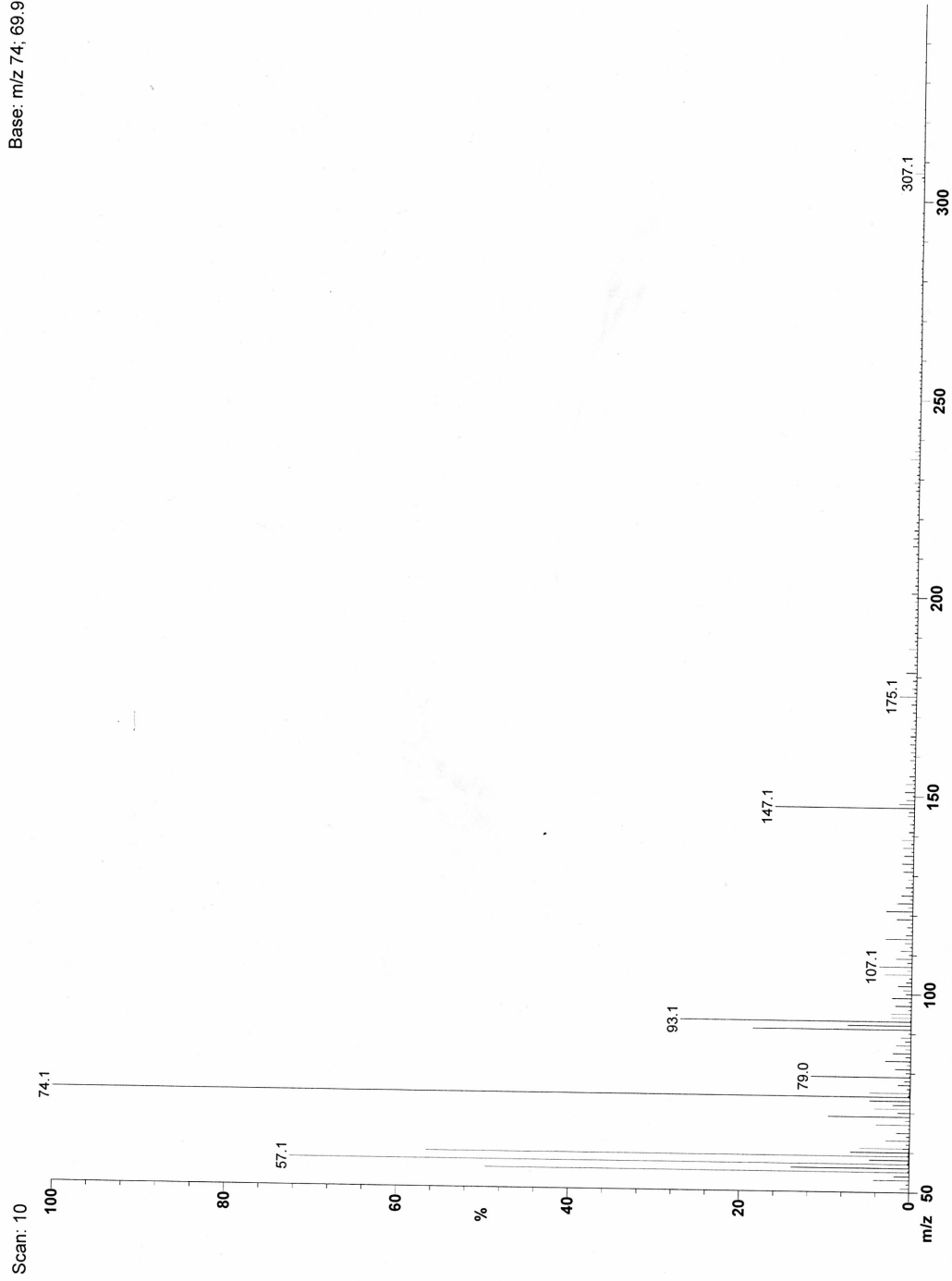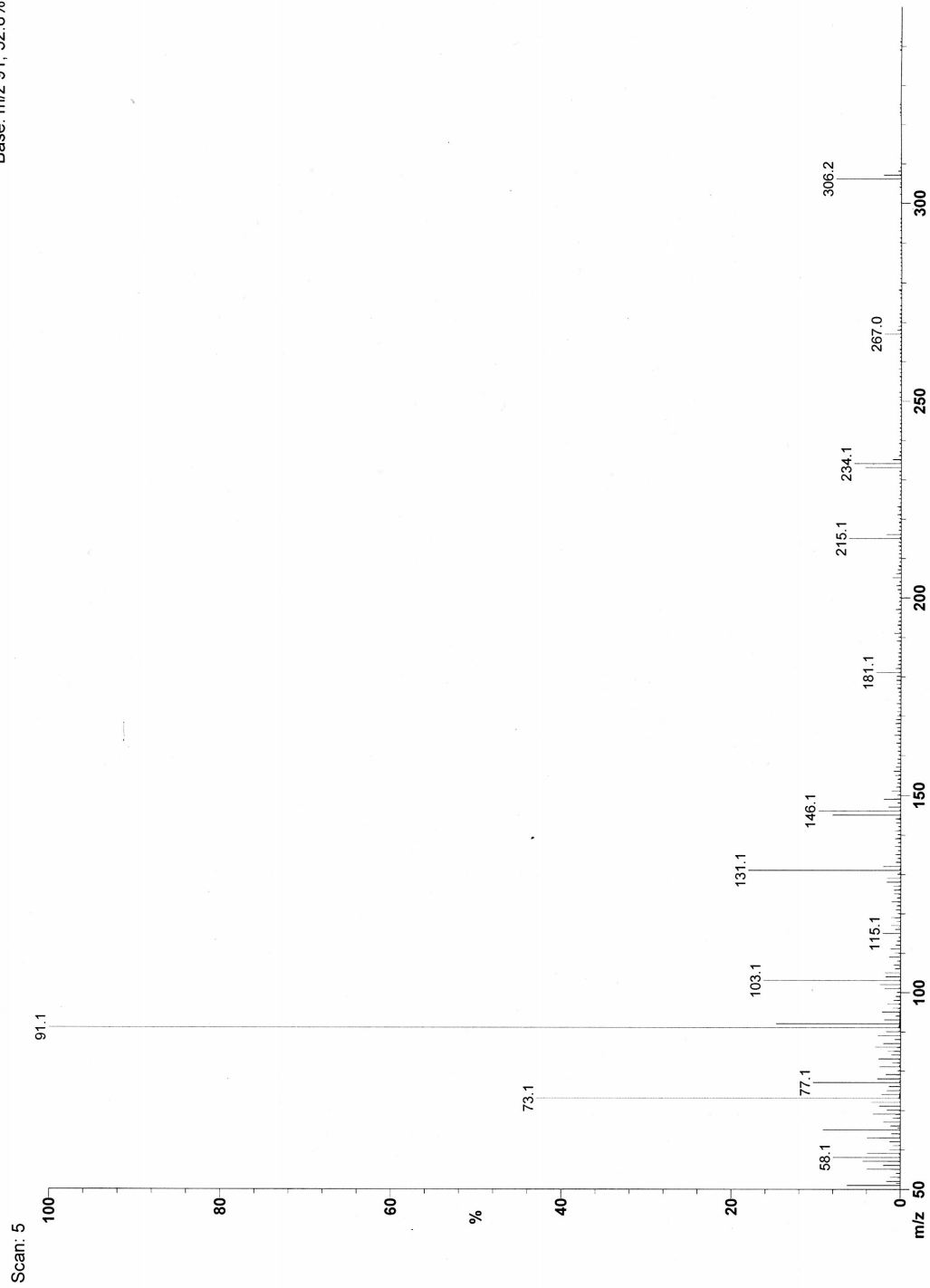
University of Illinois SCS Mass Spectrometry Laboratory

File: oh137band2hr
Sample: OH-1-37-Band 2

Date Run: 06-12-2012 (09:36:30)

Ionization mode: EI+

Instrument: 70-VSE(C)

Base: m/z 290; 8.3%FS

Scan: 11

Selected Isotopes : C H O$_{0-3}$

Error Limit : 5 mmu

Unsaturation Limits : -5 to 30

Measured Mass	% Base	Formula	Calculated Mass	Error	Unsaturation
290.13107	100.0%	C$_{20}$H$_{18}$O$_2$	290.13068	0.4	12.0

NS-Phenol

+//../../info

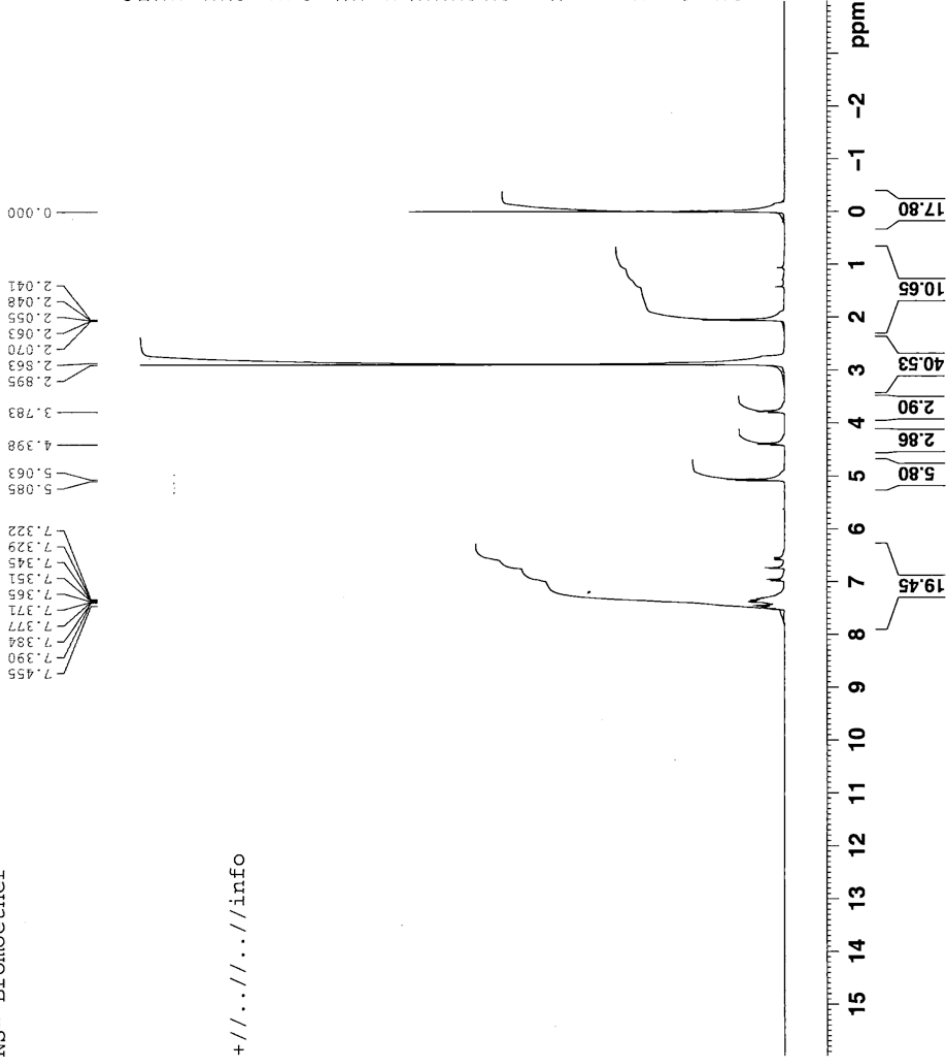Current Data Parameters
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EXPNO   50
PROCNO   1

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PROBHD   5 mm BBO BB-1H
PULPROG   zg30
TD   32768
SOLVENT   Acetone
NS   16
DS   0
SWH   5995.204 H
FIDRES   0.182959 H
AQ   2.7329011 s
RG   362
DW   83.400 u
DE   6.00 u
TE   295.2 K
D1   2.00000000 s
TD0   1

======= CHANNEL f1 =======
NUC1   1H
P1   9.00 u
PL1   -1.00 d
SFO1   300.1318008 M

F2 - Processing parameter
SI   16384
SF   300.1300038 M
WDW   EM
SSB   0
LB   1.00 H
GB   0
PC   1.00

-0.037
0.000

2.037
2.044
2.051
2.058
2.065
2.836
2.868

5.021
5.071
6.396
6.405
6.425
6.435
6.564
6.573
6.906
6.935
7.310
7.335
7.352
7.374
7.397
7.402
7.452
7.465
7.488
7.819

14.01
17.52
15.69
52.79

ppm   -2 -1   0   1   2   3   4   5   6   7   8   9   10 11 12 13 14 15

NS-Phenol CDCl3

Current Data Parameters
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PROCNO   1
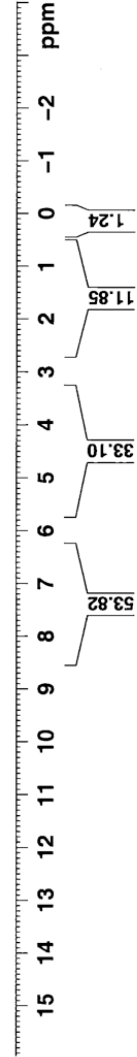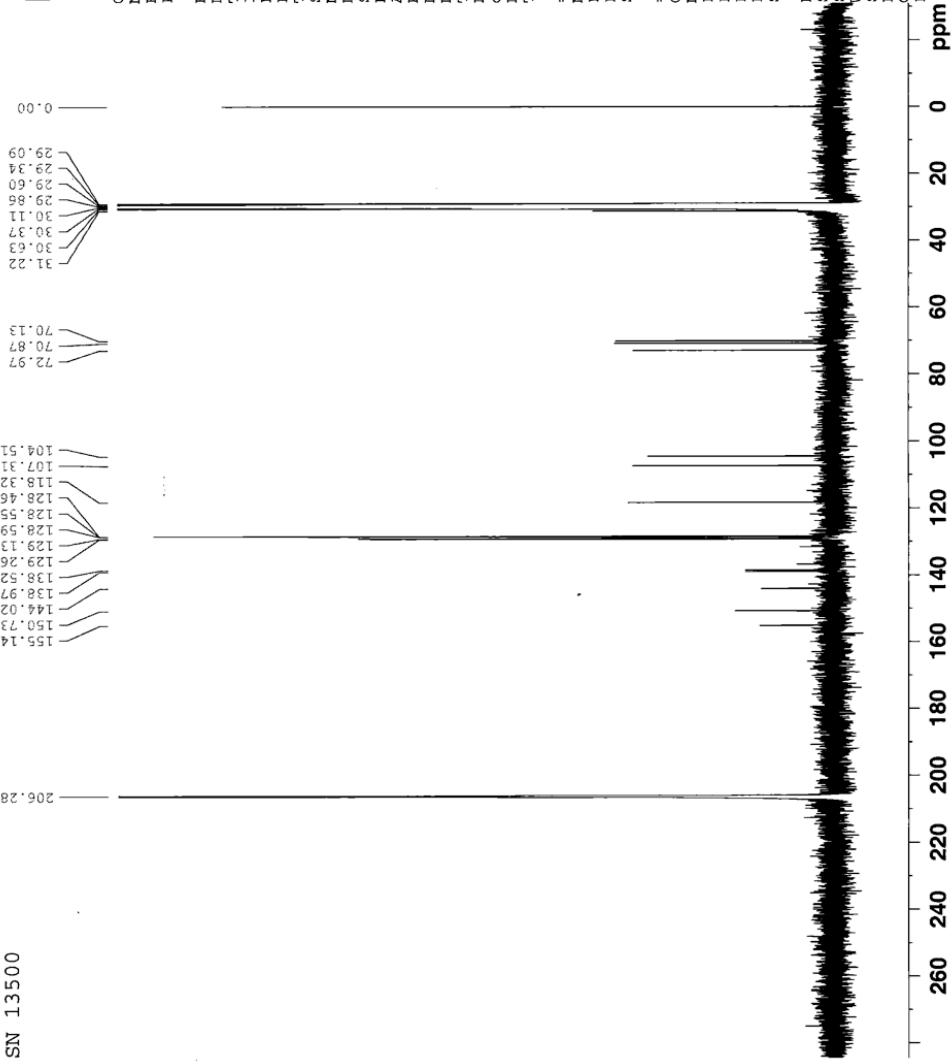
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PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   16
DS   0
SWH   5995.204 H
FIDRES   0.182959 H
AQ   2.7329011 s
RG   645.1
DW   83.400 u
DE   6.00 u
TE   297.2 K
D1   2.00000000 s
TD0   1

======== CHANNEL f1 ========
NUC1   1H
P1   9.00 u
PL1   -1.00 d
SFO1   300.1318008 M

F2 - Processing parameter
SI   16384
SF   300.1300079 M
WDW   EM
SSB   0
LB   1.00 H
GB   0
PC   1.00

+//..//..//info

0.000

1.551
2.169

4.993
5.045
5.669
6.411
6.420
6.440
6.449
6.640
6.649
6.814
6.843
7.254
7.287
7.309
7.332
7.337
7.350
7.376
7.395

3.92
7.60
23.30
65.19

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm

File: oh137band1-2
Sample: OH-1-37-Band 1

Date Run: 06-27-2012 (11:06:36)

Ionization mode: CI+

Instrument: 70-VSE(C)

Base: m/z 74; 69.9%FS

Scan: 10

NS- Bromoether

+//../../../info

NS-2-33-Band 2

+//..//..//info

Current Data Parameters
NAME   Mar07-2013
EXPNO   20
PROCNO   1

F2 - Acquisition Parameters
Date_   20130307
Time   17.05
INSTRUM   spect
PROBHD   5 mm BBO BB-1H
PULPROG   zg30
TD   32768
SOLVENT   CDCl3
NS   16
DS   0
SWH   5995.204 Hz
FIDRES   0.182959 Hz
AQ   2.7329011 sec
RG   228.1
DW   83.400 usec
DE   6.00 usec
TE   294.2 K
D1   2.00000000 sec
TD0   1

======= CHANNEL f1 =======
NUC1   1H
P1   9.00 usec
PL1   -1.00 dB
SFO1   300.1318008 MHz

F2 - Processing parameters
SI   16384
SF   300.1300089 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.00

0.000

0.872
1.258
1.278
1.561

3.608
3.629
3.650
4.284
4.305
4.325
4.986
5.064
6.479
6.499
6.508
6.611
6.619
6.843
6.872
7.246
7.300
7.341
7.364
7.383
7.406
7.431

1.24   11.85   33.10   53.82

ppm

15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2

97

NS-Bromoether
SN 13500

NS-Protected Thiol

18.4863

0.0998

2.5967

15.0000

[ppm]

99

Mar26-2013 10 1 /opt/xwinnmr dcm_lab
protected thiol purged cdcl3

100

NS- Protected Thiol

206.03

145.91

130.26
129.00
128.53
128.26
127.29

67.02
63.39
33.69
32.40
30.57
30.28
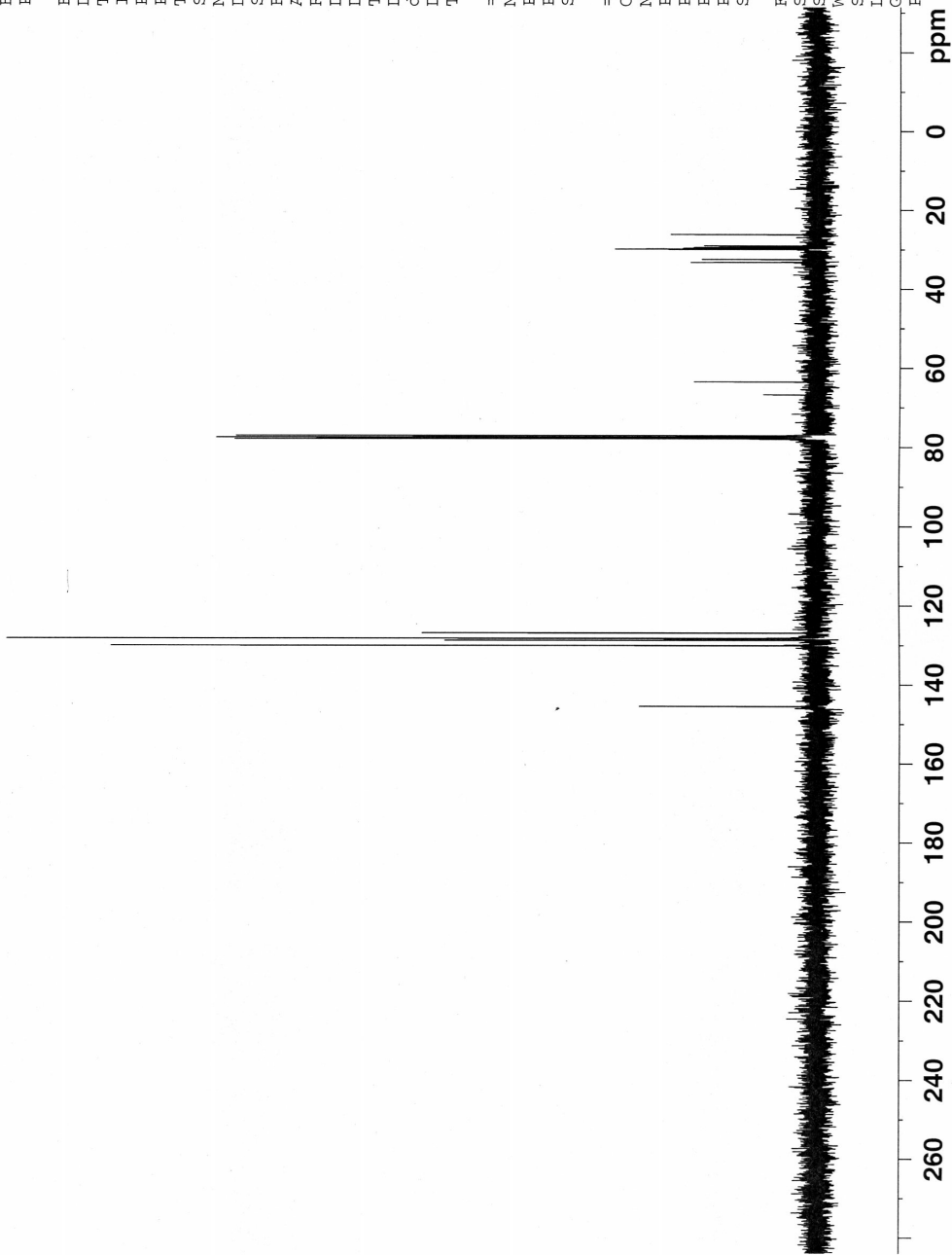30.16
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29.29
29.19
29.03
26.59
0.00

ppm

260 240 220 200 180 160 140 120 100 80 60 40 20 0

101
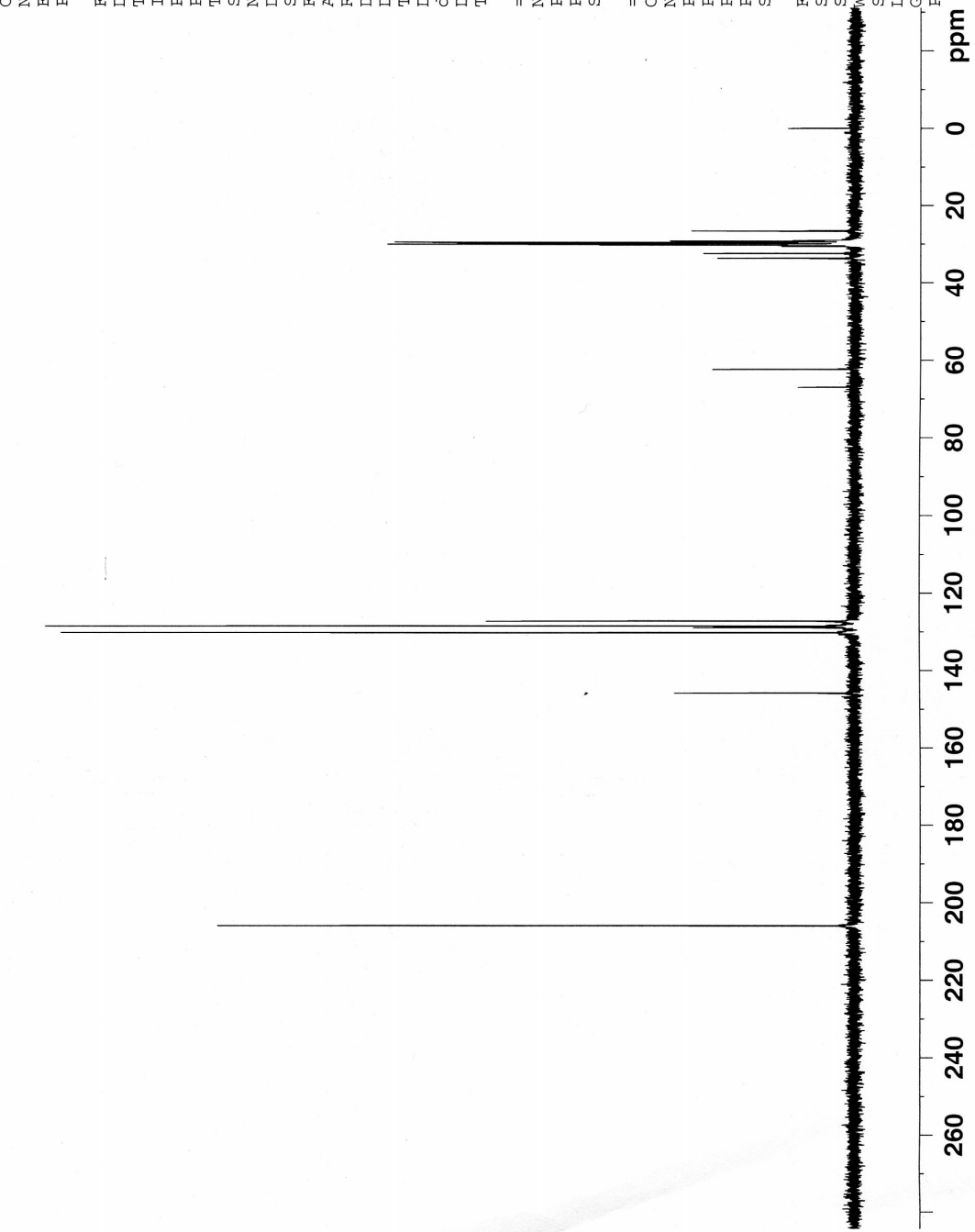
Protected Thiol Fragment CDCl3 (normal)

Peaks (13C NMR):
26.14
29.00
29.42
29.59
29.82
29.88
29.97
32.45
33.21

63.50
66.76
77.02
77.45
77.87

126.91
128.21
128.76
130.02
145.49

102