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Synthesis of a bis-Thiol Receptor for Arsenic(III) Compounds

A Thesis Presented

by

Karlee Archer

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in Partial Fulfillment of the

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We, the thesis committee for the above candidate for the

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Abstract of the Thesis

Synthesis of a bis-Thiol Receptor for Arsenic(III) Compounds

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The effects of ingesting trivalent and pentavalent arsenic compounds range from developmental problems to death. They dissolve readily in water, and more of these compounds are finding their way into groundwater due to agricultural runoff, leeching from preserved wood and mining, among other sources. Development of an easily visualized molecule that binds selectively and strongly to arsenic compounds might allow ease of both the removal and detection of these contaminants from water. The program HostDesigner was used to design a receptor containing thiol groups that would favorably bind to an arsenic(III) compound. The precursor to this receptor is a a novel dihydrodimethylisobenzofuran-diol that was synthesized via a Diels-Alder reaction followed by oxidative cleavage and then NaBH$_4$ reduction to the diol. Starting from o-Bromofluorobenzene and 2,5-Dimethylfuran, *cis*-1,3-*bis*-Hydroxymethyl-1,3-dimethyl-1,3-dihydroisobenzofuran was obtained in 10% yield. Methods to convert the diol to a dithiol were explored, including a thio-Mitsunobu reaction.

Dedication Page

This thesis is dedicated to my first Chemistry Lab TA, Alexander Santulli, who gave me the confidence and basic skills I needed to start research in Chemistry.
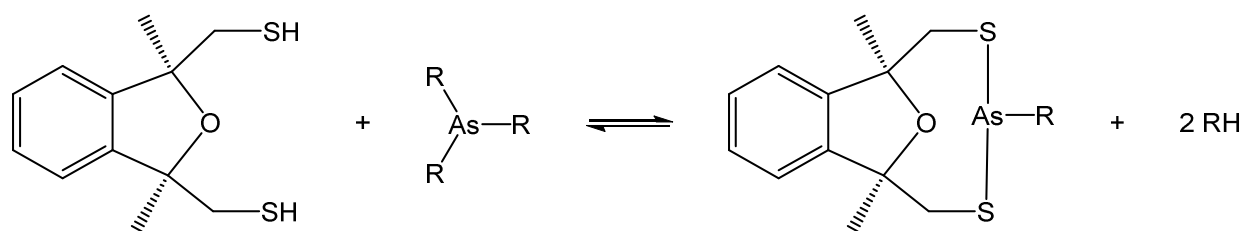
Frontispiece

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Acknowledgments

I am very grateful for the guidance from my research advisor and instructor Professor Dale Drueckhammer, my fellow group members and Dr. James Marecek.

I. Introduction

1.1 Why Arsenic?

It is well-known that ingestion of arsenic can cause death if taken in lethal doses (0.05-0.30 g within 14 days). However, chronic ingestion of small quantities of arsenic compounds can also cause a wide range of serious health issues. Arsenic is a known cause of cancer, diabetes, developmental and reproductive problems, neurological complications, and cardiovascular disease.[1] Inorganic arsenic(III) and arsenic(V) compounds are the most toxic to humans, aside from arsine gas. They occur naturally in minerals and dissolve readily in water. In recent times, more of these compounds are finding their way into groundwater than usual due to agricultural runoff, leeching from wood preservatives, and mining, among other sources.

According to the World Health Organization (WHO), the maximum amount of arsenic in groundwater should be 10 ppb. The United States Geological Survey has collected groundwater samples across the US of which 25% exceeded the maximum level.[2] Arsenic-contaminated drinking water is a worldwide problem, most notably affecting countries with low sanitation and high abundance of arsenic in the land.[3] To effectively resolve the problem of natural and anthropogenic contamination of potable water, a practical and reliable method of detecting inorganic arsenic compounds is needed.

1.2 Why Thiol-based?

Arsenic compounds are usually detected in water using a test strip that converts the inorganic arsenic to arsine gas and then further reduces it to a compound that sticks to the paper and generates a color change.[4] Table 1 shows some of the kits that operate on this principle.

Table 1: Some Available Arsenic Test Kits Relying on Arsenite Reduction

Kit	As(III) Reducing Agent	AsH$_3$(g) Reducing Agent
Merck	Zinc/hydrochloric acid	Mercury salt of chloride or bromide
Hach	Zinc/sulfamic acid	Mercury salt
Baghel[4]	Magnesium/oxalic acid	Gold chloride

These methods raise questions of how much of a risk to health they are and how easily their waste products are disposed of. Arsine gas is being generated and the method relies on all of this gas interacting with the solid test strip. Sulfides are also reduced by the test chemicals, generating toxic H$_2$S(g). Another concern is that many of the test compounds are mercury-based. The larger the area being tested, and thus the more test strips being used, the greater the risk to personal health and the environment.

Recently, bacteria are being genetically modified for the colorimetric detection of arsenic compounds in water.[5] While this would be a 'greener' method of arsenic detection, the use of genetically modified biological organisms also has its issues. The bacteria would need to be contained both before and after usage and the population controlled. This is especially true for bacteria like *E. coli* that are harmful if ingested.

A safe, efficient and low-maintenance method of arsenic detection would be greatly beneficial to environmental remediation and water sanitation. Development of a fluorescent or easily visualized molecule that binds selectively and strongly to arsenic compounds might allow ease of both the removal and detection of these contaminants from water.

By observing nature, we know that arsenic has a strong affinity for sulfur. They are seen bound together in minerals, for example realgar (AsS), orpiment (As_2S_3) and arsenical pyrites (AsFeS). One of the ways that arsenic(III) compounds disrupt cellular activity is by binding to two proximal thiol groups of a protein.[6] This interaction was the basis of the development of Lewisite as an arsenic-based war gas and of the development of British anti-Lewisite (BAL) as antidote.[6] Figure 1 shows the structural similarity between the protein moeity and BAL. Each contains two thiol groups to which Lewisite can bind. This dithiol-arsenic interaction is also the basis for the design of our arsenic(III) receptor, which after testing may be further developed for practical applications.

Figure 1: Illustration of British anti-Lewisite Development Based on Protein-Arsenic(III)

Interaction

a)

Protein   Lewisite

b)

British anti-Lewisite
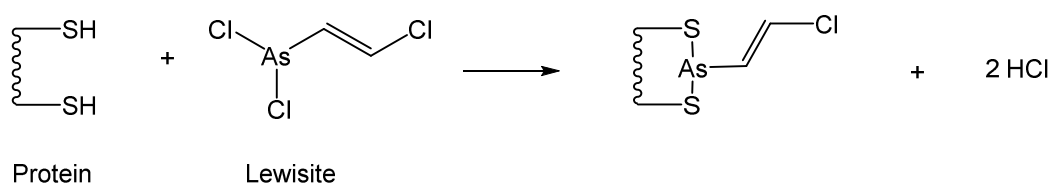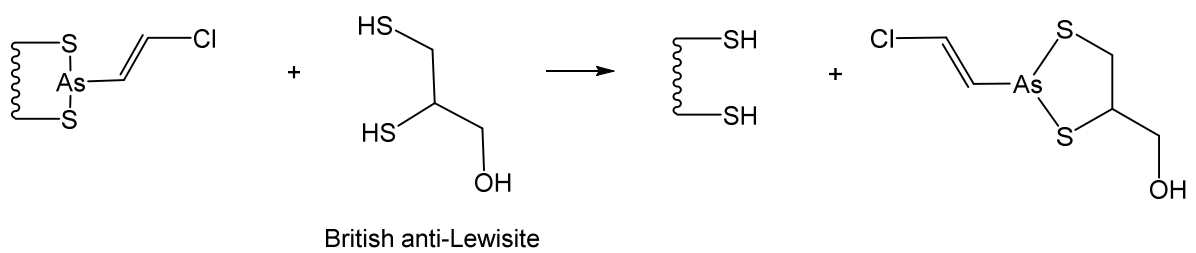
II. Designing the Arsenic Receptor

2.1 HostDesigner

HostDesigner is "a program for the de Novo structure-based design of molecular receptors with binding sites that complement metal ion guests".[7] It works on the principle of 'complementarity' so the structure of a host, in this case a receptor, may be designed with confidence that it will bind the desired guest.

HostDesigner was used by Dr. Drueckhammer to design a simple *bis*-thiol compound that would bind favorably to an As(III) compound of low toxicity. The structures of the receptor candidates were optimized on the B3LYP/6-311G(d) level using a PCM representation of water. The heat of reaction ΔH for the binding of each candidate to $As(SCH_3)_2CH_3$ (Figure 2) was calculated using the program.

Figure 2: Reaction Used as Basis for Designing Structure of Arsenic Receptor
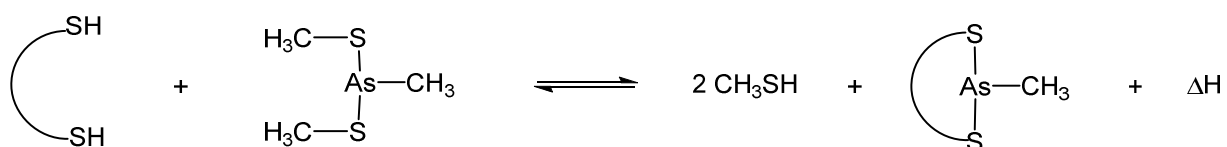
2.2 Candidates for Receptor Synthesis

From optimization of the structures shown in Figure 3 using HostDesigner, it was determined that a stabilized tetrahydrofuran structure functionalized by methanethiol groups had a suitable structure to bind favorably to the model arsenic(III) compound in Figure 2.

Figure 3: Some Candidates for Receptor Synthesis and their Calculated Heat of Reactions with As(SCH$_3$)$_2$CH$_3$

Candidates:

ΔH:

n=1			
1.6 kcal/mol	1.3 kcal/mol	-5.3 kcal/mol	R=H
n=2			-3.8 kcal.mol
2.4 kcal/mol			R=CH$_3$
			-5.5 kcal/mol
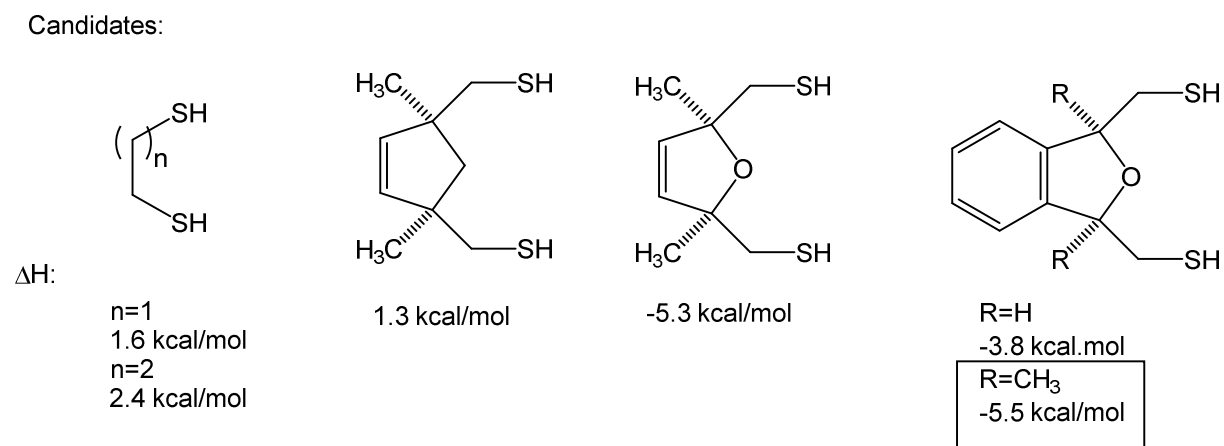
Since the dimethylisobenzodihydrofuran-*bis*-thiol structure was calculated as reacting most exothermically with the arsenic compound, it was chosen for experimental synthesis.

III. Synthesizing the Arsenic Receptor

3.1 Overview

Since the isobenzofuran-dithiol structure chosen is an isobenzofuran-diol analog, it was imagined to be easily prepared by simple functional group conversion from the diol, in a scheme similar to Figure 4.

Figure 4: Potential Conversion of Diol **2** to Dithiol **1**

Since the **2** was not a known compound, according to the literature, an effective synthesis route for this novel compound was also needed.

Tetrahydrofuran-diol and dihydrofuran-diols have been synthesized in very good yields and enantio-purity via oxidative cyclization of 1,5-dienes using catalytic osmium(IV) tetroxide[8] or oxidized ruthenium(III) chloride[9], as illustrated in Figure 5.

Figure 5: Oxidative Cyclization of 1,5-Diene to Yield Tetrahydrofuran-diol

a) 70%
b) 72%
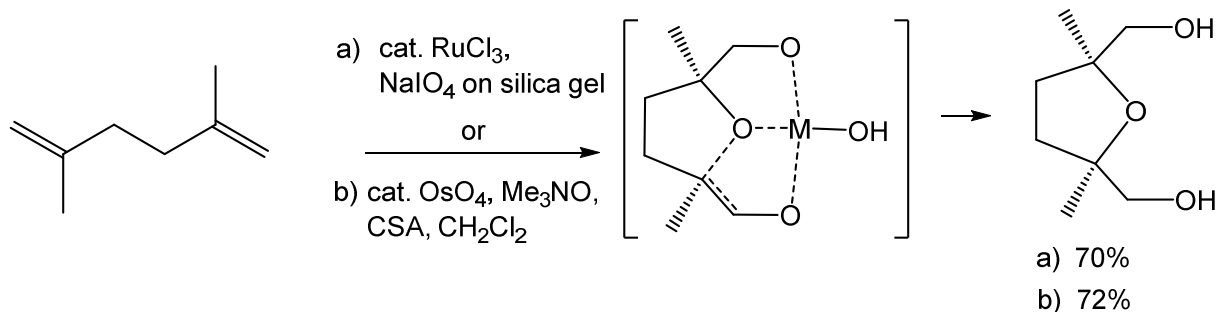
We predicted that the isobenzofuran-diol could be generated in the same manner (Figure 6).

Figure 6: Potential Oxidative Cyclization of 1,5-Diene **3** to Yield Isobenzofuran-diol **2**

3   **2**
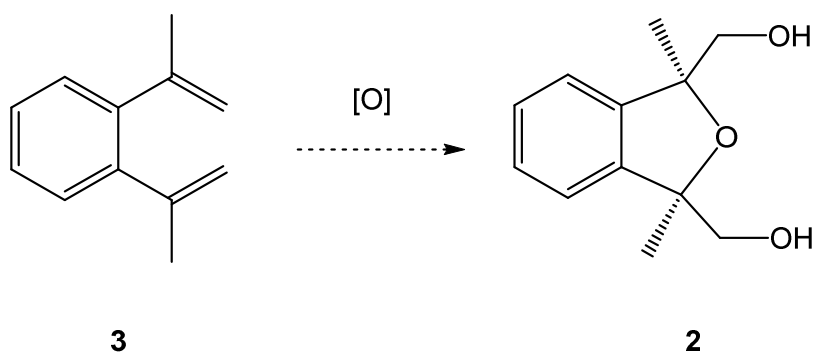
The o-diisopropenylbenzene **3** is not commercially available, and there is no literature procedure

for preparing it. To synthesize the diene, we initially chose a two-step procedure involving

exhaustive methylation of a diester to form a bis-tertiary alcohol followed by dehydration to

produce the diene (Figure 7).

Figure 7: Potential Synthesis of Diene **3** from Diethyl phthalate
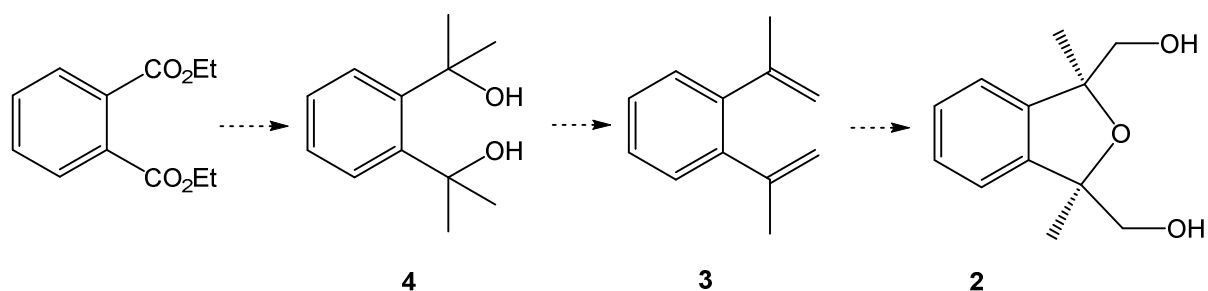
The diol was produced in decent yield via a Grignard reaction with methylmagnesiumbromide. However, multiple attempts of converting the diol to the diene did not produce the desired results.

Since alkenes are commonly prepared from ketones using the Wittig reaction, we tried to synthesize the diisopropenylbenzene from o-diacetylbenzene (ODAB) via a classic Wittig reaction (Figure 8). The ODAB was synthesized by Grignard methylation of phthaldialdehyde followed by oxidation to the diketone. No alkenes were isolated and the basic conditions of the Wittig reaction converted the diketone **5** to an undesirable cyclized product.

Figure 8: Potential Synthesis of Diene **3** from Phthaldialdehyde
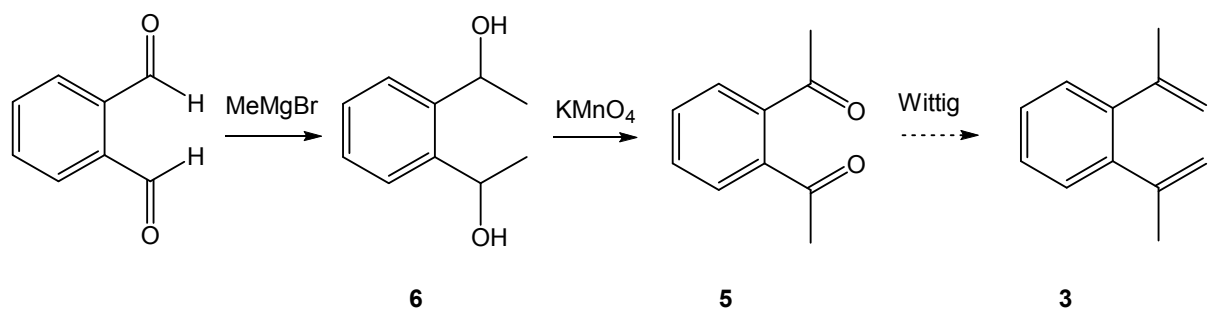
Finding a paper written by Chaubet et al. led to the realization that our desired isobenzofuran-diol might be easily synthesized via a Diels-Alder reaction followed by oxidative cleavage with reductive work-up, as shown in Figure 9.[10]

Figure 9: Synthesis of *cis*-Isobenzodihydrofuran-diol **2** from Oxidative Cleavage of Diels-Alder Adduct
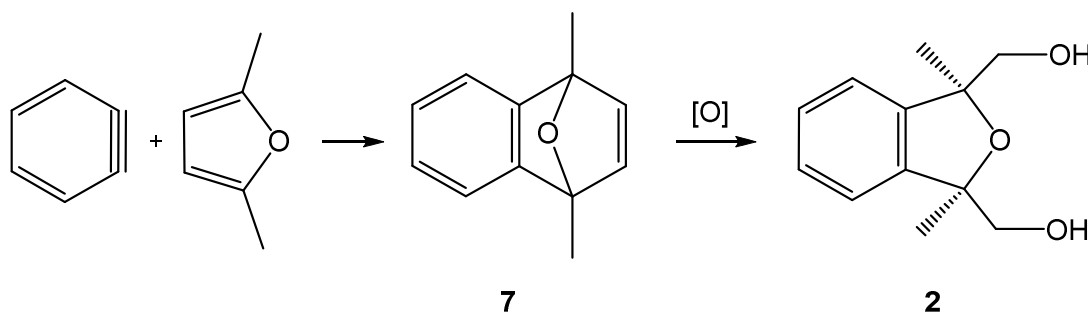
The desired compound **2** was obtained via this reaction pathway.

Final conversion of the alcohol groups of the diol to thiol groups was first attempted through mesylation followed by nucleophilic substitution by thiolacetate (Figure 4). When attempted substitution of the mesylate groups was not effective, a more aggressive approach using direct conversion of the alcohol groups to thioacetyl groups via the Mitsunobu reaction was attempted. Whether the Mitsunobu reaction works on Compound **2** has not been concluded.

3.2 Preparation of 2-[2-(1-Hydroxy-1-methylethyl)phenyl]-2-propanol **4** from Diethyl phthalate

Synthesis of the bis-tertiary alcohol **4** via exhaustive Grignard methylation (Figure 10) was

successful with a yield of 66%. Microwave-assisted reaction of N-methylphthalamide with 12

equivalents of MeMgBr gave Foitzik et al. a yield of 45% in 2 hours.[11] The classic Grignard

reaction performed gave a yield 66% with only 6 eq of MeMgBr but required at least 13 hours.

Figure 10: Exhaustive Methylation of Diethyl phthalate via Grignard Reaction
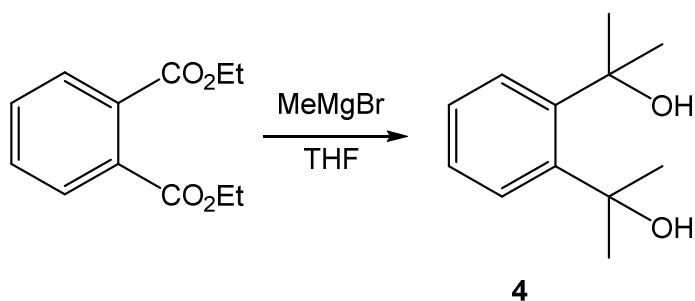
One interesting thing to note is the side-product due to cyclization of an intermediate, as shown

in Figure 11. Since it is more stable than the dianion of the diol, sufficient heating and Grignard

reagent are required to drive it to the desired product. To remove the cyclized side-product **8**, the

crude product was slowly crystallized in heated diethyl ether to give pure clear crystals of

Compound **4** (Figure 12).

Figure 11: Products of Grignard Reaction of Diethyl phthalate and MeMgBr

[+ Mg(OH)Br]
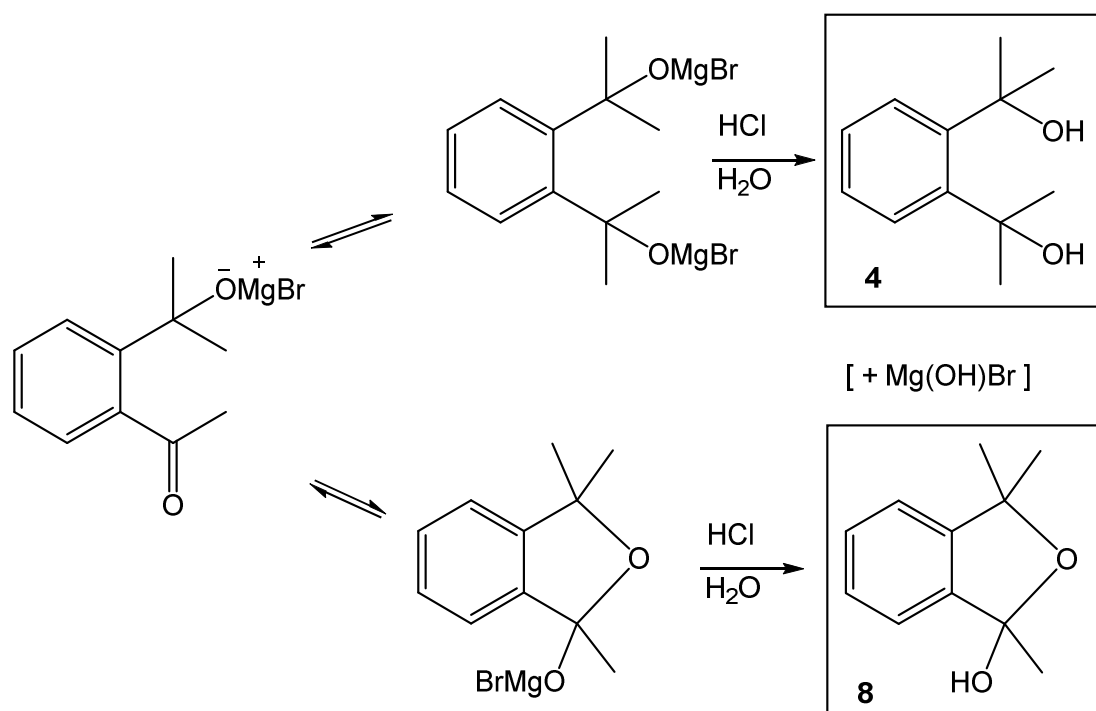
Figure 12: Purified 2-[2-(1-Hydroxy-1-methylethyl)phenyl]-2-propanol Crystals

3.3 Attempted Preparation of Diene **3** via 1,2-Elimination of bis-tertiary Alcohol **4**

An efficient method of dehydrating tertiary alcohols to alkenes using silica-chloride was developed by Firouzabadi et al.[12] The silica-chloride reagent was easily prepared by refluxing silica gel and thionyl chloride. However, the SiO_2-Cl was not able to dehydrate the diol **4** but instead catalyzed cyclization of the diol to 1,1,3,3-tetramethyl-1,3-dihydroisobenzofuran **9**, shown in Figure 13. This cyclization is explained by the mechanism of SiO_2-Cl in reacting with alcohols. The silica-chloride acts as a Lewis acid and anchors the compound so that E2 elimination can quickly take place. For the diol **4**, though, intramolecular attack by the *ortho* hydroxyl group was quicker, and no alkene was isolated.

Figure 13: Reaction of bis-tertiary Alcohol **4** and Silica chloride
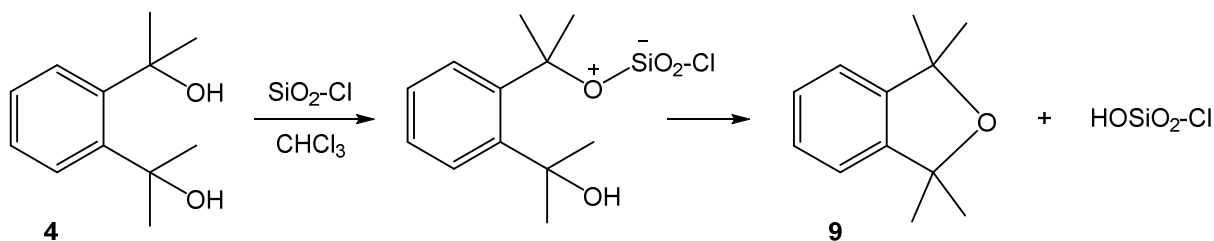
Attempted conversion of the alcohol groups to mesylate groups followed by elimination with base also produced the tetramethyl isobenzofuran **9**, suggesting the mesylate group of the mono-mesylated compound left before the compound could react with the second equivalent of mesyl chloride (Figure 14).

Figure 14: Reaction of bis-tertiary Alcohol **4** and Mesyl chloride
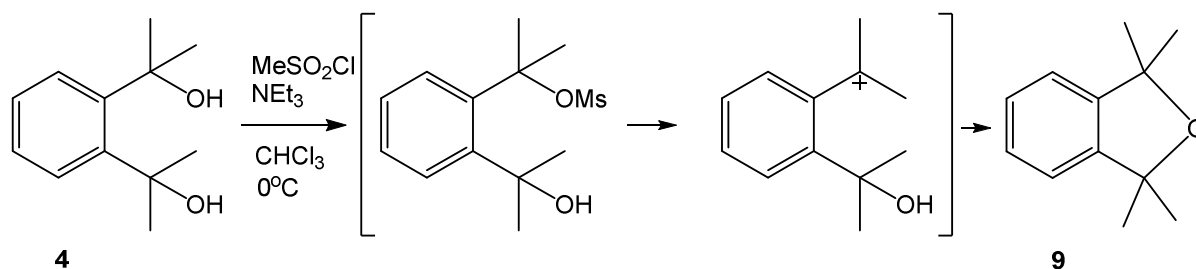
To avoid formation of the carbocation, the hydroxyl groups might be converted to groups less likely to leave than the mesylates. Attempts to convert the diol to a *bis*-carbamate ester by reaction with cyclohexylisocyanate were nearly successful (Figure 15). The mono-ester **10** was formed. The diester was not formed, but that is unsurprising due to steric hindrance from the methyl and cyclohexyl groups. The strong base should have been able to eliminate the carbamate ester, freeing CO_2 and amine, but no alkene peaks were observed by NMR.

Figure 15: Attempted Synthesis of Diene **3** via Carbamate ester **10**
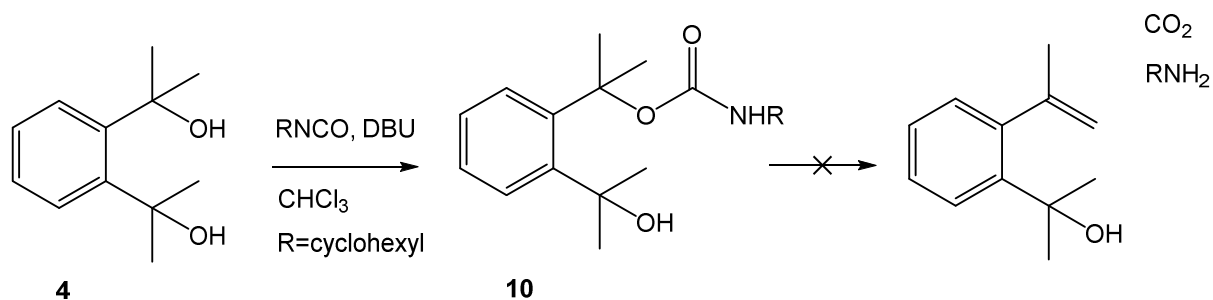
3.4 Preparation of o-Diacetylbenzene **5** from Phthaldialdehyde

Although o-Diacetylbenzene (ODAB) is commercially available, it was more practical to prepare it from phthaldialdehyde. A Grignard reaction with MeMgBr was easily performed and gave 85% yield of a diastereomeric mixture of 1,2-bis(1-hydroxyethyl)benzene **6**, which was confirmed with the ^{1}H-NMR data of Landis et al.[13] The procedure by Shabaani et al. for 'green' oxidation using a solvent-free $KMnO_4/MnO_2$ mixture, which converted hydroxyethylbenzene to acetophenone in 5 hrs with 92% yield,[14] was performed on the diol **6**. The desired ODAB **5** was obtained in about 67%, but from ^{1}H-NMR it was seen that some of the diketone reacted further with base to form a more stable cyclic compound **11**, shown in Figure 16. This hypothesis was confirmed by the ^{1}H-NMR of 3-Hydroxy-3-methyl-1-indanone **11** obtained by Ruan et al.[15] Since $KMnO_4$ can react with water to form MnO_2 and OH^-, it is likely the source of base.

Figure 16: Base-catalyzed Cyclization of o-Diacetylbenzene **5** to Indanone **11**
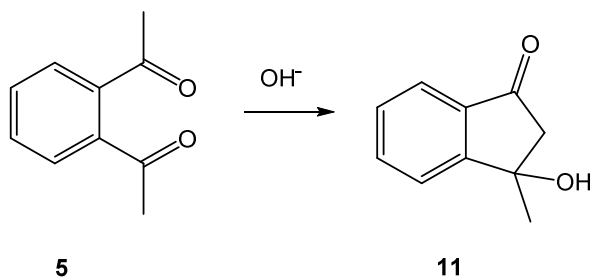
3.5 Attempted Preparation of o-Diisopropenylbenzene **3** from o-Diacetylbenzene **5**

A simple Wittig reaction was performed on the ODAB **5** in attempts to obtain the diene **3**. Because of the basic conditions, however, only the indanone **11** was isolated. The diene might be synthesized by carbonyl methylenation reagents that don't require basic conditions, such as the Tebbe or Petasis reagents.

3.6 Preparation of *cis*-Isobenzofuran-diol **2** from 2,5-Dimethylfuran and Benzyne Precursor

The Diels-Alder reaction is the method of choice to obtain structure, functionality and stereospecificity. However, it was not immediately clear that we could employ the Diels-Alder to make the desired isobenzofuran-diol. A paper by Chaubet et al. showed that the furan-diol moiety could be generated by ozonolysis of a bicyclic alkene followed by reductive work-up with sodium borohydride.[10] The bicyclic alkene was synthesized via [4+2] cycloaddition between a highly reactive dienophile and 2,5-dimethylfuran, as shown in Figure 17.

Figure 17: Literature Preparation of a *cis*-Dihydrofuran-diol via Oxidative Cleavage of a Diels-Alder Adduct
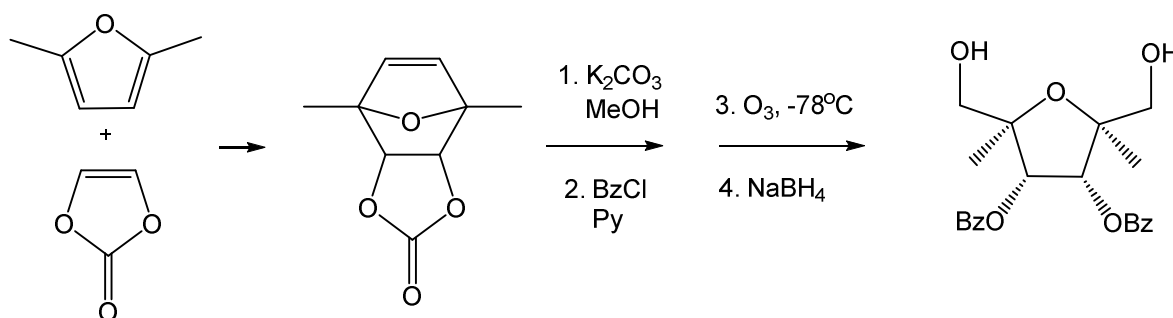
This work inspired the reaction scheme in Figure 18. A Diels-Alder reaction between benzyne and 2,5-dimethylfuran yielded 1,4-dihydro-1,4-dimethylepoxynaphthalene **12**. Instead of performing ozonolysis, which involves compressed gases and low temperature, the alkene **12** is dihydroxylated to 1,4-epoxy-2,3-dihydroxy-1,4-dimethyl-tetralin **13** and the glycol **13** is cleaved to the dialdehyde **14** by $NaIO_4$. Reaction with $NaBH_4$ results in the desired

cis-isobenzodihydrofuran-diol **2**.

Figure 18: Practical Synthesis of *cis*-Benzodihydrofuran-diol **2** via Oxidative Cleavage of Diels-Alder Adduct **12**
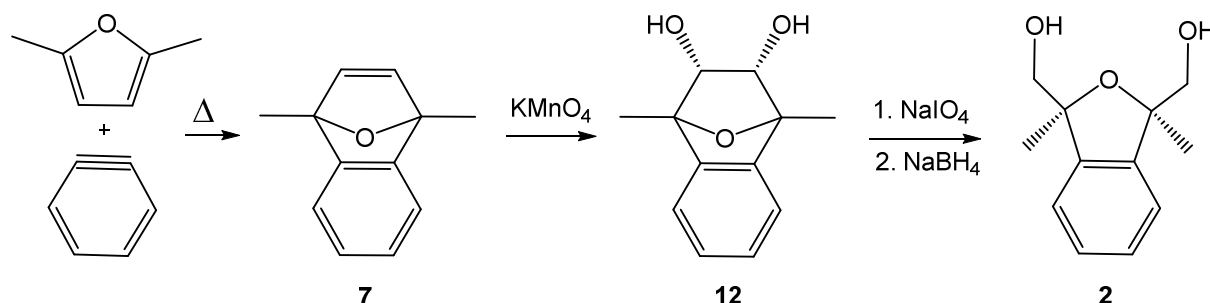
The bicycloalkene **7** has been synthesized by several groups for many reasons, but not usually for the purpose of cleaving the resultant double bond. The benzyne must be generated *in situ*, since it is highly unstable and it undergoes [2+2] cycloaddition with itself to form biphenylene if no diene is present. One popular method of generating benzyne involves the decarboxylation of benzene diazonium-2-carboxylate releasing CO_2 and N_2. Since this compound is explosive and sensitive to shock, it is commonly not isolated but synthesized *in situ* by the reaction of anthranilic acid with a nitrite, as shown in Figure 19.[16]

Figure 19: In situ Preparation of Benzyne from Anthranilic acid
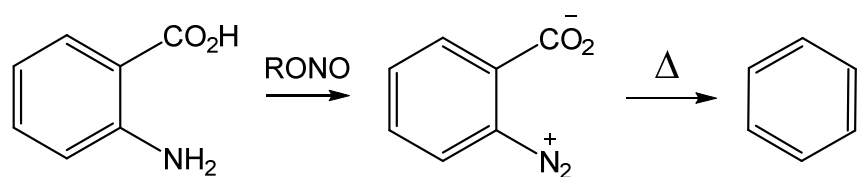
The transformation was effective, as confirmed by TLC and ^{1}H-NMR,[17] but suffered from low yields around 36% and a difficult work-up. Isoamyl nitrite was used and converted to isoamyl alcohol, as confirmed by ^{1}H-NMR and a fruity undertone to the scent of the product. It was removed by washing with aq. KOH or evaporation under reduced pressure. The more

problematic byproduct was a small amount of 1,4-dimethyl-2-naphthol **14** produced by acid-catalyzed opening of the epoxy group. As shown by Fétizon, ring-opening occurs with even a trace amount of BrØnsted or Lewis acid.[18] The mechanism is shown in Figure 20.

Figure 20 : Acid-catalyzed Ring-opening of 1,4-Dihydro-1,4-dimethylepoxynaphthalene **7** to 1,4-dimethyl-2-naphthol **14**
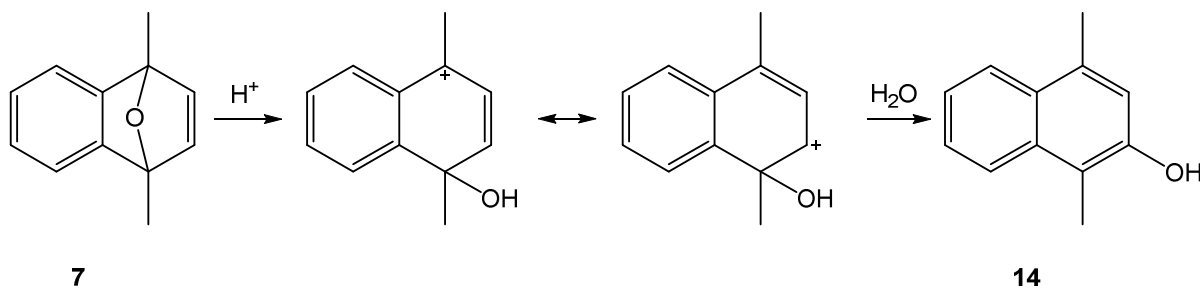
The use of o-bromofluorobenzene (OBFB) instead of anthranilic acid as benzyne precursor resulted in a purer crude epoxynaphthalene **7** product in higher yield and reduced the chance of acid-catalyzed ring-opening during the reaction and aqueous work-up. The intermediate is a Grignard reagent and the byproduct MgBrF(s) is easily filtered from the product mixture. The reaction mechanism is shown in Figure 21. The reaction would also work using o-dibromobenzene, but the yield would be lower since the magnesium could couple to both bromo groups and prevent benzyne formation. This also applies to o-Bromochlorobenzene. Since the C-F bond in oBFB is not easily disrupted, it is the best option of the three for benzyne formation. This trend is seen in the yields of 1,4-dihydroepoxynaphthalene prepared by Wittig starting with each of these o-bromohalobenzenes.[19]

Figure 21: Benzyne Generation from o-Bromofluorobenzene
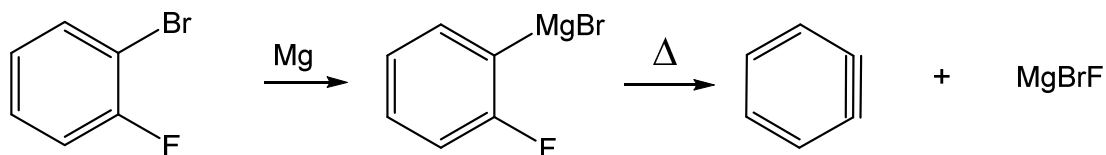
KMnO$_4$ oxidation of the Diels-Alder product yielded a significant amount of o-diacetylbenzene **5** in addition to the desired glycol **12**. The somewhat unexpected product can be explained by generation of the 1,4-dimethyl-2-naphthol **14** and its subsequent oxidation to the diketone **5**, which has been effected by the oxidants KMnO$_4$,[20] CrO$_3$,[20] and O$_3$[21]. To avoid the ring-opening, OsO$_4$ could be used for the dihydroxylation to the glycol. This was done by Fétizon using a stoichiometric amount of OsO$_4$.[18] Osmium tetroxide is a highly toxic volatile solid that is expensive to obtain and to dispose of, so this procedure was not chosen. More recently, the Upjohn dihydroxylation is performed using a catalytic amount of OsO$_4$ with N-methylmorphoniline N-oxide (NMO) to reoxidize it.[22] However, hindered alkenes are very slow to react by this method, so it has been recommended against.[23] Potassium permanganate is a much safer and cheaper alternative to osmium tetroxide. However, it is a stronger oxidant and can act through a variety of mechanisms, some of which are pH dependent. Column chromatography of the glycol **12** and ODAB **5** is difficult since their polarities are very similar. Very pure glycol crystals could be obtained by slow evaporation in a 1:1 mixture of ether and hexane (Figure 22). The permanganate dihydroxylation produced the low yield of 21% pure **12**, which might be improved by running the reaction at higher pH.

Figure 22: Purified Crystals of 1,4-Epoxy-2,3-dihydroxy-1,4-dimethyl-tetralin **12**
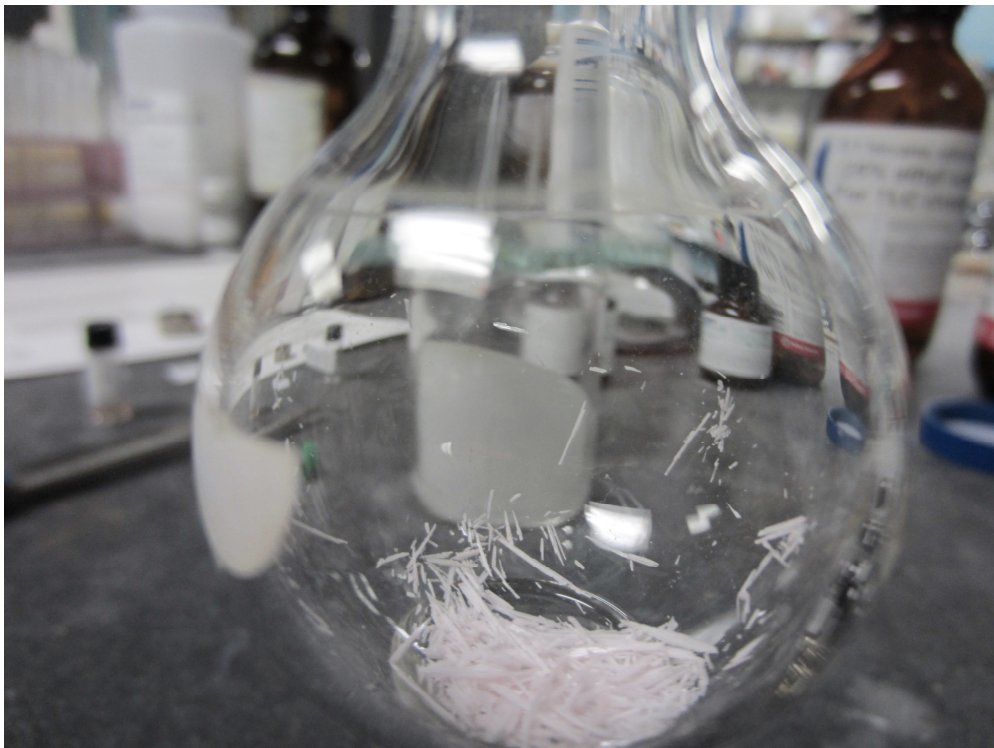
An aqueous solution of sodium meta-periodate was used to cleave the glycol to the dialdehyde with no issues. Since ODAB **5** does not react with $NaIO_4$, the $KMnO_4$ oxidation product mixture can be reacted without purification. The dialdehyde **13** and ODAB **5** are more easily separated by column chromatography than the glycol **12** and oDAB **5**. The dialdehyde **13** was easily reduced to the isobenzofuran-diol **2** using $NaBH_4$. Loss of diol **2** in an aqueous workup was avoided by using a procedure similar to the one by Yakabe et al., which utilizes $NaBH_4$ on silica in aprotic solvent and collection of product by washing with solvent.[24] This cleavage/reduction step only had a yield of 47% so far, but it should be quantitative. It has only been done on the 0.5 mmol scale so far, so a larger amount of reactant might give the expected results. The overall percent yield of isobenzofuran-diol **2** from oBFB, essentially 5 reactions, is about 10%.

3.7 Attempted Preparation of *cis*-1,3-*bis*-Sulfhydrylmethyl-1,3-dimethyl-1,3-dihydroisobenzofuran **1** from **2**

Alcohols are often converted to thiols by nucleophilic substitution by thioacetate followed by reduction of the thioacetic ester to obtain the thiol. Preparation of the dithioester **16** from isobenzofuran-diol **2** was attempted by first converting the alcohol groups to mesylate groups and then substituting with thioacetate, as shown in Figure 23. The mesylation and substitution with thioacetate has been done on similar compounds.[25]

Figure 23: Potential Preparation of Dithioacetic ester **16** from Isobenzofuran-diol **2**
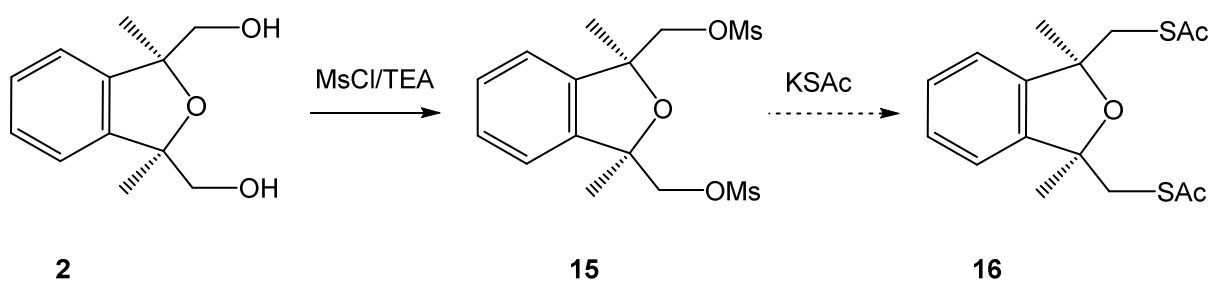
The isobenzofuran-diol **2** was easily converted to the dimesylate **15** by reaction with methanesulfonylchloride/triethylamine. However, attempts to displace the mesylate groups by potassium thioacetate were unsuccessful. One part of the likely explanation is that the isobenzofuran-dimesylate is very hindered and does not allow for direct nucleophilic substitution. The mesylate groups are also unlikely to leave on their own to produce a primary carbocation. The other part of the explanation is that thioacetate is too soft a nucleophile due to delocalization of charge between sulfur and oxygen. Sulfur nucleophiles displace bromide and iodide much more quickly than mesylate and tosylate groups.[26]

The primary hydroxyl groups of sugar molecules are recently commonly converted to thioacetate groups via the 'thio-Mitsunobu' reaction, which is a Mitsunobu reaction using a thiol as the acid/nucleophile source.[27] Nicol et al. have also used this reaction to convert alcohol groups on polymers to thiols.[28] The mechanism is shown in Figure 24.

Figure 24: Mechanism of a General Thio-Mitsunobu Reaction
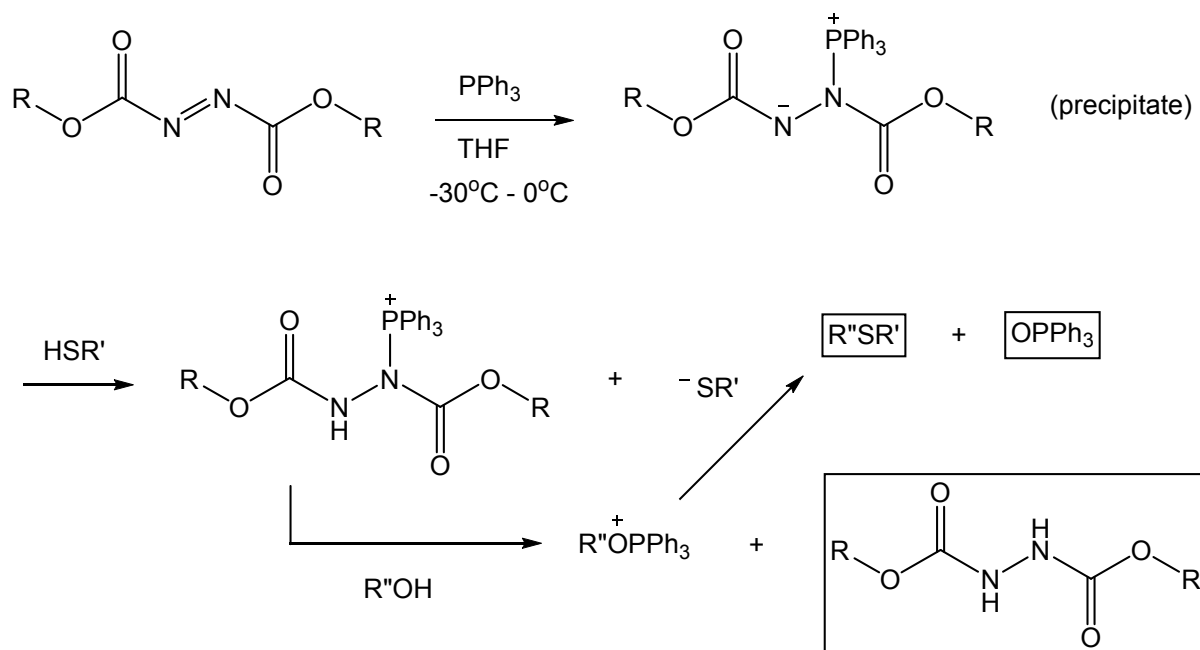
From the mechanism, it is clear why the thio-Mitsunobu reaction is an attractive choice. In one pot, a hydroxyl is converted to an unstable betaine susceptible to nucleophile attack and an active sulfur nucleophile is generated. The Mitsunobu reaction does have disadvantages of strict condition requirements and byproducts that may be difficult to remove. The reaction requires anhydrous conditions since H_2O can act as a nucleophile and regenerate the starting materials. Most of the triphenylphosphine oxide and hydrazinedicarboxylate byproducts can be removed by crystallization followed by filtration. Diisopropyl azodicarboxylate (DIAD) was used instead of the standard diethylazodicarboxylate (DEAD) because it was already available in the laboratory.

DIAD is advantageous over DEAD because the isopropyl groups hinder formation of hydrazide side-products due to nucleophilic attack instead of the desired deprotonation by the diisopropylhydrazide-dicarboxylate intermediate. Unlike DEAD, it can also be stored without stabilization in solvent.

The first attempts to convert the isobenzodihydrofuran-diol to the dithioester were unsuccessful, but this could be due to the small scale that it was done at and insufficient drying of reagents and equipment. To test whether the laboratory conditions were suitable for a Mitsunobu reaction, as the thio-Mitsunobu was performed on a simpler diol, *E*-2-Butene-1,4-diol, with positive results (Figure 25). The *bis*-Thioacetic ester **17** was isolated by column chromatography and characterized by TLC and ¹H-NMR. The thio-Mitsunobu reaction will be tried on the isobenzofuran-diol **2** again once a larger amount of it has been synthesized (Figure 26).

Figure 25: Synthesis of *bis*-Thioacetic ester of *E*-2-Butene-1,4-diol via Thio-Mitsunobu
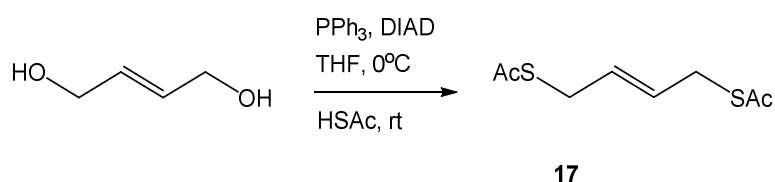
Figure 26: Potential Conversion of Isobenzofuran-diol **2** to Isobenzofuran-dithioester **16** via Thio-Mitsunobu Reaction
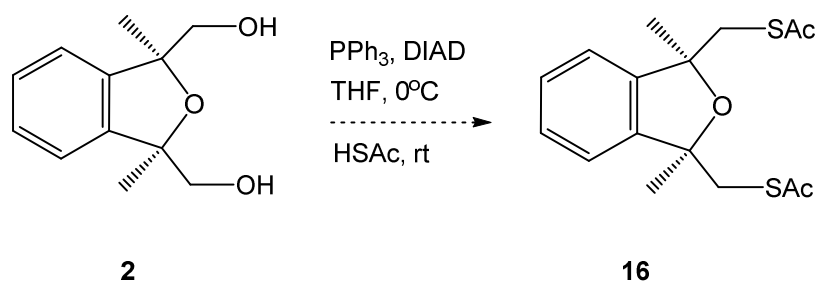
The dithioester **16** obtained would then be converted to the dithiol **1** by reaction with KOH to eliminate acetic acid and form the disulfide salt, which would then be neutralized with HCl in an aqeous workup (Figure 27). To limit the chance of disulfide bond formation, this conversion could be done under N_2. Anhydrous anaerobic conversion using $LiAlH_4$ or DIBAL-H have also been done, but should be avoided if possible since they react violently with water and alcohols and can rapidly form explosive $H_2(g)$.[25,28]

Figure 27: Potential Conversion of Dithioester **16** to Dithiol **1**
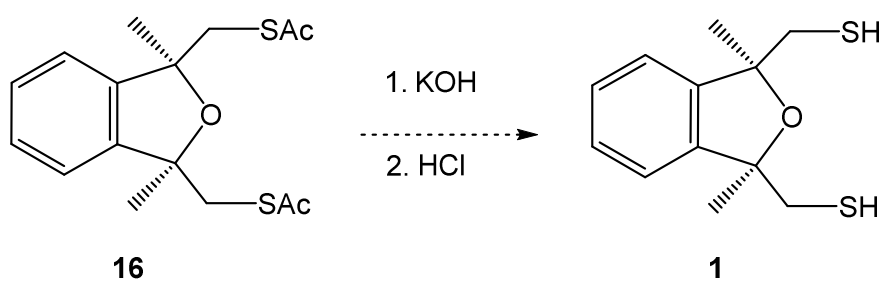
IV. Conclusions

A novel isobenzofuran-diol, *cis*-1,3-*bis*-Hydroxymethyl-1,3-dimethyl-1,3-dihydroisobenzofuran, was synthesized in 10% yield from benzyne precursor o-bromofluorobenzene and 2,5-dimethylfuran. The diol was obtained via oxidative cleavage of a Diels-Alder adduct after attempts of synthesizing it from diethyl phthalate and phthaldialdehyde failed due to inability to obtain o-diisopropenylbenzene. Improvements of the dihydroxylation step with potassium permanganate might improve the yield greatly. Two ways of converting the diol to the desired arsenic receptor *cis*-1,3-*bis*-Sulfhydrylmethyl-1,3-dimethyl-1,3-dihydroisobenzofuran were explored. Substitution of a dimesylated intermediate did not seem to be effective. The thio-Mitsunbou reaction was effective on a small model diol and might be able to convert the synthesized diol to the desired *bis*-thiol receptor. The receptor will then be tested and further developed to help detect and remove toxic arsenic(III) compounds from drinking water.

V. Experimental

General Information: Reagents were obtained from Sigma Aldrich and used without purification unless otherwise noted. Flash chromatography was performed on neutral silica gel. ^{1}H NMR spectra were recorded on a Bruker Fourier 300 MHz spectrometer or Bruker Nanobay 400 MHz spectrometer (compounds **12**, **13**, **2**) at room temperature in CDCl$_3$ as solvent and internal standard (δ_H 7.28). ^{12}C NMR spectra were recorded on the Bruker Nanobay 400 MHz spectrometer in CDCl$_3$ (δ_C 77.00). TLC was performed on aluminum-backed silica plates with hexane/ethyl acetate mixture as eluent, denoted R_f(V_{Hex}:V_{EtOAc}). ATR-IR spectra were recorded with neat samples on a Thermo Scientific Nicolet iS10 FT-IR spectrometer.

Experiment 1: Exhaustive Methylation of Diethyl phthalate by Methylmagnesiumbromide

To a 100-mL rbf under N$_2$ in an ice bath was added dry THF (20 mL) and 3 M ether solution of MeMgBr (15.0 mL, 45.0 mmol). To stirring solution was dripped diethyl phthalate (3.0 mL, 15.1 mmol). Solution turned yellow and then white precipitate formed. Solution was stirred for 1 hr at rt and then refluxed at 80° overnight. Resulting yellow-white gel was quenched with aqeuous 1M HCl (30 mL) and extracted with ether (3×50 mL). The yellow ether layer was dried over MgSO$_4$ and rotary evaporated to give viscous orange oil as crude product that partially crystallized on standing. The product was recrystallized in ether to give clear needles as pure **4** (1.940 g, 9.99 mmol) in 66% yield.

diol, 4

R_f(3:1) 0.27

δ_H 1.74 (s, 12H, CH$_3$), 4.89 (br s, 2H, OH), 5.31 (d, 0.36, OH-CH$_3$), 7.17-7.21 (m, 2H, ArH), 7.33-7.37 (m, 2H, ArH)

Experiment 2: Dehydration of **4** by Silica chloride

Silica chloride was prepared by refluxing silica gel (10.011 g) and thionyl chloride (38.0 mL) in a 250-mL rbf under N$_2$ for 48h at 53°C. Excess SOCl$_2$ (17 mL) was distilled off at 73°C. The white-grey solid product (14.934g) was further dried by rotary evaporation and stored in a tightly sealed container. The yield was calculated as 94%.

To a 100-mL rbf, SiO$_2$-Cl (4.534 g) was added and then **2** (4.219 g, 21.72 mmol) dissolved in CHCl$_3$ (10 mL), producing a black solution. The mixture was refluxed at 75°C for 2h. To the resulting viscous black-green mixture, silica gel was added until it became dry and grainy. Hexanes (25 mL) were used to transfer the mixture to fluted filter paper and wash the nonpolar components into a 50-mL rbf. After rotary evaporation, the pure product (2.534 g, 14.4 mmol) was confirmed by TLC and ^{1}H-NMR as the tetramethyl isobenzofuran **9** in 66% yield.

tetramethyl isobenzofuran, 9

R$_f$(3:1) 0.58

δ_H 1.52 (s, 12H, CH$_3$), 7.09-7.12 (m, 2H, ArH), 7.28-7.30 (m, 2H, ArH)

Experiment 3: Reaction of **4** with Methanesulfonyl chloride

To a 25-mL rbf under N$_2$ in an ice bath, anhydrous triethylamine (0.40 mL, 2.87 mmol) and MeSO$_2$Cl (0.20 mL, 2.58 mmol) were added. Stirring produced a yellow solid. A few mgs of 2 dissolved in CHCl$_3$ was slowly dripped into the rbf, resulting in a thin orange layer on top of the mixture. More CHCl$_3$ was added until the solid dissolved into a yellow solution. The mixture

was stirred at 0°C for 1.5 hrs. Water was added to the solution and the organic layer was extracted with 3×4 mL of $CHCl_3$, dried over $MgSO_4$, and rotary evaporated. The product **9** was confirmed by ^{1}H-NMR.

Experiment 4: Reaction of **4** with Isocyanate

To a 25-mL rbf under N_2 was added diol (0.017 g, 0.082 mmol), $CDCl_3$(1 mL), cyclohexyl isocyanate (0.03 mL, 0.157 mmol) and DBU (2 drops). After stirring 12 hrs the white precipitate was filtered and ^{1}HNMR was taken. Column chromatography with 3:1 hexane/ethyl acetate gave a small amount of pure mono-carbamate ester **10**.

mono-carbamate ester, 10

δ_H 1.61 (s, 6H, CH_3), 2.00 (s, 6H, CH_3), 3.38 (m, 11H, C_6H_{11}), 3.68 (br s, 1H, OH), 5.15 (s, 1H, NH), 7.15-7.40 (m, 4H, ArH)

Experiment 5: Grignard Reaction of Phthaldialdehyde and Methylmagnesiumbromide

To a 100-mL rbf under N_2 in an ice bath was added OPA (0.987 g, 7.36 mmol) and dry THF (15 mL), creating a bright yellow solution. A 3 M ether solution of MeMgBr (7.4 mL, 22 mmol) was dripped via syringe at 1 drop/s. Solution became pale transparent yellow and a white precipitate formed.   Mixture was stirred at rt for 19 hrs. Then, sat. aq. NH_4Cl was added dropwise until the solution was transparent brown. Mixture was extracted with chloroform (3×20 mL). Transparent violet/pink organic layer was dried over $MgSO_4$ and rotary evaporated to yield a dark brown viscous oil (1.042 g, 6.27 mmol). TLC and ^{1}H-NMR confirmed pure diol **6** was obtained in 85% yield.

diol, 6

R$_f$(1:1) 0.12

δ$_H$ 1.57-1.60 (dd, 12H, CH3); 2.17 (br s, 2H, OH), 2.47 (br s, 2H, OH); 5.24-5.29 (m, 4H, CH), 5.31-5.34 (m, 4H, CH); 7.34 (m, 4H, ArH), 7.53 (m, 4H, ArH)

Experiment 6: 'Green' Oxidation of **6** by KMnO$_4$/MnO$_2$

To a 50-mL rbf containing **6** (0.234 g, 1.41 mmol)was added finely ground KMnO$_4$ (1.025 g, 6.49 mmol) and MnO$_2$ (3.029 g, 34.8 mmol). The oily mixture was rapidly stirred overnight and then diluted with ether and vacuum filtered through a sintered 30-mL 10-15M funnel. The pale yellow filtrate was dried over MgSO$_4$. Rotary evaporation yielded a yellow liquid (0.154 g). Flash column chromatography with 9:1 hexane/ethyl acetate gave pure oDAB **5** (0.104 g, 0.641 mmol) in 45% yield. The byproduct **8** was also collected and analyzed.

o-diacetylbenzene, 5

R$_f$(1:1) 0.52

δ$_H$ 2.55 (s, 6H, CH$_3$), 7.57 (br s, 4H, ArH)

3-hydroxy-3-methyl-1-indanone, 11

R$_f$(1:1) 0.35

δ$_H$ 1.72 (s, 3H, CH$_3$), 2.89 (s, 2H, CH$_2$), 7.46 (m, ArH), 7.68 (m, ArH)

Experiment 7: Wittig Reaction of **5** and Phosphorous Ylide

The phosphorous ylide Ph_3PCH_2 was prepared by stirring $MePh_3PBr$ (3.836 g, 10.7 mmol) with NaH (1.182 g, 49.3 mmol) and THF (20 mL) under N_2 at 70° for 30 min to make a pale yellow suspension and then stirring at rt overnight. The resulting yellow-white mixture was vacuum filtered and washed with ether. Drying the filtrate over $MgSO_4$ and rotary evaporation yielded an orange liquid (2.484 g, 9.00 mmol).

To the 25-mL rbf containing Ph_3PCH_2 was added **5** (0.104 g, 0.641 mmol) and heptane (5 mL). After 10 min the orange layer on bottom turned red-brown. After stirring 20 hrs, extraction with hexane, drying over $MgSO_4$ and rotary evaporation gave small white crystals. TLC and ^{1}H-NMR confirmed product was 3-Hydroxy-3-methyl-1-indanone **11**.

Experiment 8: Diels-Alder Reaction of Anthranilic Acid and 2,5-Dimethylfuran

A 50-mL rbf was added dry THF (30 mL) and DMFu (6.0 mL, 56.8 mmol) and isopentyl nitrite (4.8 mL, 35.7 mmol). Anthranilic acid (4.0 g, 29.2 mmol) was added in small portions to the mixture stirring at 65°. The solution turned red and foamy, then black. After 1 hr, the mix was cooled to rt, decanted into a 50-mL rbf and rotovaped to remove most of the solvent. To the black-yellow liquid was added sat. aq. KOH (30 mL). The mixture was extracted with ether (3x50 mL). The yellow ether layer was dried over $MgSO_4$ and rotovaped to yield red-yellow liquid (4.225 g). ^{1}H-NMR showed THF and isoamyl alcohol still present so the mixture was rotovaped again at 80° and then extracted with hexane (3x30 mL) and brine (10 mL) to give a viscous yellow oil as pure 1,4-dihydro-1,4-dimethylepoxynaphthalene **7** (1.786 g, 10.4 mmol) in 36% yield. In some cases, a small amount of naphthol **14** was also produced and isolated.

1,4-dihydro-1,4-dimethylepoxynaphthalene, 7:

R_f(9:1) 0.52; R_f((1:1) 0.83

δ_H 1.94 (s, 6H, CH$_3$), 6.82 (s, 2H, CH), 7.01-7.03 (m, 4H, ArH), 7.16-7.19 (m, 4H, ArH)

δ_C 15.20, 118.25, 124.64, 146.73, 152.67

1,4-dimethyl-2-naphthol, 14:

R_f(1:1) 0.47

δ_H 2.40 (s, 3H, CH$_3$), 2.62 (s, 3H, CH$_3$), 5.12 (br s, 1H, OH), 7.11 (s, 1H, CH), 7.50 (m, 1H, ArH), 7.53 (m, 1H, ArH), 7.94 (m, 1H, ArH), 8.18 (m, 1H, ArH)

Experiment 9: Diels-Alder Reaction of o-Bromofluorobenzene and 2,5-Dimethylfuran

Magnesium turnings (1.091 g, 45 mmol) were activated by washing with a few mLs of sat. aq. NH$_4$Cl and vacuum filtration while washing with several portions of anhydrous ether. To a 3-neck 100-mL rbf equipped with rubber stoppper, reflux condenser and 15-mL pressure-equalizing addition funnel was added the shiny white-silver Mg turnings. After vacuum and placement under N$_2$, dry THF (15 mL) was added to the rbf and gently refluxed at 80°. To the addition funnel was added dry THF (10 mL), OBFB (2.4 mL, 22 mmol) and DMFu (2.6 mL, 24 mmol). The clear solution was dripped at 1 drop/s and the reaction mixture refluxed for 19 hrs. To the cloudy yellow solution was added ether to precipitate more byproduct and vacuum filtered into a 100-mL rbf and rotovaped to yield a yellow viscous oil (3.466 g, 20 mmol). TLC and ^{1}H-NMR confirmed pure **7** was obtained in 90% yield.

Experiment 10: Potassium Permanganate Oxidation of **7**

To a 25-mL rbf containing **7** (0.160 g, 0.930 mmol) and DCM (10 mL) vigorously stirring in cool water bath was added in small portions a dark purple solution of $KMnO_4$ (0.208 g, 1.32 mmol) and water (10 mL). The mixture changed from cloudy yellow to pink/brown and to black in 15 mins. A solution of sat. aq. sodium bisulfite was stirred in until no purple/pink color was detected. TLC showed disappearance of **7** and appearance of one spot more polar and one spot less polar. The dark green suspension was vacuum filtered through a 60-mL 40-60M sintered funnel and extracted with DCM (3×15 mL) to obtain a pale golden solution. Rotary evaporation gave a white crystals in a yellow oil (0.112 g). Crystallization was performed by dissolving the oil in 10 mL of ether, transferring to 25-mL Erlenmeyer flask, adding 20 mL hexane and boiling off the ether until white crystals formed on bottom. After cooling, the shiny clear/white crystals (0.041 g, 0.199 mmol) were obtained after washing with warm hexane. Characterization by TLC, ^{1}H-NMR and IR confirmed that the crystals were purified glycol **12** in 21% yield.

1,4-epoxy-2,3-dihydroxy-1,4-dimethyl-tetralin, 12

R_f(1:1) 0.50

δ_H 1.77 (s, 6H, CH3), 3.12 (br s, 2H, OH), 3.77 (s, 2H, CH), 7.19 (m, 2H, ArH), 7.24 (m, 2H, ArH)

δ_C 1.01, 12.89, 73.42, 87.43, 119.22, 127.62

IR(cm^{-1}) 3428, 3350, 2953, 2911, 1457

Experiment 11: Sodium meta-Periodate Cleavage of **12** to **13** followed by Sodium Borohydride-Silica Reduction of **13** to **2**

To a 25-mL rbf containing crystals of **12** (0.115 g, 0.558 mmol) was added $NaIO_4$ (0.154 g, 0.720 mmol), ether (10 mL) and water (5 mL). After vigorously stirring for 30 mins, the ether layer was washed with water (3×5 mL) and brine (10 mL), dried over $MgSO_4$ and filtered into a 25-mL rbf. To the rbf was added $NaBH_4$ powder (0.063 g, 1.67 mmol) and silica gel (8 mL). The mixture was stirred for 4 hrs and then vacuum filtered through a sintered 60-mL funnel. The clear filtrate was rotary evaporated to give a clear oil, which precipitated white crystals when hexane was added. The solvent was evaporated again to yield tiny white crystals and white film (0.055g, 0.26 mmol) of pure **2** in 47% yield.

dialdehyde, 13:

R_f(1:1) 0.64

δ_H 1.71 (s, 6H, CH_3), 7.25 (m, 2H, ArH), 7.41 (m, 2H, ArH), 9.75 (s, 2H, HCO)

***cis*-1,3-*bis*-Hydroxymethyl-1,3-dimethyl-1,3-dihydroisobenzofuran, 2**:

R_f(1:1) 0.26

δ_H 1.44 (s, 6H, CH_3), 3.78-3.86 (dd, 4H, CH_2), 7.12-7.15 (m, 2H, ArH), 7.35-7.38 (m, 2H, ArH)

δ_C 26.32, 69.35, 87.80, 121.06, 128.51, 142.99

Experiment 12: Mesylation of **2**

To a 50-mL rbf containing **2** (0.011 g, 0.053 mmol) in an ice bath was added TEA (0.18 mL, 1.29 mmol) and ether (5 mL). Addition of MsCl (0.10 mL, 1.29 mmol) created white precipitate and then yellow-white solid. Water (20 mL) was added and the product was extracted with ether (20 mL). The ether layer was dried over $MgSO_4$ and rotary evaporated to give a mixture of **15**

and triethylamine hydrochloride as an orange film (0.056 g), which was confirmed by TLC and
^{1}H-NMR.

dimesylate, 15

R$_f$(1:1) 0.68

δ$_H$ 1.61 (s, 6H, CH$_3$), 2.98 (s, 6H, CH$_3$), 4.27-4.38 (dd, 4H, CH$_2$), 7.21 (m, 2H, ArH), 7.40 (m, 2H, ArH)

Experiment 13: Reaction of **15** with Thioacetate

Potassium thioacetate was prepared by stirring in 50-mL Erl for 1 hr a solution prepared from KOH chips (1.093 g, 19.5 mmol), ethanol (15 mL, 200 proof) and thiolacetic acid (1.2 mL, 16.8 mmol). The bright yellow solution was decanted into a 50-mL rbf and rotary evaporated. The yellow/white solid was washed with ether and a mostly white powder (1.030 g, 9.02 mmol) were obtained after vacuum filtration. The KSAc was stored in the refridgerator in an amber vial.

To a 25-mL rbf containing impure **15** (0.056 g) was added KSAc (0.159 g, 1.39 mmol) and THF (10 mL). The solution was stirred overnight with no change. Solution was then heated at 50° for 10 mins. No conversion was seen by TLC or ^{1}H-NMR.

Experiment 14: Thio-Mitsunobu Reaction on *E*-2-butene-1,4-diol

To a 50-mL rbf in ice bath under N$_2$ was added triphenylphospine (1.915 g, 7.30 mmol), dry THF (10 mL) and DIAD (1.4 mL, 7.11 mmol). A yellow solid precipitated. To a 10-mL conical bottom flask was added butenediol (0.2 mL, 2.4 mmol), dry THF (2.5 mL) and distilled thiolacetic acid (0.5 mL, 7.1 mmol) to form a golden solution. The solution from cbf was transferred via syringe to the rbf solution. The mixture was stirred for 1 hr in ice bath. ^{1}H-NMR

showed no diol and both mono- and di-thioester products. The mixture was stirred overnight at rt. ^{1}H-NMR showed more of the di-thioester and still some mono-thioester. Column chromatography of the yellow metallic-smelling liquid was done using 9:1, then 3:1 hexane/ethyl acetate. Collection of the first eluted fraction and rotary evaporation gave an orange oil of mostly pure butene-bis-thioacetic ester **17** in ethyl acetate (0.666 g).

E-2-butene-bis-thioacetic ester, 17

R$_f$(1:1) 0.72

δ$_H$ 2.36 (s, 6H, CH$_3$), 3.63 (d, 4H, CH$_2$), 5.56 (t, 2H, CH)

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