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Green approaches to salicylaldehydes and heteroaromatics

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Green approaches to salicylaldehydes and heteroaromatics

by

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The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this thesis. The Graduate College will ensure this thesis is globally accessible and will not permit alterations after a degree is conferred.

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ABSTRACT

Organic chemistry has been used over the decades to solve a myriad of problems facing our society. From pharmaceutical drug design and food additives, to plastics and fuels, organic synthesis is at the heart of these industries. Recently, a new focus has emerged to use greener syntheses in order to meet the demands of a modern society. Research has focused on the use of less toxic, more bio-renewable materials, while maintaining cost-effectiveness and industrially viable syntheses.

In this work, we strived for direct routes to both biologically active compounds, and compounds useful for industrial materials. We sought relatively cheap alternatives to the non-renewable sources that are used industrially today.

GENERAL INTRODUCTION

In this dissertation, we will detail direct routes to biologically active and industrially relevant compounds.

In Chapter 1 we will describe a pathway to tether triphenylphosphine to an antioxidant molecule using radical hydrophosphonation. This is done in order to increase the free radical scavenging capability of the antioxidant by aggregating the molecule in the mitochondria, the principal location for free radical generation.

Chapter 2 will show several routes to heteroaromatic polycarboxylates, using fermentation products as the starting material. The resulting compounds are intended to be used as a monomer in order to supplant the need for petroleum product in plastic production.

Chapter 1: SYNTHESIS OF TRIPHENYLPHOSPHINE TETHERED SALICYLALDEHYDES

Introduction

The mitochondria is an important part of cellular biology, responsible for the generation of energy for the cell. The oxidative process by which this occurs has potential to release harmful reactive oxygen species, which can in turn damage the mitochondria.[1,2] Mitochondrial dysfunction accounts for a wide array of diseases, including Alzheimer's muscular dystrophy, Lou Gehrig's, various cancers, and diabetes, to name a few.[2,3] Additionally, it is believed that a primary cause of aging is due to free radical damage to the mitochondria.[1,2]

Previously, our group developed chemically modified antioxidants with the ability to aggregate in the mitochondria, with the goal that these molecules can help to neutralize free radicals before damage to the mitochondria can occur. We developed a method to synthesize vitamin E tethered to triphenyl phosphonium (TPP) salts (Figure 1). The molecule was subsequently shown to reduce oxidative stress in the mitochondria, as well as lowering lipid and hydrogen peroxide levels in mice.[4]

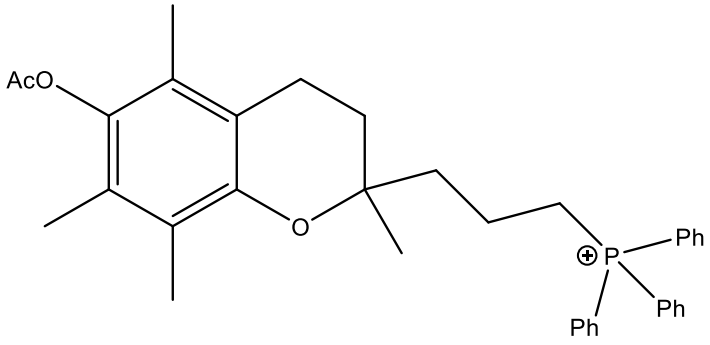


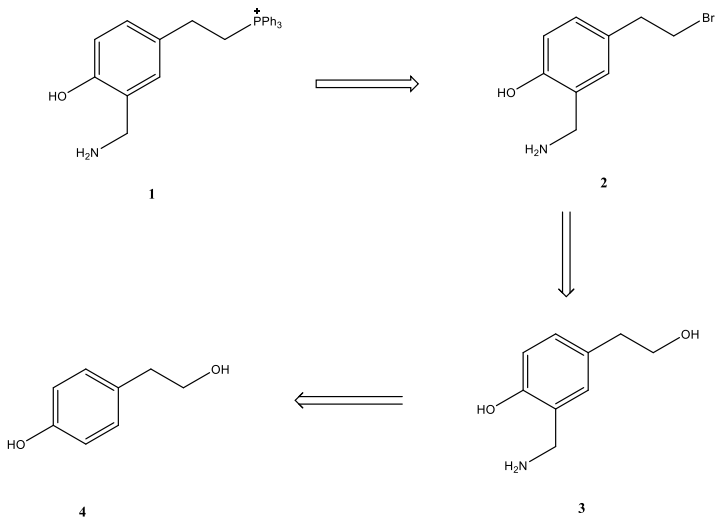
Figure 1. Triphenylphosphonium tethered vitamin E

The TPP salt helps the molecule localize in the mitochondria; the bulky hydrophobic phenyl groups allow the compound to pass the bilayer of the mitochondrial membrane, while the charged nature of the salt holds it in the inner-membrane space.[2]

We wanted to expand upon this work, by using other known antioxidants. Through our work with Metabolic Technologies, Inc (MTI), we decided to employ salicylamine as our target antioxidant. This compound was chosen because MTI had stockpiles of the compound, and it's known antioxidant properties.[5] Initially, we tethered the TPP para to the phenol, as we did not want to interrupt the phenol-methylamine interactions. After we achieved this synthesis, we tethered the TPP directly to the amine in order to study the effects of different tether locations on the compound's properties.

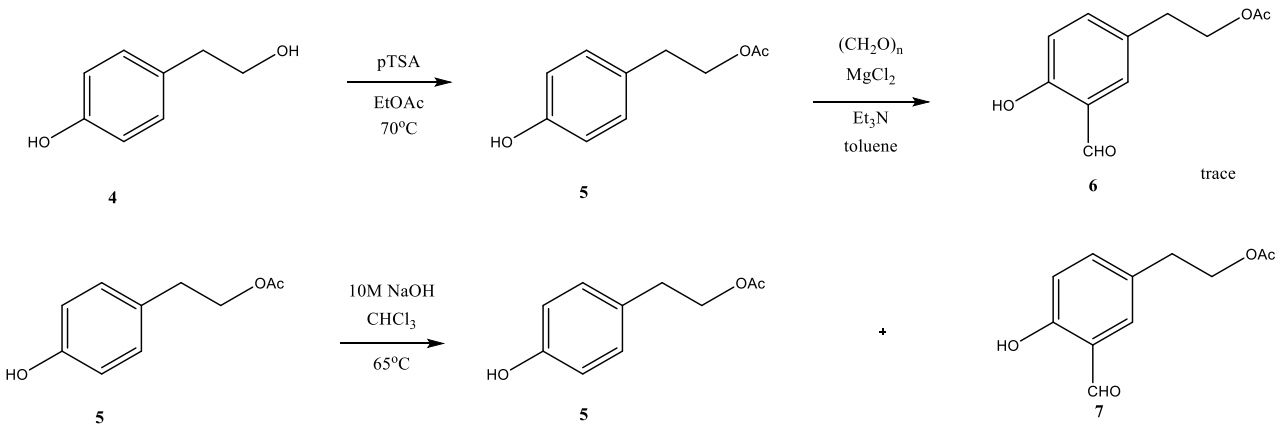
Results and Discussion

Our initial attempts to synthesize the molecule began with 2-(4-hydroxyphenyl)ethanol. We planned to protect the primary alcohol, then formylate ortho to the phenol. Reductive amination followed by deprotection would yield compound **3**. Then, conversion of the primary alcohol to halide **2**, followed by the S_N2 reaction of the halide with triphenyl phosphine to yield the desired product **1** (Scheme 1).



Scheme 1. Retrosynthesis of triphenylphosphonium tethered salicylamine

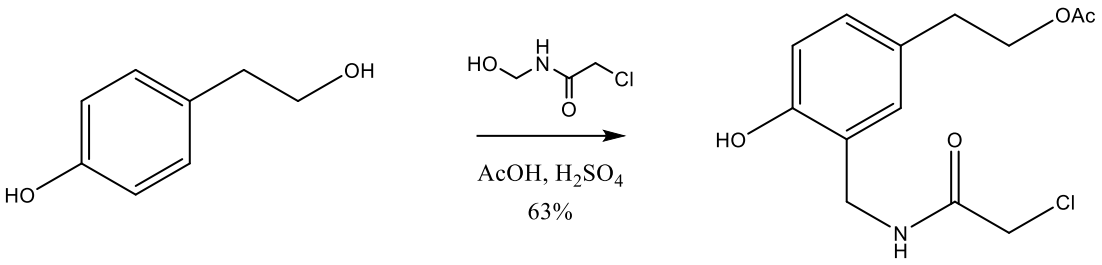
Protection of the primary alcohol **4** via acetylation was successful in quantitative yield.[6] However, the initial formylation attempt of **5** yielded only trace amounts of desired product **6**.[7] Furthermore, other attempts at formylation utilizing the Reimer-Tiemann[8] reaction led to an inseparable mixture of starting material **5** and product **7** (Scheme 2).



Scheme 2. Attempts at formylation of the phenol.

We decided to employ a method utilized by Zerkowski to directly attach a nitrogen containing group ortho to the phenol, which would later be cleaved to our desired salicylamine.

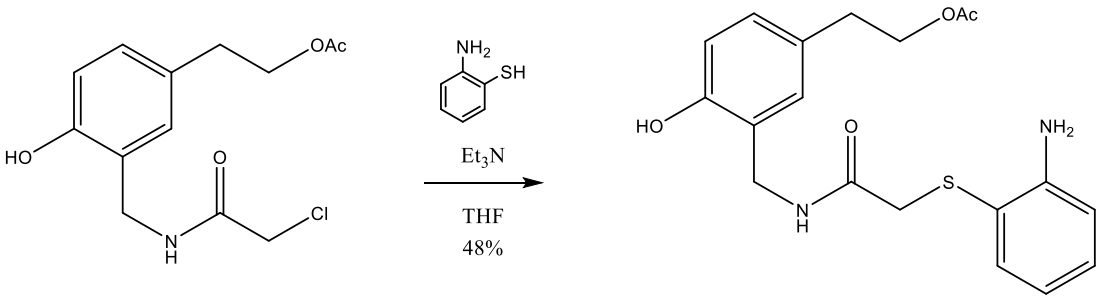
Phenol **4** was reacted with 2-chloro-N-(hydroxymethyl)acetamide in acetic acid and sulfuric acid to yield amide **8** in 63% yield (Scheme 3).[9]



4 **8**

Scheme 3. Methylamination of the phenol.

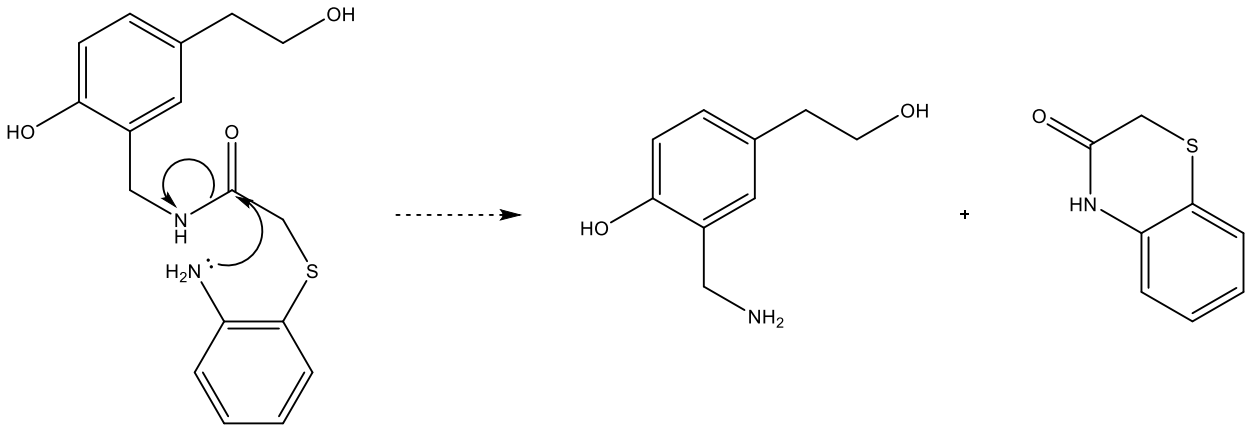
Unfortunately, traditional acid and base catalyzed attempts to cleave the amide were unsuccessful. We decided to try to utilize the alpha-halogen to install a group which could facilitate cleavage of the amide bond. Using 2-aminothiophenol and triethylamine in tetrahydrofuran we were able to synthesize compound **10** in 48% yield (Scheme 4).



9 **10**

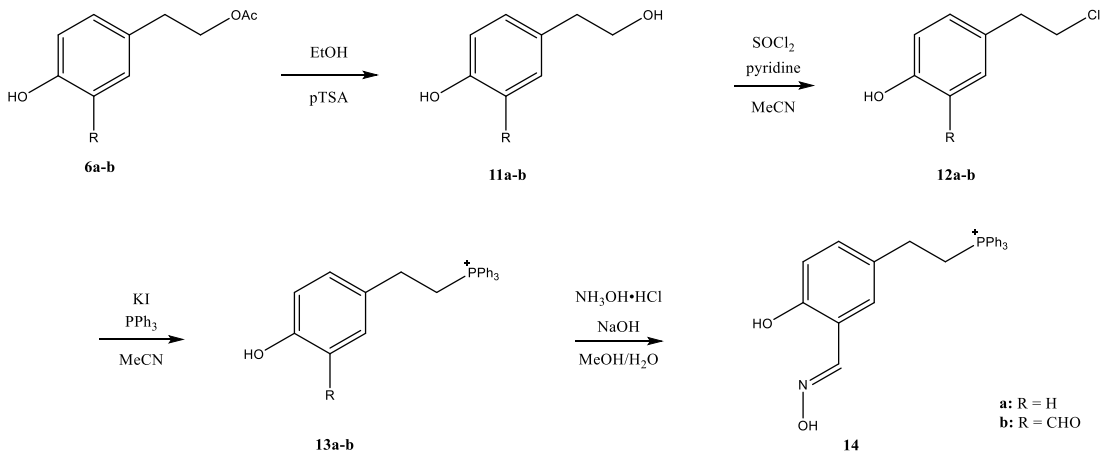
Scheme 4. Attachment of the intramolecular cleavage group.

We planned to use the aniline group six atoms away from the carbonyl to intramolecularly cleave the amide bond, leaving the desired amine (Scheme 5).



Scheme 5. Proposed mechanism for intramolecular cleavage.

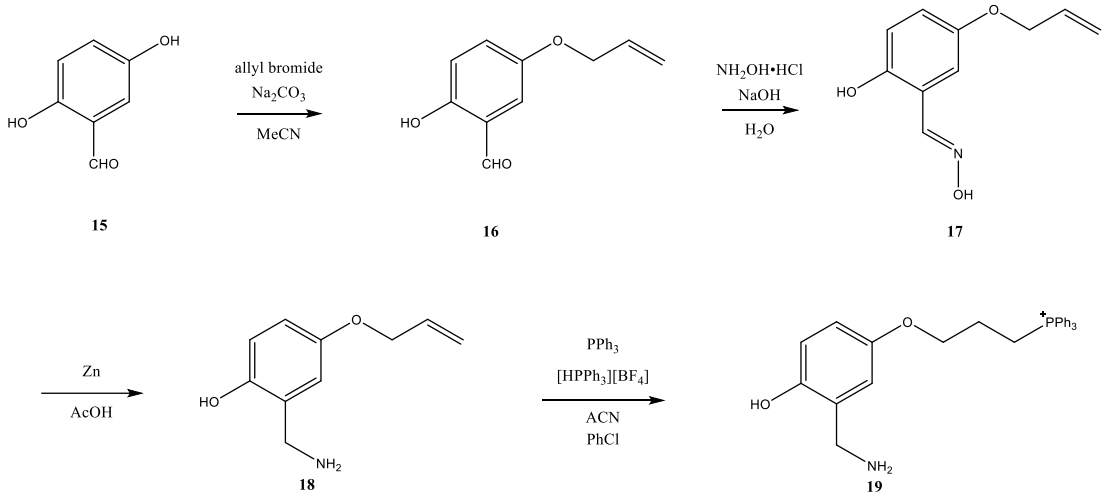
We again tried a variety of acid and base catalyzed conditions, none of which yielded the desired amide cleavage. With this information, we decided to go back to the inseparable mixture of formylated and non formylated product. We began by cleaving acetates **6a-b** using ethanol and p-toluenesulfonic acid, yielding primary alcohols **11a-b**. Using thionyl chloride and pyridine in acetonitrile, we synthesized chlorides **12a-b**. Next, were able to attach the triphenylphosphonium moiety yielding **13a-b** using potassium iodide and triphenylphosphine in acetonitrile. It was at this point in the synthesis that the two compounds were separable, and were purified by flash chromatography. Finally, using the separated aldehyde, we synthesized oxime **14** using hydroxylamine[10] hydrochloride and sodium hydroxide in a methanol/water mix, with 12% yield over 5 steps (Scheme 6).



Scheme 6. Alternate route to amination of the phenol.

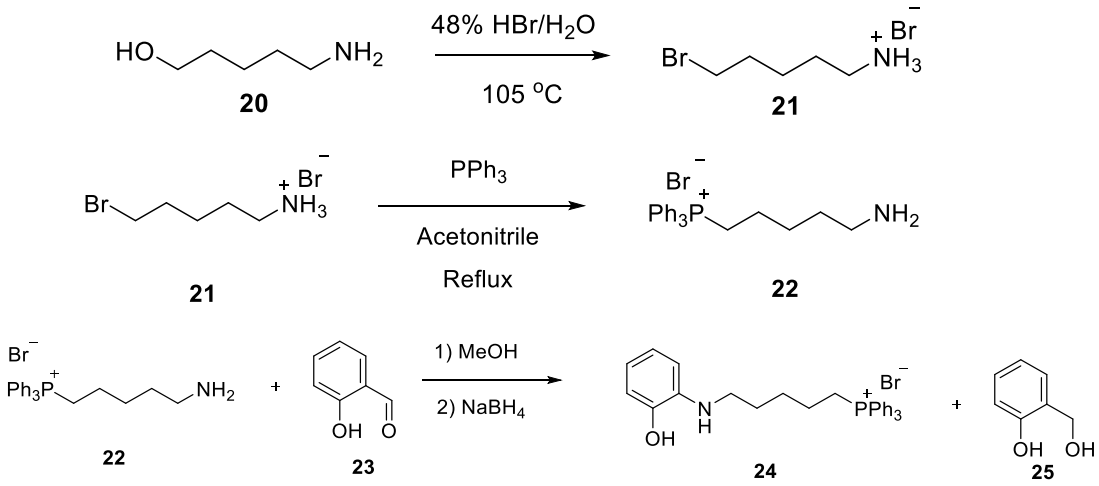
Due to the low overall yield, we decided to take a different approach to the synthesis of the TPP tethered compound. We instead started with 2,5-dihydroxybenzaldehyde **15**, as it was readily available and had the aldehyde preinstalled. Using **15** with allyl bromide and sodium carbonate in acetonitrile, we were able to selectively introduce and allyl group at the 5-position phenol with 19% conversion.[11] We were able to achieve selective allylation due to the hydrogen bonding of the 2-position phenol and the aldehyde, that lowers the 2-position phenol's acidity.

While the conversion was poor, starting material was readily recovered from the crude mixture by acidifying the aqueous phase and extracting. Thus, we were able to enrich our material and generate a large quantity of material to carry on to the next step. We converted aldehyde **16** to oxime **17** in 85% yield utilizing the same conditions as for oxime **14**.[10] From **17** we used zinc dust in acetic acid to reduce to the methylene amine,[12] followed by radical hydrophosphonation using triphenylphosphine, $[HPPh_3][BF_4]$, 1,1-azobis-1-cyclohexanenitrile (ACN), and chlorobenzene,[13] in 48% yield over 2 steps (Scheme 7).



Scheme 7. Attachment of the triphenylphosphonium salt.

We sought to synthesize another related compound, with the TPP tethered directly to the amine. Starting with 5-amino-1-pentanol **20**, we converted the alcohol to primary bromide **21** using hydrobromic acid in water,[14] in quantitative yield. From there, we reacted triphenylphosphine with primary bromide **21**, yielding triphenylphosphonium salt **22**. Finally, we oxidatively aminated salicylaldehyde **24** with triphenylphosphonium salt **22** to generate the desired compound **24** (Scheme 8).



Scheme 8. Route to anchoring off the amine.

In summary, we developed syntheses to TPP tethered salicylamine. We chose the salicylamine moiety due to the abundance our collaborators had in stock, as well as the antioxidant properties it exhibits. We were able to attach the TPP tether to the aromatic ring and the amine in order to study the different effects these locations would have on biological activity.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and use without purifications. All experiments were performed under ambient atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with a Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^1H NMR) unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. Standard grade silica gel (60 A, 32-63 μm) was used for flash chromatography.

3-((2-chloroacetamido)methyl)-4-hydroxyphenethyl acetate (8)

2.07g of 4-(2-hydroxyethyl)phenol and 1.89g of 2-chloro-N-(hydroxymethyl)acetamide was placed in a 50mL round bottom flask. 3 mL of concentrated sulfuric acid and 27 mL of acetic acid were added to the flask. The solution was stirred for 16 hours. The flask was poured into 40 mL of saturated sodium bicarbonate. Additional sodium bicarbonate was added as necessary to adjust the pH to 5. The aqueous layer was extracted with 3x90 mL of ethyl acetate, dried over sodium sulfate, and solvent was removed in vacuo. The compound was purified by

column chromatography 1:1 ethyl acetate: hexanes. 2.74g of 3-((2-chloroacetamido)methyl)-4-hydroxyphenethyl acetate was recovered in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.48 (t, 1H, J = 4 Hz), 7.06-6.84 (m, 2H), 6.72 (d, 1H, J = 8 Hz), 4.19 (d, 2H, J = 5.8 Hz), 4.10 (s, 2H), 4.09 (t, 2H, J = 7 Hz), 2.73 (t, 2H, J = 7Hz), 1.96 (s, 3H).

3-((2-((2-aminophenyl)thio)acetamido)methyl)-4-hydroxyphenethyl acetate (10)

0.12g of 2-aminothiophenol was added to 2 mL of THF in a 25 mL flame dried round bottom flask. The flask was placed under an argon atmosphere. 0.14 mL of triethylamine was added to the flask. The thiophenol crashed out of solution upon addition of triethylamine, 3 mL of THF was added to dissolve the salt. 0.23g of 3-((2-chloroacetamido)methyl)-4-hydroxyphenethyl acetate in 2 mL of THF was added to the flask. Solution was stirred for 6 hours. Reaction was filtered and solvent removed in vacuo. Compound was purified with column chromatography 9:1 ethyl acetate: hexanes, yielding 0.14g 3-((2-((2-aminophenyl)thio)acetamido)methyl)-4-hydroxyphenethyl acetate in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 8.33 (t, 1H, J = 5.6 Hz), 7.22 (d, 2H, J = 7.5 Hz), 7.00 (t, 1H, J = 7.3 Hz), 6.93-6.79 (m, 2H), 6.67 (d, 2H, J = 7 Hz), 6.45 (t, 1H, J = 7.4 Hz), 5.39 (s, 1H), 4.14 (d, 2H, J = 5.9), 3.48 (q, 2H, J = 7.2 Hz), 3.41 (s, 2H), 2.55 (t, 2H, J = 7.1), 2.07 (s, 3H).

2-hydroxy-5-(2-hydroxyethyl)benzaldehyde (11b)

0.62g of 3-formyl-4-hydroxyphenethyl acetate was placed in 10 mL of ethanol. 0.20g of p-toluenesulfonic acid was added was added and allowed to stir overnight. Solvent was removed in vacuo, and compound was purified by column chromatography 1:1 ethyl acetate: hexanes. Cleaved product was obtained in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.59 (t, 1H, J = 2.2 Hz), 7.47 (dd, 1H, J = 8.4, 2.2 Hz), 6.89 (d, 1H, J = 8.5 Hz), 3.78 (t, 2H, J = 7.6 Hz), 2.81 (t, 2H, J = 6.8 Hz).

5-(2-chloroethyl)-2-hydroxybenzaldehyde (12b)

0.54g of 2-hydroxy-5-(2-hydroxyethyl)benzaldehyde was placed in 3 mL of acetonitrile. 0.15 mL of thionyl chloride and 0.1 mL of pyridine was added to the flask. The solution was stirred for 2 hours, until the TLC indicated complete conversion. The compound was brought on to the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.45 (t, 1H, J = 2,2 Hz), 7.32 (dd, 1H, J = 8.4, 2.2 Hz), 7.01 (d, 1H, J = 8.4 Hz), 3.63 (t, 2H, J = 7.5 Hz), 2.94 (t, 2H, J = 6.9 Hz).

(3-formyl-4-hydroxyphenethyl)triphenylphosphonium salt (13b)

To the 5-(2-chloroethyl)-2-hydroxybenzaldehyde solution, 0.16g of potassium iodide was added. 1.30g of triphenylphosphine was added, and the solution was refluxed overnight. At this point, the compounds became separable. The product was purified by gradient column

chromatography 1:1 ethyl acetate: hexanes to 1:9 methanol: ethyl acetate yielding the phosphonium salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 7.96-7.24 (m, 18H), 3.77 (t, 2H, J = 7.4 Hz), 3.01 (t, 2H, J = 7.2 Hz).

(4-hydroxy-3-((hydroxyimino)methyl)phenethyl)triphenylphosphonium salt (14)

0.41g of (3-formyl-4-hydroxyphenethyl)triphenylphosphonium salt was dissolved in 5 mL of methanol. 0.36g of hydroxylamine hydrochloride was dissolved in 0.7 mL of water and added to the phosphonium salt. 0.21g of sodium hydroxide was added. The solution was refluxed for 30 minutes. Solvent was removed in vacuo and purified by gradient column chromatography ethyl acetate to 1:9 methanol: dichloromethane. 0.15g of (4-hydroxy-3-((hydroxyimino)methyl)phenethyl)triphenylphosphonium salt was obtained in 35% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H), 7.93-7.28 (m, 18H), 3.47 (t, 2H, J = 6.4 Hz), 2.65 (t, 2H, J = 7 Hz).

5-(Allyloxy)-2-hydroxybenzaldehyde (16)

To a 25 mL round bottom flask was added 2,5-dihydroxybenzaldehyde (1.48 g, 10.7 mmol), acetonitrile (11 mL), sodium carbonate (2.27 g, 21.4 mmol), and allyl bromide (0.93 mL, 10.7 mmol). Reaction was heated to 80 °C and allowed to reflux overnight. The resulting solution was cooled to room temperature, poured into 20 mL 1M NaOH, and extracted with 20 mL of ethyl acetate to remove 2,5-bis(allyloxy)benzaldehyde side product. The aqueous layer was acidified with concentrated HCl to pH 1, and extracted with 3x20 mL of ethyl acetate. The

organic layer was dried with magnesium sulfate and filtered. Solvent was removed under reduced pressure. Product was purified via column chromatography 1:4 ethyl acetate: hexanes, giving 5-(allyloxy)-2-hydroxybenzaldehyde (0.35 g, 1.99 mmol) in 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 9.82 (s, 1H), 7.14 (dd, 1H, J = 9.1, 3.2 Hz), 7.00 (d, 1H, J = 3 Hz), 6.90 (d, 1H, J = 9.1 Hz), 6.13-5.92 (m, 1H), 5.39 (d, 1H. J = 17.2 Hz), 5.29 (d, 1H, J = 10.7 Hz), 4.50 (d, 2H, J = 5.3 Hz).

5-(Allyloxy)-2-hydroxybenzaldehyde oxime (17)

To a 25 mL round bottom flask was added 5-(allyloxy)-2-hydroxybenzaldehyde (0.16 g, 0.9 mmol). Hydroxylamine hydrochloride (0.10 g, 1.37 mmol) and sodium hydroxide (0.06 g, 1.37 mmol) were dissolved in 1.5 mL deionized water. This aqueous solution was added, and the reaction was heated to 80 °C for 1 hour. The mixture was allowed to cool to room temperature and was poured into 20 mL of an HCl solution (pH 1). The solution was extracted with 3x20 mL of ethyl acetate, dried with magnesium sulfate, and filtered. Solvent was removed under reduced pressure, giving 5-(allyloxy)-2-hydroxybenzaldehyde oxime (0.17 g, 0.9 mmol) in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.03-6.84 (m, 2H), 6.72 (t, 1H, J = 1.6 Hz), 6.14-5.93 (m, 1H), 5.40 (d, 1H, J = 17.2 Hz), 5.28 (d, 1H. J = 10.7 Hz), 4.48 (d, 2H, J = 5.3 Hz).

(5-(Allyloxy)-2-hydroxyphenol)methanaminium acetate (18)

To a 10 mL round bottom flask was added 5-(allyloxy)-2-hydroxybenzaldehyde oxime (0.17 g, 0.9 mmol), then acetic acid (2 mL) and zinc dust (0.20 g, 3 mmol). Reaction was allowed

to stir overnight at room temperature. Solution was diluted with methanol (5 mL), and zinc dust was filtered off, and solvent was removed under reduced pressure. Several washes with toluene followed by removal of solvent under reduced pressure were required to remove trace amounts of acetic acid. (5-(allyloxy)-2-hydroxyphenol)methanaminium acetate (0.21g, 0.9 mmol) was recovered in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (s, 1H), 6.78-6.52 (m, 2H), 6.10-5.89 (m, 1H), 5.33 (d, 1H, J = 17.2 Hz), 5.19 (d, 1H, J = 10.7 Hz), 4.48 (d, 2H. J = 5.3 Hz).

Triphenylphosphonium tetrafluoroborate

To a 125 mL Erlenmeyer flask was added triphenylphosphine (2.91 g, 11 mmol) and dissolved in Et2O (15 mL). Tetrafluoroboric acid diethyl ether complex (1.36 mL, 10 mmol) was added, and a white precipitate formed. The precipitate was collected via filtration and recrystallized from chloroform giving triphenylphosphonium tetrafluoroborate (0.97 g, 2.7 mmol) in 27% yield.

(3-(3-(ammoniomethyl)-4-hydroxyphenoxy)propyl)triphenylphosphonium salt (19)

To a 50 mL round bottom flask was added (5-(allyloxy)-2-hydroxyphenol)methanaminium acetate (0.14 g, 0.6 mmol), chlorobenzene (25 mL), and acetic acid (2 mL). After the compound completely dissolved, 1,1’-azobis(cyclohexanecarbonitrile) (0.03 g, 0.12 mmol), triphenylphosphonium tetrafluoroborate (0.51 g, 2.64 mmol), and triphenylphosphine (0.03 g, 0.12 mmol) were added. Reaction vessel sealed with a septum and sparged with argon gas for 5 minutes. Reaction was heated to 110 °C under balloon pressure

and allowed to react overnight. Mixture was cooled to room temperature and solvent was removed under reduced pressure. Several washes with toluene followed by removal of solvent under reduced pressure were required to remove trace amounts of acetic acid and chlorobenzene. Resulting crude solid was triturated several times with chloroform, giving (3-(3-(ammoniomethyl)-4-hydroxyphenoxy)propyl)triphenylphosphonium acetate tetrafluoroborate (0.14 g, 0.29 mmol) in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.54 (m, 15H), 6.97-6.64 (m, 3H), 5.01-4.67 (m, 4H), 4.07 (t, 2H, J = 7 Hz), 3.34 (q, 2H, J = 15.4 Hz).

5-bromopentan-1-amine (21)

1.11g 5-amino-1-pentanol (10 mmol) is added to a 25 mL round bottom flask. 10 mL of 48% HBr in H_2O is added. The reaction vessel is refluxed for three hours. The solvent is removed under reduced pressure yield a brown, sticky solid in quantitative yield. The compound is used in the next step without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.37 (t, 2H, J = 6.8 Hz), 3.01 (t, 2H, J = 6.9 Hz), 1.97-1.54 (m, 6H).

(5-aminopentyl)triphenylphosphonium salt (22)

2.47g 5-bromopentan-1-amine hydrobromide (10 mmol) is placed in a 100 mL round bottom flask. 50 mL acetonitrile is added to the flask. 5.27g triphenylphospine (20 mmol) is added to the flask. The flask is heated under reflux for 60 hrs. Solvent is removed under reduced pressure yielding brown crude oil. The oil is dissolved into 30 mL water and washed 3x30 mL diethyl ether. Aqueous phase is basified with sodium carbonate, then extracted 3x30

mL dichloromethane. Solvent was removed under reduced pressure, giving 5.08g of (5-aminopentyl)triphenylphosphonium in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13-7.54 (m, 15H), 3.61 (t, 2H, J = 6.9 Hz), 2.72 (t, 2H, J = 7 Hz), 1.72-1.35 (m, 6H).

(5-((2-hydroxybenzyl)amino)pentyl)triphenylphosphonium salt (24)

0.30g (5-aminopentyl)triphenylphosphonium bromide (0.7 mmol) placed in 10 mL round bottom flask. 5 mL methanol added. 0.07 mL salicylaldehyde (0.7 mmol) added. Flask stirred overnight. 0.04g sodium borohydride (1.05 mmol, 1.5 eq) added to flask. Reaction allowed to proceed until gas formation stopped. Solution poured into 20 mL water and extracted 3x 20 mL dichloromethane. Solvent removed under reduced pressure. Crude solid dissolved in minimal amount of dichloromethane and flooded with diethyl ether. White crystals collected forming mixture of products in a 4:5 ratio. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11-7.46 (m, 15H), 6.86 (t, 1H, J = 7.8 Hz), 6.74 (d, 1H, J = 7.4 Hz), 6.47 (t, 1H, J = 7.4 Hz), 6.39 (d, 1H, J = 7 Hz), 4.50 (s, 2H), 3.75 (t, 2H, J = 12.9 Hz), 2.48 (t, 2H, J = 2 Hz), 1.65-1.22 (m, 6H).

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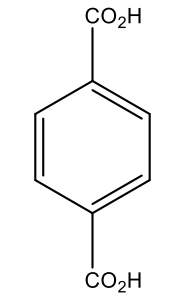
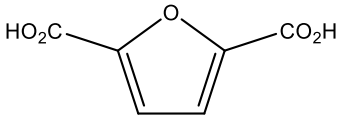
Chapter 2: BIO-RENEWABLE SYNTHESES OF HETEROAROMATIC POLYCARBOXYLATES

Introduction

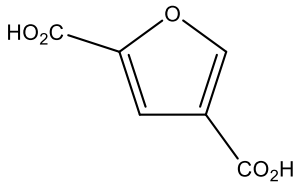
Terephthalic acid is an important molecule for the polymer industry. It is produced from xylenes,[1] a petroleum product, making it an extremely cheap precursor to polymers, and is used for the production of polyethylene terephthalate (PET).[2] Polyethylene terephthalate is ubiquitous in modern society, being the 4th most produced polymer and seeing uses from clothing, to plastics, to engineering resins.[3] Unfortunately, since it is currently synthesized from petroleum, it is non-renewable, and the production can have huge environmental impact. Accordingly, there is interest in developing an alternative to PET that is both environmentally friendly, and renewable.



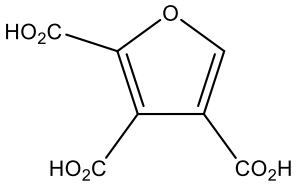
terephthalic acid



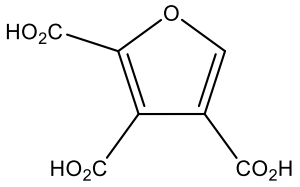
furan-2,5-dicarboxylic acid



furan-2,4-dicarboxylic acid



furan-2,3,4-tricarboxylic acid



furan-2,3,4-tricarboxylic acid

Figure 1. Terephthalic acid and desired furan polycarboxylates.

Recently there has been interest in furan carboxylates as such a replacement. Specifically, polymers from furan 2,5-dicarboxylate have been shown to have similar properties to PET.[4] The properties of the other furan polycarboxylate polymers are less known, partly because syntheses to their precursors are less common. As such, we set out to develop syntheses for various furan dicarboxylates and tricarboxylates.

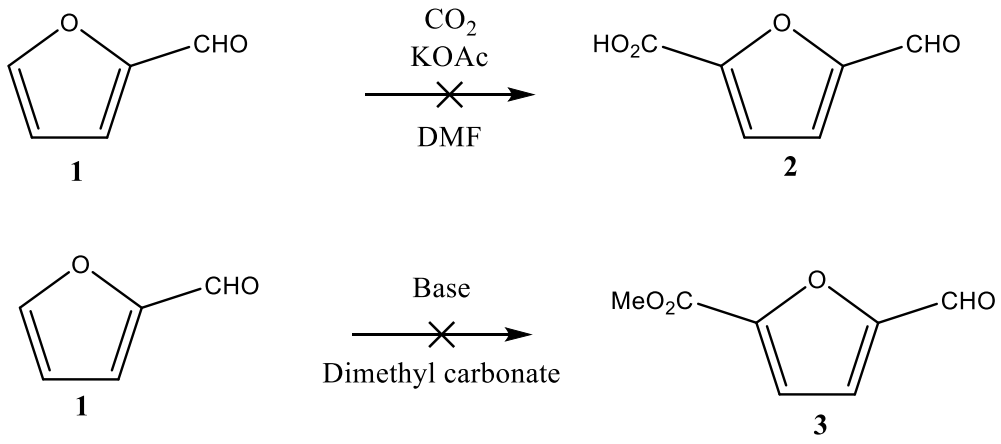
In designing our synthesis, we wanted to keep in mind the goals of replacing terephthalic acid. Specifically, using bio renewable starting materials to achieve our synthesis. Furthermore, we would have to use relatively cheap materials in order to keep any synthesis developed economically competitive with terephthalic acid. Finally, we wanted to make sure the synthesis was as few steps as possible for it to be commercially viable.

We had two primary strategies in mind to achieve our synthesis. Initially, we sought to carboxylate furfural, as it is a relatively inexpensive starting material, and the synthesis route to the product is short. Additionally, furfural is commercially made by dehydrating five-carbon sugars in biomass waste, so it satisfied the requirement of a bio renewable starting material.[5]

The second strategy was to cyclize various compounds from the citric acid cycle. These molecules are an excellent bio renewable resource, as bacterial fermentation of agricultural products can be tuned to produce the desired product from the cycle. As such, should a large enough demand for a particular citric acid cycle product arise, fermentations could be easily developed to cheaply produce the required compound.

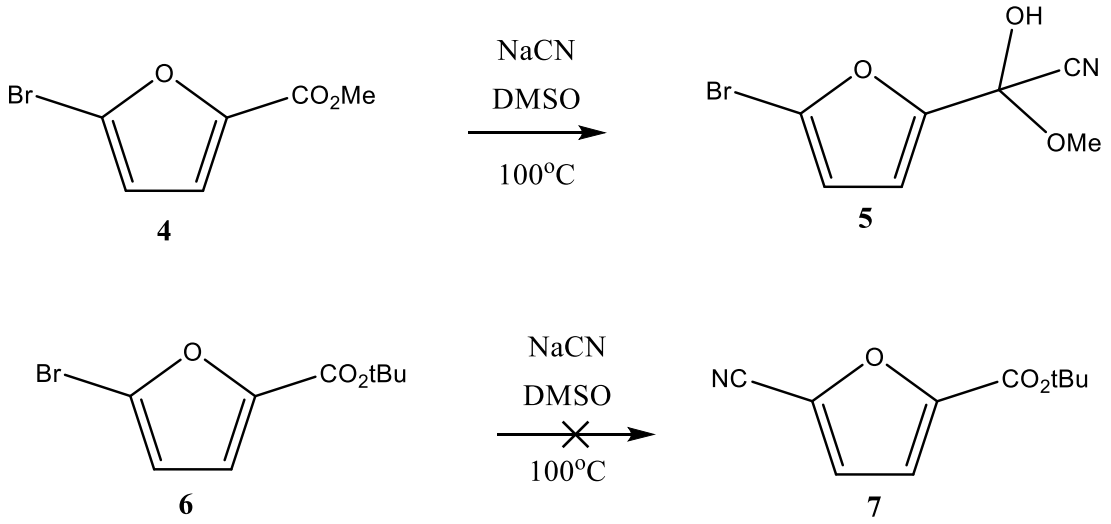
Results and Discussion

Our focus began with the dicarboxylates of furan. We tried furfural **1** and potassium acetate under a carbon dioxide atmosphere with no success.[6] Hypothesizing that we needed a more accessible carbonyl source, we again tried furfural **1** with various bases, and dimethyl carbonate, but still had no success (Scheme 1).



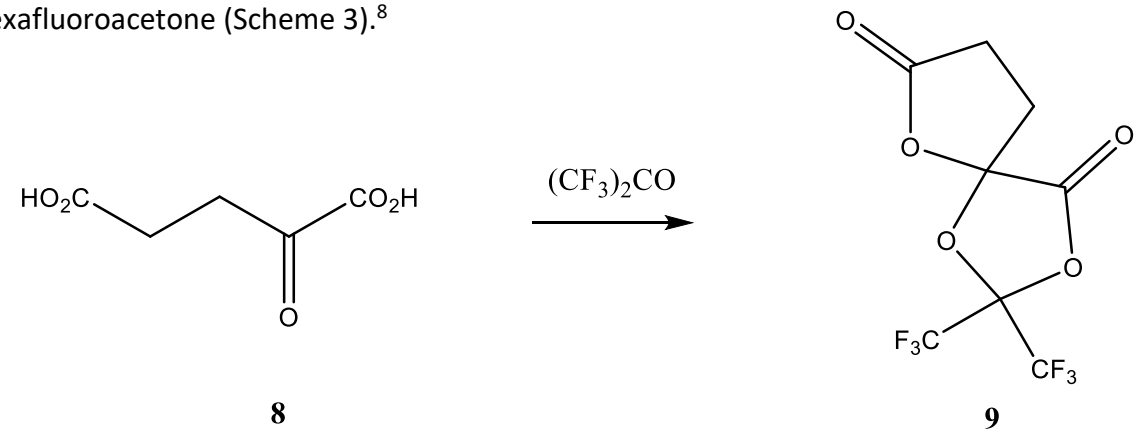
Scheme 1. Initial attempts at furan dicarboxylates.

With this lack of success, we decided to start with a halogen installed on the furan ring in order to help convert to the carbonyl. We choose 5-bromo-2-methyl furoic acid as our electrophile for its availability, and cyanide as our nucleophile due to ease of transformation into the carboxylic acid. After converting to the ester using thionyl chloride in methanol, we reacted the ester **4** with sodium cyanide in DMSO. To our surprise, the cyanide attacked the ester instead of the halogen, giving **5.** We synthesized the t-butyl ester of 5-bromo-2-methyl furoic acid using t-butanol, magnesium sulphate, and sulfuric acid in dichloromethane[7] in an attempt to prevent attack on the ester. However, this compound showed to be unreactive (Scheme 2).



Scheme 2. Further attempts at furan dicarboxylates.

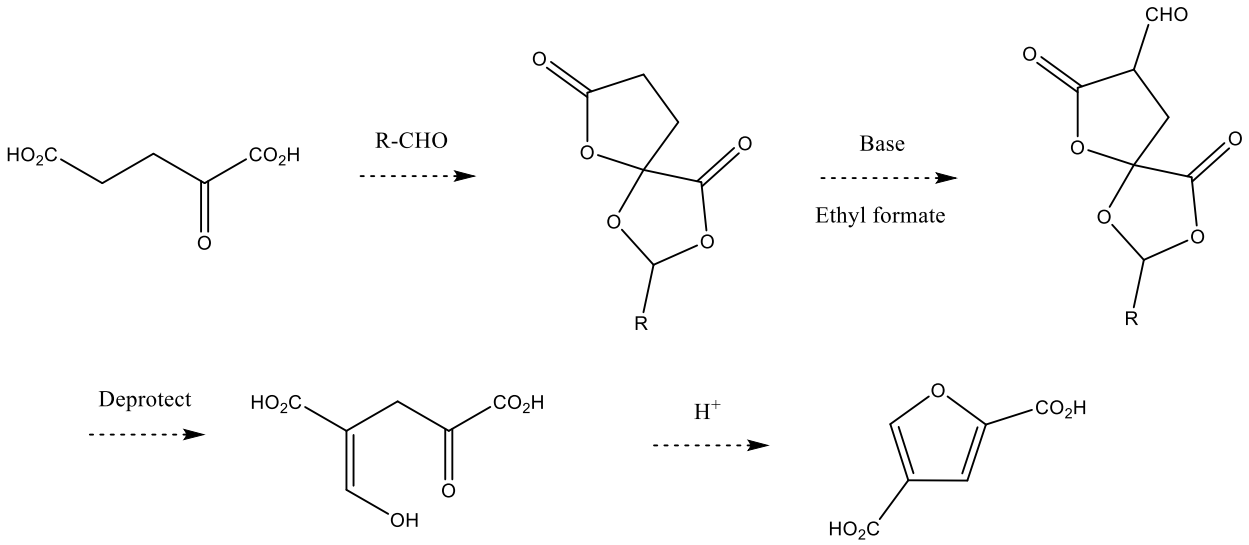
With still no success, we decided to try our second strategy to synthesize the desired furan. Inspired by the work of Spengler, we decided to use alpha-ketoglutarate (aKG) **8** as our starting material. Using the equilibrium between the open chain form and the cyclic form of aKG **8**, Sprengler was able to cyclize aKG by capturing the molecule in its cyclic form using hexafluoroacetone (Scheme 3).[8]



Scheme 3. Previous work done to trap the spirocyclic form of aKG.

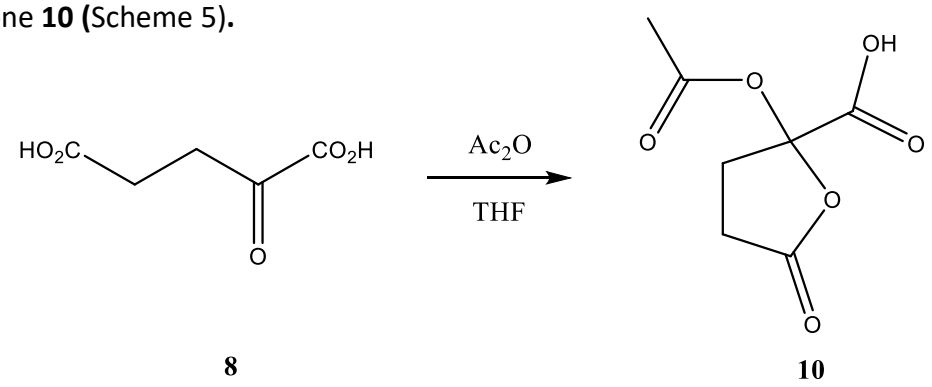
Our goal was to cyclize aKG in a similar matter, formylate the compound, then deprotect the spirocyclic compound so the furan could be synthesized. We knew we had to use a very

electrophilic carbonyl, however due to the expense and toxicity of using hexafluoroacetone, we set out to find a different carbonyl to achieve the desired spirocyclic compound (Scheme 4).



Scheme 4. Our attempts to trap the spirocyclic form of aKG.

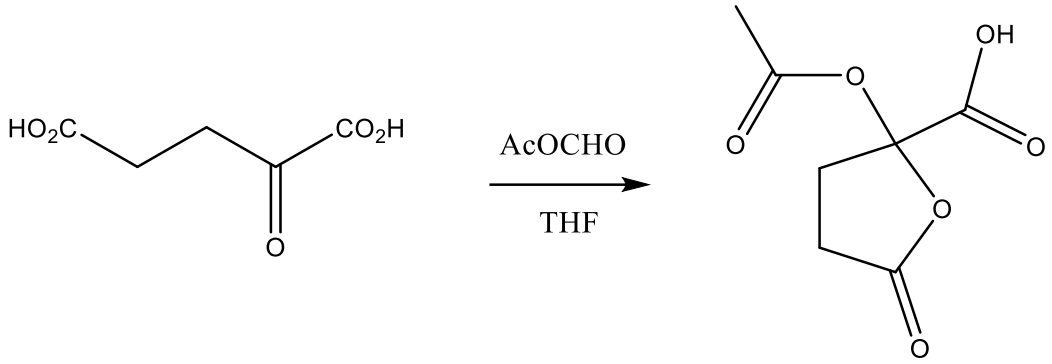
We tried several compounds to achieve the desired spirocyclic compound, including paraldehyde, benzaldehyde, 1,3,5-trioxane, isobutyraldehyde, paraformaldehyde, phosphorous trichloride, phenylboronic acid, and dichlorodimethylsilane, none of which afforded the desired spirocycle. We were, however, able to capture aKG **8** in its cyclic form using acetic anhydride, giving lactone **10 (**Scheme 5**).**



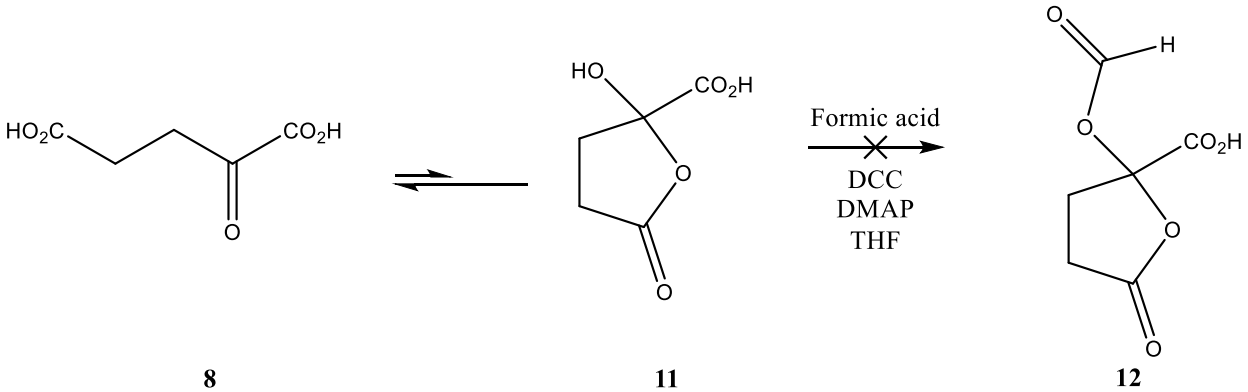
8 **10**

Scheme 5. Trapping the molecule as the lactone.

Unfortunately, due to the two acidic alpha carbons, this route turned out to be unfruitful as we were unable to control the selectivity of the deprotonation. We attempted to instead use acetic formic anhydride to achieve the cyclization, however the reaction yielded the same product as with acetic anhydride (Scheme 6). Additionally, the reaction with formic anhydride yielded starting materials (Scheme 7).



Scheme 6. Alternate trapping mechanism of aKG.

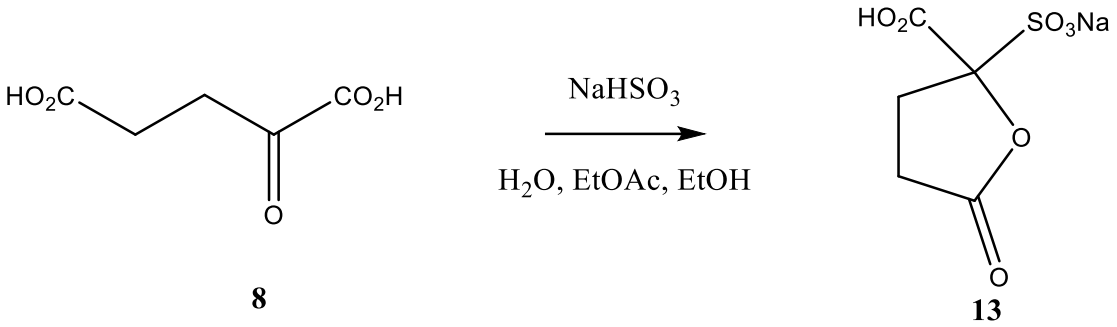


Scheme 7. Attempts to manipulate lactone of aKG.

The fact that we could isolate the gamma lactone form of aKG suggested to us that the cyclic form was present long enough to undergo chemical manipulation and capture. With this information in hand, we tried to esterify the transient alcoholic form of aKG to mimic the

reaction with formic anhydride in order to achieve our desired lactone. We reacted formic acid with DCC and DMAP in THF, however we only recovered starting material.

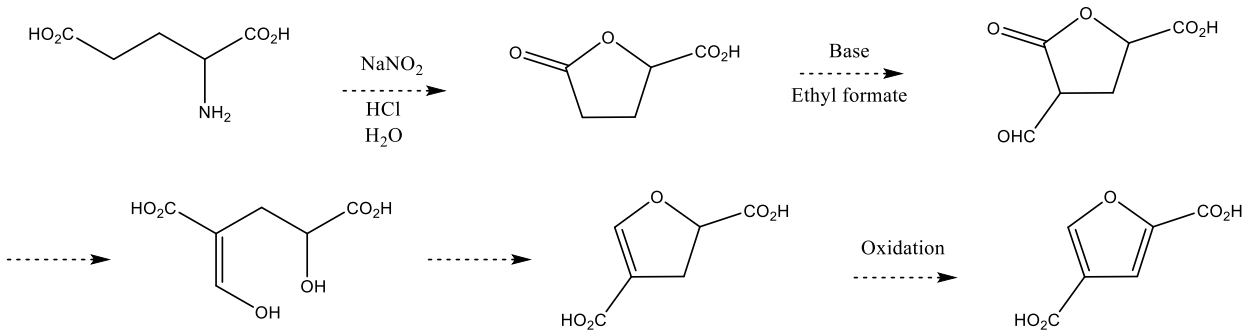
Utilizing a procedure our group has previously been successful with, we were able to cyclize aKG **8** into what appeared to be a productive form. Using sodium bisulfite as a reagent to convert the ketone into the corresponding alcohol, we formed gamma lactone **13** (Scheme 8).[9] Promising as this compound appeared, it was insoluble in all tested solvents, including DMSO, water, ethanol, and methanol. Unfortunately, this rendered our compound impractical toward the formylation step of the synthesis.



Scheme 8. Alternate trapping mechanism of aKG.

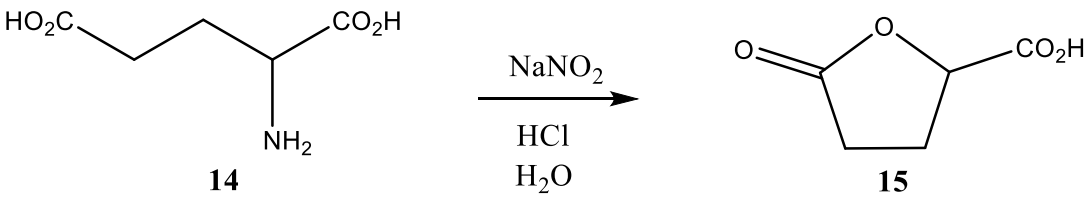
Feeling as we had exhausted our options with aKG, we decided to use glutamic acid **14** as our starting material. We proposed to cyclize glutamic acid into the corresponding gamma-lactone using sodium nitrite. With this lactone in hand, we would selectively formylate alpha to the carbonyl of the lactone. We reasoned the carboxylate would lower the pKa of the 2-position proton enough to achieve selective formylation. After formylating our lactone, we

would open the lactone and cyclize to the dihydrofuran, followed by oxidation to the desired product (Scheme 9).



Scheme 9. Proposed route to furan dicarboxylate.

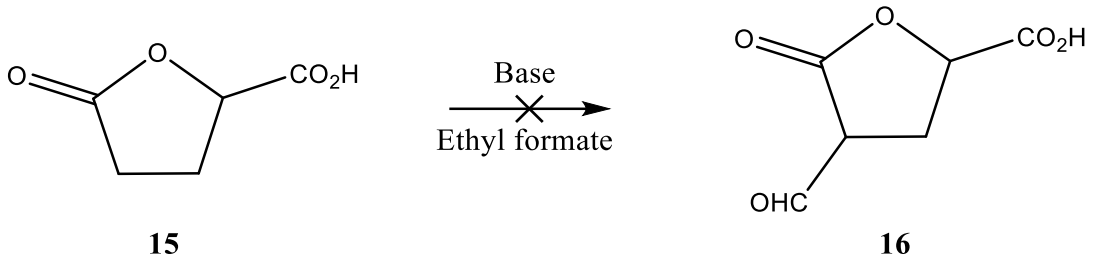
Following the procedure of Montagnat, we were successfully able to convert glutamic acid **14** to gamma lactone **15** in one pot using hydrochloric acid and sodium nitrite in water (Scheme 10).[10]



Scheme 10. Lactone formation from glutamic acid.

With gamma lactone **15** in hand, we attempted selective formylation. We tried a host of solvents and bases with ethyl formate in order to afford the selective formylation, including 2-4 equivalents potassium tert-butyl hydroxide in tetrahydrofuran, 4 equivalents potassium tert-butoxide in 1:3 dimethylformamide: tetrahydrofuran, and 2 equivalents lithium diisopropylamide in tetrahydrofuran. Unfortunately, none of these conditions gave the desired

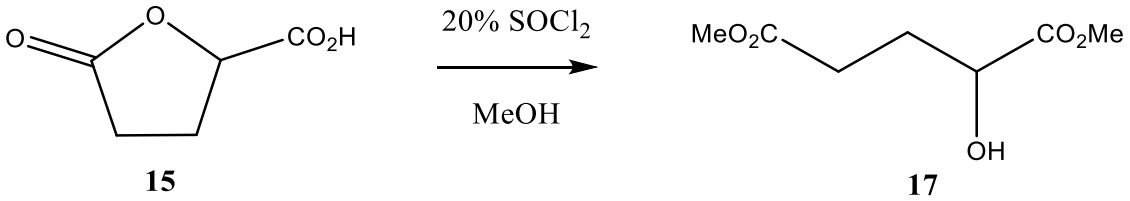
product, yielding only starting material. We speculated that the dianion was too insoluble in the organic solvents as we observed precipitate formation upon addition of the base (Scheme 11).



15 **16**

Scheme 11. Attempts at modification of the lactone.

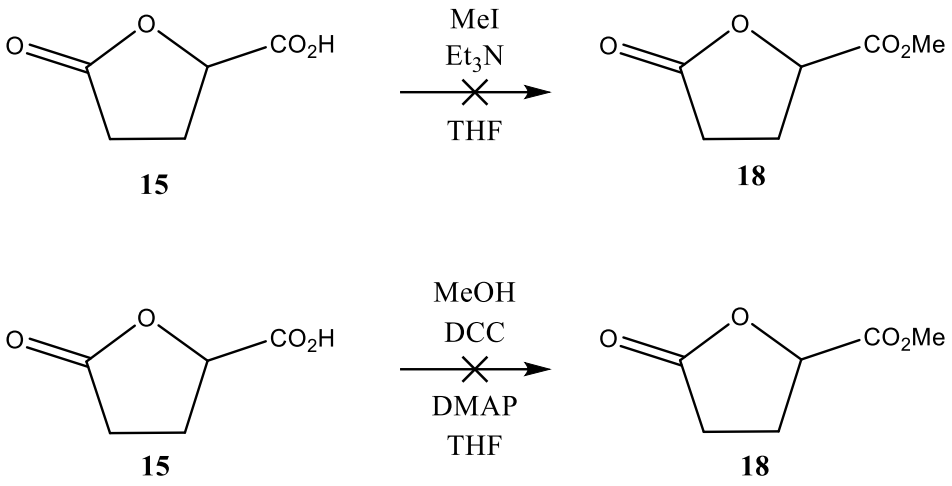
In an effort to increase solubility, we decided to esterify the compound. While this could have reduced regioselectivity, we wanted to test our formylation conditions on the lactone. The reaction of lactone **15** in methanol with various acid sources did in fact esterify the compound, but with the unintended consequence of opening the lactone to the open-chain form **17** (Scheme 12).



15 **17**

Scheme 12. Further attempts at modifying the lactone.

We tried to circumvent this problem by utilizing other esterification methods. Both triethylamine and methyl iodide in THF, and DCC, DMAP, and methanol in THF were unsuccessful in yielding the desired ester (Scheme 13).

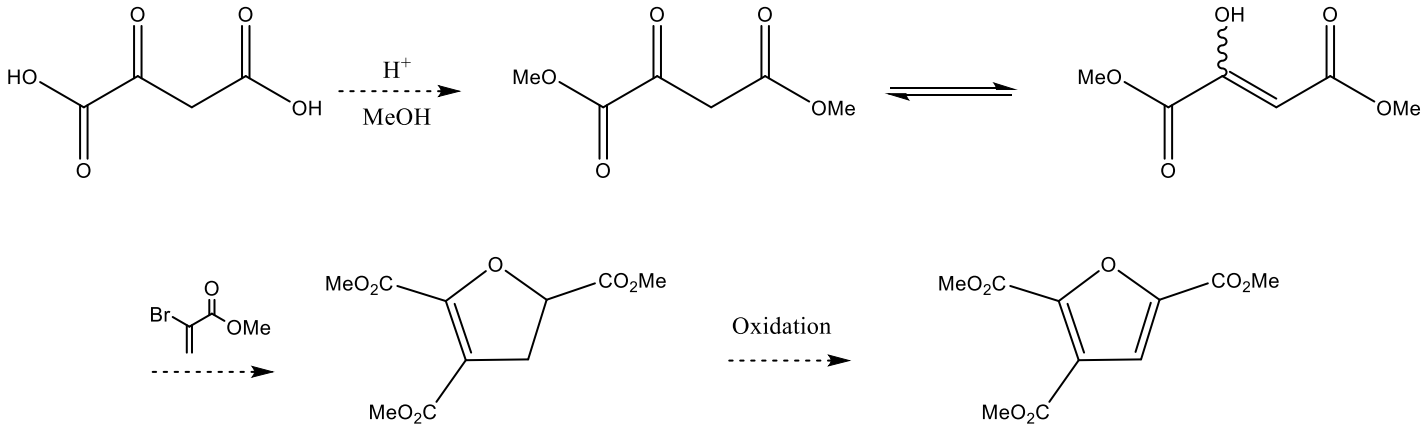


Scheme 13. Attempts to form the lactone ester.

Even though we were unsuccessful in esterifying the lactone, we decided to attempt formylation of the open chain compound. We hypothesized that we would still be able to achieve regioselectivity due to the increased electron density around the hydroxyl group, allowing us to deprotonate and formylate the ester distal to the hydroxyl group. We tried various bases and solvents with ethyl formate, including potassium tert-butoxide in ethanol, lithium diisopropylamide in tetrahydrofuran, and sodium hydride in tetrahydrofuran. Unfortunately, these conditions only yielded starting material.

Having made little progress with both aKG and glutamic acid as a precursor, we switched our starting material to oxaloacetic acid (OAA). Our proposed synthesis used both OAA and methyl alpha-bromoacrylate to create the carbon skeleton for our furans. Using

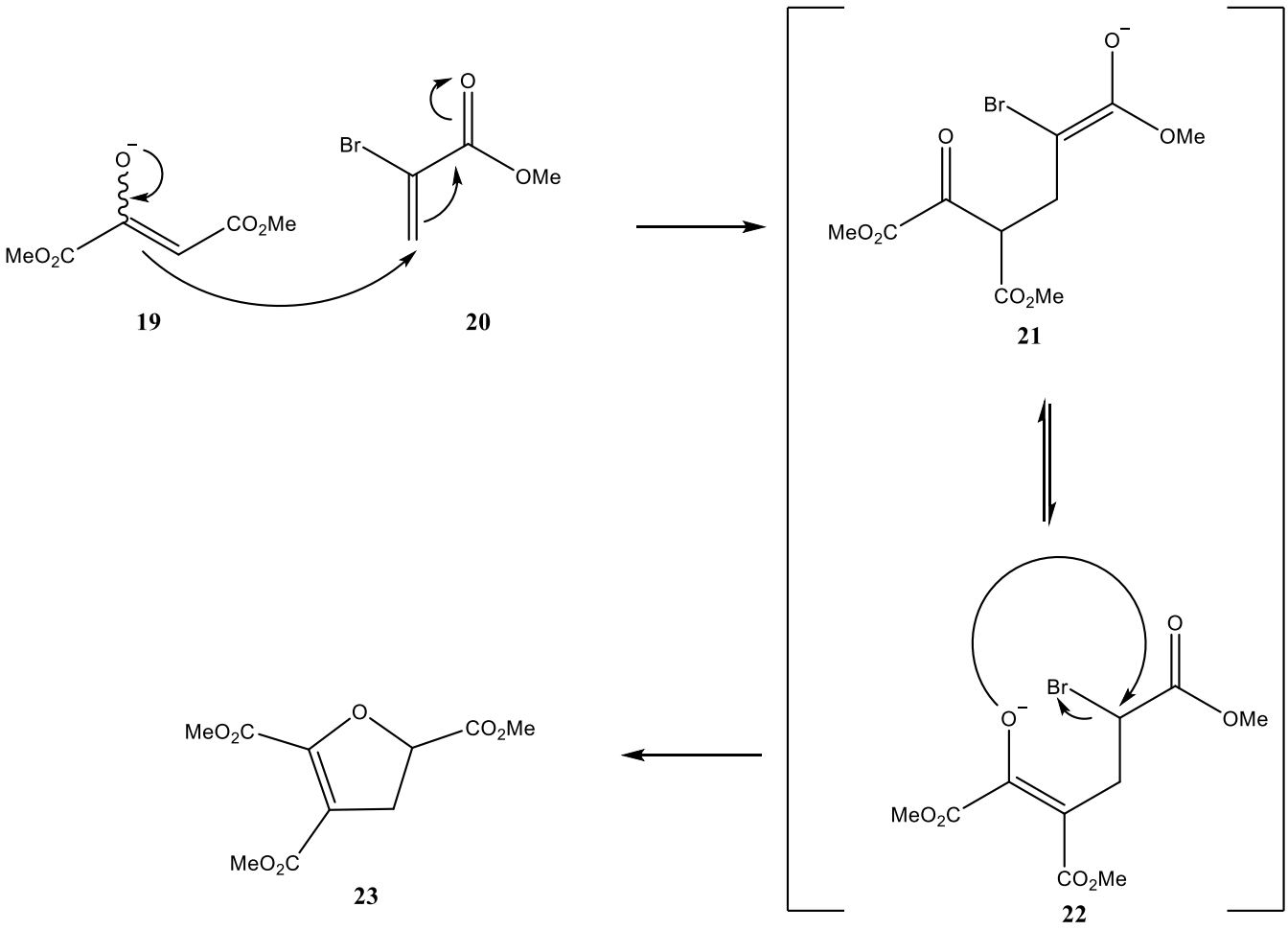
dimethyl oxaloacetate, we would facilitate a Michael addition with methyl alpha-bromoacrylate to form the dihydrofuran, followed by oxidation to form the desired furan (Scheme 14).



Scheme 14. Alternate proposed route to furan polycarboxylate.

Using methanol and thionyl chloride, we were able to esterify OAA in excellent yield. Interestingly, the NMR of the esterified compound showed almost that the compound was almost exclusively in the enol form. This was thought to be due to the stabilizing effect of the oxygen on the carbonyl 6 atoms away.

Separately, we synthesized methyl alpha-bromoacrylate from methyl acrylate, bromine, and triethylamine in chloroform.[11] We then deprotonated compound **19** using 1,8-diazabicylco[5.4.0]undec-7-ene (DBU), and reacted with methyl alpha-bromoacrylate **20**.[12] Two substitution patterns for the resulting dihydrofuran were possible, depending on whether C- or O-alkylation happened first. We correctly predicted the 2,3,5 substitution pattern over the 2,3,4 pattern due to the softer nature of the enolate anion when compared to the alkoxide anion (Scheme 15).

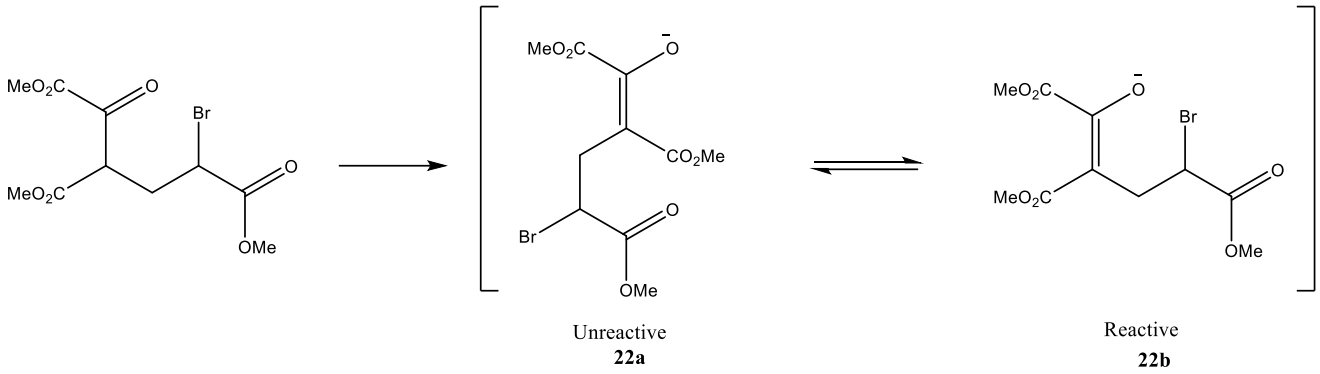


Scheme 15. Proposed mechanism to dihydrofuran tricarboxylate.

Upon further study, we discovered that the choice of base was imperative in the reaction, as substituting sodium hydride for DBU yielded no reaction. We predict that the chosen base is crucial in the proton transfer, thereby necessitating an equilibrating base like DBU.

Unfortunately, we were unable to purify dihydrofuran **23** by flash chromatography. Upon inspection of the proposed mechanism, we can see that the enolate has two possible

geometries **22a** and **22b.** Only **22b** is the correct orientation for the second substitution reaction to occur. We hypothesized that the impurities present in the compound **23** were due to side reactions with the unreactive geometry (Scheme 16).

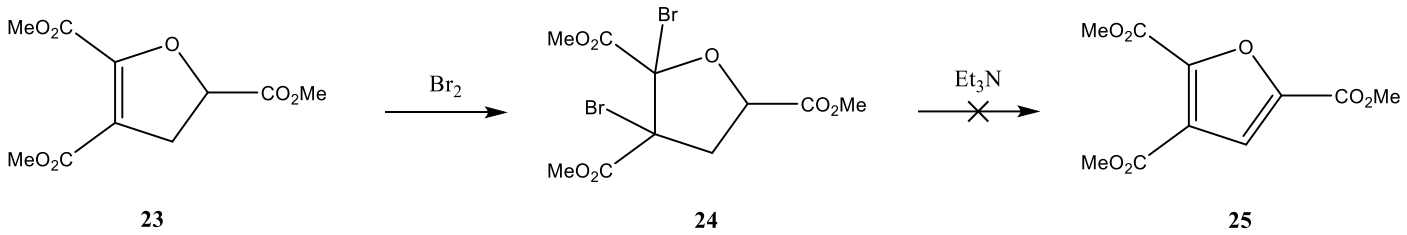


Scheme 16. Equilibrium between reactive and unreactive geometry.

In order to disfavor side reactions, we needed to either increase the favorability of the reactive geometry **22b** or allow for more equilibration to the reactive geometry **22b**. Due to the intramolecular nature of the second reaction, we speculated that once in the correct geometry, the ring would close quickly, thereby driving the equilibrium to the correct orientation. To our delight, by heating up the reaction from 0^{o}C to 40^{o}C, we were able to increase the rate of the equilibration and got a crude mixture which was able to purify by flash chromatography.

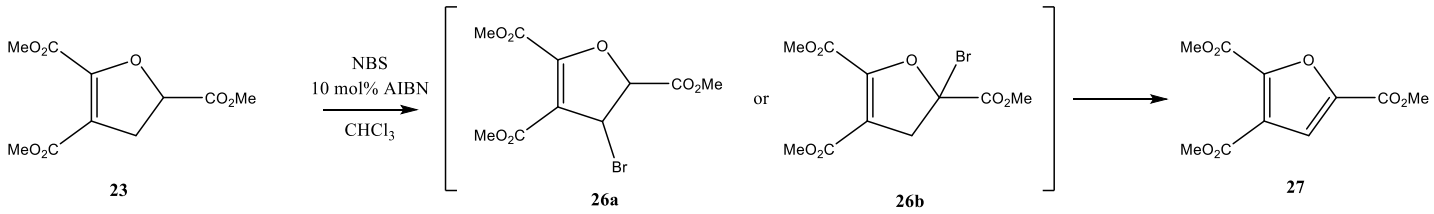
With a route to purified dihydrofuran **23**, we began to test oxidation conditions. Our initial test with manganese (IV) oxide caused the compound to decompose. We then tried

brominating the dihydrofuran, with subsequent elimination. While we were successful with the bromination step to get dihalide **24**, the subsequent elimination was unsuccessful (Scheme 17).



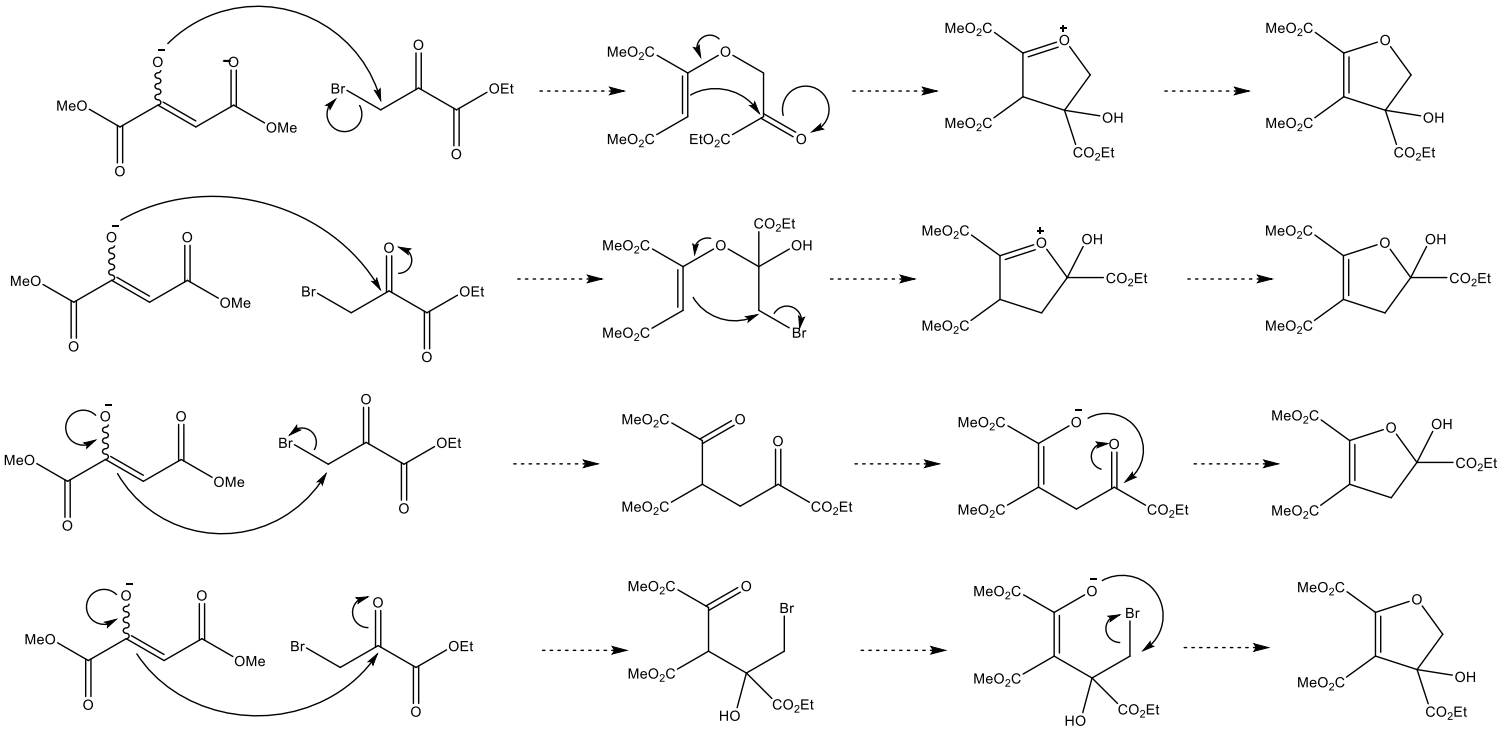
Scheme 17. Attempts at oxidation of dihydrofuran tricarboxylate.

Considering the nature of the dihydrofuran, we decided that it was a good candidate to undergo radical halogenation, followed by elimination to the desired furan. To our delight, we found that the compound not only underwent radical halogenation to form compounds **26a-b**, but also spontaneously eliminated to desired furan **27** in one pot (Scheme 18). Due to the multitude of stabilizing factors for the radical, as well as the spontaneous elimination of the halide, we were unable to determine on the regioselectivity of halogenation, however for our purposes this did not matter.



Scheme 18. Alternate attempt at oxidation of dihydrofuran tricarboxylate.

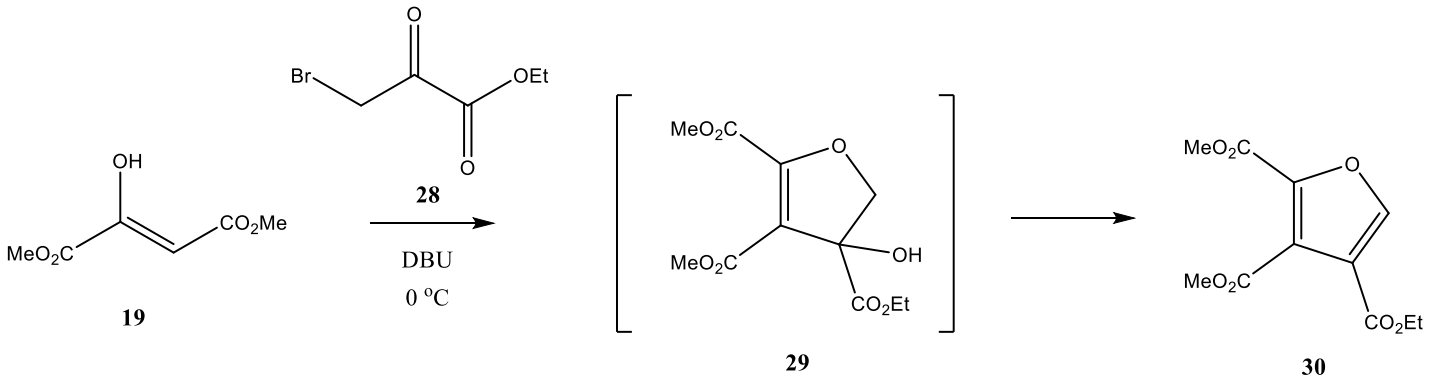
With the synthetic route for trimethyl furan-2,3,5-tricaboxylate **27** in hand, we set out to develop a route to furan-2,3,4-tricarboxylate **30**. Instead of using an acrylate derivative, we decided to change our electrophile to ethyl bromopyruvate **28**. Ethyl bromopyruvate is easily synthesized from bromine and ethyl pyruvate, another fermentation product. The challenge with this system is that our OAA ester has two possible nucleophilic sites, and ethyl bromopyruvate has two possible electrophilic sites, yielding 4 possible reactions pathways and 2 possible products. Unlike with the methyl alpha-bromoacrylate, there was not a clear indication as to which pathway the molecule would undergo (Scheme 19).



Scheme 19. Possible mechanisms for formation of dihydrofuran tricarboxylate.

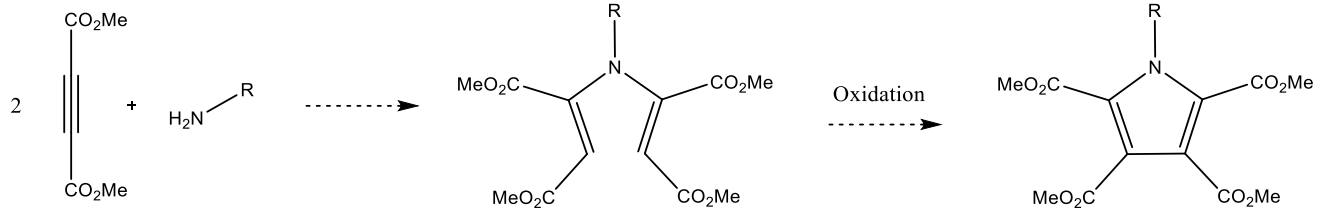
We hypothesized that the primary bromide would be more electrophilic than the ketone, and as such wanted to promote the alkoxide attack over the enolate. We reacted our

OAA ester **19** with potassium hydride in DMF at 0°C and ethyl bromopyruvate **28**, followed by reflux in toluene, but saw no reaction. Based on the requirement for an equilibrating base in the previous synthesis, we decided to again try DBU as our base. To our delight, not only did the two compounds react to form dihydrofuran **29**, but also underwent the requisite elimination to yield furan-2,3,4-tricarboxylate **30** (Scheme 20).



Scheme 20. Route to alternate isomer of furan tricarboxylae.

With routes to both isomers of the furan-tricarboxylate, we wanted to achieve synthesize a heteroaromatic tetracarboxylate. In our initial attempts, we tried to dimerize dimethyl aspartate into the corresponding pyrrole. Using manganese (III) acetate, copper (II) acetate, and sodium acetate Zhou was able to achieve this.[13] Unfortunately, our attempts to reproduce the synthesis were not successful. We decided to instead use dimethyl ethylene dicarboxylate, an alkyl amine, and an oxidizing agent to synthesize our pyrrole.



Scheme 21. Proposed route to pyrrole tetracarboxylate.

Our initial attempt used ceric ammonium nitrate as the oxidizing agent, and benzyl amine as the alkyl amine.[14] Unfortunately, we were unable to recover any of the desired product. Upon further analysis of literature we noticed that Liu had been successful using (diacetoxyiodo)benzene and silver tetrafluoroborate as the oxidizing agent in dioxane at 100^{o}C.[15] We were indeed able to replicate the results, and were thus able to synthesize a heteroaromatic tetracarboxylate, in addition to the furan tricarboxylates for polymer studies (Scheme 21).

In summary, we developed a bio renewable, cheap, and short route to both isomers of furan triester. Additionally, we were able to replicate the synthesis of a pyrrole tetraester. We did so in order to further study these molecules for their polymer properties as a potential future replacement for terephthalic acid derived polymers.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and use without purifications. All experiments were performed under ambient atmosphere unless otherwise noted. Nuclear magnetic resonance experiments were performed with a Varian 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.26 ppm for ^{1}H NMR) unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet. Standard grade silica gel (60 A, 32-63 μm) was used for flash chromatography.

2-(5-bromofuran-2-yl)-2-hydroxy-2-methoxyacetonitrile (5)

0.15g of sodium cyanide was added to a 25 ml round bottom flask and placed under and argon atmosphere. 0.42g of 5-bromo-2-methyl furoate was added to a separate flask and placed under an argon atmosphere followed by the addition of 7 mL of DMSO. The flask containing the furoate was transferred via cannula to the flask containing the sodium cyanide. The flask was heated to 100^{o}C and stirred for 24 hours. The reaction contents were quenched with 10 mL of saturated ammonium chloride and extracted with 20 mL ethyl acetate. The organic layer was washed with 3x20 mL water. The aqueous layer was acidified with sulfuric acid and extracted with 3x40mL ethyl acetate. The organic layers were combined, dried over sodium sulfate, and solvent was removed in vacuo. 0.46g of 2-(5-bromofuran-2-yl)-2-hydroxy-2-methoxyacetonitrile was collected in 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (t, 1H, J = 3.5 Hz), 6.78 (t, 1H, J = 2.5 Hz), 2.52 (s, 3H).

2-acetoxy-5-oxotetrahydrofuran-2-carboxylic acid (10)

0.44g of alpha-ketoglutaric acid, 2 mL of acetic anhydride, and 2 mL of THF were added to a 25 mL round bottom flask, and the solution was stirred for 2 days. 0.45 mL of triethylamine was added to the flask, and the reaction contents were poured into 10 mL of water. The aqueous phase was extracted with 3x10 mL dichloromethane. Then the aqueous phase was acidified with sulfuric acid and extracted with 3x10 mL ethyl acetate. The organic layers were combined, dried over sodium sulfate, and solvent was removed in vacuo. The residue was purified by column chromatography 1:9 methanol: dichloromethane, giving 0.22g of 2-acetoxy-

5-oxotetrahydrofuran-2-carboxylic acid in 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64-3.59 (m, 2H) 2.09 (s, 3H), 1.60-1.53(m, 2H).

Sodium 2-carboxy-5-oxotetrahydrofuran-2-sulfonate (13)

0.76g of alpha-ketoglutaric acid and 0.59g of sodium bisulfite were added to a 25 mL round bottom flask. 3.5 mL of ethyl acetate, 2.3 mL of ethanol, and 0.8 mL of water were added, and the flask was stirred at 40^{o}C. After 16 hours, the flask was cooled to 0^{o}C, and a white solid precipitated out. The solid was collected through filtration and washed with ethanol, giving 0.75g of sodium 2-carboxy-5-oxotetrahydrofuran-2-sulfonate in 65% yield.

5-oxotetrahydrofuran-2-carboxylic acid (15)

10.13g of glutamic acid was added to a 500 mL round bottom flask. 70 mL of water was added, followed by 40 mL of 2M hydrochloric acid. The solution was cooled to 0^{o}C. 5.59g of sodium nitrite was dissolved in 40 mL of water and added to the glutamic acid solution over 15 minutes. The reaction mixture was stirred for 16 hours and allowed to warm to room temperature. The reaction mixture was extracted 3x100 mL of ethyl acetate. The organic layer was dried over sodium sulfate, and solvent was removed in vacuo, giving 3.96g 5-oxotetrahydrofuran-2-carboxylic acid in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21-4.88 (m, 1H), 2.01-1.46 (m, 4H).

Dimethyl-2-hydroxyfumarate (19)

0.27g oxaloacetic acid was placed in 5 mL methanol in a 25 mL round bottom flask. 0.02 mL thionyl chloride was added, and the reaction was stirred for 3 hours. 5 mL brine was poured into the solution and extracted 3x10 mL ethyl acetate. Organic layer was dried over sodium sulfate and solvent was removed in vacuo. 0.25g dimethyl (E)-2-hydroxypent-2-enedioate was obtained in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.57 (s, 1H), 6.02 (s, 1H), 3.87 (s, 3H), 3.80 (s, 3H).

Methyl 2-bromoacrylate (20)

0.9 mL of methyl acrylate was placed in 5 mL of chloroform. 0.51 mL elemental bromine was added over 20 mins. The solution was stirred overnight. Solvent was removed in vacuo, then 7.5 mL diethyl ether and 7.5 mL pentanes were added. 1.39 mL triethyl amine was added dropwise and the solution was stirred for 3 hours. A precipitate formed and was filtered off. The organic phase was washed with 10 mL water, dried over sodium sulfate, and solvent was removed in vacuo. 0.62g of methyl 2-bromoacrylate was obtained in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.24 (s, 1H), 3.81 (s, 3H).

Trimethyl 4,5-dihydrofuran-2,3,5-tricarboxylate (23)

0.48g dimethyl-2-hydroxyfumarate was placed in 10 mL tetrahydrofuran. The flask was placed under an argon atmosphere and cooled to 0^{o}C. 1.35 mL DBU was added, and the

solution was stirred for 20 minutes. 0.4 mL methyl 2-bromoacrylate was added, and the solution was stirred 1 hour. The solution was quenched with 10 mL concentrated ammonium chloride and extracted 3x10 mL ethyl acetate. Organic layer was dried over sodium sulfate, and solvent was removed in vacuo. Residue was purified by column chromatography 1:1 ethyl acetate: hexanes, giving 0.20g trimethyl 4,5-dihydrofuran-2,3,5-tricarboxylate in 28% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (dd, 1H, J = 11.8, 7.4 Hz), 3.83 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.25-3.07 (m, 2H).

Trimethyl furan-2,3,5-tricarboxylate (25)

0.37g of trimethyl 4,5-dihydrofruan-2,3,5-tricarboxylate was placed in 5 mL chloroform. 0.27g N-bromosuccinimide and 0.03g AIBN were added. Solution was refluxed for 3 hours. Solvent was removed in vacuo and purified by column chromatography, 1:2 ethyl acetate: hexanes, giving 0.16g of trimethyl furan-2,3,5 tricarboxylate in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H).

4-ethyl 2,3-dimethyl furan-2,3,4-tricarboxylate (30)

0.40g of dimethyl-2-hydroxyfumarate was placed in 15 mL THF. The flask was placed under an argon atmosphere and cooled to 0^{o}C. 0.37 mL DBU was added and the solution was stirred for 20 minutes. 0.32 mL ethyl bromopyruvate was added, and the solution was stirred for 3 hours. The solution was poured into 30 mL 1M sulfuric acid and extracted 3x30 mL ethyl

acetate. The solvent was removed in vacuo and refluxed in 25 mL toluene for 16 hours. Solvent was removed in vacuo and the residue was purified by column chromatography, giving 0.26g 4-ethyl 2,3-dimethyl furan-2,3,4-tricarboxylate in 41% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 4.19 (q, 2H, J = 7.3 Hz), 3.85 (s, 3H), 3.80 (s, 3H), 1.22 (t, 3H, J = 7.2 Hz).

Tetramethyl 1-benzyl-1H-pyrrole-2,3,4,5-tetracarboxylate

0.70g of dimethyl acetylenedicarboxylate was placed in a 50 mL flame dried round bottom flask. 10 mL dioxane was added, followed by 0.28 mL benzylamine, 0.02g silver tetrafluoroborate, and 0.97g of (diacetoxyiodo)benzene. Solution was refluxed for 3 hours, then poured into 15 mL water and extracted 3x30 mL diethyl ether. Organic layer was washed with 30 mL brine, dried over sodium sulfate, and solvent was removed in vacuo, giving 0.15g of tetramethyl 1-benzyl-1H-pyrrole-2,3,4,5-tetracarboxylate in 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.31 (m, 5H), 7.16 (s, 2H), 3.71 (s, 6H), 3.60 (s, 6H).

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GENERAL CONCLUSION

In this dissertation, we explored direct routes to biologically active and industrially relevant compounds.

Chapter 1 describes how to tether triphenylphosphine to an antioxidant molecule using radical hydrophosphonation, in order to increase the free radical scavenging capability of the antioxidant.

Chapter 2 shows several routes to heteroaromatic polycarboxylates, using fermentation products as the starting material in order to supplant the need for petroleum product in plastic production.

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