2011

Chemistry from Nature: From Natural Products to Biorenewables

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Chemistry from nature: from natural products to biorenewables

by

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A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

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Iowa State University

Ames, Iowa

2011

GENERAL INTRODUCTION

There is no chemistry without nature. Every living creature, from the smallest bacteria to the blue whale, is all the result of billions upon billions of years of chemistry. One of the main challenges in organic chemistry, then, is achieving in the laboratory what nature is able to do every day and building upon the foundation that which the natural world has given us.

With this in mind, this thesis is divided into two fronts: the chemical synthesis of naturally occurring compounds and the preparation of chemicals from biobased sources. The first part will focus on the total synthesis of natural products, in particular the compound salvinorin A and a new class of antimicrobials. In each case, the total synthesis of the material will be considered, as well as the preparation of analogues to that material. The second part will address the issue of renewable chemicals. The current preparation of chemicals is largely based on petroleum sources. This section will focus on the large-scale preparation of chemical intermediates, not from petrochemical feedstocks, but from biobased sources.

CHAPTER 1. SYNTHESIS OF ANALOGUES TO NATURAL PRODUCT SALVINORIN A

Introduction

Salvinorin A is a potent kappa opioid receptor agonist that originates from the Mexican plant *Salvia Divinorum*, a member of the Sage family. It was previously used in divination ceremonies by the Mazatecs, and has become more commonly used recreationally in the past decade. It is the most potent naturally occuring hallucinogen, with an activity in doses as low as 200 μg.[1] Its activity is comparable to morphine, and thus has potential for use as a therapeutic agent in medicine.

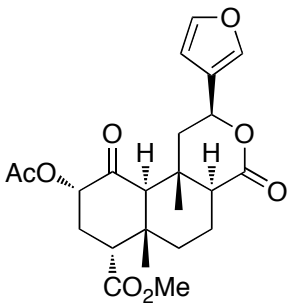

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Figure 1. The structure of salvinorin A

The structure consists of a tricyclic core with seven stereogenic centers, four of which are alpha to carbonyl moieties and are therefore epimerizable by basic conditions. A fifth chiral center can be epimerized by hydrolysis and reformation of the lactone via a known procedure.[2] Interestingly, unlike morphine and similar compounds, salvinorin A lacks an amine group (and thus is not an alkaloid.)

The structure/function relationship of the various functional groups in the compound has been extensively studied,[3] the results of which are summarized in Figure 2. In general, reduction is tolerated, and in some cases simple modification is tolerated as well. Certain modifications actually gave increased activity; for example, changing the C2 acetyl ester group to a methoxymethyl protected ether lead to a more active derivative. Interestingly, the methyl groups do not seem to be critical for the biological activity and are presumably an artifact of the biosynthesis from terpene subunits.

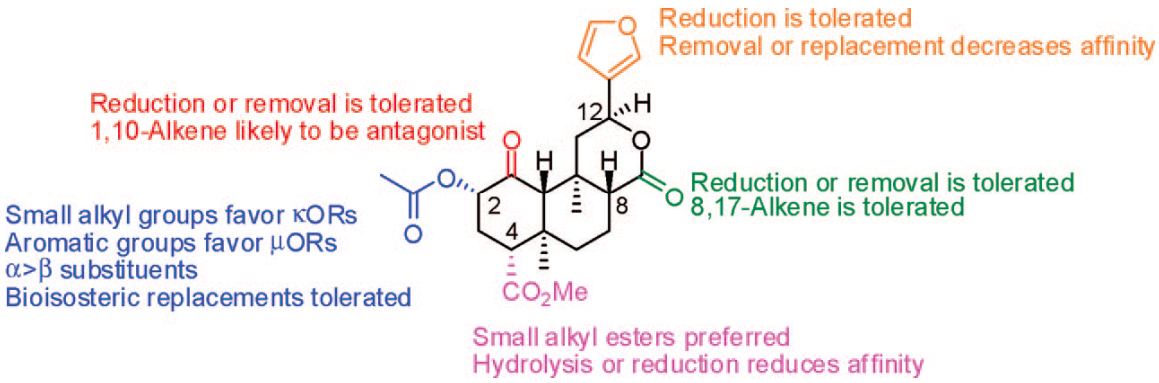


Figure 2. Structure-activity relationships within salvinorin A (taken from ref. 3)

The total synthesis of the compound has been studied for many years by various groups,[4] but was first achieved in 2007 by Evans.[5] This elegant synthesis utilizes a *bis*-Michael Addition pathway as the key step (Figure 3) to prepare the title compound **1** in 23 steps with an overall yield of 1.8% as a single enantiomer. A later synthesis by

Hagiwara and coworkers produced 12-epi-salvinorin A over a 20-step series with a 2.6% overall yield from known starting materials.[6]

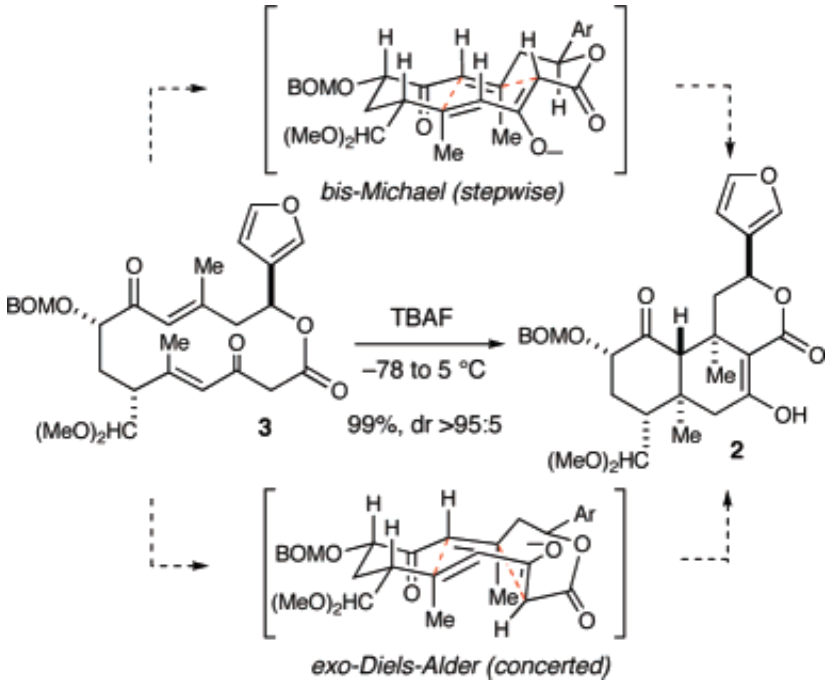


Figure 3. Key step in the Evans synthesis of salvinorin A (taken from ref. 5)

The Kraus lab had attempted to achieve the total synthesis as well, but were unsuccessful. The retrosynthetic analysis is shown in Figure 4. The key step in this sequence was a Diels-Alder cyclization utilizing enone **4** as the dienophile. If the Diels-Alder pathway was unsuccessful, a Michael Addition pathway would also be considered, again using compound **4** as a Michael acceptor. The advantage of using **4** as the starting material is that the cyclic lactone fixes the relative stereochemistry of the C2 and C4 functional groups and and can be opened by simple hydrolysis.

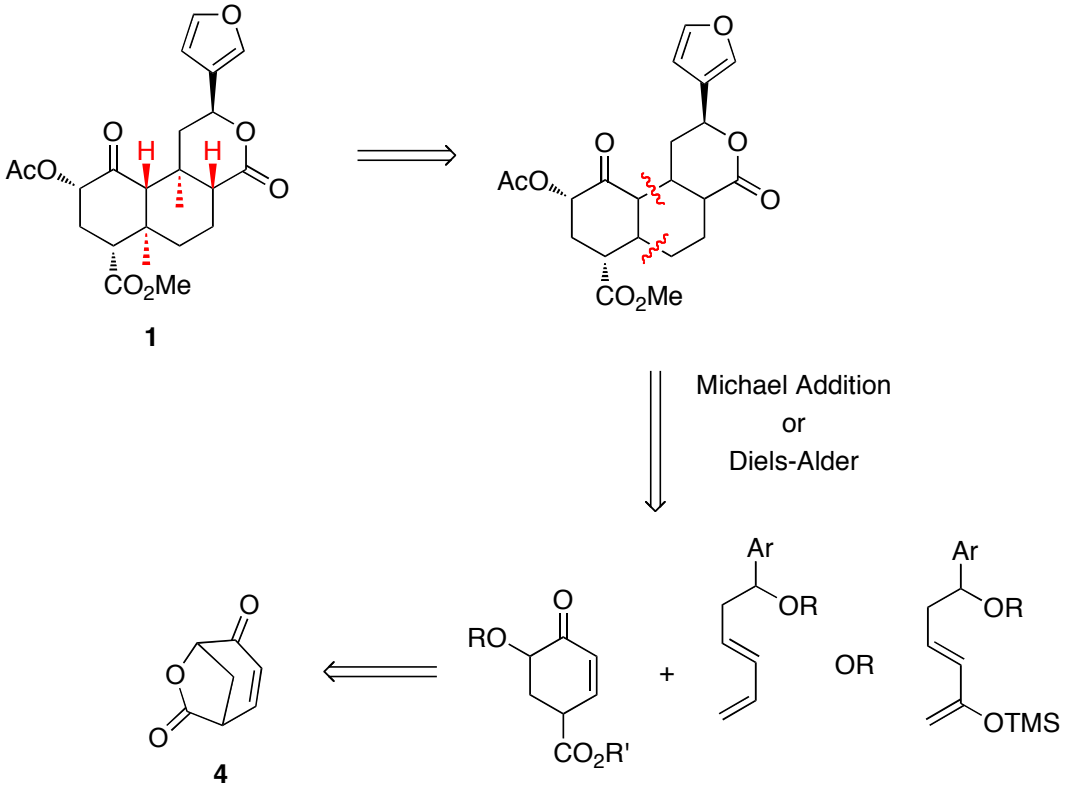
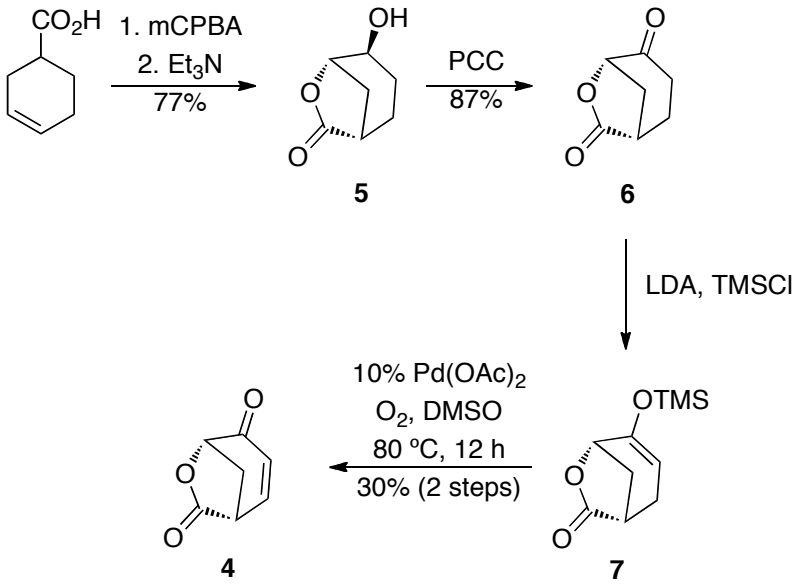


Figure 4. Retrosynthetic analysis of salvinorin A

The preparation of **4** was accomplished based on a procedure by Corey [7] starting from commerially available 3-cyclohexene-1-carboxylic acid (Scheme 1). Epoxidation of the starting alkene with *meta*-chloroperoxybenzoic acid (*m*CPBA), followed by treatment with base lead to formation of lactone **5** in good yield. Oxidiation of the resulting alcohol to the ketone using pyridinium chlorochromate (PCC) lead to ketone **6**.

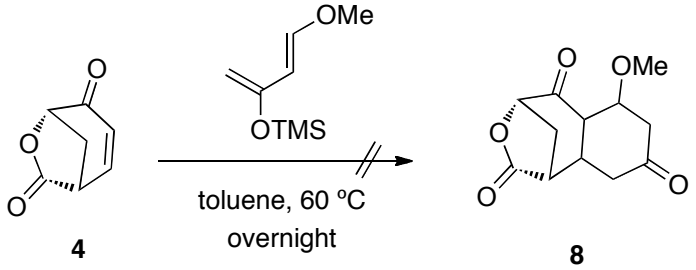
Transformation of **6** to the alpha-beta unsaturated ketone proved to be more difficult than originally expected. The typical selenoxide elimination procedure (i.e. selenation alpha to the ketone using base and diphenyl diselenide, oxidation of the

selenide to the selenoxide, and spontaneous elimination of the selenoxide to form the enone via a retro hetero *ene*-reaction) was ineffective in this case.[8] The only method that was moderately successful to produce the compound was a procedure by Larock and Kraus[9] involving forming the enol silyl ether of the ketone using lithium diisopropyl amide (LDA) and trimethylsilyl chloride (TMSCl). Treatment of enol silane **7** with palladium acetate in DMSO using an atmosphere of oxygen lead to formation of desired compound **4** in 30% maximum yield over the two-step sequence.



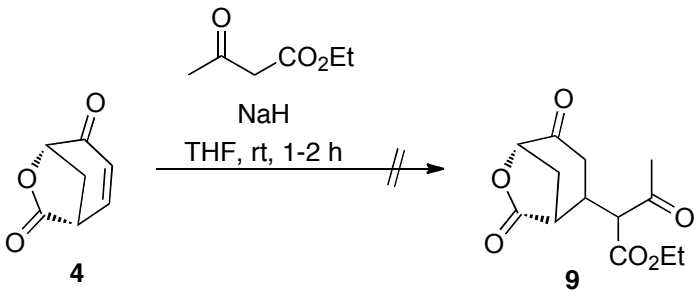
Scheme 1

Compound **4** underwent various Diels-Alder cyclization conditions, including the use of Lewis acids to help catalyze the reaction,[10] but with no success. The use of Danishefsky's diene,[11] *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene a very reactive diene molecule, also failed (Scheme 2.)



Scheme 2

With the lack of success of the Diels-Alder pathway, a Michael Addition strategy was employed. A 'soft' nucleophile such as the anion of ethyl acetoacetate was utilized (Scheme 3) to produce the desired compound **9**, unfortunately without success. Other Michael addition substrates were attempted, such as allyl cuprate, but were either unsuccessful or plagued with low yields. The rationale for this unusual result was the strain of the lactone ring prevented proper attack by the nucleophile.



Scheme 3

The failure to functionalize **4**, coupled with the fact that several syntheses of salvinorin A were published, suggested that the focus of the project needed to change. Instead of the total synthesis of the natural product, the focus would be on producing analogues to salvinorin A.

The most logical direction to move was to synthesize compounds with structures analogous to salvinorin A, with the hope that they exhibit a similar biological activity as the true natural product. Of course, the new targets would have to have a similar structural framework as salvinorin A, but with decreased molecular complexity. The advantage of this new strategy is that even if the new target compounds show decreased biological activity than the actual natural product, the overall synthesis would be shortened, thus allowing easier access to the target compound. Compare this to a total synthesis, which, although worthwhile chemically, may take too many steps to be practical. Likewise, because salvinorin is such a highly active molecule, a compound with even a fraction of activity would still be a significant find.

This strategy is similar to that employed on morphine (that is, decreasing the molecular complexity while retaining morphine-like activity) which lead to the formation of the so-called Morphine Rules.[12] These state that a molecule will have morphine-like activity if it meets the following requirements:

1. A tertiary amine, typically attached to a non-bulky group such as methyl
2. An aromatic ring or steric equivalent
3. A quaternary center directly attached to the aromatic ring
4. A two-carbon linker connecting the amine and the quarternary center

If the compound meets these minimum requirements, it will exhibit some morphine-like activity, regardless of the rigidity of the structure. Morphine and selected analogues are shown in Figure 5. In each case, the overall molecular complexity is decreased, although some are simpler than others (methadone versus pentazocine). Along the same lines, the activity of analoguous compounds is decreased. Therefore this strategy could be seen as a compromise between biological activity for ease of synthesis.

The rationale for why these compounds exhibit similar activity as morphine is that the necessary functional groups are allowed to freely rotate to the desired conformation for the required mu opioid receptors that are activated by morphine.

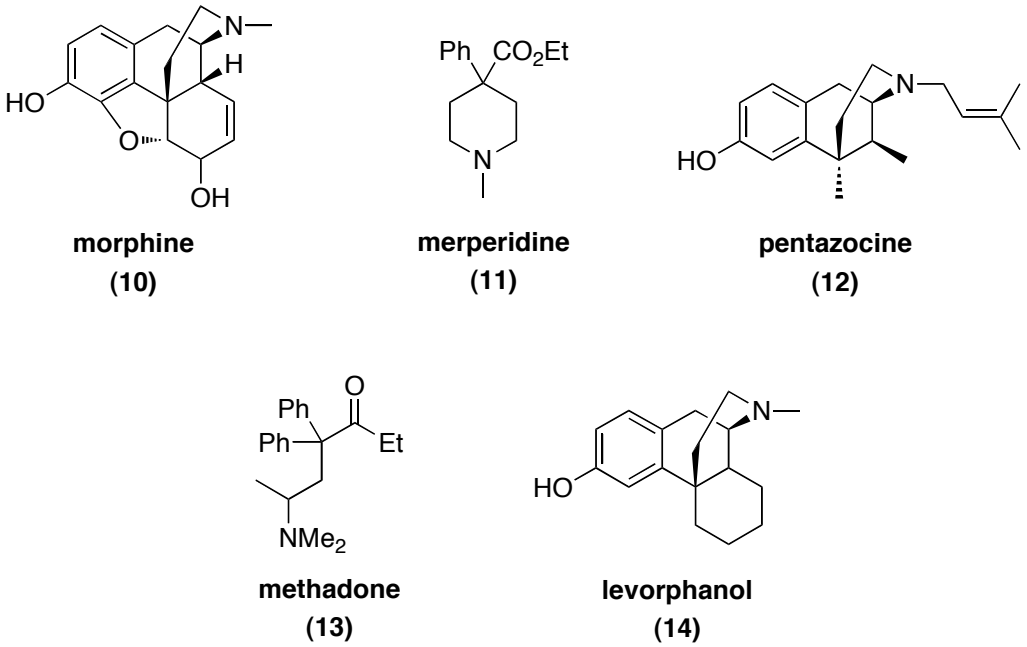


Figure 5. Morphine Analogues

With this in mind, a similar strategy could be employed for salvinorin A. That is, eliminating the rigidity of the compound, while still retaining the required functionality. This is shown in Figure 6. The tricyclic core structure could be simplified to a simple monocyclic compound. By extension, this would also eliminate four of the seven stereogenic centers in the molecule, with the remaining three all in easily epimerizible positions. All of the necessary functional groups of salvinorin A are present, but without the rigidity of the core structure. The hope is that the groups will orient themselves in the same conformation as in the natural product, and thus giving a similar activity.

Retrosynthetically, the compound could arise from simple conjugate addition and

oxidation of a 4-cyclohexanone ester. The aromatic side-chain could be easily formed via an esterification reaction from the corresponding carboxylic acid and 3-furanmethanol.

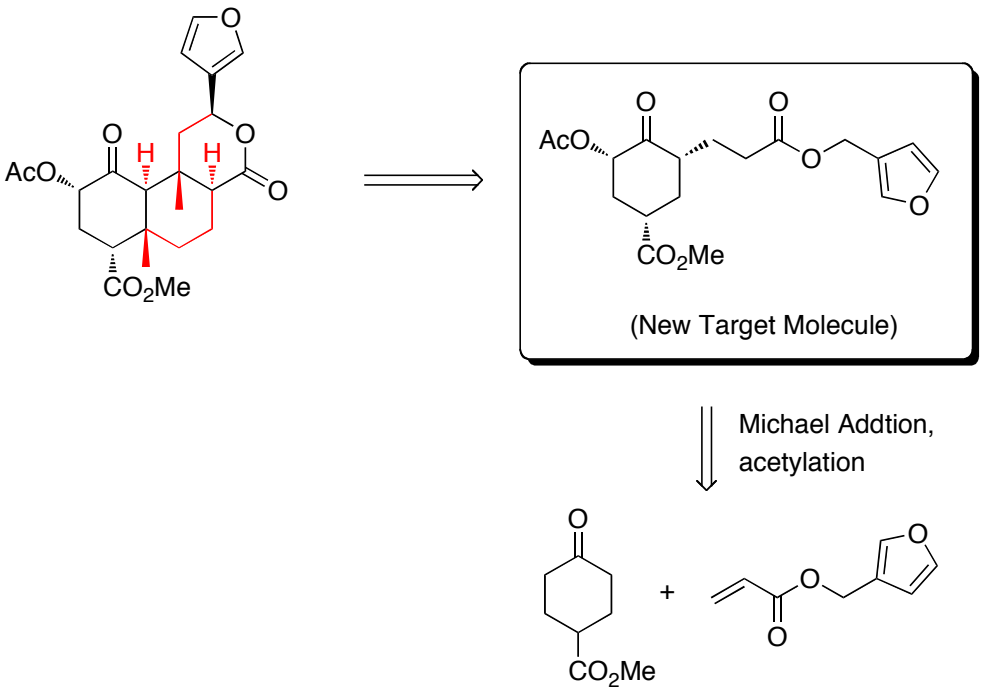
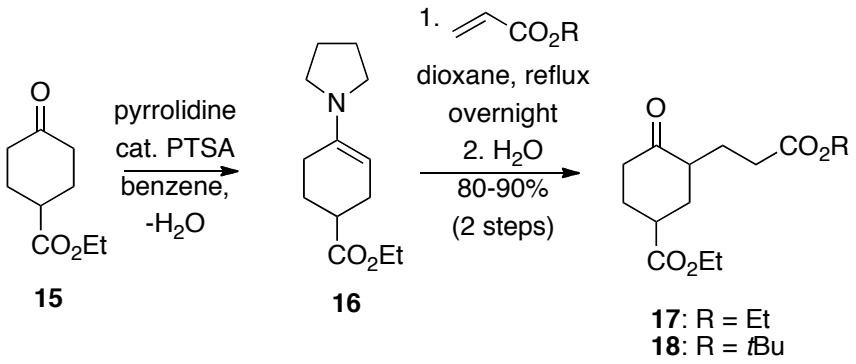


Figure 6. Retrosynthetic analysis of a salvinorin A analogue

Results and Discussion

The synthesis of the first salvinorin A analogue commenced from the formation of enamine **16** from commercially available ethyl cyclohexanone-4-carboxylate **15**. The first method employed was using stoichiometric titanium tetrachloride.[13] However, subsequent Michael addition reactions with acrylates failed, presumably due to trace amounts of unwanted excess titanium tetrachloride and side product titanium dioxide. A simpler method to produce the enamine was reaction of 4-cyclohexanone carboxylic acid

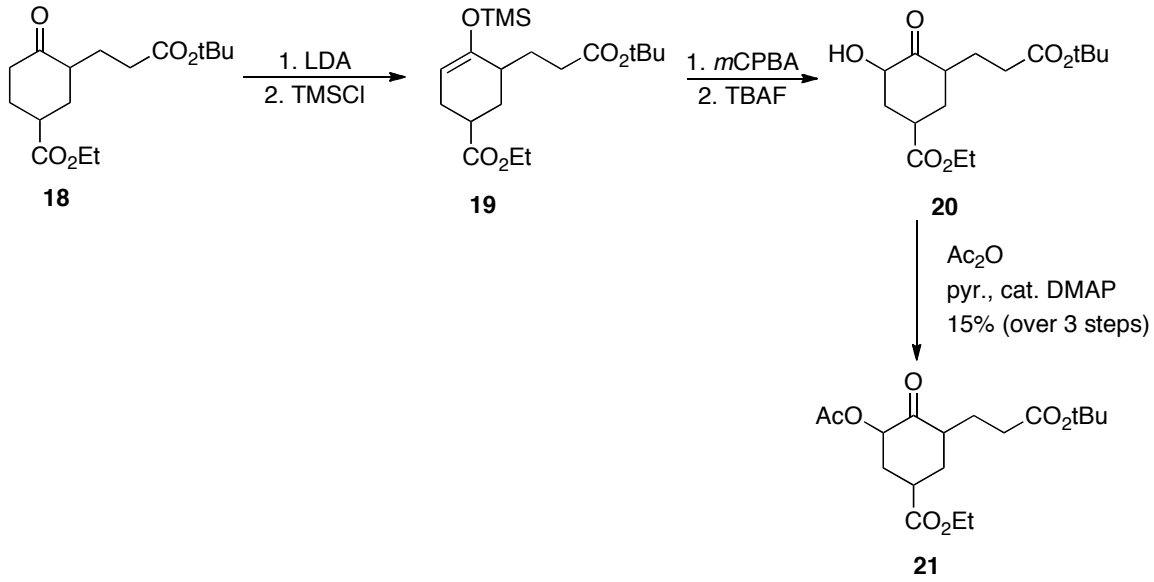
ethyl ester with pyrrolidine using *para*-toluene sulfonic acid (PTSA) as the catalyst and azeotropic distillation of water.[14] Treatment of the enamine with a variety of acrylates, followed by hydrolysis gave the desired conjugate addition products in good yield.



Scheme 4

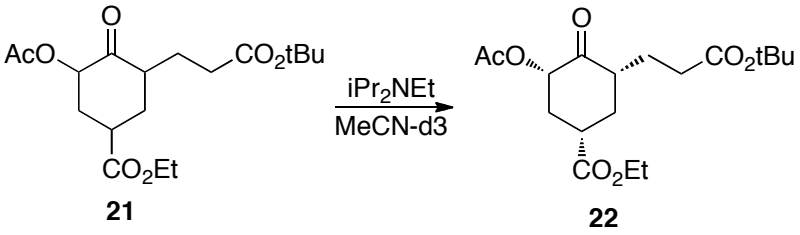
With the Michael addition product in hand, we looked towards the remaining functional group modifications: the oxidation/acetylation alpha to the ketone, hydrolysis of the ester, and coupling of the ester with 3-furanmethanol. Direct Michael addition of **16** with acrylic acid was unsuccessful. Likewise, using the ester of 3-furanmethanol also failed. With this in mind, the next steps of the synthesis are shown in Scheme 5. The trimethylsilyl ether of ketone **18** was made via typical conditions[15] (i.e. treatment with LDA and quenching with trimethylsilyl chloride). Oxidation of the enol silane via Rubottom conditions,[16] (epoxidation using *m*CPBA, followed by cleavage of the silane with tetrabutylammonium fluoride) gave intermediate alcohol **20**. This was taken

directly in the acetylation step without purification using acetic anhydride in pyridine, giving product **21** in 15% yield over the three-step sequence.



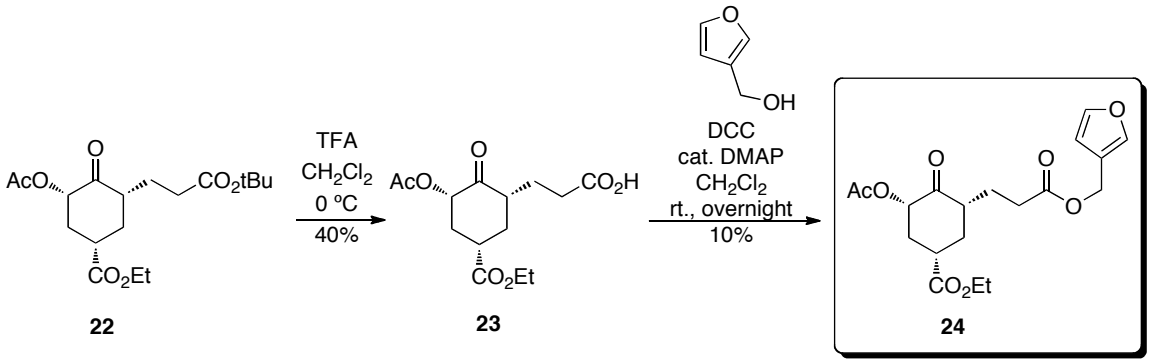
Scheme 5

At this point, the compound was a mixture of stereoisomers and therefore needed to be epimerized with diisopropylethylamine in order to give the desired product. The three stereogenic centers are all on the cyclohexane ring and were therefore expected to all fall into the more favorable equatorial positions. The reaction was done in acetonitrile-d3, monitoring by ^{1}H NMR, using the diagnostic alpha acetoxy ketone peak at 5.3 ppm. By integration it showed a roughly 2:1 ratio of epimers by integration.



Scheme 6

With the epimerized product in hand, the final steps of the synthesis were completed (Scheme 7). The *tert*-butyl ester moiety of **22** was cleaved with treatment with trifluoroacetic acid (TFA) to give the requisite acid **23**.[17] The acid was finally coupled with 3-furanmethanol under Steglich Esterification conditions[18] to give the desired product **24** in 10% isolated yield.



Scheme 7

One must note that the order of operations is extremely important in this case. Previous efforts involved cleavage of the *tert*-butyl ester with TFA and subsequent DCC coupling before the oxidation using *m*CPBA. However, this lead to a complex mixture

due to epoxidation of the furan ring moiety. Doing the Rubottom oxidation first, followed by cleavage of the ester to the acid, and coupling avoids the competition of the oxidation of the enol silane versus the furan ring.

The product was submitted to Dr. Prisinzano at the University of Kansas for biological testing, but it was found to have no KOR activity. It was suggested that the compound might be too flexible to allow the molecule to find the correct conformation for biological activity. In particular, the ring system of salvinorin A fixes the C-O single bond of the ester in the s-*cis* conformation (shown in red in Figure 7), whereas the open-chain analogue favors the s-*trans* conformation over s-*cis*. Therefore, new analogues were considered that lock the degrees of freedom of the molecule and lock the functionality in the approximate positions they are in salvinorin A.

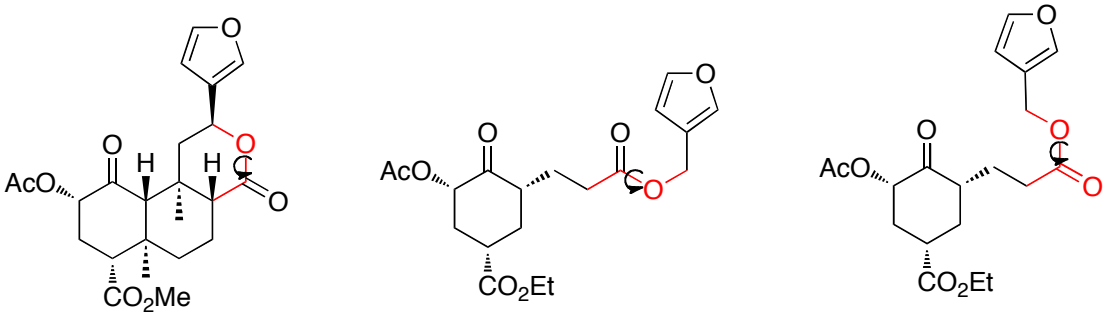
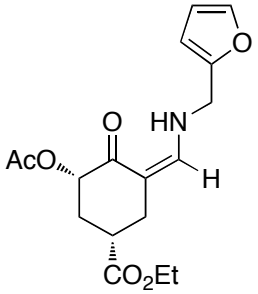


Figure 7. S-*cis* versus s-*trans* conformations in salvinorin

The new analogue considered is shown in Figure 8. In this case, a double bond is employed to limit the conformational freedom of the molecule and to place the furan moiety in roughly the same position it is in the ring-locked salvinorin. Additionally, the hydrogen bonding of the amine proton with the ketone would fix the tethered furan ring moiety in the desired 'up' position, as it is in the natural product. It would arise simply from an alpha-keto aldehyde intermediate coupling with furfuryl amine.



(26)

Figure 8. New salvinorin A analogue structure

The retrosynthesis of **26** is shown in Figure 9. Starting from the same 4-cyclohexanone carboxylic acid ethyl ester used previously, an aldehyde moiety can be introduced in a similar fashion as a known procedure.[19] Of note is that the aldehyde precursor greatly favors the enol form due to the hydrogen-bonding motif with the ketone. The same is true of enamine derivative; the hydrogen bond of amine fixes the nitrogen in the desired position.[20] This also simplifies the molecule in that it further reduces the amount of stereogenic centers from three to two, both of which are still easily epimerizable via basic conditions.

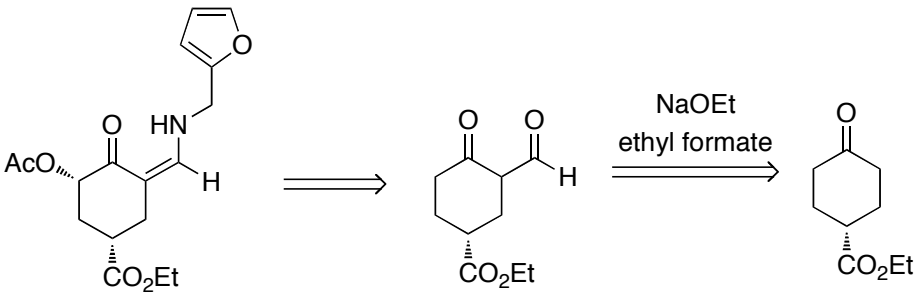
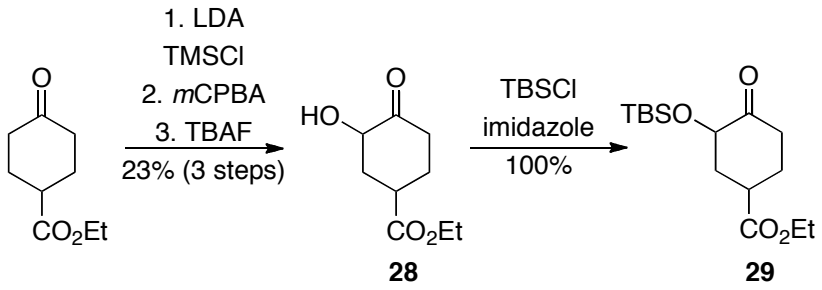


Figure 9. Retronsynthetic analysis

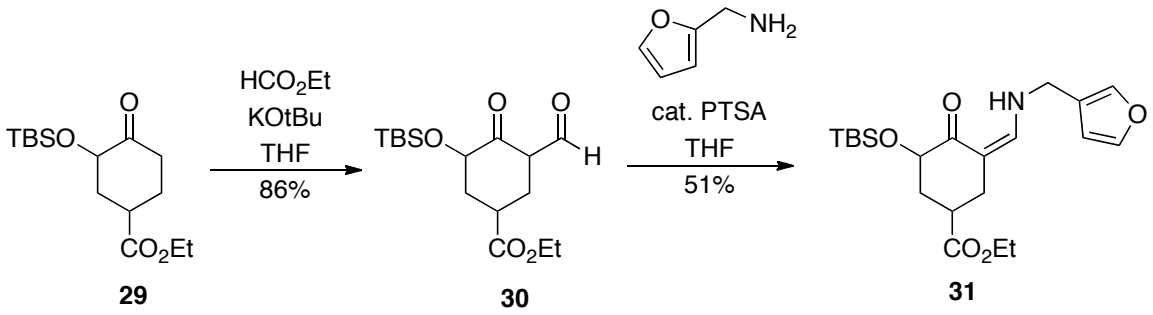
The synthesis began with typical Rubottom oxidation to give the desired alcohol (compound **28** in Scheme 8). This was protected as the *tert*-butyldimethylsilyl (TBS) ether (**29**) using well-known conditions.[21]



Scheme 8

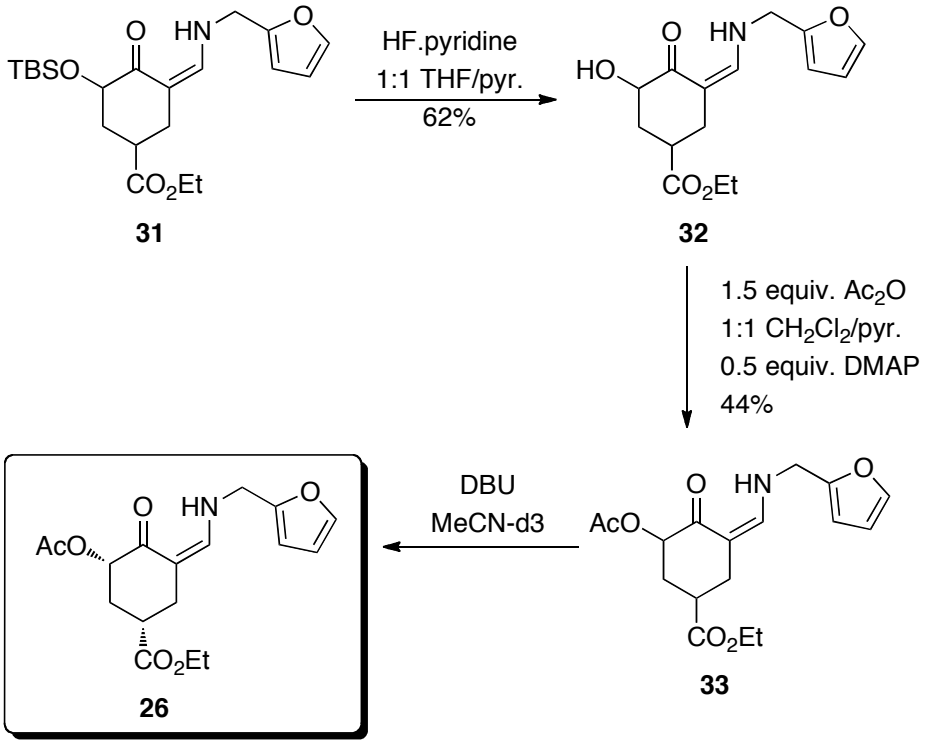
Preparation of the desired aldehyde intermediate proved more difficult than expected (Scheme 9). The typical reaction procedure using ethyl formate and either sodium ethoxide or sodium hydride gave the desired product in unsatisfactory yields (i.e. less than 30%). Switching the base to potassium *tert*-butoxide was able to afford the

product (**30**) in much better yield (86%). Compound **30** was transformed into **31** via treatment of the furfuryl amine with catalytic PTSA.[22]



Scheme 9

The TBS ether moiety of the enamine adduct (**31**) was deprotected with hydrogen fluoride in pyridine[23] and acetylated with acetic anhydride in a similar fashion as used previously to give compound **36**. Epimerization with DBU afforded the salvinorin A derivative **26**.



Scheme 10

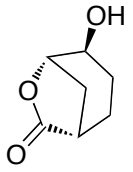
The new product was also submitted for biological testing, but unfortunately, was not found to have any desired KOR activity.

In conclusion, two structural analogues of salvinorin A were prepared. The first compound, **24**, involved the Michael addition of an enamine to acrylates as the key step. The second analogue, **26**, was prepared from the same starting material and utilized the preparation of an alpha-keto aldehyde and formation of an enamine.

Experimental

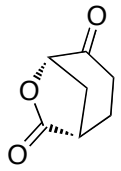
Unless otherwise noted, materials were obtained from commercial suppliers and

used without purification. Tetrahydrofuran was distilled from sodium and benzophenone. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with a Varian 300 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet, ABq = AB quartet. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



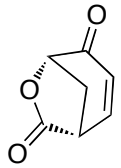
4-Hydroxy-6-oxabicyclo[3.2.1]octan-7-one (5)

To a solution of 3-cyclohexene-1-carboxylic acid (2 mL, 17.1 mmol) in dichloromethane at 0 ºC was added *m*CPBA (4.226 g, 18.9 mmol). The reaction was allowed to stir at this temperature for 4 hours, followed by treatment with triethylamine (2.4 mL, 17.2 mmol) and stirring at room temperature for 3 hours. The reaction was worked-up by subsequent washing with NaS_2O_3 and $NaHCO_3$. The crude material was purified by flash silica gel chromatography (1:2 hexanes/ethyl acetate) to yield product **5** as a white power (1.879 g, 77% yield). ^1H NMR (300 MHz, $CDCl_3$): ∂ 4.66 (t, J = 6 Hz, 1H), 4.18 (m, 1H), 2.60 (br, 1H), 2.22-2.16 (m, 3H), 1.92-1.76 (m, 4H).



6-Oxabicyclo[3.2.1]octane-4,7-dione (6)

To a solution of **5** in dichloromethane (318 mg, 2.2 mmol) was added PCC (721 mg, 3.3 mmol), where the solution darkened immediately. The mixture was stirred at room temperature for 3 h, where it was filtered through a pad of Celite. The product was purified through flash silica gel chromatography (1:1 hexanes/ethyl acetate) to yield **6** as a white powder (270 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 4.66 (d, J = 6 Hz, 2H), 2.89-2.74 (m, 3H), 2.31-2.27 (m, 2H), 2.12-2.06 (m, 2H).



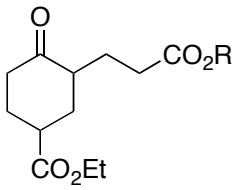
6-Oxabicyclo[3.2.1]oct-2-ene-4,7-dione (4)

In an oven-dried flask under argon, freshly distilled diisopropylamine (0.2 mL, 1.3 mmol) was dissolved in THF at -78 ºC. To this was added a 2.5 M solution of *n*-butyllithium in hexanes (0.5 mL, 1.4 mmol), and the reaction was allowed to stir at -78 ºC for 30 minutes.

A solution of keto lactone **6** (182 mg, 1.3 mmol) dissolved in THF was added to the solution of LDA at -78 ºC. After stirring for 1 hour, chlorotrimethylsilane (TMSCl) was added (0.15 mL, 1.2 mmol), warming to 0 ºC for 1 hour. The solution was filtered through a pad of Celite in order to remove the precipitated lithium salts and washed with

hexanes. The crude product **7** was concentrated via rotary evaporator and used in the next step without further purification.

Enol silane **7** was dissolved in freshly distilled dimethyl sulfoxide (DMSO) under an oxygen atmosphere. To this was added palladium acetate (29 mg, 0.13 mmol) and the reaction was heated to 80 ºC over a 12-16 hour period. After cooling to room temperature, dilution with dichloromethane, and aqueous work-up, the product was purified via flash silica gel chromatography (1:1 hexanes/ethyl acetate) as a yellow oil (53 mg, 30% yield, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 6.87 (d, J = 6 Hz, 1H), 6.11 (d, J = 6 Hz, 1H), 4.82-4.78 (m, 1H), 3.75 (t, J = 6 Hz, 1), 2.50-2.40 (m, 2H).



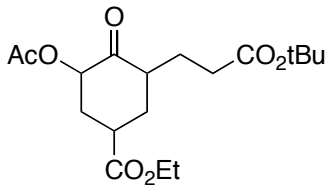
Ethyl 3-(3-alkoxy-3-oxopropyl)-4-oxocyclohexanecarboxylate (17-18)

The ethyl ester of 4-cyclohexanone carboxylic acid (0.5 mL, 3.1 mmol) was dissolved in 20 mL benzene. To this was added pyrrolidine (0.26 mL, 3.2 mmol) and a single crystal of *para*-toluenesulfonic acid (PTSA). The reaction mixture was heated to reflux overnight with a Dean-Stark trap to azeotropically remove the water byproduct. The reaction flask was cooled, and the product concentrated to give the crude enamine product, which was used immediately in the next step without further purification. Unpurified enamine **16** was dissolved in 20 mL dry dioxane. The corresponding acrylate (R = Et or tBu, 1 equiv.) was added to the solution, where it was heated to reflux over a 6

hour period. The reaction is quenched by cooling to room temperature and addition of 5 mL water, stirring for 1 hour. The product was extracted with ethyl acetate, and the organic layer was dried over $MgSO_4$ and concentrated. The product was purified by flash silica gel chromatography (2:3 hexanes/ethyl acetate) to yield the desired Michael Addition products **17** and **18**.

(**17**) Yellow liquid (439 mg, 80% yield, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 4.25-4.08 (m, 4 H), 2.84-2.80 (m, 2H), 2.51-2.44 (m, 6H), 2.10-2.00 (m, 2H), 1.65-1.53 (m, 2H) 1.24 (t, J = 6 Hz, 6H).

(**18**) Yellow liquid (853 mg, 91% yield, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 4.21-4.13 (m, 2H), 2.73 (t, J = 7 Hz, 2H), 2.44-1.80 (m, 10H), 1.43 (s, 9H), 1.26 (t, J = 7 Hz, 3H).

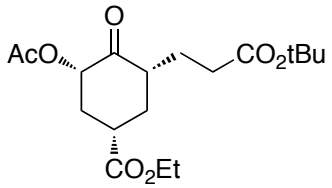


Ethyl 3-acetoxy-5-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxocyclohexanecarboxylate (22)

In an oven-dried flask, LDA was prepared at -78 ºC using 2.5 M *n*-BuLi (0.37 mL, 0.9 mmol) and diisopropylamine (0.15 mL, 1.0 mmol) in 10 mL THF. To this was added a solution of **19** (251 mg, 0.8 mmol) in 3 mL THF at -78 ºC. The reaction was stirred for 30 minutes. TMSCl (0.12 mL, 0.9 mmol) was added to the solution, where it was allowed to warm to 0 ºC over a 1 hour period. The product **20** was concentrated and used directly in the next step without further purification.

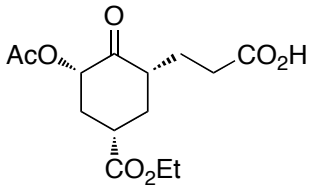
Enol silane **20** was dissolved in dry dichloromethane at 0 ºC. To this was added solid *m*CPBA (209 mg, 0.9 mmol), which was warmed to room temperature over a 1 hour period. The reaction was treated with a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (1 mL, 1 mmol), and stirred for 2 hours. The reaction was worked up by dilution with dichloromethane, washing sequentially with saturated solutions of NaS_2O_3 and $NaHCO_3$, drying over $MgSO_4$, and concentration. The product was purified by flash silica gel chromatography (1:1 hexanes/ethyl acetate) to give **21** as a yellow oil. ^{1}H NMR (crude) (300 MHz, $CDCl_3$): ∂ 4.20 (m, 1H), 4.12-4.09 (m, 2H), 2.88-1.63 (m, 10H), 1.86 (s, 1H), 1.42 (s, 9H), 0.94 (t, J = 7 Hz, 3H).

Hydroxy ketone **21** was dissolved in 5 mL dichloromethane, along with 1 mL pyridine, 1 mL acetic anhydride, and 20 mg DMAP. The reaction was allowed to stir at room temperature overnight before being worked up with $NaHCO_3$ solution, extraction with dichloromethane, drying over $MgSO_4$, and concentration. Purification by silica gel chromatography (1:1 hexanes/ethyl acetate) produced the desired product as a yellow oil (150 mg, 15% yield over 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 5.34, 5.32 (ABq, J = 6 Hz, 1H), 5.20, 5.15 (ABq, J = 6 Hz, 1H), 4.17-4.12 (m, 2H), 2.51-1.91 (m, 10H), 2.14 (s, 3H), 1.41 (s, 9H), 1.33-1.29 (m, 2H).



(1*S*,3*S*,5*R*)-ethyl 3-acetoxy-5-(3-(*tert*-butoxy)-3-oxopropyl)-4-oxocyclohexanecarboxylate (23)

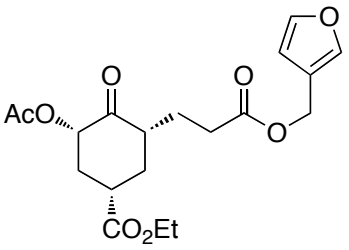
Compound **22** (150 mg, 0.4 mmol) was dissolved in 2 mL of acetonitrile-d3. Two drops of diisopropylethylamine were added, and the reaction was stirred at room temperature for 5 h, monitoring by proton NMR every hour until it reached an equilibrium of peak ratios. The epimerized product **23** was concentrated in vacuo and recovered quantitatively (150 mg). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 5.34, 5.32 (ABq, J = 6 Hz, 1H), 5.20, 5.15 (ABq, J = 6 Hz, 1H), 4.13 (q, J = 6 Hz, 2H), 2.51-2.01 (m, 5H), 1.91-1.5 (m, 5H), 2.14 (s, 3H), 1.41 (s, 9H), 1.29 (t, J = 6 Hz, 3H).



3-((1*R*,3*S*,5*S*)-3-acetoxy-5-(ethoxycarbonyl)-2-oxocyclohexyl)propanoic acid (24)

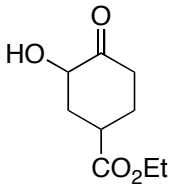
Compound **23** (150 mg, 0.4 mmol) was dissolved in 5 mL dichloromethane. 0.5 mL trifluoroacetic acid (TFA) was added, stirring at room temperature for 3 hours. The solvent and excess TFA were removed via rotary evaporator and the product purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to yield the product as an orange oil

(50 mg, 40% yield) ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 5.38, 5.33 (ABq, J = 6 Hz, 1H), 4.20 (q, J = 6 Hz, 2H), 2.95-1.94 (m, 10H), 2.15 (s, 3H), 1.27 (t, J = 6 Hz, 3H).



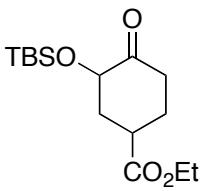
(1*S*,3*S*,5*R*)-ethyl 3-acetoxy-5-(3-(furan-3-ylmethoxy)-3-oxopropyl)-4-oxocyclohexanecarboxylate (25)

Compound **24** (50 mg, 0.16 mmol) was dissolved in 3 mL dichloromethane. To this was added 3-furanmethanol (17 μL, 0.19 mmol), 39 mg DCC (0.18 mmol), and DMAP (39 mg, 0.02 mmol). The reaction mixture was filtered through a pad of Celite to remove the precipitated urea byproduct, and concentrated in vacuo. The product was purified by preparative TLC (1:1 hexanes/ethyl acetate) as a white solid (10 mg, 16% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.46 (s, 1H), 7.39 (s, 1H), 6.41 (s, 1H), 5.33, 5.38 (ABq, J = 6 Hz, 1H), 4.97 (s, 2H), 4.23 (q, J = 6 Hz, 2H), 2.91-1.53 (m, 10H), 2.15 (s, 3H), 1.25 (t, J = 6 Hz, 3H).



Ethyl 3-hydroxy-4-oxocyclohexanecarboxylate (28)

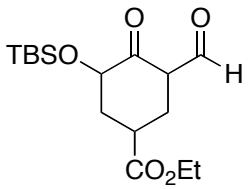
Starting from ethyl cyclohexanone-4-carboxylate (1 mL, 6.2 mmol), a similar procedure which was used to prepare compound **21** was utilited (i.e. formation of the enol silane via LDA and TMSCl, oxidation using *m*CPBA, and epoxide ring opening using TBAF). Purification of crude product **28** via flash silica gel chromatography (1:1 hexanes/ethyl acetate) produced the required compound as a yellow oil (266 mg, 23% over 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 4.17 (q, J = 6 Hz, 4H), 2.65-2.57 (m, 3H), 2.49-2.43 (m, 2H), 2.07-2.04 (m, 2H), 1.27 (t, J = 6 Hz, 3H).



Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexanecarboxylate (29)

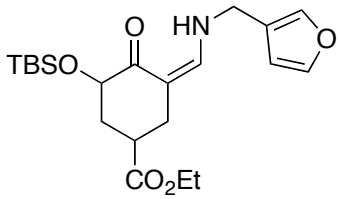
Compound **28** (200 mg, 1.1 mmol) was dissolved in 5 mL CH_2Cl_2, where imidazole (80 mg, 1.2 mmol) and TBSCl (178 mg, 1.2 mmol) were added, respectively. The mixture was allowed to stir at room temperature for 12-16 hours. After aqueous workup, the product was purified by flash silica gel chromatography (1:1 hexanes/ethyl acetate) to yield product **29** as a yellow oil (322 mg, 100%). ^{1}H NMR (300 MHz,

$CDCl_3$): ∂ 4.16 (q, *J* = 6 Hz, 2H), 2.65-2.61 (m, 2H), 2.44-2.28 (m, 4H), 2.09-2.01 (m, 2H), 1.27 (t, *J* = 6 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H).



Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-5-formyl-4-oxocyclohexanecarboxylate (30)

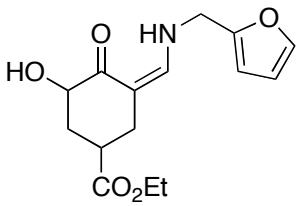
Starting material **29** (300 mg, 1.0 mmol) was dissolved in 5 mL dry THF. To this was added HCO_2Et (0.12 mL, 1.5 mmol) and a 1 M solution of KOtBu in THF (1.1 mL, 1.1 mmol). The reaction was stirred for 12 hours. After aqueous workup and purification by silica gel chromatography (1:1 hexanes/ethyl acetate), pure **30** was produced as a pale yellow oil (282 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 8.69 (s, 1H), 4.15 (q, *J* = 6 Hz, 2H), 2.71-2.65 (m, 2H), 2.60-2.56 (m, 2H), 2.47-2.44 (m, 2H), 1.24 (t, *J* = 6 Hz, 3H), 0.9 (s, 9H), 0.06 (s, 6H).



(*Z*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(((furan-3-ylmethyl)amino)methylene)-4-oxocyclohexanecarboxylate (31)

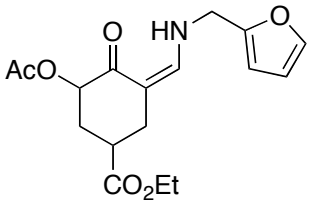
Compound **30** (147 mg, 0.4 mmol) was dissolved in methanol, where furfuryl amine (0.06 mL, 0.67 mmol) and a single crystal of PTSA was added, stirring for a 24

hour period. The crude product was concentrated in vacuo and purified via silica gel chromatography (1:1 hexanes/ethyl acetate) to yield **31** as a pale yellow amorphous solid (92 mg, 51% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.35 (s, 1H), 6.31 (s, 1H), 6.13 (s, 1H), 4.31 (s, 2H), 4.21 (q, *J* = 6 Hz, 2H), 2.85-2.70 (m, 3H), 2.66-2.5 (m, 3H), 1.30 (t, *J* = 6, 3H), 0.9 (s, 9H), 0.06 (s, 6H).



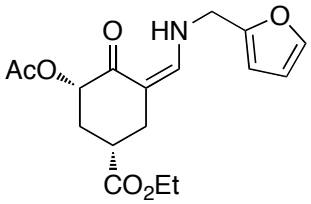
(*Z*)-Ethyl 3-(((furan-2-ylmethyl)amino)methylene)-5-hydroxy-4-oxocyclohexanecarboxylate (32)

Compound **31** (67 mg, 0.16 mmol) was dissolved in 5 mL of a 1:1 mixture of THF and pyridine. The reaction flask was cooled to 0ºC in an ice bath and treated with a solution of hydrogen fluoride pyridine (~70% HF, 0.08 mL, 2.8 mmol) The reaction was warmed to room temperature, where it was stirred for 6 hours. The reaction was worked up with a 10% solution of copper sulfate, extracted with ethyl acetate, dried, and concentrated. Purification via flash silica gel chromatography (1:1 hexanes/ethyl acetate), produced pure alcohol as an amorphous solid (30 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.36 (s, 1H), 6.24 (s, 1H), 6.05 (s, 1H), 4.46 (s, 2H), 4.35-4.32 (m, 1H), 4.10-4.06 (m, 2 H), 2.61-2.50 (m, 2H), 2.17-2.04 (m, 3H), 1.25 (t, *J* = 6 Hz, 3H).



(*Z*)-Ethyl 3-acetoxy-5-(((furan-2-ylmethyl)amino)methylene)-4-oxocyclohexanecarboxylate (33)

In 1 mL of a 1:1 solution of CH_2Cl_2 and pyridine was dissolved **32** (30 mg, 0.1 mmol), followed by acetic anhydride (0.02 mL, 0.2 mmol) and 4-dimethylaminopyridine (DMAP, 6 mg, 0.05 mmol). The reaction was stirred at room temperature for 12 hours before aqueous workup and purification via preparative TLC (1:1 hexanes/ethyl acetate) gave product as a white amorphous solid (15 mg, 44% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.2-10.0 (br, 1H), 7.36 (s, 1H), 6.31 (s, 1H), 6.22 (s, 1H), 5.28-5.26 (m, 1H), 4.31 (s, 2H), 4.13-4.10 (m, 2H), 2.90-2.74 (m, 3H), 2.59-2.36 (m, 3H), 2.13 (s, 3H), 1.24 (t, J = 6 H, 3H).



(1*S*,3*S*,*Z*)-Ethyl 3-acetoxy-5-(((furan-2-ylmethyl)amino)methylene)-4-oxocyclohexanecarboxylate (26)

A similar experimental procedure was used as in the preparation of compound **23**. ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.2-10.0 (br, 1H), 7.36 (s, 1H), 6.31 (s, 1H), 6.22 (s,

1H), 5.28-5.26 (m, 1H), 4.31 (s, 2H), 4.13-4.10 (m, 2H), 2.90-2.74 (m, 3H), 2.59-2.36 (m, 3H), 2.13 (s, 3H), 1.24 (t, J = 6 H, 3H).

References

1. (a) Imanshahidi, M.; Hosseinzadeh, H. *Phytother. Res.* **2006**, *20*, 427. (b) Prisinzano, T. E. *Life Sci.* **2005**, *5*, 527.
2. (a) Bikbulatov, R. V.; Stewart, J.; Jin W.; Yan, F.; Roth, B. L.; Ferreira, D.; Zjawiony. J.K. *Tetrahedron Lett.* **2008**, *49*, 937; (b) Béguin, C.; Duncan, K. K.; Munro, T. A.; Ho, D. M.; Xu, W.; Liu-Chen, L.; Carlezon W. A.; Cohen, B. M. *Bioorg. & Med. Chem.* **2009**, *17*, 1370.
3. Prisinzano, T.E.; Rothman, R. B. *Chem. Rev.* **2008**, *108*, 1732.
4. (a) Bergman, Y.E.; Mulder, R.; Perlmutter, P. *J. Org. Chem.* **2009**, *74*, 2589; (b) Burns, A. C.; Forsyth, C. J. *Org. Lett.* **2008**, *10*, 97.
5. Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968.
6. Nozawa, M.; Suka, Y.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2008**, *10*, 1365.
7. Corey, E. J.; Huang, H. C. *Tetrahedron Lett.* **1989**, *30*, 5235.
8. Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1.
9. Larock, R. C.; Hightower, T. C.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.
10. Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.

11. Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc*. **1974**, *96*, 7807.

12. Block, J.; Beale, J. M.; G. A. *Wilson & Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 11th ed.; 1998, p 629.

13. White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213.

14. Fraenkel, G.; Gallucci, J.; Rosenzweig, H. S. *J. Org. Chem.* **1989**, *54*, 677.

15. Okabayashi, T.; Iida, A.; Takai, K.; Nawate, Y.; Misaki, T.; Tanabe, Y. *J. Org. Chem.*, **2007**, *72*, 8142.

16. Rubottom, G. M.; Vasquez, M. A.; Pelegrina, D.R. *Tetrahedron Lett*. **1974**, 4319.

17. Bryan, D. B.; Hall, R. F.; Holden, K. G.; Huffman, W. F.; Gleason, J. G. *J. Am. Chem. Soc.* **1977**, *99*, 2353.

18. Neises, B.; Steglich, W. *Angew. Chem. Int. Ed*. **1978**, *17*, 522.

19. Ainsworth, C. *Org. Synth.* Coll. Vol. 4, **1963**, 536.

20. Walter, W.; Fleck, T. *Liebigs Ann.* **1976**, *4*, 670.

21. (a) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons: New York, 1999, p 127; (b) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

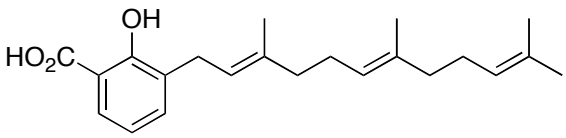
22. Wen, J.; Lin, C.; Li, J. *J. Chem. Res.* **2008**, *1*, 3.

23. Tully, S. E.; Mabon, R.; Gama, C. I.; Tsai, S. M.; Liu, X.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.*, **2004**, *126*, 7736.

CHAPTER 2. SYNTHESIS OF NEW ANTIMICROBIAL COMPOUNDS

Introduction

Piper multiplinervium C. DC. is a climbing shrub in tropical rainforests. It grows from Nicaragua to Peru and is used as a treatment for stomach aches by the native people of Panama.[1] The methanolic leaf extracts were recently isolated and characterized, revealing a highly active compound, 3-farnesyl-2-hydroxybenzoic acid (**1**), the structure of which is shown in Figure 1. To date, there are no known chemical preparations of the compound.



(1)

Figure 1. Structrure of the natural product from *Piper multiplinervium*

Compound **1** is a very potentent antimicrobial agent, showing activity of 100 µg/mL against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Mycobacterium smegmatis*, *Klebsiella pneumoniae* and *Candida albicans*.[2] It is also effective against *Helicobacter pylori* with a minimum inhibitory concentration (MIC) of 12.5 µg/mL. Of note is the fact that the compound is effective against Gram-negative bacteria, which tend to be resistant to antibiotics due to their outer membrane structure.

Because there is considerable interest in the field of antimicrobials, coupled with the intriguing activity of this new natural product, the chemical synthsis of **1** was pursued.

The retrosynthetic analysis is shown in Figure 2. The carboxylic acid moiety could arise from lithium-halogen exchange of an aryl halide, trapping with carbon dioxide, and acidification. The farnesyl side chain would likewise arise from a similar process (i.e. lithiation of an aryl halide and alkylation using farnesyl bromide as the electrophile), leading to the hydroxyl protected 2,6-dibromophenol. To accomplish these transformations, the phenol would have to be protected with group R. The R protecting group would be chosen so to stabilize an *ortho* lithium species arising from lithium-halogen exchange of aryl halides, typically a methoxymethyl (MOM) ether. One advantage of this sequence is that, potentially the final carboxylic acid can be acidified and the phenol can be deprotected in a single step by aqueous acid, as MOM groups are well known to be cleaved under such conditions.[3]

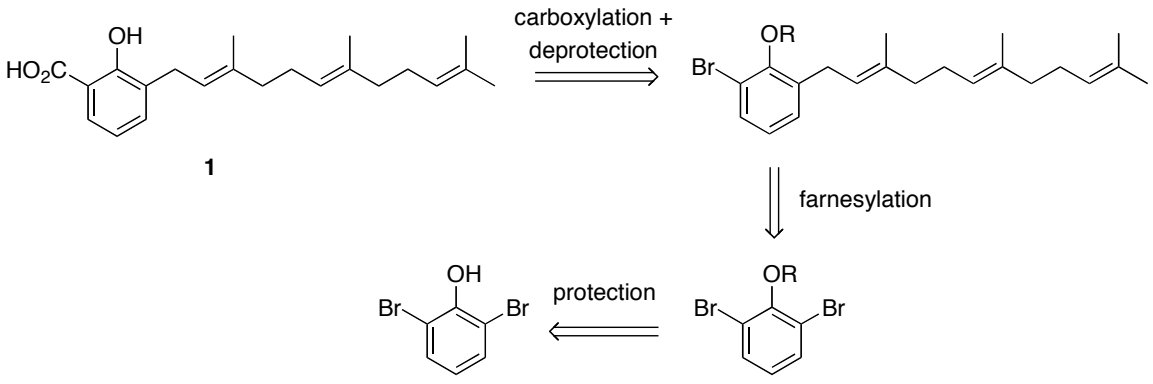
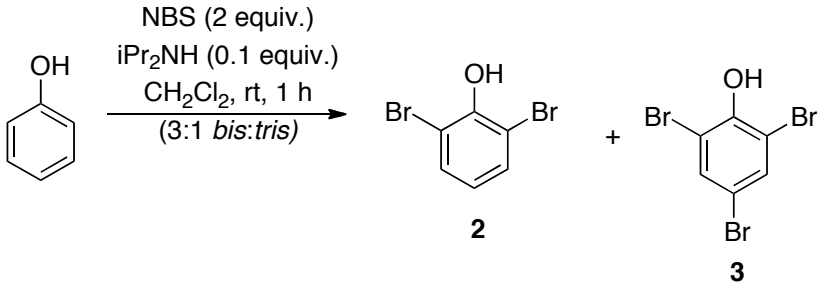


Figure 2. Retrosynthetic analysis of **1**

Results and Discussion

The first step towards the natural product was to produce the 2,6-dibromophenol. The literature has reported the preparation of the *ortho*-dibromophenol using *N*-bromosuccinimide (NBS) and diisopropylamine.[4] However the results were irreproducible, giving a 3:1 mixture of the desired product and 2,4,6-tribromophenol as an inseparable mixture (Scheme 1). Although the desired *bis*-brominated product **2** is the major product in this case, the presence of *tris*-bromophenol **3** will create difficulties in subsequent lithium-halogen exchange reactions. Therefore, commercially available 2,6-dibromophenol was chosen as the starting material, even though it is fairly expensive when compared to the inexpensive phenol.

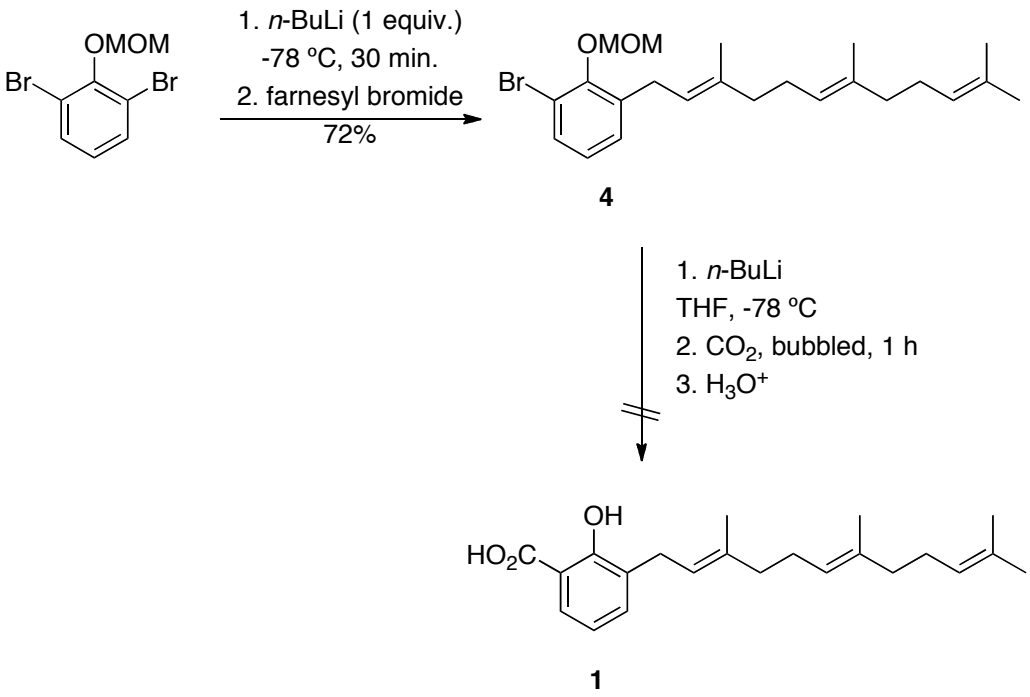


Scheme 1. Attempts to prepare 2,6-dibromophenol

The original synthetic plan involved a methoxymethyl (MOM) protected phenol as the *ortho*-directing group.[5] Preparation of farnesylated compound **4** from known MOM-protected 2,6-dibromophenol[6] proceeded smoothly (Scheme 2). The final step was the second lithiation using *n*-butyllithium, quenching with bubbling gaseous carbon

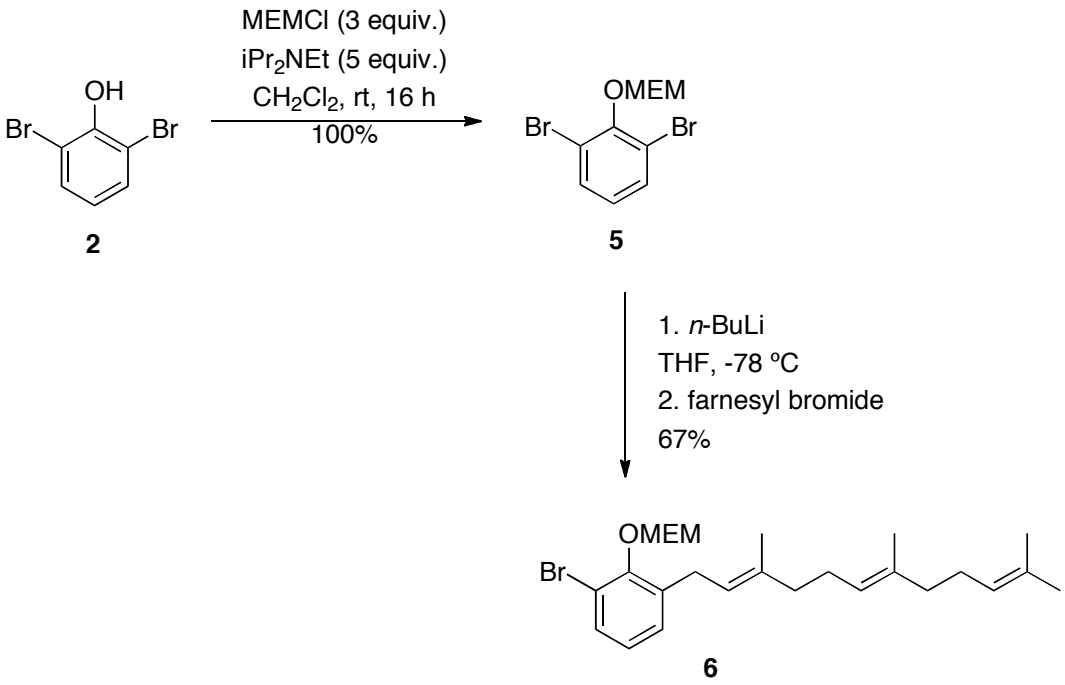
dioxide, acidification of the carboxylate, and cleavage of the MOM ether with dilute aqueous hydrochloric acid (1 N HCl). Unfortunately, the reaction was found to be a complex mixture upon work up. The theory is that the acid was too harsh and caused the phenol to cyclize upon the farensyl group. The side chain has the potential to form tertiary cations on the double-bonds on which the phenol could potentially cyclize. Because there are three possible tertiary cations that could be produced on the farnesyl group, this could help explain why the reaction lead to a complex mixture.

Therefore, a similar protecting group was used, one that is more labile and could be cleaved by milder conditions. The group would also have to have the ability to stabilize *ortho* lithiation of the aryl bromide in a similar fashion as the MOM group. This led to the use of the methoxyethoxymethyl (MEM) protecing group. The advantage of the MEM group is that, although it is less stable than the MOM group, it is much more labile and can be cleaved through treatment with mild Lewis acids that would otherwise not affect MOM-protected ethers.[6] The disadvantage would be that it adds another step to the synthesis, where the acidifation of the carboxylate and the cleavage of the MEM protection group would be two distinct steps.



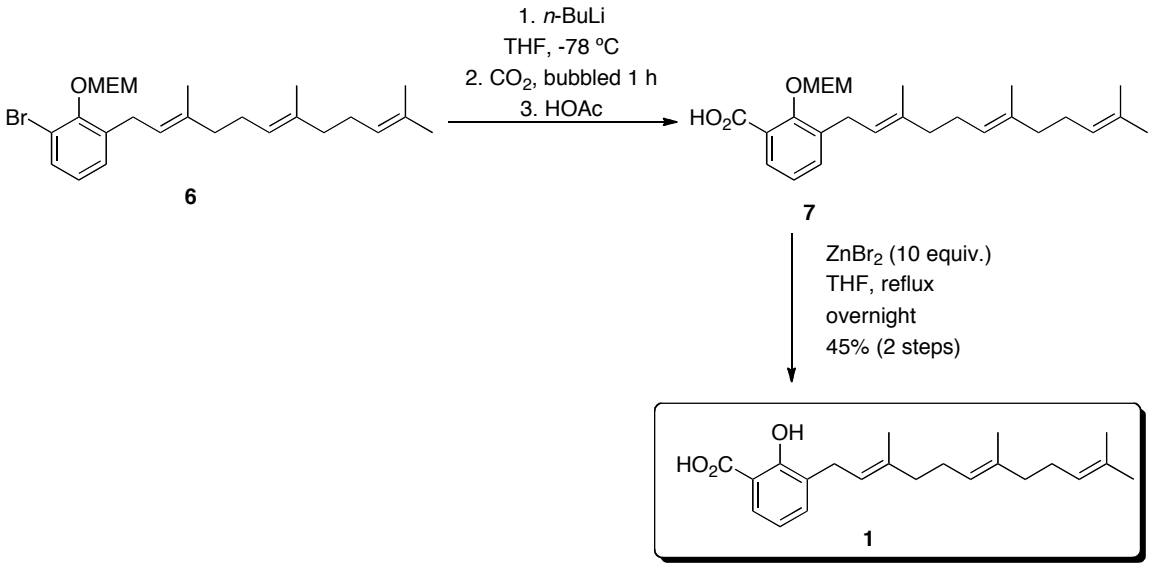
Scheme 2

Gratifyingly, the MEM protection of 2,6-dibromophenol proceded in quantitative yield using the method developed by Corey.[7] This masked phenol compound (**5** in Scheme 3) was treated with *n*-butyllithium at -78 ºC to give the aryllithium species, followed by alkylation with faresyl bromide (freshly prepared from *trans*, *trans*-faresol and phosphorus tribromide)[8] to give compound **6** in 67% yield. The reaction also contains traces of the difarnesylated compound, arising from lithium-halogen exchange of both bromides within the molecule and subsequent alkylation. However, the product is predominantly the required monofarnesylated product and easily separatable via silica gel column chromatography.



Scheme 3

With the required compound in hand, the final steps of the synthesis were achieved (Scheme 4). Lithium-halogen exchange on **6** was done using *n*-butyllithium, and the resulting anion was trapped by bubbling carbon dioxide. After acidification with acetic acid, the crude product **7** was taken to the deprotection step over zinc dibromide (prepared from 1,2-dibromoethane and zinc metal)[9] to give the natural product in moderate yield over two steps.



Scheme 4

With the natural product in hand, we looked toward the scope this chemistry by synthesizing some analogues to the natural product. The first modification was to change the farnesyl group (C15) to the smaller, but similar geranyl (C10) and prenyl (C5) groups (**8** and **9** in Figure 3, respectively) in order to probe the structure-function relationship of the side-chain on the salicylic acid. Presumably, the prenyl and geranyl compounds would have similar activity as the natural product due to their similarity to the farnesylated compound, as they are expected to arise from the common prenyl subunit. Surprisingly, neither of these compounds are known in the chemical literature, so their preparation would also represent the first known synthesis of compounds of this type.

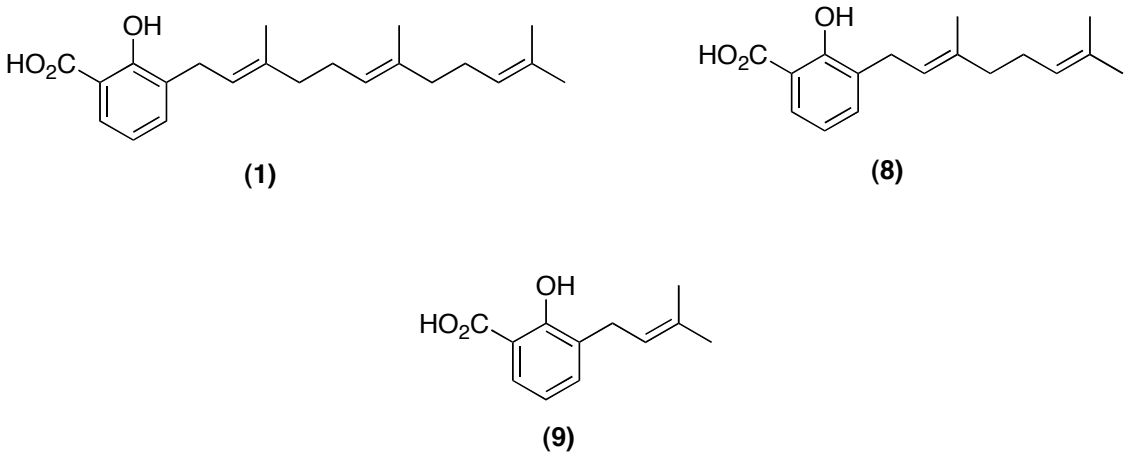
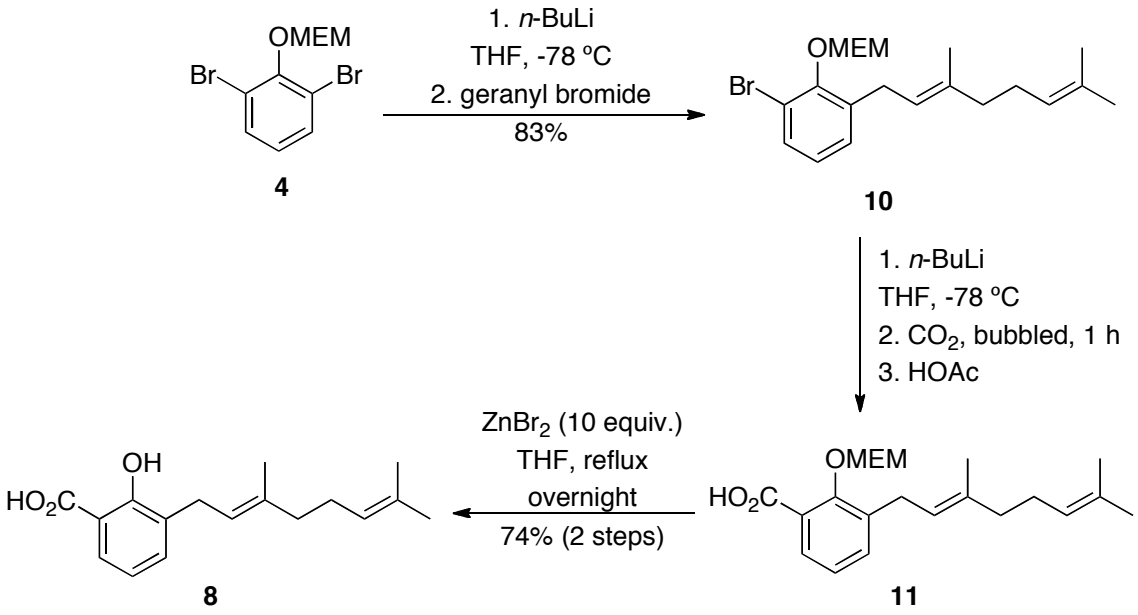


Figure 3. Natural product **1** and its proposed analogues

The preparation of 3-geranyl salicylic acid **7** utilized the same method as the one used to prepare **1** (Scheme 5). Lithiation of MEM-protected 2,6-dibromophenol **4** using *n*-butyllithium, followed by alkylation with geranyl bromide, cleanly produced monoalkylated product **10**. A second lithiation and carboxylation using carbon dioxide produced crude **11**, which was deprotected with zinc bromide to produce the desired product **8** in 74% yield over a two-step sequence.



Scheme 5

Several different methods were explored to produce the simplest prenylated salicyclic acid **9**. This is in part due to the expense and difficulties of purification of 2,6-dibromophenol, which would make preparation of large amounts of material impractical. The first idea considered started from simple phenol, which is readily available, inexpensive, and can be selectively *C*-prenylated via a literature procedure[11] (the retrosynthetic analysis is shown in Figure 4). The final step would be carboxylation under Kolbe-Schmitt conditions.[12]

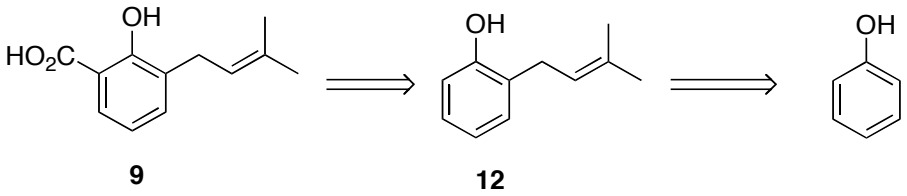
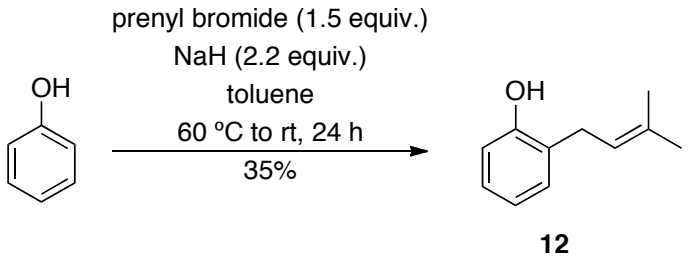


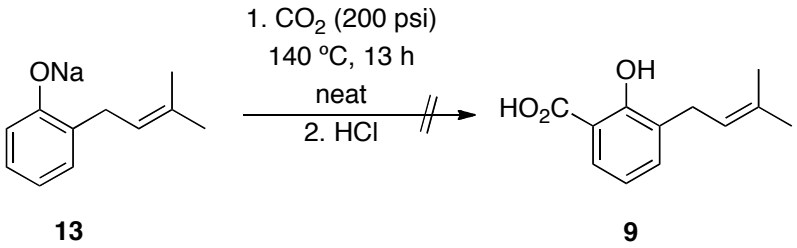
Figure 4

The *C*-prenylation of phenol proceded as shown in Scheme 6. The choice of metal counteranion and solvent is critical in this case. Ideal conditions involved an excess of sodium hydride in toluene. The use of more polar solvents (e.g. THF) leads to primarily *O*-prenylation. The reaction produced the required product **12**, albeit in low yield.



Scheme 6

The next step of the sequence required Kolbe-Schmitt conditons (Scheme 7). The sodium salt of the prenylated phenol was made by treating **12** with metallic sodium, where it was heated in an autoclave under high carbon dioxide pressure. However, upon acidification it was clear there was no reaction, as only starting material was recovered.



Scheme 7

Due to the failure of the carboxylation pathway, the synthetic strategy was modified. Starting from commercially-available coumarin (Figure 5), 2,2-dimethyl chromene (**15**) can be made in two steps following a known procedure.[13] The remaining oxygen atom can then act as a directing group for directed *ortho* metalation, and trapping with carbon dioxide, giving aromatic acid **14**. Finally, opening of the C5 ring under acidic conditions would produce desired prenylated salicylic acid **9**.

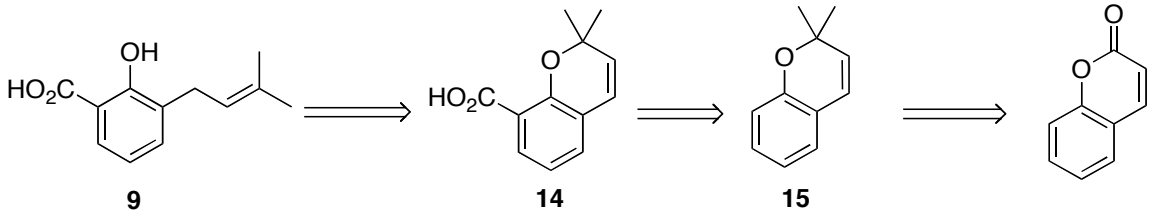
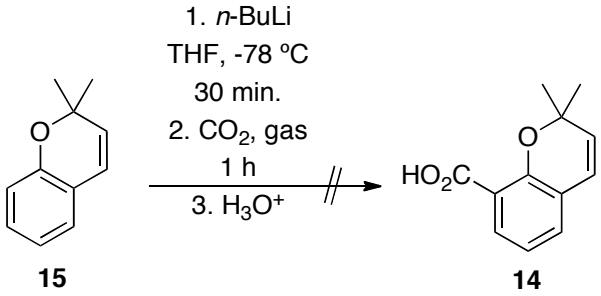


Figure 5

Preparation of **15** from coumarin proceeded without complications. However, metalation and subsequent carboxylation failed (Scheme 8), giving only recovered starting material. This may be due to the fact that the oxygen from the phenol may not be

as strongly directing towards *ortho* lithiation as other functional groups (i.e. a MEM-protected phenol) and thus would lead to difficulties in the required lithium-hydrogen exchange step.



Scheme 8

The next idea for the preparation of prenylated salicylic acid is shown in Figure 6. It was envisioned that product **9** would arise in a similar fashion as in Figure 5, that is, from hydrolysis and ring opening of **16**. This compound would in turn arise from prenylation of the very common methyl salicylate and isoprene, which follows a similar procedure for the prenylation of phenols.[11] The reaction uses an acidic resin catalyst, Amberlyst 15, to form dimethylchromans from phenols.

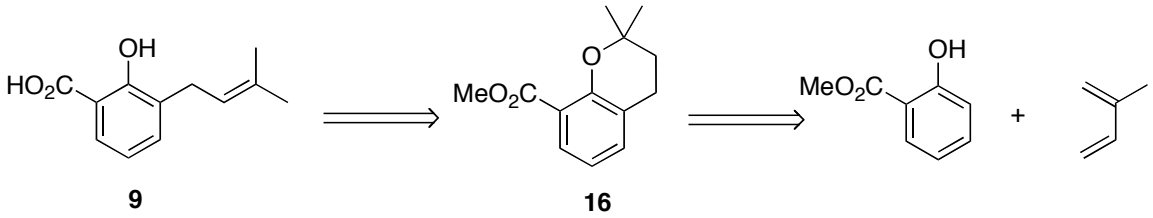
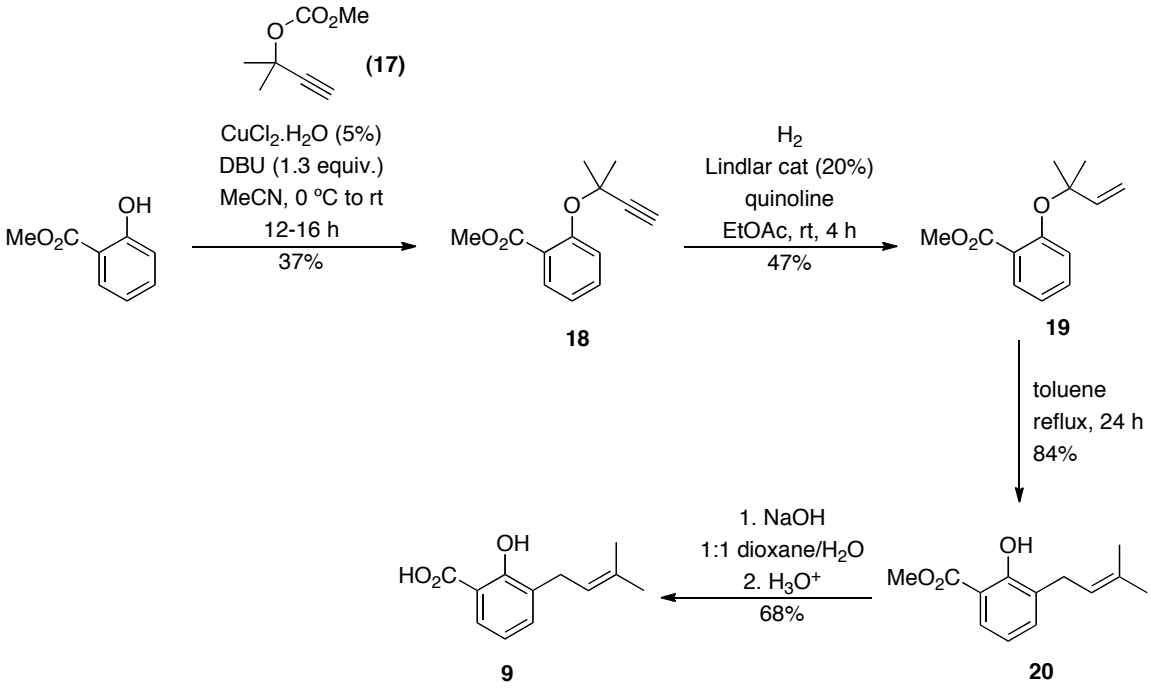


Figure 6

Unfortunately, the preparation of **16** failed, only giving recovered methyl salicylate. The reason for this is that the prenylation conditions described in the literature were used on aromatic rings with at least two phenol moieties (i.e. either phloroglucinol, hydroquinone or resorcinol derivatives). This makes the aromatic ring more electron-rich and likely to undergo substitution from electrophiles. Methy salicylate, however, only has a single phenol activating group, as well as the methyl ester, making it relatively electron-poor and thus less reactive under these conditions.

The final route towards the prenylated salicylate is shown in Scheme 9. Starting wih methyl salicylcate, 1,1-dimethyl-2-propynyl methyl carbonate (prepared from the corresponding alcohol and methyl chloroformate)[14] is coupled with a copper catalyst[15] to give **18** in fair yields. The resulting alkyne was catalytically semi-hydrogenated over Lindlar catalyst[16] to give alkene **19**. This *O*-prenylated compound then underwent thermal Claisen Rearrangement to give the *C*-prenylated product **20** in good yield. Simple hydrolysis and acidification of the methyl ester produced the corresponding prenylated salicylic acid **9**, with an overall yield is 10% over 4 steps.

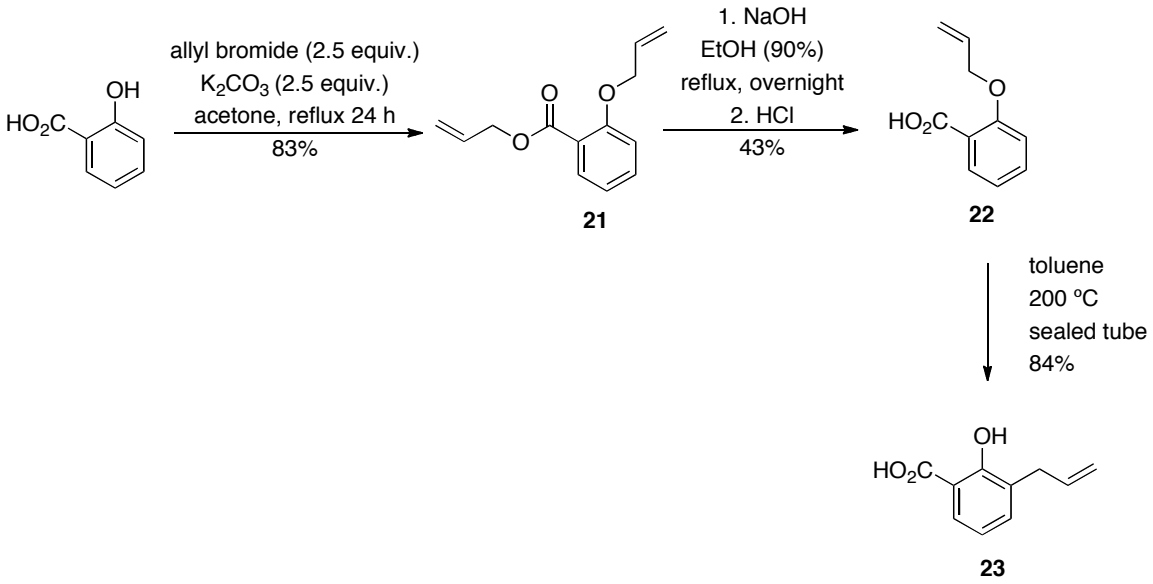


Scheme 9

With the simple prenylated salicylic acid in hand, the next step was to analyze different 3-alkyl-substituted salicylic acid derivatives to find the smallest possible group that could possibly have antimicrobial activity as well. The rationale was if the prenyl group was active, perhaps even smaller carbon-numbered side chains could also have activity. The simplest carbon chain would be a methyl group, which would correspond to commercially available 3-methylsalicylic acid. Unfortunately, that compound showed none of the desired antimicrobial activity.

3-Allylsalicylic acid was prepared in order to compare the replacement of the prenyl side chain with an allyl side chain. The advantage of this compound is that it is structurally analoguous to the prenyl group and thus could be synthesized in a similar manner. Likewise, the similarity could also lead to a similar activity.

The synthesis follows a similar route as the prenylated salicylate (i.e. *O*-allylation followed by thermal Claisen Rearrangement to give *C*-allylation). Allylation of salicylic acid with an excess of allyl bromide produced the *bis* allylated compound **21** (Scheme 10).[17] Hydrolysis of the ester with sodium hydroxide produced *O*-allylated salicylic acid **22**, which underwent clean thermal electrocyclic rearrangement to produce the target compound 3-allylsalicylic acid **23**.



Scheme 10

Compound **23** was tested and it was not found to have any required antimicrobial activity. Therefore, one can conclude that the prenyl group is the mininum group necessary for the compound to have any desired activity. Currently, the mechanism of action of the within cells is being tested.

The various functionalized salicylic acids prepared, including the C15, C10, and C5 compounds were tested by Dr. Gregory Phillips at Iowa State University for antimicrobial activity using a disc diffusion assay as shown in Figure 7. The bacteria (either *E. coli* or *S. typhimurium*) were grown in top agar, filter discs are placed in the center of nutrient agar plates.

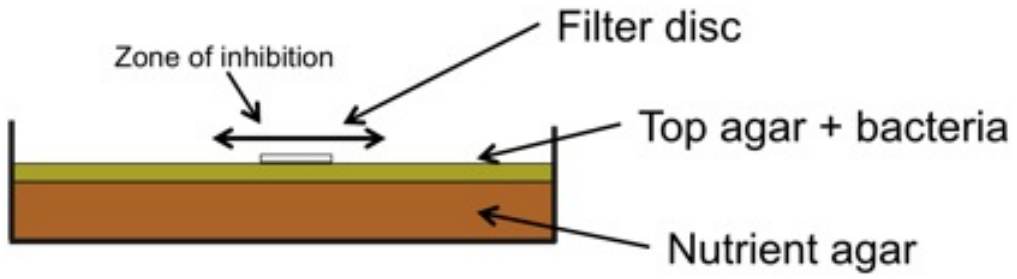


Figure 7. Disc assay to measure zone of inhibition of compounds

Zones of inhibition were measured and reported as mm in Figure 8. Not unexpectedly, the simple salicylic acid and methyl salicylic acid showed no activity, as evidenced by a zone of inhibition of zero (columns A and B, respectively). The synthesized C15 natural product was tested and had the required activity. The C10 geranyl functionalized compound had a zone of inhibition of 6 mm (column F). Interestingly, the C5 compound had the highest activity, with a zone of inhibition of 15 mm (column E). Known antibiotics amicillin and chloramphenicol are represented in columns H and I, respectively. Oddly, the C15 compound (which had identical spectra to the previous samples) showed no activity upon scale-up (column G).

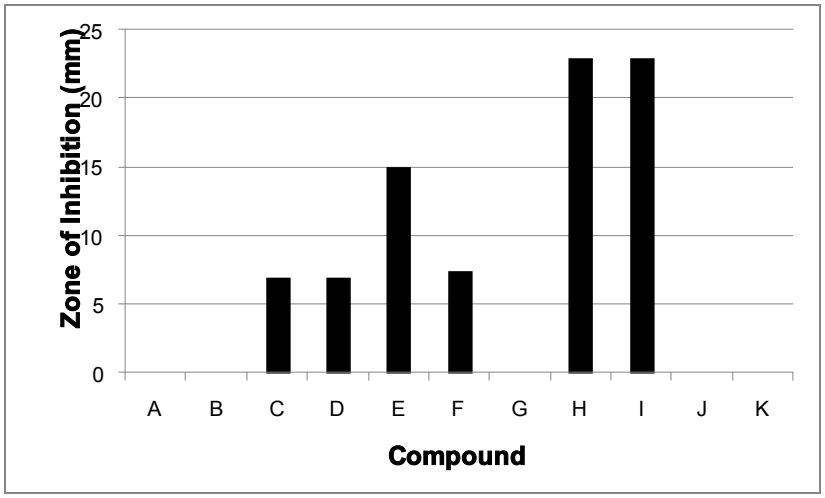


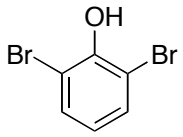
Figure 8. Results of zone of inhibition measurements. Compounds tested include: A. salicylate; B. salicylate+C1; C. salicylate+C3; D. salicylate+O-C3; E. salicylate+C5; F. salicylate+C10; G. salicylate+C15; H. ampicillin; I. chloramphenicol; J. DMSO (solvent control); K. H_2O (solvent control). Salicylate derivatives and antibiotics were applied at a concentration of ~50 µg/µl. Shown are the results with *E. coli*, with similar results obtained for compound E and controls with *S. enterica*.

This project represents the first known preparation of the natural product 3-farnesylsalicylic acid **1** from 2,6-dibromophenol through a 4-step sequence with a 29% overall yield. Additionally, the the first synthesis of 3-geranyl and 3-prenyl salicylic acids were achieved in over a 3-4 step sequence with good overall yields. Both products had similar antimicrobial activity as described for the natural product, with the C5 prenyl having the greatest activity overall. The 3-allylsalicylic acid derivative was prepared as well, but did not have any biological activity, thus proving that the prenyl subunit is

absolutely required for activity. Future work involves further biological assays in order to determine the mode of activity within the cell. Additionally, different side chains are also being considered, including fully hydrogenated prenyl units.

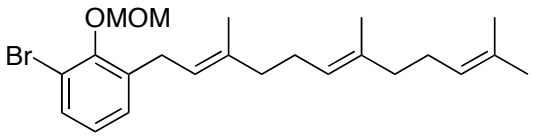
Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran was distilled from sodium and benzophenone. Dichloromethane and toluene was dried over calcium hydride prior to use. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^{1}H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.



2,6-Dibromophenol (2)

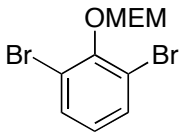
Phenol (189 mg, 2.0 mmol) and diisopropylamine (0.55 mL, 3.9 mmol) were dissolved in 5 mL of dry CH_2Cl_2. Freshly recrystalized NBS (718 mg, 4.0 mmol) was carefully added to the solution in portions, were it was allowed to stir for 1 hour. After quenching with concentrated sulfuric acid, the product was extracted with CH_2Cl_2, dried over $MgSO_4$, concentrated, purified through silica gel chromatography (2:1 hexanes/ethyl acetate) to produce a inseparable mixture (3:1 by ^{1}H NMR peak integration) of 2,6-dibromophenol and 2,4,6-dibromophenol as a white solid (401 mg). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.59 (s, 2H), 7.44 (d, 2H), 6.70 (t, 1H), 5.88 (1H).



1-Bromo-2-(methoxymethoxy)-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (4)

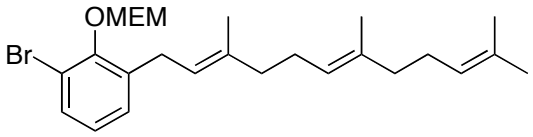
MOM-protected 2,6-dibromophenol (284 mg, 1.0 mmol) was dissolved in THF at -78 ºC. This was treated with a 2.5 M solution of *n*-butyllithium in hexanes (0.38 mL, 1.0 mmol), and the reaction mixture was stirred at -78 ºC for 30 minutes. A solution of freshly-prepared farnesyl bromide (274 mg, 1.0 mmol, made by treatment of farnesyl alcohol with PBr_3) in 5 mL THF was added, and the solution was stirred for a 12-16 hour period, warming to room temperature. After aqueous workup, the crude product was

purified by flash silica gel chromatography (10:1 hexanes/ethyl acetate) to yield pure **4** as yellow oil (292 mg, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.40 (d, J = 6 Hz, 1H), 7.13 (d, J = 6 Hz, 1H), 6.93 (t, J = 6 Hz, 1H), 5.31 (t, J = 6 Hz, 1H), 5.17-5.09 (m, 2H), 5.09 (s, 2H), 3.65 (s, 3H), 3.46 (d, J = 6 Hz, 2H), 2.13-1.97 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H).



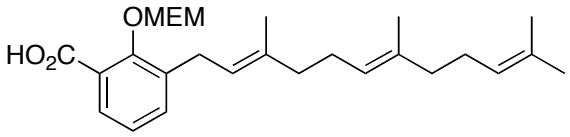
1,3-Dibromo-2-((2-methoxyethoxy)methoxy)benzene (5)

In an oven-dried flask under argon, 2,6-dibromophenol (253 mg, 1.0 mmol) was dissolved in 10 mL dry CH_2Cl_2. To this were added diisopropylethylamine (0.87 mL, 5.0 mmol, 5 equiv.) and MEMCl (0.35 mL, 3.1 mmol, 3 equiv), respectively. The mixture was allowed to stir at room temperature overnight, where it was worked up with saturated $NaHCO_3$ (5 mL), extracted with dichloromethane, and dried over $MgSO_4$. Purfication by silica gel chromatography (4:1 hexanes/ethyl acetate) yielded pure protected phenol **5** as a yellow liquid (342 mg, 100% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.52 (d, J = 9.0 Hz, 2H), 6.88 (t, J = 9.0 Hz, 1H), 5.27 (s, 2H), 4.11 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 6.0 Hz), 3.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 59.3, 70.1, 71.9, 98.5, 118.7, 126.8, 133.1, 151.6; HRMS (EI) m/z exact mass calculated for $C_{10}H_{12}Br_2O_3$ 339.9153, found 339.9160.



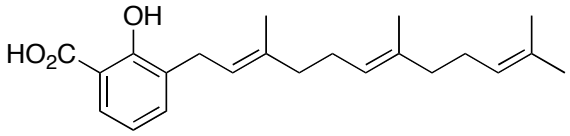
1-Bromo-2-((2-methoxyethoxy)methoxy)-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzene (6).

Compound **5** (342 mg, 1.0 mmol) was dissolved in dry THF (10 mL) under argon at -78 ºC (dry ice/acetone). To this was carefully added a solution of *n*-BuLi (0.4 mL, 2.5M in hexanes, 1.0 mmol) and the reaction was allowed to stir at -78 ºC for 30 minutes. The reaction mixture was treated with a solution of freshly-prepared farnesyl bromide (290 mg, 1.0 mmol) in 5 mL THF. The reaction was allowed to warm to room temperature with stirring for 12 hours. After aqueous work up, purification of the crude product via silica gel chromatography (4:1 hexanes/ethyl acetate) yielded compound **6** as a yellow oil (313 mg, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.38 (d, J = 6.0 Hz, 1H), 7.11 (d, J = 6.0 Hz, 1H), 6.92 (t, J = 6.0 Hz, 1H), 5.31-5.26 (m,1H), 5.17 (s, 2H), 5.13-5.06 (m, 2H), 4.01 (t, J = 6.0 Hz, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.46, 3.40 (s, 3H), 2.2-1.8 (m), 1.67, 1.59; ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 16.3, 16.4, 18.0, 26.0, 26.7, 27.0, 29.0, 39.5, 39.9, 59.3, 69.7, 71.9, 98.8, 116.4, 118.4, 123.3, 124.5, 125.9, 128.7, 129.3, 131.3, 133.6, 135.4, 137.6, 152.6; HRMS (EI) m/z exact mass calculated for $C_{25}H_{37}BrO_3$ 464.1926, found 464.1938.



2-((2-Methoxyethoxy)methoxy)-3-((2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)benzoic acid (7)

Starting material **6** (220 mg, 0.47 mmol) was dissolved in THF at -78 ºC. To this was added a 2.5 M solution of *n*-butyllithium in hexanes (0.19 mL, 0.48 mmol), stirring at -78 ºC for 30 minutes. Gaseous carbon dioxide was bubbled through solution for 1 hour, during which time the reaction flask was warmed to room temperature. The reaction was quenched with HOAc and concentrated, and the crude product **7** was taken to the next step without further purification.

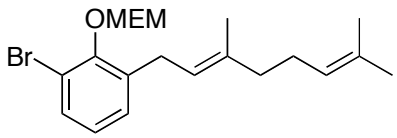


3-Farnesyl-2-hydroxybenzoic acid (1)

A solution of the **7** in THF was added to a solution of freshly prepared $ZnBr_2$ (shown below) and the mixture was stirred at room temperature overnight. The reaction was worked up with H_2O, extracted with ether, dried over $MgSO_4$, and purified by column chromatography (1:2 hexanes/ethyl acetate) to yield **1** as a white solid (72 mg, 45% yield over 2 steps). ^{1}H and ^{13}C NMR spectra correspond to those of the natural product.[2] HRMS (EI) m/z exact mass calculated for $C_{22}H_{30}O_3$ 342.2195, found 342.2201.

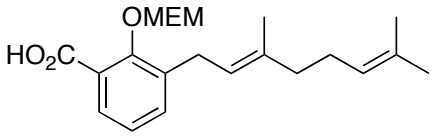
Preparation of $ZnBr_2$: oven-dried zinc powder (346 mg, 5.3 mmol, 10 equiv.) was suspended in 10 mL dry THF. To this was added 1,2-dibromoethane (0.45 mL, 5.2

mmol, 11 equiv.) and the solution was heated to reflux overnight, during which time the color turned cloudy white.



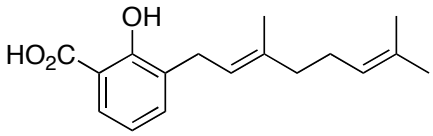
(*E*)-1-Bromo-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-((2-methoxyethoxy)methoxy)benzene (10)

Compound **5** (315 mg, 0.93 mmol) in THF was treaded with 2.5M *n*-BuLi (0.37 mL, 0.93 mmol) at -78 ºC for 30 minutes. The resultant mixture was treated with a THF solution of freshly prepared geranyl bromide (245 mg, 1.1 mmol, made from geraniol and PBr_3) and stirred overnight. The reaction was worked up with aqueous NH_4Cl, extracted with ether, dried over $MgSO_4$, and purified by flash column chromatography to yield **10** as a yellow oil (304 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.49 (d, J = 6.0 Hz, 1H), 7.11 (d, J = 6.0 Hz, 1 H), 6.93 (t, J = 6.0 Hz, 1H), 5.30 (m, 1H), 5.18 (s, 2H), 5.10 (m, 1H), 4.02 (t, 2H), 3.62 (t, 2H), 3.46 (d, 2H), 3.40 (s, 3H), 2.10-2.05 (m, 4H),1.68 (6H), 1.60 (3H); ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 16.4, 18.0, 26.0, 26.8, 29.0, 39.9, 59.3, 69.7, 71.9, 98.8, 117.6, 122.2, 124.4, 125.9, 129.3, 131.3, 131.8, 133.6, 137.3, 152.6; HRMS (EI) m/z exact mass calculated for $C_{20}H_{29}BrO_3$ 396.1300, found 396.1308.



(*E*)-1-Bromo-3-(3,7-dimethylocta-2,6-dien-1-yl)-2-((2-methoxyethoxy)methoxy)benzene (11)

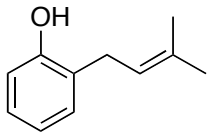
Compound **10** (304 mg, 0.77 mmol) was dissolved in 10 mL dry THF at -78 ºC, where it was treated with 2.5M *n*-BuLi (0.31 mL, 0.78 mmol) for 30 minutes. Carbon dioxide gas was bubbled through solution and warmed to room temp for a 2 hour period. The reaction was worked up with acetic acid and concentrated. The crude product **11** was used in the next step without further purification.



(*E*)-3-(3,7-Dimethylocta-2,6-dien-1-yl)-2-hydroxybenzoic acid (8)

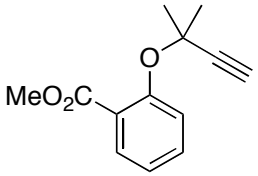
Preparation of **8** was done in a similar fashion as in the preparation of **1**. The starting material was added to a solution of zinc bromide in THF, stirring at room tempertature overnight. The reaction was worked up with H_2O, extracted with ether, dried over $MgSO_4$, and purified by column chromatography (1:1 hexanes/ethyl acetate)to yield **8** as an off-white solid (155 mg, 74% yield over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.72 (br, OH), 8.02 (d, J = 6.0 Hz, 1H), 7.38 (d, J = 6.0 Hz), 7.03 (t, J = 6.0, 1H), 5.31-5.29 (m, 1H), 5.12-5.09 (m, 1H), 3.51 (d, 2H), 2.03-1.96 (m, 4H), 1.68 (s, 6H), 1.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 19.9, 23.1, 32.0, 39.8, 41.2, 47.8, 116.0, 119.7, 121.6, 124.2, 131.2, 132.0, 136.0, 136.8, 153.1, 169.5; HRMS (EI) m/z exact mass

calculated for $C_{17}H_{22}O_3$ 274.1569, found 274.1575.



2-(3-Methylbut-2-en-1-yl)phenol (12)

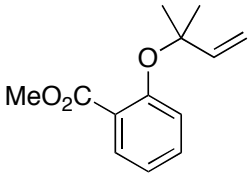
A suspension of NaH (469 mg, 11.7 mmol, 60% in parafin oil) was made in toluene. A solution of phenol (500 mg, 5.3 mmol) in 5 mL toluene was added slowly and carefully to the suspension, where gas began to evolve. The mixture was heated to 60 ºC for 30 minutes before cooling to room temperature and treated with prenyl bromide (0.92 mL, 8.0 mmol). The reaction was stirred at room temperuture for 24 hours before aqueous workup. Purification by silica gel chromatography (15:1 hexanes/ethyl acetate) produced **12** as a yellow liquid (306 mg, 35% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.09 (d, 1H), 6.89-6.79 (m, 3H), 5.32 (t, J = 6 Hz, 1H), 3.36 (d, J = 6 Hz, 2H), 1.78 (s, 6H).



Methyl 2-((2-methylbut-3-yn-2-yl)oxy)benzoate (18)

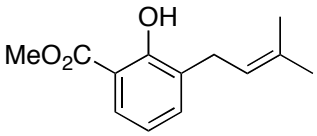
Methyl salicylate (1.46 mL, 11.1 mmol) was dissolved in 10 mL acetonitrile at 0 ºC. To this was added a solution of **17** in 5 mL acetonitrile (1.738 g, 12.2 mmol), 1,8-diazabicycloundec-7-ene (DBU, 2.2 mL, 14,7 mmol), and copper(II) chloride dihydrate

(96 mg, 0.6 mmol), respectively. The reaction mixture was warmed to room temperature, stirring for 12 hours. After aqueous work up, the product was purified by silica gel chromatography (10:1 hexanes/ethyl acetate) to yield pure **18** as a white solid (890 mg, 37% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.77 (d, J = 6 Hz, 1H), 7.56 (d, J = 6 Hz, 1H), 7.43 (t, J = 6 Hz, 1H), 7.11 (t, J = 6 Hz, 1H), 3.88 (s, 3H), 2.56 (s, 1H), 1.67 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 29.6, 52.1, 74.6, 82.1, 86.2, 122.5, 123.1, 125.7, 131.4, 132.6, 155.3, 166.6. HRMS (EI) m/z exact mass calculated for $C_{13}H_{14}O_3$ 218.0943, found 219.1016 (MH^+).



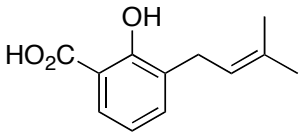
Methyl 2-((2-methylbut-3-en-2-yl)oxy)benzoate (19)

Compound **18** (860 mg, 3.9 mmol) was dissolved in 4 mL of ethyl acetate in a three-necked flask. To this was added Lindlar catalyst (180 mg) and quinoline (0.25 mL, 2.1 mmol). The flask was placed under a hydrogen gas atmosphere, and the reaction stirred for 4 hours. The solution was filtered through a pad of Celite to remove the catalyst, where the filtrate was concentrated. Purification via silica gel chromatography (10:1 hexanes/ethyl acetate) to yield pure **19** as a translucient oil (400 mg, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.70 (d, J = 6 Hz, 1H), 7.31 (t, J = 6Hz, 1H), 7.13 (d, J = 6 Hz, 1H), 7.01 (t, J = 6 Hz, 1H), 5.16 (dd, J = 18 Hz, 1H, J = 7 Hz, 2H), 3.88 (s, 3H), 1.48 (s, 6H).



Methyl 2-hydroxy-3-(3-methylbut-2-en-1-yl)benzoate (20)

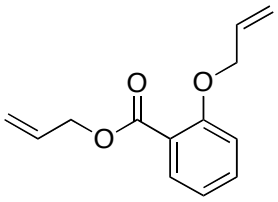
Compound **19** (400 mg, 1.8 mmol) was boiled in toluene (12 mL) for a 24 hour period. The product was concentrated and purified via silica gel chromatography (10:1 hexanes/ethyl acetate) to give **20** as a yellowish oil (336 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.79 (d, J = 6 Hz, 1H), 7.44 (t, J = 6 Hz, 1H), 6.98 (d, J = 6 Hz, 1H), 5.50 (t, J = 6 Hz, 1H), 4.62 (d, J = 6Hz, 2H), 3.88 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H).



3-Prenylsalicylic acid (9)

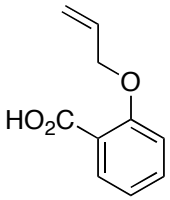
Starting material **20** (293 mg, 1.3 mmol) was dissolved in 5 mL of a 1:1 mixture of dioxane and water. Solid NaOH (235 mg, 5.9 mmol) was added and the solution was heated to reflux. After 3 hours, the reaction was cooled to room temperature and quenched with 1.5 mL a 4 N solution of HCl. The product was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. Purification through silica gel chromatography (1:1 hexanes/ethyl acetate) produced pure **9** as an orange solid (187 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.71 (s, 1H), 7.78 (d, J = 6Hz, 1H), 7.39 (d, J = 6 Hz, 1H), 6.86 (t, J = 6 Hz, 1H), 5.32 (t, J = 6 Hz, 1H), 3.38 (d, J = 6 Hz, 2H), 1.76 (s, 3H), 1.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 18.0, 23.6, 26.0, 115.8, 117.6, 119.1, 121.9, 123.9, 132.1, 133.5, 148.7, 161.4. HRMS (EI) m/z exact mass calculated for

$C_{12}H_{14}O_3$ 206.0943, found 206.0940.



Allyl 2-(allyloxy)benzoate (21)

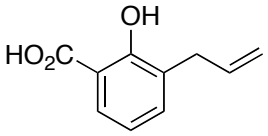
Salicylic acid (501 mg, 3.6 mmol), allyl bromide (0.8 mL, 9.2 mmol), and K_2CO_3 (1.267 g, 9.2 mmol) were dissolved in acetone. The mixture was boiled to reflux for 24 hours. Aqueous workup and purification by flash silica gel chromatography (4:1 hexanes/ethyl aetate) produced pure **21** (657 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.84 (d, J = 6 Hz, 1H), 7.44 (t, J = 6 Hz, 1H), 6.98 (t, J = 6 Hz, 1H), 6.96 (d, J = 6 Hz, 1H), 6.12-5.97 (m, 4H), 5.48 (dd, J = 18 Hz, 2H), 5.28 (dd, J = 6 Hz, 2H), 4.81 (d, J = 6 Hz, 2H), 4.63 (d, J = 6 Hz, 2H).



2-(Allyloxy)benzoic acid (22)

21 (657 mg, 3.0 mmol) was dissolved in 7 mL anhydrous ethanol. NaOH (492 mg, 12.3 mmol) was added, and the reaction mixture was stirred for 12-16 hours. After acidification with 4 N HCl, extratction with CH_2Cl_2, drying, concentration, and purification by recrystalization produced compound **22** as a light yellow solid (230 mg,

43%). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.48 (s, 1H), 8.20 (d, *J* = 6 Hz, 1H), 7.53 (t, *J* = 6 Hz, 1H), 7.15 (t, *J* = 6 Hz, 1H), 7.05 (d, *J* = 6 Hz, 1H), 6.15-6.04 (m, 1H), 5.46 (dd, *J* = 18 Hz, *J* = 7 Hz, 2H), 4.80 (d, *J* = 6 Hz, 2H).



3-Allyl-2-hydroxybenzoic acid (23)

The *O*-allylated compound **22** (230 mg, 1.3 mmol) was dissolved toluene in a thick glass sealable tube with a screw cap. The reaction vessel was heated to 200 ºC in an oil bath for 8 hours. The product was concentrated and purified by flash silica gel chromatography (1:1 hexanes/ethyl acetate) to yield pure **23** (194 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 10.97-10.52 (br, 2H), 7.82 (d, *J* = 6 Hz, 1H), 7.39 (d, *J* = 6 Hz, 1H), 6.88 (t, *J* = 6 Hz, 1H), 6.05-5.96 (m, 1H), 5.11 (dd, *J* = 17 Hz, *J* = 7 Hz, 2H), 3.44 (d, *J* = 3Hz, 2H).

Reference

1. Gupta, M. P.; Correa, M. D.; Solís, P. N.; Jones, A.; Galdames, C.; Guionneau-Sinclair, F. *Journal of Ethnopharmacology*, **1993**, *40*, 77.
2. Rüegg, T.; Calderón, A. I.; Queiroz, E. F.; Solís, P. N.; Marston, A.; Rivas, F.; Ortega-Barría, E.; Hostettmann, K.; Gupta, M. P. *Journal of Ethnopharmacology*, **2006**, *103*, 461.
3. Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John

Wiley & Sons: New York, 1999, pp 708-711.

4. Fujisaki, S.; Eguchi, H.; Omura, A.; Okamoto, A.; Nishida, A. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576.
5. Snieckus, V. *Chem. Rev*. **1990**, *90*, 879.
6. Nicolaou, K. C.; Snyder, S. A.; Huang, X.; Simonsen, K. B.; Koumbis, A. E.; Bigot, A. *J. Am. Chem. Soc.*, **2004**, *126*, 10162.
7. Corey. E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P. Keck, G. E.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.
8. Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150.
9. Bellassoued, M.; Grugier, J.; Lensen, N. *J. Organomet. Chem.* **2002**, *662*, 172.
10. Kalena, G. P.; Jain, A.; Banerji, A. *Molecules*, **1997**, *2*, 100.
11. Yamada, S.; Ono, F.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 750.
12. Masayuki, F.; Fukuoka, O.; Nagatomo, A. Masaru, W. Process for Preparing Hydroxybenzoic Acids. EP 0 834 494 A1. April 8, 1998.
13. de Boer, J. D.; Brown, W. R.; Harutyunyan, S. R.; Bini, L.; Tiemersma-Wegman, T. D.; Alsters, P. L.; Hage, R. L.; Feringa, B. L. *Chem. Comm.* **2008**, 3747.
14. Tisdale, E. J.; Vong, B. G.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59*, 6873.
15. Godfrey, J. D.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405.
16. Nicolaou, K. C.; Lister, T.; Denton, R. M.; Gelin, C. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7501.

17. Ye, T.; García, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1373.

CHAPTER 3. PREPARATION OF ALPHA OLEFINS FROM FATTY ACIDS

Introduction

Alpha olefins are a class of compounds that consist of an alkene at the terminal end of an alkyl chain with a typical structure as shown in Figure 1. The market for alpha olefins is approximately 2.5 million tons per year, and they are used in detergents, surfactants and specialty chemicals. Likewise, short chain linear alpha olefins are commonly used as monomers in the preparation of polyethylene.

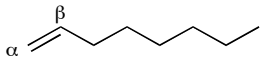


Figure 1. Structure of an alpha olefin

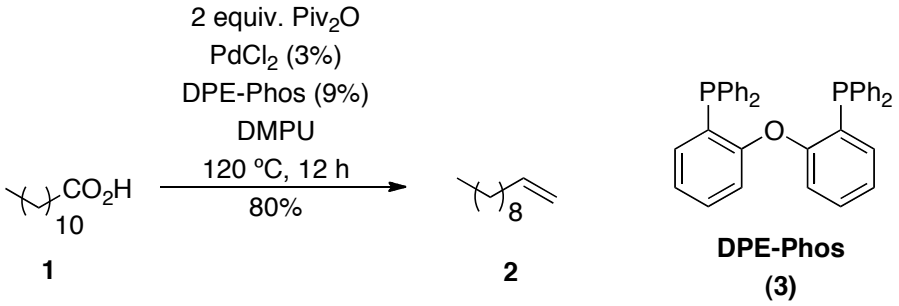
The most common method of preparing linear alpha olefins industrially is oligomerization of ethylene,[1] which comes from petroleum cracking.[2] Of note is that only even carbon-numbered alpha olefins can be made through this process as it involves the joining of a series of C2 carbon units. Other preparations of alpha olefins include dehydration of alcohols[3] and thermal cracking of waxes.[4] Unfortunately, there are few biorenewable-based counterparts for alpha olefins, as terminal olefins are not common components in biomass.

In contrast to ethylene, fatty acids are common components of plant material. Typical biobased sources of fatty acids are corn oil, palm oil, and soybean oil. Owing to the demand of alpha olefins, it is clear that new, renewable methods of production need to be explored. Biological engineers at the Center for Biorenewable Chemicals (CBiRC)

at Iowa State University have designed strains of microbes that can produce large amounts of fatty acids. Thus, the main goal of this project is to find a method of converting these biologically-derived fatty acids into alpha olefins with as high yields as possible. Additionally, the process must utilize inxpensive reagents in order to be economically viable. Although there is interest in biobased preparations of commodity chemicals, one must always keep in mind that the process should be cost effective as well.

Results and Discussion

The first attempt to synthesize olefins was based on the work of Gooßen,[5] the general form is shown in Scheme 1. Palladium chloride is the catalyst and *bis*-(2-diphenylphosphinophenyl)ether (DPE-Phos) **3** is the ligand. The use of an anhydride activator is essential, typically pivalic anhydride. The reaction produces an olefin of one less carbon atom than the starting acid, and thus procedes with loss of either carbon dioxide or carbon monoxide.



Scheme 1. Gooßen preparation of alpha-olefins

The proposed mechanism of this reaction by Gooßen is shown in Figure 2.[6] First, starting acid **1** forms a mixed anhydride with pivalic anhydride (compound **5** where R' is a *tert*-butyl group). Palladium then oxidatively inserts into the anhydride C-O bond on the side away from the R' group to form the aceyl-palladium species **6**. Carbon monoxide is eliminated, which was confirmed via experiment (i.e. collection and IR analysis of the evolved gas). The resulting alkyl palladium **7** rapidly undergoes beta-hydride elimination[7] to give alkene **2**. The palladium catalyst is reformed and the catalytic cycle begins again.

The rate-limiting step in the reaction is the loss of carbon monoxide from the acyl-palladium species, which is a difficult process. Although carbonylation of palladium species is fairly well known,[8] the reverse process is not as common. The elevated temperature is required to overcome the energetic barrier of the step. The use of pivalic anhydride directs the oxidative addition through steric bulk, where palladium inserts in the side of the mixed anhydride to minimize steric hindrance. In this case, the catalyst is directed away from the bulky *tert*-butyl group, which is the desired position for further chemistry. Insertion into the other anhydride bond would be nonproductive. Therefore, this process could be considered an equilibrium, where only one species is able to proceed forward.

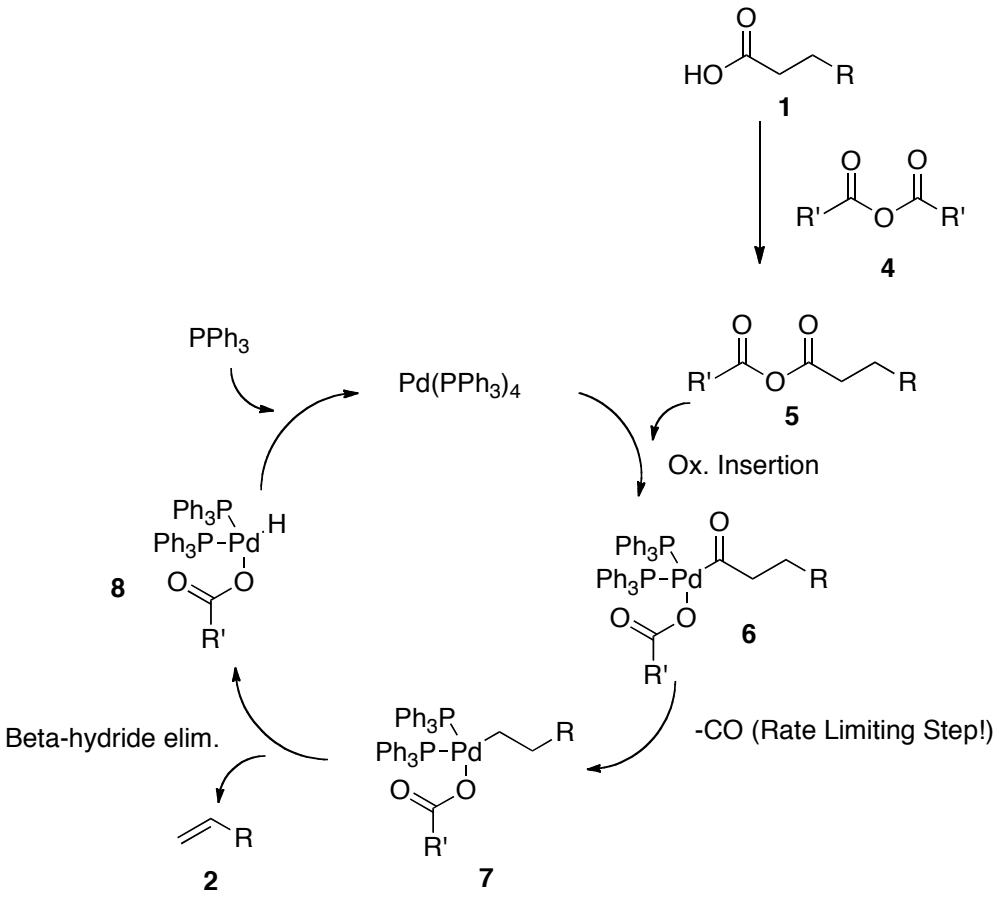


Figure 2. Gooßen's proposed mechanism

This reaction proved to be readily reproducible on a laboratory scale (1-2 g) with typical yields around 80%. However, there are several limitations that prevent it from being feasible on a larger scale. First, it requires the use of an uncommon and expensive ligand. Other, more common ligands were screened, such as triphenylphosphine, and were not found to be as effective as DPE-Phos. The loading is high (3 equivalents of ligand relative to catalyst), which also would increase the cost industrially.

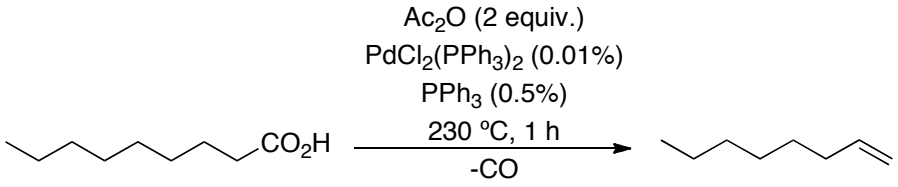
Second, the necessity of pivalic anhydride activator would be expensive upon scale-up. Relative to other anhydrides (e.g. acetic anhydride, butyric anhydride), pivalic

anhydride is more expensive. As a test, the reaction was attempted on a 1 gram scale with acetic anhydride as the activator, but the yield was only around 50%, thus verifying the necessity of pivalic anhydride on this reaction.

The reaction mixture must be heated for long time periods in order to achieve high conversions. A typical experiment requires a temperature of 120 ºC for 12-16 hours, which represents a large input of energy. This sustained heating may not be economically feasible on larger scales and is another disadvantage.

The solvent, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), is also problematic to the reaction. It has a high boiling point and a high polarity required to help solubilize the palladium species. Once the reaction is complete, it is necessary to separate the products from the solvent, typically done in the laboratory via silica gel chromatography. On an industrial scale, solvent recovery would be critical, as DMPU is an uncommon and expensive solvent relative to other organic solvents.

With these difficulties in mind, other methods to synthesize alpha olefins were considered. This led to the work of Miller,[9] which follows a similar decarboxylative preparation of alpha olefins from fatty acids (Scheme 2). The reaction uses an anhydride as an activator, palladium, triphenylphosphine ligand, and high temperatures (greater than 200 ºC). The alpha-olefin product is distilled in order to prevent isomerization via palladium-hydride species. All that remains in the reaction flask is recovered starting material, inactive catalyst, and triphenylphosphine.



Scheme 2

There are a few advantages of this reaction over the previous example. First, it requires no solvent; the reaction is done neat with the starting material and acetic anhydride. Removing the solvent greatly simplifies the reaction and thus lowers the overall cost. Second, the catalyst loading is extremely low, at only 0.01%. This is significantly lower than the 3% used previously and, considering the expense of the palladium catalysts, decreases the cost. Acetic anhydride is the typical anhydride activator in this case, which is more common and cheaper than pivalic anhydride. Additionally, the excess acetic anhydride (as well as acetic acid byproduct) is distilled along with the product, and is thus recoverable. This is in contrast to Gooßen's procedure, where the issue of recovering the anhydride is not considered. Finally, the heating, while at a fairly high temperature, is only maintained for a an hour before the reaction is complete. This would be less of an input of energy than heating at lower temperatures for a much longer time period.

A variety of fatty acid substrates were transformed to the corresponding alpha olefins using the following conditions: 0.1% palladium chloride, 2.5% triphenylphosphine, 2 equivalents of acetic anhydride, and heating up to 230 ºC for a one

hour period, at which point the palladium becomes inactive and precipitates out of solution, turning it black.

The results of these reactions are summarized in Table 1. The conversions (based on recovered starting material) are generally in the 50-70% range and work well for simple acids a on multigram scale (Table 1, entries 1-4). For larger carbon chain fatty acids (i.e. containing twelve carbons or greater, entries 5-6), the olefin products had boiling points higher than the 230 ºC used. For these cases, mild vacuum distillation of the product was employed, as it is essential to remove the product from the reaction flask as soon as it is prepared in order to prevent olefin isomerization.

Additionally, the reaction is effective on both unsaturated and saturated olefins. For example, using oleic acid (Table 1, entry 6), a monounsaturated fatty acid, as the substrate cleanly gives a diene with comparable conversion as similar fully saturated acids. Likewise, the reaction works well on diunsaturated fatty acids (entry 7) to cleanly produce the corresponding triene compound. Previous efforts to produce trienes from linoleic acid were impractical, using stoichiometric amounts of lead tetraacetate.[10] The conversion of oleic acid to the diene using this reaction is known in the literature.[11] However this is the first example of the catalytic conversion of linoleic acid to the triene using this chemistry. In both cases, vacuum distillation was employed, as the products are too involatile to distill under atmospheric pressure.

Entry	Acid Substrate	Conv.
1	octanoic acid (C8)	50%
2	nonanoic acid (C9)	67%
3	undecanoic acid (C11)	45%
4	lauric acid (C12)	51%
5	palmitic acid (C16)	56%
6	oleic acid (C18:1)	60%
7	linoleic acid (C18:2)	69%
8	myristic acid (C14) = 41.3% palmitic acid (C16) = 18.8% palmitoleic acid (C16:1) = 35.5% stearic acid (C18) = 4.4%	52%
9	myristic acid (C14) = 34% palmitic acid (C16) = 25% palmitoleic acid (C16:1) = 36% stearic acid (C18) = 5%	57%

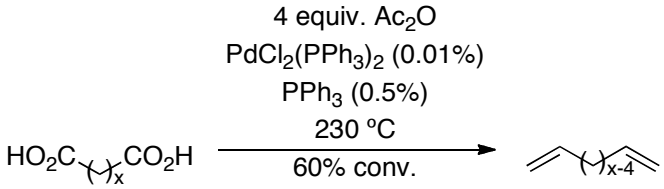
Table 1. Conversion of different fatty acid substrates

With the success of the reaction on simple fatty acids, other substrates were considered. Samples came from biobased sources through CBiRC collaborators containing a mixture of acids. These samples were prepared via engineered strains of bacteria that produce large amounts of fatty acids. After extraction of the desired starting

material and separation from cellular impurities, the catalytic conversion to olefin compounds was achieved in good yield (Table 1, entries 8-9) using vacuum distillation. Notably, the product composition directly matches that of the starting material by GCMS analysis. Thus, there is no preference in the selectivity of reaction.

One of the main goals of CBiRC is the preparation of bifunctional molecules from biobased sources. Because this reaction was found to be effective on monoacids, the next logical step was to attempt the reaction on diacid molecules. This would produce dialkene molecules with 2 less carbon units than the starting diacids, which could have potential use in polymer chemistry as linker molecules.

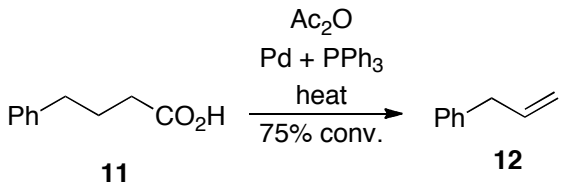
The reaction to convert diacids to dialkenes is shown in Scheme 3. Of note is that 4 equivalents of acetic anhydride were used in this case. Using only the minimum required 2 equivalents of acetic anhydride only leads to insoluble polymer products in the reaction flask with no conversion to the product. An excess of activator alleviates this problem.[12] The conversions are in the same 60% range as the monoacids, where x=6-10 in Scheme 3. Likewise, the diolefin is distilled immediately as it is prepared, giving predominantly the desired terminal olefin product.



9 **10**

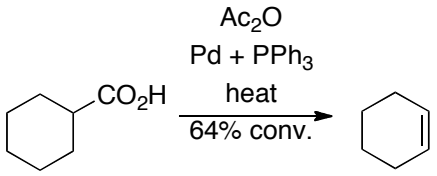
Scheme 3

With these simple acids and diacids complete, the next idea was to extend this chemistry to different acid substrates. One example is 4-phenylbutanoic acid **11** (Scheme 4), which underwent decarboxylative reaction to give allylbenzene with very nice conversion. Although it is not necessarily a bio-based starting material, it represents another succesful example of this chemistry, thus increasing the overall scope of the reaction.



Scheme 4

One might notice that, up until this point, only primary acids were being employed as substrates. This begs the question: if the reaction works well on primary acids, will it be successful on secondary and tertiary acids? Cyclohexane carboxylic acid was the perfect substrate for this reaction (Scheme 5), as cyclohexene would be the only product due to symmetry. Gratifyingly, the reaction gave satisfactory conversion to **14**, thus proving that both primary and secondary acids are both suitable substrates and increasing the scope of this reaction.

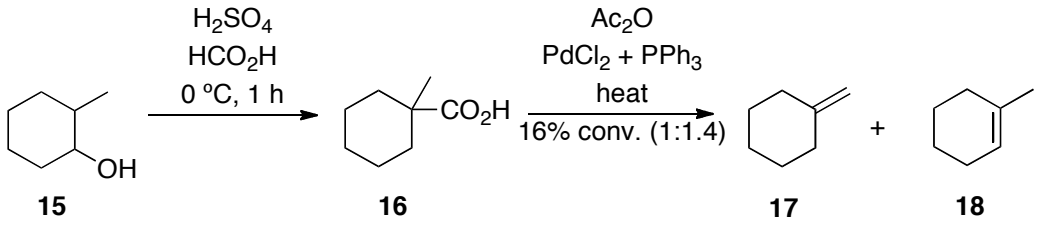


13 **14**

Scheme 5

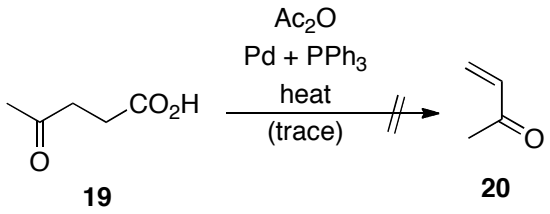
An example of the reaction on tertiary acid is shown in Scheme 6. Alcohol **15** was converted to carboxylic acid **16** via a literature procedure.[13] **16** was transformed via the same decarboxylation procedure to give a mixture of alkenes **17** and **18**. The low yields may be either due to the steric constraints of the bulky tertiary center, or the impurities with crude **16**, which was used directly in the decarboxylation reaction without intermediate purification. In any case, regardless of yields, it is proof that this reaction is indeed possible on tertiary acids as well.

The selectivity of this reaction is worth mentioning. It is the first case of competing products being produced in the reaction, whereas all the previous reactions had a single possible product (aside from traces of isomerized alkene). Integration of ^{1}H NMR peaks in the product mixture showed a 1:1.4 ratio of external **17** to internal alkene **18**. Thus, there is essentially no preference towards a primary or secondary hydrogen atom of the beta-hydride elimination step. Perhaps **18** may be the dominant species because it contains a trisubstituted double bond, while **17** contains a less stable disubstituted double bond.



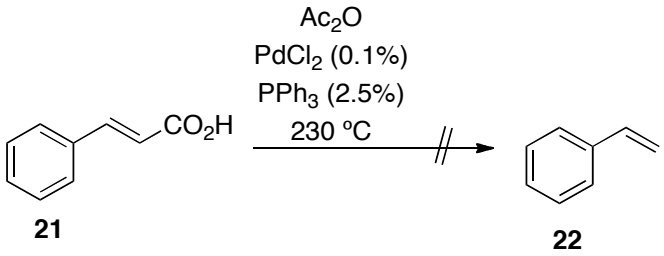
Scheme 6

Other substrates screened in this reaction include levulinic acid, which can be prepared by heating sucrose with concentrated hydrochloric acid.[14] The reaction on levulinic acid is shown in Scheme 7, where the product is methyl vinyl ketone **20**. Due to the volatility of the product, the reaction setup was modified to trap the product in an ice bath. The reaction did give the required product, albeit in very small quantities. The conversion to product is very low, mostly due to thermal instability of the product.



Scheme 7

The next substrate was cinnamic acid, a readily available compound that can come from biorenewable sources. The difference in this case is that the acid is on an sp^2 center, as opposed to previous examples which have an sp^3 center adjacent to the acid (Scheme 8). The expected product of reaction would be styrene, which, of course, is a well-known monomer for polymerization reactions.



Scheme 8

Unfortunately, the reaction did not produce the desired product, only returning primarily unreacted starting material. The rationale for this is that the palladium catalyst undergoes oxidative addition to the anhydride as expected (intermediate **24** in Figure 3 below). Upon loss of carbon monoxide, however, the resultant vinyl-palladium species **25** cannot undergo elimination and becomes "trapped". This is evidenced by the rapid darkening of the reaction solution, which could come from the inactivation of palladium catalyst. The next idea was to add a reducing agent to the reaction to act as a hydride source and drive the catalytic cycle; typically this is done with formic acid.[15] For our reaction, in order to alleviate difficulties with volatility of formic acid, ammonium formate was used. Unfortunately, the reaction still did not produce the required styrene product.

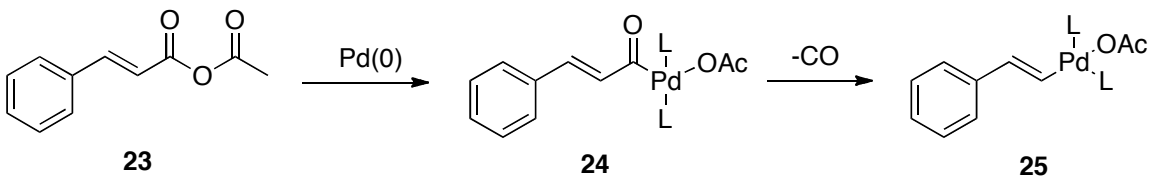
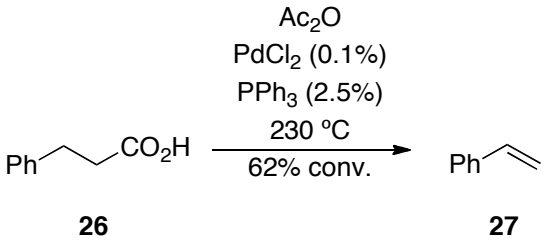


Figure 3. Inactivation of palladium catalyst with cinnamic acid

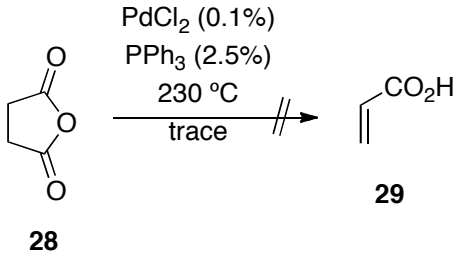
With the difficulties of the sp^2 center in cinnamic acid in mind, the similar hydrocinnamic acid was considered (Scheme 9). The difference with this substrate is that the acid is attached to an sp^3 center, which would allow clean beta-hydride elimination. Gratifyingly, the reaction cleanly produced styrene with 62% conversion. Therefore, it is clear that the acid must be attached to an sp^3 center in order to effectively produce the alkene product.



Scheme 9

One of the key steps in this chemistry is the insertion of a palladium species into an anhydride. In theory, the palladium could insert into other types of anhydrides with subsequent loss of carbon monoxide, etc. In particular, there was interest in the addition of palladium into cyclic anhydrides. The advantage of these substrates over carboxylic acids is that no activator is necessary to form the mixed anhydride. The first example is succinic anhydride **28** (Scheme 10). The resulting product would be acrylic acid, a product of interest. Typical reaction conditions were used in this case (i.e. palladium dichloride, triphenylphosphine, and heating) minus the usual acetic anhydride activator. Similar to the reaction of the anhydride of cinnamic acid, the reaction solution underwent rapid darkening, indicating inactivation of catalyst. However, traces of the

acrylic acid was found in the distillate. The vast majority of the reaction mixture was unconverted starting material.



Scheme 10

With the small promise of the first reaction, a second attempt was done with higher palladium loading (0.5% $PdCl_2$ and 12.5% PPh_3), the rationale being that it would give a higher conversion. Unfortunately, this proved to be unfruitful, as there were still only traces of the acrylic acid product. To try and solve this problem, we look towards the mechanism of reaction (shown in Figure 4). Palladium inserts into the anhydride as expected, forming acyl-palladium species **30**. Loss of carbon monoxide would give alkylpalladium compound **31**. However, due to the fixed ring structure of succinic anhydride, the palladium is unable to reach the required hydrogen atom in **31** for beta-hydride elimination, and thus is unable to go towards the product. This could be evidenced by the rapid darkening of solution, presumably due to trapping of the catalyst as either **30** or **31**.

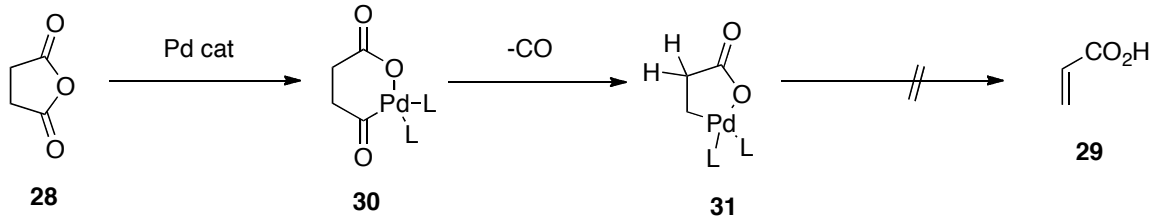
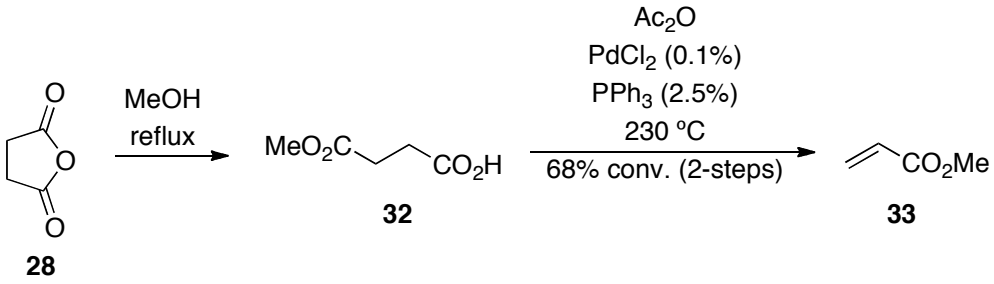


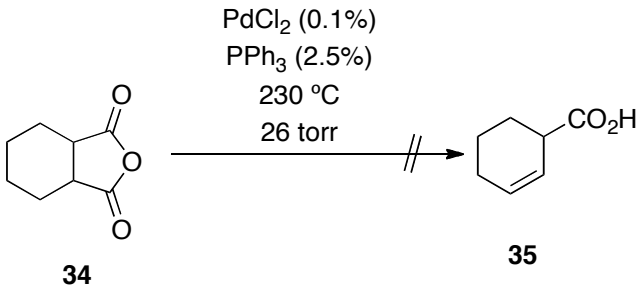
Figure 4

With the hypothesis that the ring structure is inhibiting the elimination of the catalyst, it was postulated that the open-chain configuration of the compound would be more effective at producing the acrylate product. With this in mind, succinic anhydride underwent methanolysis in refluxing methanol to produce succinic anhydride monomethyl ester (**32** in Scheme 11). This intermediate underwent the typical decarboxylation procedure to give methyl acrylate **33**, with reasonable conversion over a 2-step process. The effectiveness of the conversion of the open-chain molecule versus the closed-ring derivative verifies the hypothesis that the beta-hydride elimination step in the closed-ring structure is difficult and prevents the reaction from moving forward. This represents the first and only known method of converting succinates into acrylates via a 2-step, one-pot procedure.



Scheme 11

Utilization of this chemistry on different cyclic anhydride substrates was also considered. 1,2-Cyclohexanedicarboxylic anhydride **34** was used, which, unlike succinic anhydride, has the potential to undergo beta-hydride elimination in two directions. It has been previously proven that elimination of hydride across the ring is impossible due to ring constraints. However, it was postulated that elimination of a hydrogen atom on another adjacent carbon atom is entirely possible. The reaction was the first attempted using vacuum distillation (Scheme 12), but none of the requisite alkene products were formed, even in the reaction flask. Again, a rapid darkening of the reaction solution is seen. This may be proof that, although it is possible for palladium to insert into anhydride bonds, in the case of cyclic anhydrides, the fixed geometry of the cyclic acylpalladium species prevents it from moving forward in the reaction process.



Scheme 12

With, all of these reactions completed, we looked at optimization of the reaction conditions. After all, in order to even be considered practical, the yields must be as high as possible in order to be effective. There are a few variables to change in order to achieve optimal conversion. These are as follows: temperature, type of palladium catalyst, type of anhydride activator, catalyst loading, and triphenylphosphine loading. Each will be looked at in turn. One note is that each example, and all subsequent examples, were done on a 10 gram scale on nonanoic acid. The percent conversion is based on recovered starting material.

First, let us look at the effect of the temperature on the overall conversion of the starting material to the product (Table 2). As reported by Miller, no reaction occurs until the internal temperature reaches 190 ºC. This was verified by heating the reaction in 20 degree increments starting at 110 ºC and monitoring the reaction by taking aliquots from the reaction flask and checking by proton NMR. As expected, no olefin product was seen until the flask had reached an internal temperature of 190 ºC.

With this in mind, the percent conversion of acid to product is monitored. As shown in Table 2, the difference in conversion between 200 ºC and 240 ºC shows a general trend showing that increased temperature leads to increased conversion. However, the conversion seems to have reached the limit of around 60-70%. Perhaps heating to temperatures higher than 250 ºC would lead to higher conversions, but due to limitations in the reaction set-up and for safety reasons, the temperature was not heated beyond 250 ºC.

Table 2. Effect of temperature

Entry	Pd Cat	Anhydride	Temp.	Pd loading	PPh_3 loading	Conv.
1	$PdCl_2$	Ac_2O	240 ºC	0.1 %	5 %	67 %
2	$PdCl_2$	Ac_2O	220 ºC	0.1 %	5 %	63 %
3	$PdCl_2$	Ac_2O	200 ºC	0.1 %	5 %	63 %

Different activating anhydrides were also considered for the reaction. With the idea of the mixed anhydride directing the palladium insertion, the anhydrides considered would have to be significantly bulky so that the insertion occurs in the desired position away from the bulky group. This would lead to less chance of undesired insertions in the opposite position and thus one would expect higher conversions when compared to the simple acetic anhydride. This leads to pivalic anhydride (containing a *tert*-butyl group) and butyric anhydride (containing an *iso*-propyl group). One point of note is that although both pivalic and *iso*-butyric anhydride are more expensive than acetic anhydride, the

excess anhydride and corresponding acid (i.e. pivalic acid and butyric acid, respectively) distill along with the product, and therefore they are recoverable. The results of experiments are summarized in Table 3. Interestingly, the new anhydrides give conversions comparable to that of acetic anhydride, albeit pivalic anhydride giving slightly increased conversions and *iso*-butyric anhydride slightly lower conversions.

Table 3. Effect of anhydride activator

Entry	Pd Cat	Anhydride	Temp.	Pd loading	PPh_3 loading	Conv.
1	$Pd(OAc)_2$	Ac_2O	240 ºC	0.1 %	5 %	61 %
2	$Pd(OAc)_2$	Piv_2O	240 ºC	0.1 %	5 %	63 %
3	$Pd(OAc)_2$	iBu_2O	240 ºC	0.1 %	5 %	58 %

The effect of the anhydride activator was further studied. Several fatty acids were converted using either 1 equivalent pivalic anhydride or acetic anhydride. The results shown in Figure 5. It is clear that, in all cases, pivalic anhydride (blue) gives higher conversions than acetic anhydride (red). In some cases, the conversion utilizing pivalic anhydride was higher by greater than 10 percent.

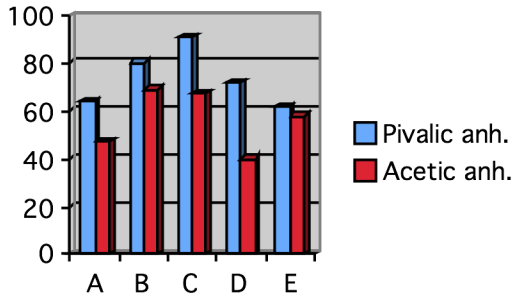


Figure 5. Decarboxylation of various carboxylic acids using different anhydride activators (% conversion) A. undecanoic acid B. palmitic acid C. myristic acid D. lauric acid E. nonanoic acid

The next variable to be looked at was the effect of the type of catalyst used, shown in Table 4. In the original Miller paper, only palladium bistriphenylphosphine dichloride, and palladium dichloride were considered. Rhodium was also used, but the expense of rhodium precludes its use on an industrial scale, so it was not considered. In our case, five different catalysts were screened: four homogeneous catalysts (palladium dichloride, palladium *bis*-triphenylphosphine dichloride, palladium tetrakistriphenylphosphine, and palladium acetate and one heterogeneous catalyst (10% palladium on activated carbon). Of the homogeneous catalysts, is seems that in general Pd(II) (entries 2 and 3 in Table 4) tend to give higher conversions than Pd(0) (entries 1 and 4 in Table 4), although each tend to give similar conversions in the 60% range. Palladium tetrakistriphenylphosphine gives the lowest relative conversion presumably due to the thermal instability of the catalyst. Using palladium on activated carbon (a

heterogeneous catalyst) gave no conversion. In any case, palladium dichloride gave the highest overall conversions and was considered the optimal catalyst for reaction.

Table 4. Effect of catalyst type

Entry	Pd Cat	Anhydride	Temp.	Pd loading	PPh_3 loading	Conv.
1	$Pd(PPh_3)_4$	Ac_2O	240 ºC	0.1 %	5 %	60 %
2	$PdCl_2(PPh_3)_2$	Ac_2O	240 ºC	0.1 %	5 %	64 %
3	$PdCl_2$	Ac_2O	240 ºC	0.1 %	5 %	67 %
4	$Pd(OAc)_2$	Ac_2O	240 ºC	0.1 %	5 %	61 %
5	Pd/C	Ac_2O	240 ºC	0.1 %	5 %	0 %

The final variables explored were the loading of catalyst and triphenylphosphine ligand. The literature reports a 0.01% catalyst and 0.5% triphenylphosphine loading, a fifty-fold excess of triphenylphosphine relative to palladium. The catalyst loading is already very low, at milligram quantities for tens of grams of substrate. Therefore the next logical question is if increasing the catalyst loading will increase the conversion signifcantly. In the case where palladium tetrakistriphenylphosphine is the palladium source, an increase of the catalyst loading from 0.01% to 0.1% increased the conversion by 16% (Table 5, entries 2 and 3). When palladium chloride is the catalyst (Table 5, entries 4 and 8), increasing the catalyst loading 10-fold has less of an effect (only a 5% increase in conversion), due to the effectiveness and stability of the catalyst used. In any

case, the overall trend is that higher catalyst loading leads to higher conversion, which is not a surprising result.

Because the catalyst loading is extremely low, and the anhydride activator has the potential to be recovered, triphenylphosphine loading is one of the limiting factors to the viability of the reaction, as it is used in large excess relative to the catalyst. The first experiment was to simply eliminate the triphenylphosphine altogether (entry 1). However, only a low conversion was achieved. Likewise, using a 1:1 catalyst to triphenylphosphine loading (entry 7) only produced trace amounts of the desired product. Changing the ligand to the previously used DPE-Phos did not have any increase in yields. Due to its expense it was not considered any further. Based on these experiments, it is clear that an excess of triphenylphosphine ligand is absolutely required for the reaction.

The next question to be answered was how low can the triphenylphosphine loading can go without the subsequent loss in conversion. Decreasing the ligand loading in half (i.e. from a 50-fold excess to a 25-fold excess) showed no significant decrease in overall conversion. For example using a 0.1% amount of catalyst, decreasing the ligand loading from 5% to 2.5% (Table 5, entries 4 and 5) gave only a 1% decrease in conversion. Likewise, using a 0.01% catalyst loading, decreasing the amount of ligand used from 0.5% to 0.25% (Table 5, entries 8 and 9) also only gave a 1% decrease in conversion of fatty acid to olefin.

Decreasing to a 10-fold excess of ligand gave different results. Only a slight decrease in conversion (4%) was seen using a 0.1% catalyst and 1% triphenylphosphine loading level (Table 5, entries 4 and 6). However, at the 0.01% catalyst and 0.1% ligand

loading level, a large change in the overall conversion was seen (Table 5, entries 8 and 10), decreasing from 62% to 28%. This may be a case of concentration, as the amount of nonanoic acid substrate and acetic anhydride were not changed in any of these experiments, even with lower catalyst/ligand loading.

Table 5. Effects of catalyst and triphenylphosphine loading

Entry	Pd Cat	Anhydride	Temp.	Pd loading	PPh_3 loading	Conv.
1	$Pd(PPh_3)_4$	Ac_2O	240 ºC	0.1 %	0 %	2 %
2	$Pd(PPh_3)_4$	Ac_2O	240 ºC	0.1 %	5 %	60 %
3	$Pd(PPh_3)_4$	Ac_2O	240 ºC	0.01 %	0.5 %	44 %
4	$PdCl_2$	Ac_2O	240 ºC	0.1 %	5 %	67 %
5	$PdCl_2$	Ac_2O	240 ºC	0.1 %	2.5 %	66 %
6	$PdCl_2$	Ac_2O	240 ºC	0.1 %	1 %	63 %
7	$PdCl_2$	Ac_2O	240 ºC	0.1 %	0.1 %	trace
8	$PdCl_2$	Ac_2O	240 ºC	0.01 %	0.5 %	62 %
9	$PdCl_2$	Ac_2O	240 ºC	0.01 %	0.25 %	61 %
10	$PdCl_2$	Ac_2O	240 ºC	0.01 %	0.1 %	28 %

There are a few main conclusions gleaned from Table 5. First is that an excess of triphenylphosphine ligand is required, although not necessarily at a 50-fold equivalents; 25-fold and, in certain cases, 10-fold excess of ligand is also tolerated. Secondly, changing the catalyst loading from 0.1% to 0.01% does not have a large effect on the conversion of reaction.

In all of the examples above, even with optimized reaction conditions, the conversion never seemed to go above 70%. This is a large problem if this process is to be used industrially, as high yields will be required. One possible solution to this problem is the addition of additional catalyst to the reaction mixture once it becomes inactivated. Thus, an experiment was undertaken in that, after a first round of reaction, additional catalyst, ligand, and acetic anhydride was added to the reaction mixture. Additional heating and further distillation of the product produced the alpha olefin product with an overall conversion of approximately 90% for the 2-step process. The addition of a third round of catalyst would presumably push the reaction further and increase the overall conversion.

In conclusion, the large scale preparation of alpha olefins from fatty acids was achieved. A wide variety of carboxylic acids were used as substrates, including those derived from biological sources. A similar method was used to prepare methyl acrylate from succinic anhydride in a 2-step, one-pot procedure. Future work includes utilizing heterogeneous palladium catalysts instead of the homogeneous catalysts currently used. This would allow for recycling of the palladium catalyst and would increase the economic viability of this chemistry.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. All experiments were performed under ambient atmospheric pressure unless otherwise noted. Nuclear magnetic resonance experiments were performed with a Varian 300 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Gas chromatography experiments were performed on a Micromass GC-TOF MS.

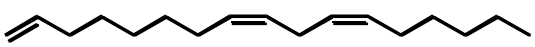
Typical reaction procedure on nonanoic acid:

Nonanoic acid (10 g), triphenylphosphine (0.5%), palladium dichloride (0.01%), and acetic anhydride (2 equivalents) are all mixed together in a 50 mL round bottom flask attached to a short path distillation apparatus with an attached collecting flask. The reaction flask is heated in an oil bath (Dow Corning fluid) up to 230 ºC with stirring. Initially, excess acetic anhydride and acetic acid distills off. Around 190 ºC, 1-octene begins to distill off the reaction flask and heating is continued to around 230 ºC. After approximately 45 minutes to 1 hour, the reaction solution darkens to black and inactive palladium catalyst precipitates out, indicating completion of the reaction. The remainder in the flask is inactive palladium, triphenylphosphine, unreacted nonanoic acid, and small amounts of mixed anhydride. The percent conversion is determined by the mass of remaining starting material remaining in the reaction flask (typical conversion is ca. 60%). The ratio of alpha-olefin to isomerized olefin is determined by integration of the

olefinic hydrogens by proton ^{1}H NMR of the product, which found to be around 95:5 of the desired alpha olefin over the isomerized olefin. ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 5.87-5.73 (m, 1H), 5.41-5.43 (m, 2H, isomerized product), 4.96 (dd, J = 12 Hz, J = 6 Hz, 2H), 2.17-1.99 (m, 4H), 1.38-1.24 (m, 6H), 0.86 (t, J = 6 Hz, 3H).

Preparation of triene from linoleic acid

To a single-necked, 25 mL round-bottom flask equipped with a teflon stirbar is added linoleic acid (2.081 g, 7.4 mmol), palladium dichloride (6 mg, 0.03 mmol), triphenylphosphine (64 mg, 0.2 mmol), and acetic anhydride (3 mL, 32 mmol). The flask is equipped with a short-path distillation apparatus with a thermometer and a 25 mL collecting flask in an ice bath. The reaction mixture is gradually heated to a temperature of 240 ºC in an oil bath over a 15 minute period, where the desired triene compound is disstilled under vacuum (26 torr), along with excess acetic anhydride and acetic acid byproduct. The reaction is complete after approximately 45 minutes heating at 240 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The reaction flask is cooled to room temperature and weighed to determine how much starting material was removed due to reaction (1.429 g, 69% conversion).



(8*Z*,11*Z*)-Heptadeca-1,8,11-triene: ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 5.71-5.57 (m, 1H), 5.26-5.12 (m, 4H), 4.79 (dd, J = 18 Hz, J = 9 Hz, 2H), 2.62 (t, J = 6 Hz, 2H), 2.05-1.97

(m, 6H), 1.22-1.15 (m, 12H), 0.74 (t, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 139.0, 130.1, 129.9, 128.1, 128.0, 114.2, 33.8, 31.6, 29.5, 29.4, 29.2, 28.9, 28.8, 27.2, 25.6, 22.6, 14.0. HRMS (EI) m/z exact mass calculated for $C_{17}H_{30}$ 234.2342, found 234.2340.

Preparation of cyclohexene from cyclohexane carboxylic acid:

To a single-necked, 50 mL round-bottom flask equipped with a teflon stirbar is added 10 g nonanoic acid, 14 mg palladium dichloride, and 512 mg triphenylphosphine, and 15 mL of acetic anhydride, respectively. The flask is equipped with a short-path distillation apparatus with a thermometer, argon balloon, and an attached 50 mL collecting flask in an ice bath. The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and cyclohexene product. The reaction is complete after approximately 30 min heating at 230 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of product by comparison to commercially available materials. The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (6.4 g, 64% conversion).

Preparation of methyl acrylate from succinic anhydride:

To a single-necked, 100 mL round-bottom flask equipped with a teflon stirbar, is added 20 g of succinic anhydride dissolved in 50 mL methanol. The flask is equipped

with a reflux condenser topped with a septa and argon balloon, and the reaction mixture is heated to reflux (70 ºC) in an oil bath (Dow Corning Fluid) for a 16 hour time period. The reaction flask is then allowed to cool to room temperature, the stir bar removed, and the excess methanol removed via rotary evaporator to give 26.4 g of succinic acid monomethyl ester.

In the same 100 mL flask containing succinic acid monomethyl ester is added a teflon stirbar, 35 mg palladium dichloride, 1.31 g triphenylphosphine, and 38 mL acetic anhydride, respectively. The flask is equipped with a short-path distillation apparatus with a thermometer, argon balloon, and an attached 100 mL collecting flask in an ice bath. The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and methyl acrylate. The reaction is complete after approximately 30 min of heating at 230 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of methyl acrylate, comparing to spectra of commercially available material. The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (17.9 g, 68% conversion).

Preparation of styrene from hydrocinnamic acid:

To a single-necked, 100 mL round-bottom flask equipped with a teflon stirbar is added 20.1 g hydrocinnamic acid, 25 mg palladium dichloride, and 899 mg triphenylphosphine, and 25 mL of acetic anhydride, respectively. The flask is equipped

with a short-path distillation apparatus with a thermometer, argon balloon, and an attached 100 mL collecting flask in an ice bath. The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and styrene product. The reaction is complete after approximately 30 min of heating at 230 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of styrene, a commercially-available compound. The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (12.3 g, 61% conversion).

Preparation of a mixture of alpha olefins under reduced pressure:

To a single-necked, 100 mL round-bottom flask equipped with a teflon stirbar is added myristic acid (20.72 g), palmitic acid (27.23 g), and of stearic acid (2.21 g). Palladium dichloride (45 mg), and triphenylphosphine (1.338 g), and acetic anhydride (50 mL) are also added, respectively. The flask is equipped with a short-path distillation apparatus with a thermometer, argon balloon, an attached 100 mL collecting flask in an ice bath, and placed under vacuum by means of a small vacuum pump (26 torr). The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and olefin products. The reaction is complete after approximately 30 min of heating at 230 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of styrene.

The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (36.26 g, 72% conversion).

A second experiment was run in a 25 mL round-bottom flask using a mixture of myristic acid (0.42 g), palmitic acid (0.56 g), and stearic acid (0.05 g). Palladium dichloride (2 mg), triphenylphosphine (32 mg), and acetic anhydride (5 mL) are employed in this case. The flask is equipped with a short-path distillation apparatus with a thermometer, argon balloon, an attached 25 mL collecting flask in an ice bath, and placed under vacuum by means of a small vacuum pump (26 torr). The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and olefin products. The reaction is complete after approximately 30 min of heating at 230 ºC when no more product distills off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of styrene. The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (0.77 g, 75% conversion).

Preparation of alpha olefins from a mixture of fatty acids from a biological sample:

To a single-necked, 25 mL round-bottom flask equipped with a teflon stirbar is added 0.51 g of a mixture of fatty acids with the following composition: 41.3% of C14, 35.5% of C16:1, 18.8% of C16, and 4.4% of C18. This sample came from the petroleum ether extraction of a biological sample. 5 mg palladium dichloride, 50 mg triphenylphosphine, and 5 mL of acetic anhydride are added to the reaction flask as well.

The flask is equipped with a short-path distillation apparatus with a thermometer, an attached 25 mL collecting flask in an ice bath, and placed under vacuum by means of a small vacuum pump (26 torr). The reaction flask is heated to a temperature of 230 ºC in an oil bath over a 30-40 minute time period, distilling out the excess acetic anhydride, acetic acid byproduct, and olefin products. The reaction is complete after approximately 30 min of heating at 230 ºC when no more products distill off and the solution darkens to a black color due to inactivation of the catalyst. The distillate is then analyzed by NMR to verify the presence of alpha olefins. The reaction flask is cooled and weighed to determine how much starting material was removed due to reaction (0.26 g, 51% conversion). The mixture of products was analyzed by GC-MS. GC-MS data: 7.06 min (m/z = 182.2, C13 alkene, 0.42), 8.74 min (m/z = 208.3, C15 monounsaturated alkene, 0.36), 8.90 min (m/z = 210.3, C15 alkene, 0.18), 10.37 min (m/z = 236.3, C17 alkene, 0.04).

The reaction was repeated under similar reaction conditions (i.e. 26 torr pressure, 230 ºC heating) using a sample (3.7 g) of a mixture of fatty acids with the following composition: 34% of C14, 36% of C16:1, 25% of C16, and 5% of C18. 6 mg of palladium chloride, 60 mg triphenylphosphine, and 25 mL acetic anhydride were employed in this case. The conversion of this reaction is 2.1 g (57%). GC-MS data: 7.33 min (m/z = 182.2, C13 alkene, 0.34), 9.01 (m/z = 208.3, C15 monounsaturated alkene, 0.36), 9.16 min (m/z = 210.3, C15 alkene, 25%), 10.37 min (m/z = 236.3, C17 alkene, 5%).

References

1. Cossee, P. *J. Catal.* **1964**, *3*, 80.
2. Picciotti, M. *Oil Gas J.* **1997**, *95*, 53.
3. (a) Baba, T.; Sakai, J.; Watanabe, H.; Ono, Y. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 2555; (b) Highfield, J. G.; Moffat, J. B. *J. Catal.* **1982**, *77*, 473.
4. Worrell, G. R.; Chapman, R. F.; Woinsky, S. G. *Ind. Eng. Chem. Process Des. Dev.* **1967**, *6*, 89.
5. Gooßen, L. J.; Rodriguez, N. *Chem. Comm.* **2004**, 724.
6. Gooßen, L. J.; Koley, D.; Hermann, H.; Thiel, W. *Chem. Comm.* **2004**, 2141.
7. Forbes, J. G.; Gellman, A. J. *J. Am. Chem. Soc.* **1993**, *115,* 6277.
8. Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
9. Miller, J. A.; Nelson, J. A.; Byrne, M. P. *J. Org. Chem.* **1993**, *58*, 18.
10. Liu, F.-C.; Li, Y.-W.; Lin, J.; Zhu, H.-Y.; Li, Q.; Zong, Q.-S. *Gaodeng Xuexiao Huaxue Xuebao* **2003**, *24*, 1040.
11. Haenchen, A,; Suessmuth, R. D. *Synlett* **2009**, *15*, 2483.
12. Gao, Z.-L.; Yin, C.-X.; Liu, F.-C. *Yunnan Daxue Xuebao* **2001**, *23*, 201.
13. Haaf, W. *Org. Synth. Coll. Vol. 5.* **1973**, 739.
14. McKenzie, B. F. *Org. Synth.* **1941**, *1*, 335.
15. Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111,* 6281.

CHAPTER 4. NEW PRODUCTS FROM PYRONES

Introduction

The Diels-Alder reaction is one of the most useful tools available to organic chemists. It is a cycloaddition reaction that forms two new carbon-carbon bonds in a single step, involving the reaction of a dialkene compound (the 'diene') with an olefin (the 'dieneophile'). Typically the diene component is electron-rich, while the dieneophile is electron deficient, although this is not always the case. Some reactions involve the opposite electron demand, i.e. using an electron poor diene and an electron rich dieneophile, although they are less common.[1]

Diels-Alder reactions on 2-pyrone derivatives are fairly well known.[2] Because of a significant aromatic character (resonance forms shown in Figure 1), they are less reactive than traditional diene compounds in cycloaddition reactions.

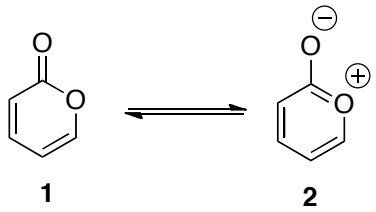
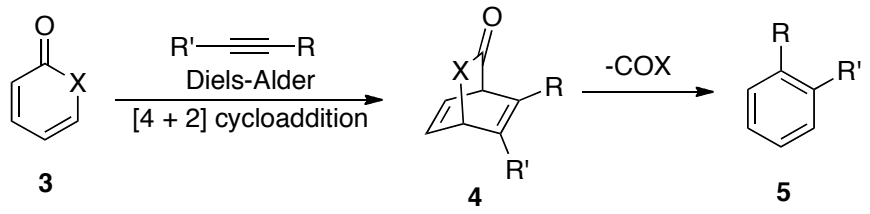


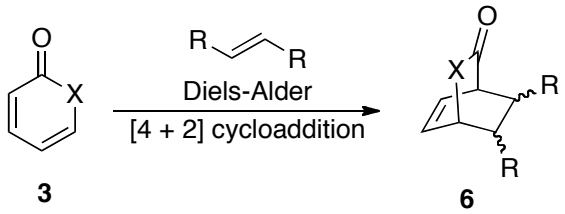
Figure 1. Resonance forms of 2-pyrone

A typical example of this type of reaction with a pyrone is shown in Scheme 1, using an alkyne as the dienophile. The two reactants undergo a [4+2] cycloaddition to form a unstable bicyclic intermediate **4**, which rapidly eliminates the elements of COX to

form an aromatic compound. For pyrones (where X=O), this involves irreversible loss of carbon dioxide. In the case where the dienophile is an alkene (Scheme 2), bicyclic compound **6** is stable and can be isolated.



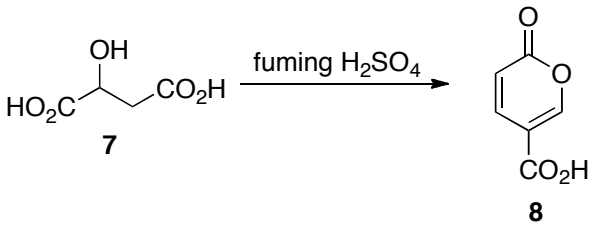
Scheme 1. Diels-Alder reaction with alkynes



Scheme 2. Diels-Alder reaction with alkenes

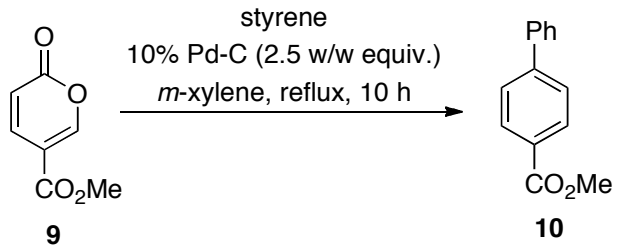
With this in mind, we wanted to utilize a pyrone that could be prepared via biorenewable pathways. Coumalic acid can be prepared from treatment of malic acid with fuming sulfuric acid, following a known procedure[3] (Scheme 3). Malic acid is an important intermediate in the citric acid cycle and a common component in fruit. Biologists could potentially engineer microbes that would utilize a metabolic pathway that siphons off malic acid, thus allowing production in large quantities from renewable

biomass. With this in mind, this makes coumalic acid a good candidate as substrate for the biorenewable chemicals platform.



Scheme 3. Preparation of coumalic acid from malic acid

Earlier work done by Matsushita and coworkers explored the decarboxylative Diels-Alder reactions of methyl coumalate with aromatic olefins to produce 4-aryl methyl benzoates[4] (Scheme 4). The reaction was done with a 10% palladium on activated carbon catalyst under thermal conditions (refluxing *m*-xylene, dodecane, or mesitylene) to produce 4'-methylbiphenyl-4-carboxylate **10** in good yield.



Scheme 4

The mechanism of reaction is shown in Figure 2. First, methyl coumalate and the olefin undergo a thermal Diels-Alder reaction to form bicylic intermediate **11**. The

palladium catalyst then serves to dehydrogenate **11** to form compound **12**, which is unstable and in turn undergoes an electrocyclic aromatization and exclusion of carbon dioxide to give product **10**. Interestingly, the regiochemistry of the reaction was reported to produce the *para* substituted product exclusively.

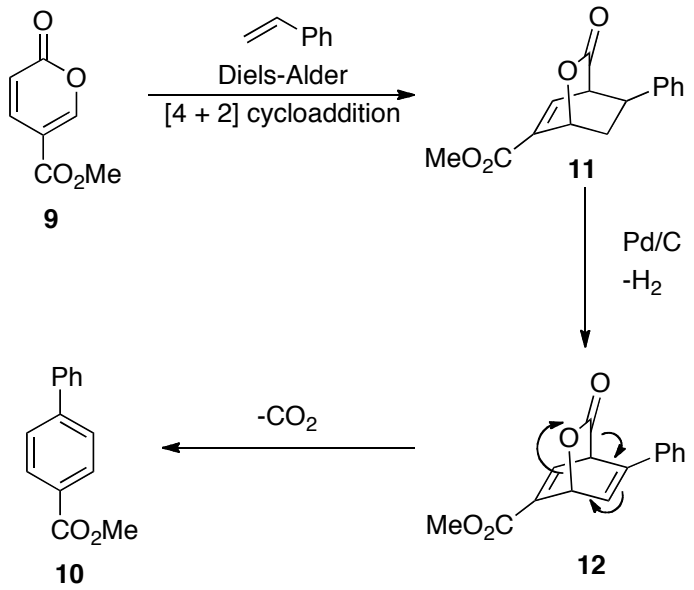


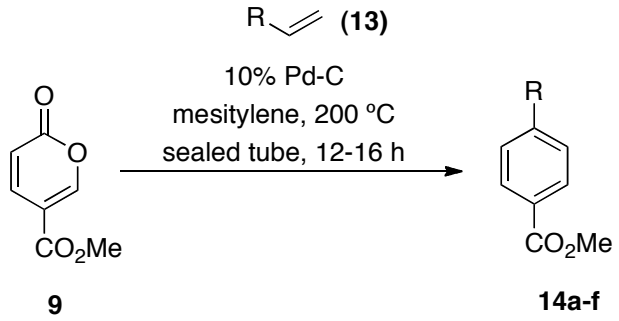
Figure 2. Mechanism for decarboxylation

Like the work with alpha-olefins, this project is in collaboration with the Center for Biorenewable Chemicals (CBiRC). One of the main goals of the center is producing commodity chemicals currently produced through petrochemical methods through new biobased methods. One of the the potential chemical targets is 1,4-benzenedicarboxylic acid or terephthalic acid. The typical prodution of this compound occurs via oxidation of *p*-xylene over manganese or cobalt acetate in acetic acid.[5] *p*-Xylene comes from naphtha, a petroleum source.

With this in mind, we evaluted a new method of producing terephthalic acid from biorenewable sources. Methyl coumalate can undergo a decarboxylative Diels-Alder reaction with simple alkyl olefins to produce *para*-substituted methyl benzoates. The resultant aromatic alkane can be oxidized to the benzoic acid, and the methyl ester hydrolyzed to produce terephthalic acid. Methyl coumalate is the methyl ester of coumalic acid.[6] The regiochemistry of the reactions is critical in order to produce the required *para* substitution on the terephthalic acid. The reaction also suggests the use of simple, inactivated olefins, in connection with previous work with alpha olefins.

Results and Discussion

The first experiments were done on methyl coumalate with various olefin substrates. The general form of the reaction is shown in Scheme 5. This was done in a similar fashion as the literature precedent: methyl coumalate, 2.5 weight equivalents (relative to methyl coumalate) of a 10% palladium on carbon catalyst, and 10 molar equivalents of 1-alkene in mesitylene heated to 200 ºC. The first example used 1-decene as the olefin substrate. Gratifyingly, this produced the alkyl-substituted benzoic acid methyl ester with the alkyl group in the *para* position as expected, with only traces of the *meta* isomer.



Scheme 5

One of the disadvantages of previous work was the very high palladium loading used. While the catalyst only contains 10% of the required palladium, 2.5 weight equivalents is still too high to be practical. Ideally, the catalyst loading would be as low as possible. Several experiments were done to decrease the catalyst loading, and it was found that using 0.25 weight equivalents of 10% palladium on carbon had no effect on both the yields or the regioselectivity of the reaction. Decreasing the loading any lower lead to greatly lowered conversions to the product. In any case, the catalyst loading was decreased from the sub-stoichiometric levels used previously to the catalytic range. This is of utmost importance commercially, as decreasing the catalyst loading will decrease the overall cost of the reaction.

The reason for the regioselectivity is still undetermined. One possible explanation is shown in Figure 3. The reaction has the possiblity of forming two intermediates, **11** and **15**, which correspond to the *para* and *meta* substituted products, respectively. Because compound **11** corresponds to the major aromatic product **10**, it is expected that intermediate **11** is also favored over **15**. With **15**, the R group is in the psuedo *meta* position and has steric hindrance between the methyl ester and the R group. However, **11**

has the R group in the psuedo *para* position, which places the two groups with minimal steric constraints; thus it is expected to be more stable and the favored intermediate to lead to the major project.

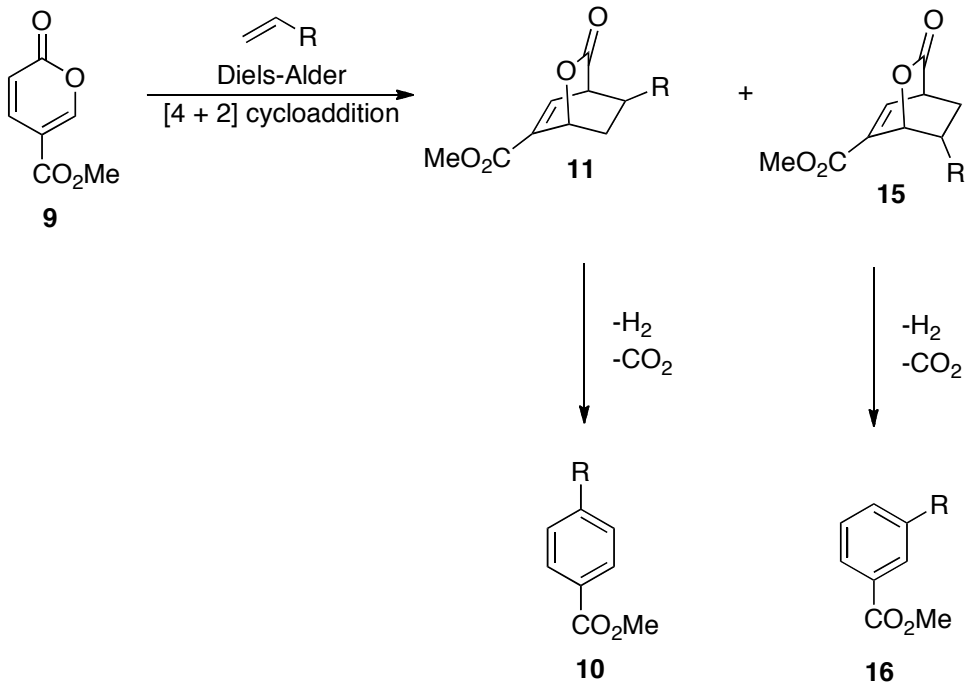


Figure 3

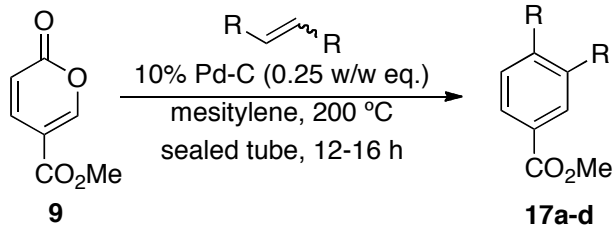
The reaction was repeated on a number of examples of alpha-olefin substrates, each of which is shown in Table 1. The reaction is tolerant of simple alkyl olefins (entries 1-4) and allyl ethers (entries 5-6). Other substrates were attempted, but with less success. For example, benzyl ethers were attempted, but the product was a complex mixture. Presumably the catalyst is well known to facilitate the deprotection of benzylic ethers to alcohols. Likewise, the reaction generally does not tolerate amines, as amines can act as

catalyst poisons. Allyl acetate was attempted, but it did not give satisfactory yields, perhaps due to the volatility of the substrate.

Table 1. Reaction of methyl coumalate with terminal olefins

Entry	Alkene	Yield	R Group	Product
1	1-nonene	52%	$-(CH_2)_6CH_3$	14a
2	1-decene	70%	$-(CH_2)_7CH_3$	14b
3	1-undecene	63%	$-(CH_2)_8CH_3$	14c
4	allyl benzene	83%	$-CH_2Ph$	14d
5	allyl phenyl ether	61%	$-CH_2OPh$	14e
6	allyl heptyl ether	51%	$-CH_2O(CH_2)_6CH_3$	14f

In an extension of this chemistry, the reaction was also tried on internal olefins (Scheme 6). In these cases, only symmetrical alkenes were chosen. This was due in order to give a single product, thus avoiding issues of regiochemistry, as well as simplifying the subsequent characterization of the products. Unlike examples with terminal olefins, where theoretically two products are possible, only a single product is possible when using a symmetrical internal olefin.



Scheme 6

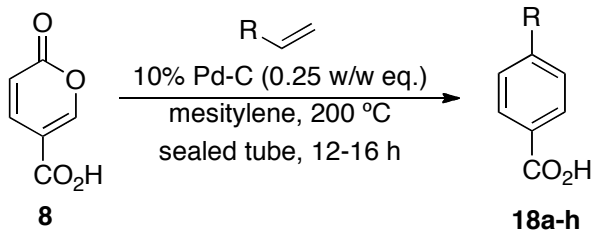
The results are shown in Table 2. Of note is that the *trans* alkene (entry 1) gave significant lower yields than *cis* alkenes, which is typical of Diels-Alder reactions. This is due to the steric hindrance of *trans* alkenes as they approach the dieneophiles, as they are more sterically encumbered and thus less reactive. The reaction was also shown to be effective on cyclic alkenes (entries 2-4) to give the fused ring product.

Table 2. Reaction of methyl coumalate with internal olefins

Entry	Alkene	Yield	R Group	Product
1	*trans*-4-octene	45%	$-(CH_2)_2CH_3$	17a
2	*cis*-cyclodecene	70%	$-(CH_2)_8-$	17b
3	*cis*-cyclooctene	62%	$-(CH_2)_6-$	17c
4	*cis*-cyclododecene	70%	$-(CH_2)_{10}-$	17d

With the successful reaction of a wide variety of olefins with methyl coumalate, the same conditions were attempted using coumalic acid (Scheme 7). The key difference in this case is that the solubility of coumalic acid in organic solvents is much lower than methyl coumalate and could potentially lead to difficulties. However, as the reaction

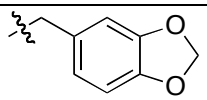
procedes towards product and the solution is heated, the compound gradually becomes soluble.



Scheme 7

The results of these experiments are shown in Table 3. Not surprisingly, the regioselectivity produces strictly the *para* substituted product in a similar fashion as with methyl coumalate. Similar olefinic substrates were screened and again both simple olefins (entries 1-4) and allyl ethers (entries 5-6) are tolerated. Additionally, dienophiles with simple alkyl esters are tolerated (entry 7). Another new alkene substrate used in this reaction was safrole (entry 8) to produce compound **18h** as the *para*-substituted product. Therefore, this reaction is not only tolerant of simple alkenes, but more complex olefin substrates as well.

Table 3. Reaction of coumalic acid with various olefins

Entry	Alkene	Yield	R Group	Product
1	1-heptene	85%	$-(CH_2)_4CH_3$	18a
2	1-decene	72%	$-(CH_2)_7CH_3$	18b
3	1-undecene	69%	$-(CH_2)_8CH_3$	18c
4	allyl benzene	79%	$-CH_2Ph$	18d
5	allyl phenyl ether	65%	$-CH_2OPh$	18e
6	allyl heptyl ether	66%	$-CH_2O(CH_2)_6CH_3$	18f
7	methyl dec-9-enoate	78%	$-(CH_2)_7CO_2Me$	18g
8	safrole	69%		18h

There are several improvements from the previous work that makes this chemistry intriguing. If this process is to be utilized to produce terephthalic acid, reaction directly with coumalic acid as opposed to methyl coumalate is an advantage commercially. Methyl coumalate is prepared from esterification of coumalic acid, and the corresponding ester must be cleaved to the acid at a later stage to produce the acid. This adds two steps (esterification and hydrolysis) to the overall synthesis. Reaction directly on coumalic acid eliminates the need for these steps and thus simplifies the process. The main advantage of methyl coumalate over coumalic acid is the solubility, but, as previously mentioned, coumalic acid will dissolve upon heating.

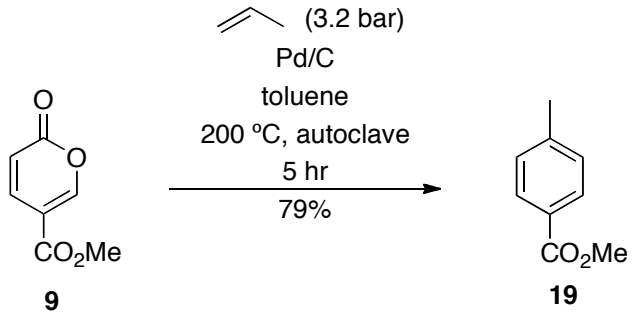
This leads to the second improvement of this reaction: the elimination of the solvent. Previous examples used high-boiling nonpolar hydrocarbons as the solvent (e.g. mesitylene, xylenes); but it was found that it is not necessary. Coumalic acid or methyl coumalate can be heated neat in an excess of olefin (typically a liquid at room temperature) using the same conditions as before to give comparable yields of the desired benzoic acid or benzoic acid ester. The excess olefin solvent could then be removed via distillation and easily recovered.

The final advantage of this reaction is that it uses inactive olefins as the dieneophiles. Examples of Diels-Alder reactions using inactivated alkenes as dienophiles are rare, which makes this example all the more interesting. The older reactions use styrene as the alkene substrate, which produces a biphenyl product. Because the end product is a stable conjugated aromatic system, styrene could be seen as a type of activated olefin towards Diels-Alder reactions. The driving force for this reaction in that case is the formation of the stable biphenyl product. However, most of our improved examples use simple alkyl groups to produce simple alkyl-substituted benzoic acids (or esters) with no clear driving force for completion. The same is true of allylic ethers, which do not have any clear electronic rationale for the formation of the product.

One of the limitations of this chemistry is that is can only be applied to higher-boiling olefins (i.e. with boiling points greater than 100 ºC) in order to achieve satisfactory yields. Lower-boiling olefins tend to give poor conversions to the product, giving mostly recovered starting material.

Another limitation to this chemistry is that, while the reaction produces the required *para* substituted compound, in order to produce the desired terephthalic acid, the long alkyl side chain must be oxidized to the acid. This process is known, however, in the case of alkyl-substituted benzoates, it involves the loss a large carbon fragment. From an atom economy standpoint, this is not a desirable situation, as a large portion of the molecule is lost in the process. The ideal olefin substrate for this reaction is the simple three-carbon unit, propene, which would produce methyl 4-methylbenzoate, which is well known to be oxidized to terephthlatic acid.[7] This is done without the subsequent loss of the large carbon fragment.

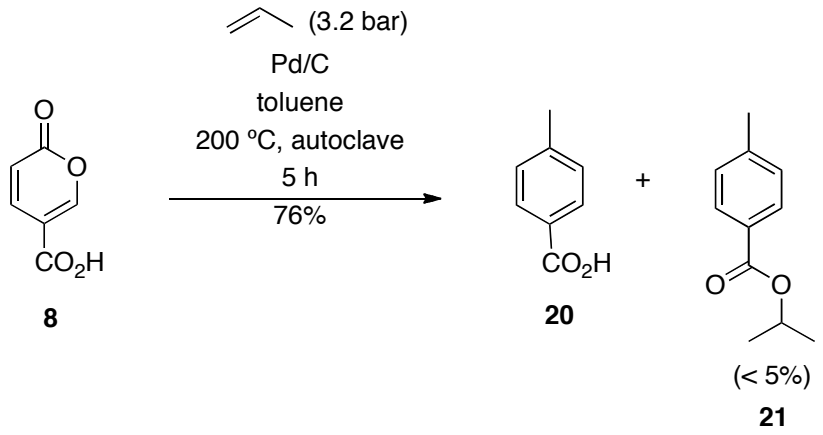
Unfortunately, propene is a gas at room temperature and is therefore unsuitable for reaction using sealed tube conditions. A reaction vessel that is able to withstand the higher pressures is required. The general form of the reaction is shown in Scheme 8. The reaction was done in an autoclave apparatus, charging multiple times with propene gas until the reaction chamber was saturated. Another modification to the reaction of methyl coumalate with propene was the use of toluene as the solvent. This is an advantage, as toluene is a much more standard solvent when compared to mesitylene. Although it is lower boiling than mesitylene, toluene is perfectly suitable at the elevated temperatures and pressures used.



Scheme 8

To our delight, the desired compound **19** was produced in good yield. Again, the *para*-substituted product is the major product. This is intriguing because even the simple methyl group, one of the least sterically-demanding functional groups, is able to direct the regiochemistry towards the desired compound.

In parallel to previous work, the next step was to attempt the reaction of propene directly on comalic acid (Scheme 9). As in the reaction using methyl coumalate, the *para* product **20** is the major compound produced. Catalytic oxidation of **20** to terephthalic acid is well-known,[8] thus representing a formal synthesis of terephthalic acid from coumalic acid.



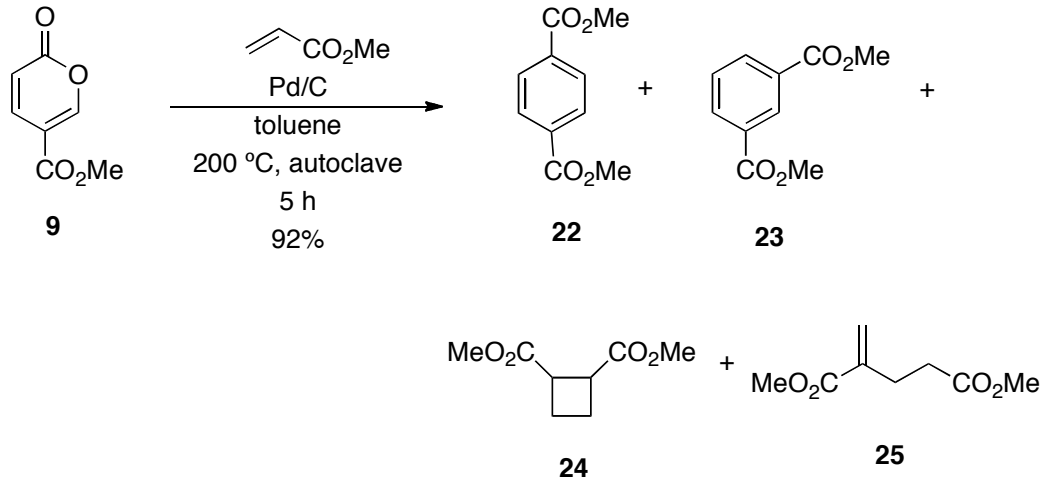
Scheme 9

Interestingly, the major byproduct in this reaction is the isopropyl ester of desired product (**21** in Scheme 9). This product represents less than 5% of the overall product via GCMS and proton NMR integration experiments. It is presumed to arise from the addition of another molecule of propene to the acid moiety of the product, which is not entirely unreasonable under the harsh conditions.

In all the cases shown, the reactions were done on inactivated olefins. However, Diels-Alder reactions are typically done using activated alkenes, usually containing an electron-withdrawing group. With this in mind, the use of an activated dienophile is the next natural step and would expand the scope of the chemistry.

The first reaction using an activated dieneophile was done with methyl coumalate as the pyrone/diene component and methyl acrylate as the dienophile (Scheme 10). Interestingly, the reaction produced a roughly 1:1 mixture of the *para* and *meta* dimethyl terephthalates (**22** and **23**, respectively) in high yield (> 90%). The only side products of the reaction were found to be traces of the dimer compounds of methyl acrylate, **24** and

25. The reaction tends to slightly favor the *para* terephthalate **22** over the *meta* **23** by GCMS and proton NMR integration, however it is not high enough to be considered selective towards the *para* isomer in any way.

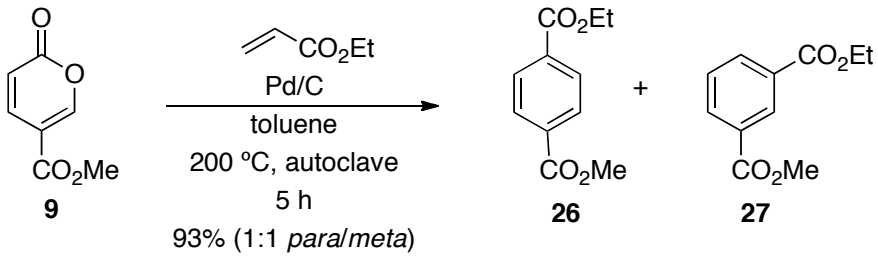


Scheme 10

Because the *para*-substituted terephthalic acid was the target compound as opposed to the *meta*, the next step was to modify the reaction conditions to favor the desired *para* isomer. Because it was postulated that the steric bulk of the dienophile directs the towards the more stable *para* product, more bulky acrylates were considered. The rationale is that, like with simple alkyl olefins, larger arcylates would also direct towards the desired product.

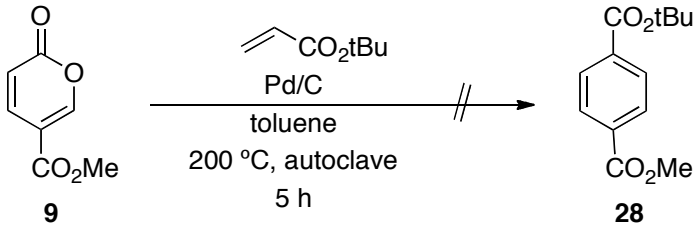
The first acrylate considered was simple ethyl acrylate (Scheme 11). The hope was that the slightly larger ethyl group would be more directing than the methyl group. Unfortunately, the reaction was identical to previous experiments, giving high yields of a

roughly 1:1 mixture of isomers. This is not entirely surprising, as methyl and ethyl groups have similar A-values and have roughly the same steric demands.



Scheme 11

The *tert*-butyl group is considerably larger than the simple methyl group, and would be thus be the most directing group from a steric standpoint. Thus, the reaction was attempted of methyl coumalate with *tert*-butyl acrylate (Scheme 12). Unfortunately, this proved to be sluggish, only giving recovered ethyl acrylate and none of the desired terephthalate product **28**. The reasoning is that, although the larger acrylate could potentially act as a directing group for the regiochemistry for the Diels-Alder reaction, it is also too bulky to appreciably react with the pyrone.



Scheme 12

The steric argument for the regiochemistry of the Diels-Alder reaction with methyl acrylate proved to be unfruitful, perhaps there is an electronic explanation to the regiochemistry. After all, the acrylate is a much different compound electronically than simple olefins and would thus have different chemical properties.

To help explain the chemistry of the reaction with methyl acrylate, various resonance forms of methyl acrylate are shown (Figure 4). Of note is that carbon 6 has a positive charge in species **29** and **30**, therefore making it net electron deficient. In contrast, carbon 3 in **31** has a negative charge, thus becoming net electron donating. Because these two carbons are involved in the carbon-carbon bond forming step of the Diels-Alder reaction, they are the most involved in directing the regiochemistry.

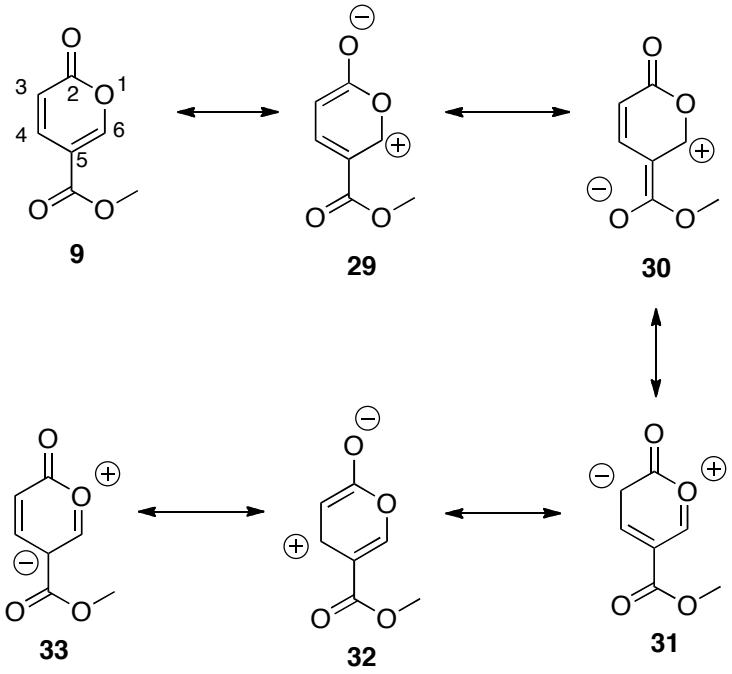


Figure 4. Resonance forms of methyl coumalate

Reaction with a dienophile containing an electron-donating group would form a bond between the partial positive charge on the pyrone in the 6 position with the partial negative charge on the dienophile (Figure 5). Thus, the ester on methyl acrylate and the electron donating group on the dienophile would end up in a 1,4 relationship in the bicyclic intermediate, which corresponds to the *para* postion in the resulting benzene ring. The other isomer involves forming a bond between the partial negatively charged atom in position 3 on the pyrone with the partially negatively charged carbon on the dienophile, which is unfavorable. For simple olefins as dienophiles, an alkyl group is a weakly electron-donating group, thus explaining the resultant regiochemistry in those products.

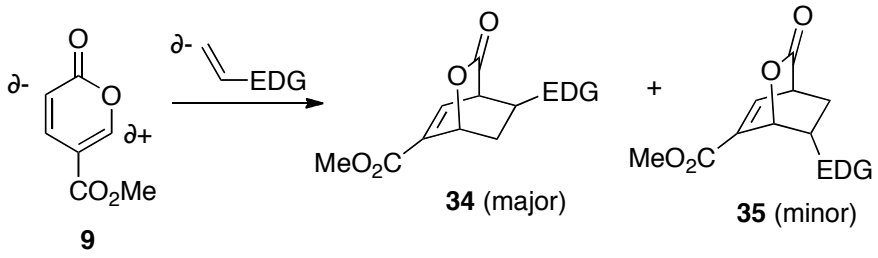


Figure 5

However, if the variable group on the dienophile is an ester (or other electron withdrawing group), the olefin becomes more positive charged in character (Figure 6). If this is the case, the reaction is expected to favor the more electronically matched intermediate **37**, forming a bond between the electron-defecient alkene and the partially negative-charged carbon at C3. Compound **37** corresponds to the *meta* substituted

benzene product while **36** corresponds to *para*. This could help to explain why the *meta* product is seen in the reaction with acrylates, although it does not completely explain why the product composition in reactions with acrylates are a 1:1 mixture.

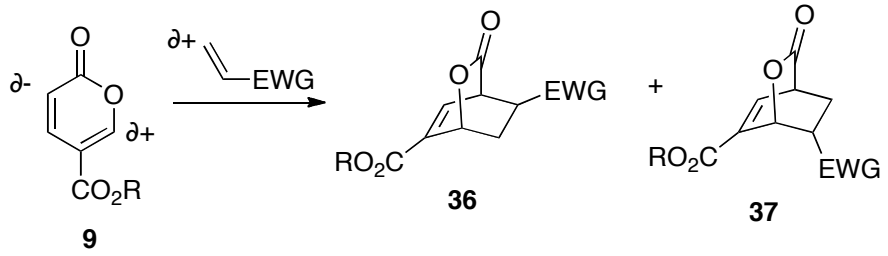
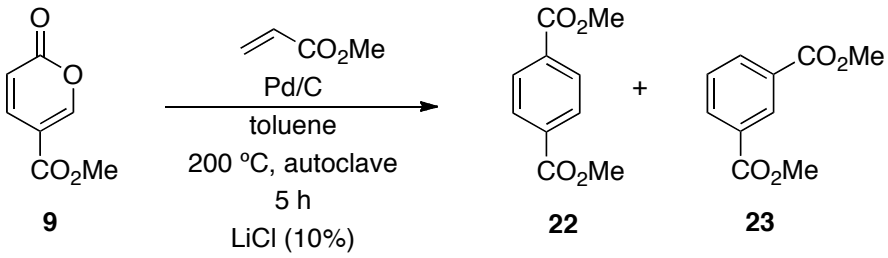


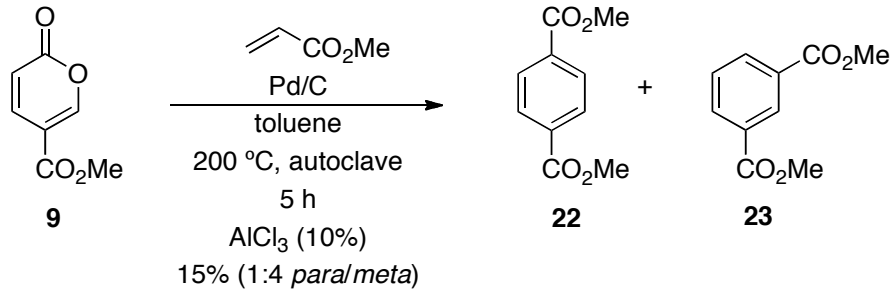
Figure 6

One of the typical modifications of the Diels-Alder reaction conditions is the use of Lewis acid catalysts.[9] Not only would this accelerate the rate of reaction, but it could also help with the issue of selectivity. One of the first Lewis acids used was a catalytic amount of lithium chloride (Scheme 13). However, there was no improvement in either the yields or selectivity.



Scheme 13

The next plan was to use a stronger Lewis acid, aluminum trichloride (Scheme 14). Although it is a harsher reagent than the very mild lithium chloride, this example will provide some valuable insights into the effect of Lewis acids on the cycloaddition reaction of methyl coumalate.

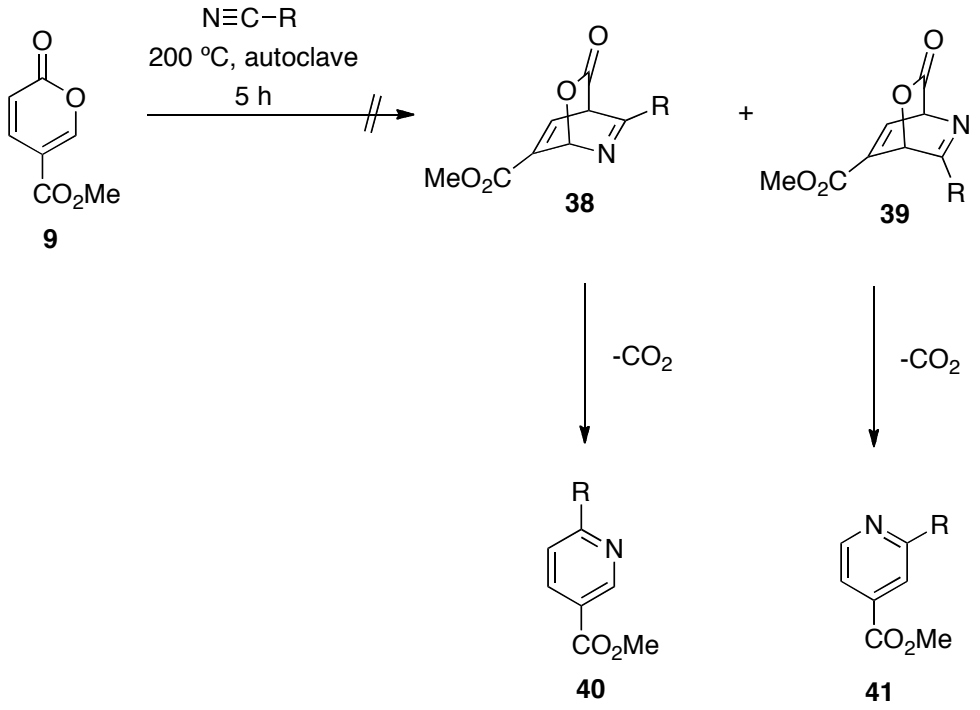


Scheme 14

The result of this reaction was unexpected; the selectivity actually favored the *meta* isomer over the *para* in a 4:1 ratio, based on peak integration of the proton NMR. The yield for reaction, unfortunately, was unsatisfactorily low, at only 15%, which could be due to the decomposition of the compounds over the acid catalyst, as no recovered starting material was seen.

The next extension of this chemistry was to utilize the reaction to produce other types of aromatic compounds. In particular, using nitriles as the dienophile component to produce pyridine compounds. The advantage of this reaction is that no catalyst is necessary, as the triple bond of the nitrile will yield the required double-bond intermediate without the need for elimination of hydrogen. The typical reaction is shown in Scheme 15. The reactants undergo a thermal [4+2] cyclization to produce

intermediates **38** and **39**, as expected, each of which should aromatize and decarboxylate as usual, forming the desired pyridines, **40** and **41** respectively. Which of the two possible compounds is expected is unknown. However, regardless of the regiochemistry issues, if this reaction is successful, it would represent a novel route to pyridines from biobased compounds.



Scheme 15

The first example tested was acetonitrile, where R = Me in Scheme 15. The advantage of using this compound as a substrate is that is a common industrial solvent. Additionally, any excess solvent can be easily recovered via distillation. The first reaction

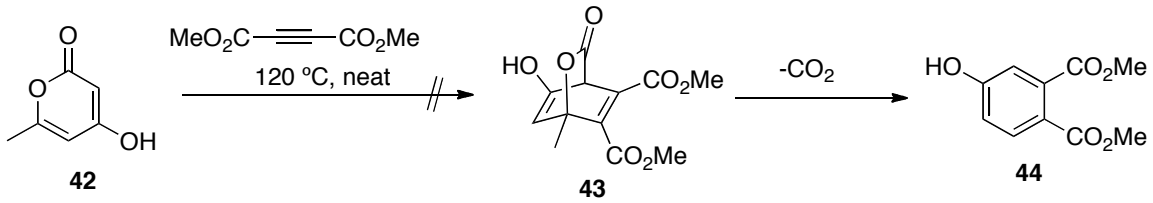
was unsuccesful, leaving only recovered methyl acrylate. A less volatile nitrile substrate was attempted, benzonitrile, (R = Ph in Scheme 15) with similar results. Even with these preliminary failures, there is some interest in this type of chemistry that warrants further investigation.

With several examples complete with coumalic acid derivatives, our effort was turned towards other pyrones as potential dienophiles. The first example considered was 2-pyrone, which has been synthesized previously from coumalic acid.[10] However, the reaction requires prohibitively high temperatures (650 ºC) and very specific equipment to be of use. Therefore, other routes towards 2-pyrone were attemped. One particular method started with readily available 2-furanmethanol.[11,12] Unfortunately, this route proved more difficult than expected, suffering from an impractical amount of steps (6 steps from 2-furanmethanol), irreproducibility of certain transformations, and low yields.

Another one of the potential starting pyrones is 4-hydroxy-6-methyl-2-pyrone, also call triacetic lactone (TAL). This compound has some value in the field of biorenewable chemicals because it is a potential intermediate in fatty acid biosynthesis and can be made on a large scale via microbes. With the previous success with Diels-Alder reactions on methyl coumalate, it is conceivable that this new pyrone molecule will also be successful with similar types of reactions.

The first Diels-Alder reaction using TAL **42** was attemped on a highly activated dienophile, dimethylacetylene dicarboxylate (Scheme 16). Because this is a reaction with a dienophile with a triple bond, no palladium on carbon catalyst is necessary as a

dehydrogenating agent. Unfortunately, neither the bicyclic intermediate **43** nor the required aromatic compound **44** was produced. Instead, the reaction produced a complex mixture of uncharacterizable compounds. Similar results were found when using methyl propiolate as the dienophile.



Scheme 16

These difficulties could be explained by the presence of the hydroxy group on the pyrone. The hydroxy group has significant ketone character (shown in Figure 7), which disrupts the diene character with the pyrone, thus making it less able to participate in the cycloaddition reactons. Likewise, the alkoxide is a reactive functional group and could react with the esters on the diene molecule. Finally, TAL could be a potential nucleophile for Michael addition, as it is a beta-keto lactone. If this is the case, then it could easily undergo conjugate addition to activated Michael acceptors, such as acetylenic esters.

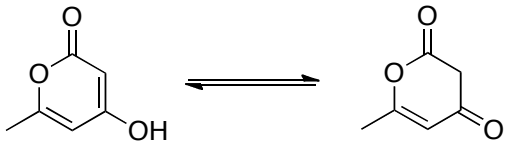
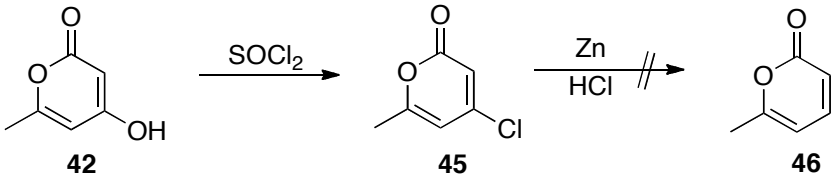


Figure 7. Tautomeric forms of triacetic acid lactone

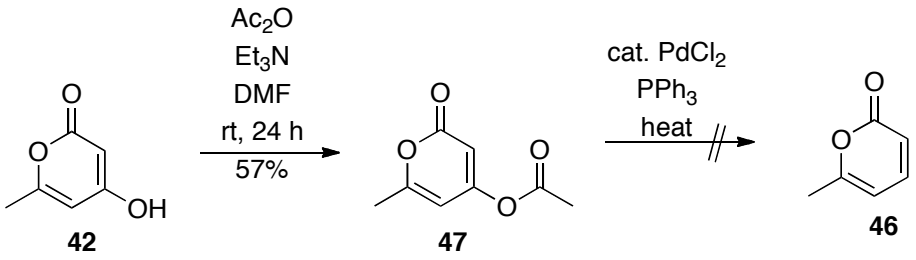
It is clear, then, that in order to procede further, the key lies in eliminating the interference from the alcohol. The simplest method is to remove the hydroxy moiety directly, to produce the simplified 6-methyl-2-pyrone **46**. A previous synthesis involved halogenation of TAL using thionyl chloride, followed by reduction using metallic zinc (Scheme 18).[13] The halogenation of **42** proceded smoothly to give **45**, however, the removal of the group proved difficult, only giving decomposition. Other reported methods to produce **46** from **42** used stoichiometric amounts of palladium,[14] which is extremely impractical, especially for potential larger scale reactions.



Scheme 18

In connection with the previous work done with decarboxylation of anhydrides, it was envisioned that a palladium catalyzed reaction may be a possible route to **46**. This started with the formation of the acetyl ester of TAL,[15] followed by the typical palladium

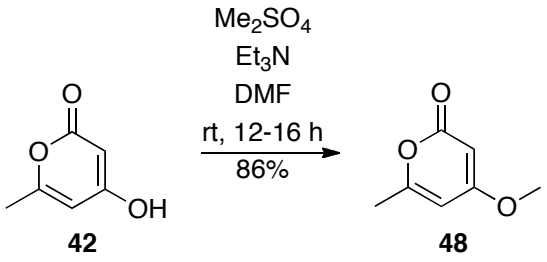
catalyzed decarboxylation conditions as outlined in Chapter 3.[16] The rationale is that the masked alcohol in **47** is also a vinylogous anhydride, and thus could facilitate insertion of palladium. Different conditions were tried, but all lead to complex mixtures (Scheme 19).



Scheme 19

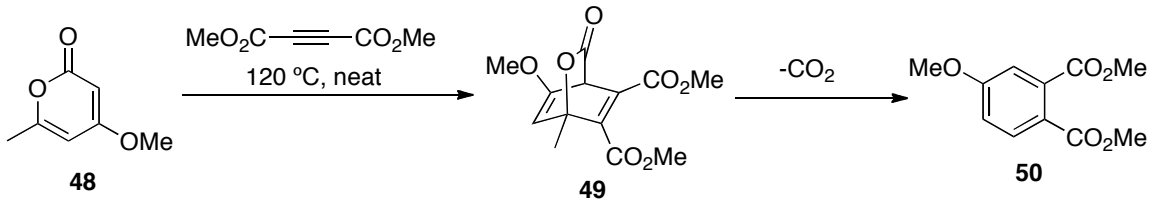
Owing to the difficulties in directly removing the hydroxy group, another possible solution would be to protect the group. This would solve the issue of the unwanted side reactions that are caused by the alcohol moiety. The choice of protecting group is crucial. For example, protecting the alcohol as the benzyl ether would not be beneficial, as the palladium catalyst will easily remove it. Nor does protection as the silyl ether, as the typical *tert*-butyldimethyl silyl (TBDMS) or trimethyl silyl (TMS) groups could be too sterically demanding and may interfere with the subsequent Diels-Alder cyclizations. In addition, the silyl group is typically removed by treatment with fluoride, which would make it impractical for larger scale reactions. It was thus settled to use a simple methyl group to mask the alcohol. Its preparation is shown in Scheme 20.[17]

The acetylated adduct to TAL **47** is also prime candidate as a protected TAL compound. In this case, the acetyl group could act as a net electron-withdrawing substituent, thus decreasing the electron density on the pyrone.



Scheme 20

Compound **48** was reacted with dimethyl acetylene dicarboylate in a similar fashion as in Scheme 16. Gratifyingly, the reaction proceded smoothly to produce **50** (Scheme 21)[18], thus confirming the hypothesis that, indeed, the hydroxyl group of TAL was interfering with the Diels-Alder reaction.



Scheme 21

The reaction of both acetyl and methyl-protected TAL was attempted with simple alpha olefins and palladium on carbon catalyst. However, neither was successful. Additionally, the more electron-deficient methyl acrylate was used as a diene substate, but that was also met with no success.

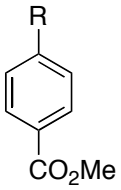
In conclusion, a new method of preparing aromatic compounds from biobased pyrones is shown. It represents one of the very few methods of creating benzene ring systems from plant-based molecules and is a potential method of producing terephthalic acid.

Experimental

Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Methyl coumalate was prepared via methylation of coumalic acid.[6] Allyl phenyl ether was prepared from phenol and allyl bromide. Allyl heptyl ether was prepared from 1-heptanol and allyl bromide. High pressure reactions were done in an Autoclave Engineers EZE-Seal 100mL aparatus. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or Bruker 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet. High resolution mass spectra were recorded on a Kratos model MS-50 spectrometer. Standard grade silica gel (60 Å, 32-63 μm) was used for flash column chromatography.

Reaction of methyl coumalate with terminal alkenes

Methyl coumalate (200 mg, 1.3 mmol), olefin (10 molar equivalents), and 50 mg of 10% Pd/C (0.25 w/w relative to methyl coumalate) were dissolved in 7 mL mesitylene in a thick walled glass sealable tube. The reaction mixture was heated in an oil bath at 200 ºC for a 12-16 hour period. The reaction vessel was then cooled to room temperature, and the catalyst was removed by filtration through a pad of Celite, washing thoroughly with ether. The filtrate was then concentrated in vacuo and purified by silica gel column chromatography (10:1 hexanes/ethyl acetate) to give the correspounding pure *para*-substituted methyl benzoate **14**.



Methyl 4-heptylbenzoate (14a) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.95 (d, J = 7 Hz, 2H), 7.23 (d, J = 7 Hz, 2H), 3.90 (s, 3H), 2.65 (t, J = 7 Hz, 2H), 1.59-1.26 (m, 10H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.4, 144.3, 129.9, 128.9, 127.3, 52.3, 32.1, 30.0, 29.2, 26.4, 22.9, 14.3; HRMS (FAB) m/z exact mass calculated for $C_{15}H_{22}O_2$ 235.1693 (MH^+), found 235.1699.

Methyl 4-octylbenzoate (14b) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.94 (d, J = 7 Hz, 2H), 7.24 (d, J = 7 Hz, 2H), 3.90 (s, 3H), 2.63 (t, J = 7 Hz, 2H), 1.59-1.26 (m, 12H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂; 167.4, 148.7, 129.8, 128.6, 127.4, 52.1,

36.2, 32.1, 31.4, 29.8, 29.7, 29.5, 22.9, 14.3; HRMS (FAB) m/z exact mass calculated for $C_{16}H_{24}O_2$ 249.1849 (MH^+), found 249.1815.

Methyl 4-nonylbenzoate (14c) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.96 (d, *J* = 7 Hz, 2H), 7.24 (d, *J* = 7 Hz, 2H), 3.90 (s, 3H), 2.64 (t, *J* = 7 Hz, 2H), 1.59-1.26 (m, 14H), 0.88 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.5, 148.7, 129.8, 128.6, 127.4, 52.1, 36.3, 32.1, 31.4, 29.8, 29.7, 29.6, 29.5, 23.5, 14.4; HRMS (FAB) m/z exact mass calculated for $C_{17}H_{26}O_2$ (MH^+) 263.2006, found 263.2005.

Methyl 4-benzylbenzoate (14d) - Spectral data matches that of previous papers[20]

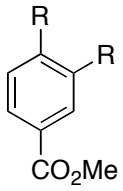
Methyl 4-(phenoxymethyl)benzoate (14e) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 8.05 (d, *J* = 7 Hz, 2H), 7.51 (d, *J* = 7 Hz, 2H), 7.31-6.91 (m, 5H), 5.13 (s, 2H), 3.92 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.1, 158.6, 142.5, 129.1, 128.9, 127.2, 121.4, 115.0, 69.5, 52.4; HRMS (FAB) m/z exact mass calculated for $C_{15}H_{14}O_3$ 243.1016 (MH^+), found 243.1009.

Methyl 4-(heptyloxymethyl)benzoate (14f) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 8.03 (d, *J* = 7 Hz, 2H), 7.39 (d, *J* = 7 Hz, 2H), 4.55 (s, 2H), 3.75 (t, *J* = 7 Hz, 2H), 1.53-1.28 (m, 10H), 0.88 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.2, 144.3, 130.3, 128.9, 127.8, 72.0, 70.7, 52.3, 32.1, 29.9, 29.4, 26.4, 22.9, 14.3; HRMS (FAB) m/z exact mass calculated for $C_{16}H_{24}O_3$ 265.1798 (MH^+), found 265.1804.

Reaction of methyl coumalate with internal alkenes

Methyl coumalate (200 mg, 1.3 mmol), olefin (10 molar equivalents), and 50 mg 10% Pd/C (0.25 w/w relative to methyl coumalate) were mixed in a sealable tube. The reaction mixture was heated in an oil bath at 200 ºC for 12-16 hours. Once complete, the

reaction vessel was then cooled to room temperature and the catalyst is removed by filtering through a pad of Celite, washing throughly with ether. The filtrate was then concentrated in vacuo and purified by silica gel column chromatography (2:1 hexanes/ethyl acetate) to give pure **17**.



Methyl 3,4-dipropylbenzoate (17a) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.82 (s, 1H), 7.78 (d, J = 6 Hz, 1H), 7.20 (d, J = 6 Hz, 1H), 3.89 (s, 3H), 2.62 (t, J = 6 Hz, 4H), 1.67-1.57 (m, 8H), 0.99 (t, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.6, 146.2, 140.8, 130.5, 129.4, 127.8, 127.2, 52.1, 35.1, 34.8, 24.5, 24.3, 14.4, 14.3; HRMS (QTOF) m/z exact mass calculated for $C_{14}H_{20}O_2$ 221.1536 (MH^+), found 221.1532.

Methyl 5,6,7,8,9,10,11,12-octahydrobenzo[10]annulene-2-carboxylate (17b) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.86 (s, 1H), 7.77 (d, J = 6 Hz, 1H), 7.23 (d, J = 6 Hz, 1H), 3.89 (s, 3H), 2.69 (t, J = 7 Hz, 4H), 1.72-1.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 167.6, 146.9, 141.1, 131.1, 129.9, 127.8, 127.0, 52.1, 30.0, 29.8, 29.6, 26.5, 26.4, 25.8, 25.7, 23.1.

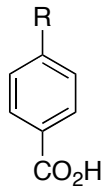
Methyl 5,6,7,8,9,10-hexahydrobenzo[8]annulene-2-carboxylate (17c) -^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.79 (d, J = 6 Hz, 1H), 7.78 (s, 1H), 7.16 (d, J = 6 Hz, 1H), 3.89 (s, 3H), 2.81-2.78 (m, 4H), 1.70-1.68 (m, 4H), 1.34-1.32 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$):

∂ 167.6, 147.2, 141.7, 130.4, 129.4, 128.2, 127.7, 52.1, 32.6, 32.5, 32.4, 32.3, 26.1, 26.0; HRMS (QTOF) m/z exact mass calculated for $C_{14}H_{18}O_2$ 219.138 (MH^+), found 219.1379.

Methyl 5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-2-carboxylate (17d) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.87 (s, 1H), 7.77 (d, *J* = 6 Hz, 1H), 7.23 (d, *J* = 6 Hz, 1H), 3.89 (s, 3H), 2.69 (t, *J* = 7 Hz, 4H), 1.72-1.39 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 167.6, 146.9, 141.4, 131.1, 129.9, 127.8, 127.0, 52.1, 30.0, 29.8, 29.5, 26.5, 26.4, 25.8, 25.7, 23.1, 23.1; HRMS (QTOF) m/z exact mass calculated for $C_{18}H_{26}O_2$ 275.2006 (MH^+), found 275.2005.

Reaction of coumalic acid with alkenes

Coumalic acid (200 mg, 1.4 mmol), olefin (10 molar equivalents), and 50 mg 10% Pd/C (0.25 w/w relative to coumalic acid) were mixed together in a sealable tube. The reaction mixture was heated in an oil bath at 200 ºC for 12-16 hours. As the reaction was heated, the insoluble coumalic acid slowly dissolves. The reaction vessel was then cooled to room temperature, where the catalyst is removed by filtering through a pad of Celite, washing thoroughly with ether. The filtrate was then concentrated in vacuo and purified by silica gel column chromatography (2:1 hexanes/ethyl acetate), giving pure *para*-benzoic acid derivative **18**.



4-Pentylbenzoic acid (18a) - ^{1}H NMR (400 MHz, $CDCl_3$): ∂ 12.06-11.6 (br, 1 H), 8.05 (d, *J* = 7 Hz, 2H), 7.29 (d, *J* = 7 Hz, 2H) 2.70 (t, *J* = 7 Hz, 2H), 1.73-1.53 (m, 2H) 1.53-1.22 (m, 4H), 0.93 (t, *J* = 7 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 172.8, 149.8, 130.5, 128.8, 127.1, 36.3, 31.7, 31.1, 22.8, 14.3; HRMS (QTOF) m/z exact mass calculated for $C_{12}H_{16}O_2$ 192.115, found 191.1078 $(M-H)^-$.

4-Octylbenzoic acid (18b) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 12.54-12.12 (br, 1 H), 8.02 (d, *J* = 7 Hz, 2H), 7.27 (d, *J* = 7 Hz, 2H), 2.67 (t, *J* = 7 Hz, 2H), 1.70-1.51 (m, 2H), 1.37-1.17 (m, 10H), 0.88 (t, *J* = 7 Hz);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 178.7, 149.8, 130.5, 128.8, 115.6, 36.4, 32.1, 31.4, 29.9, 29.7, 29.5, 22.9, 14.4; HRMS (QTOF) m/z exact mass calculated for $C_{15}H_{22}O_2$ 234.162, found 233.1547 $(M-H)^-$.

4-Nonylbenzoic acid (18c) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 12.42-11.99 (br, 1 H), 8.03 (d, *J* = 7 Hz, 2H), 7.27 (d, *J* = 7 Hz, 2H), 2.67 (t, *J* = 7 Hz, 2H), 1.70-1.55 (m, 2H), 1.40-1.20 (m, 12H), 0.89 (t, *J* = 7 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 172.8, 149.8, 130.5, 128.8, 127.1, 36.4, 32.2, 31.4, 29.9, 29.7, 29.6, 29.5, 22.9, 14.4; HRMS (QTOF) m/z exact mass calculated for $C_{16}H_{24}O_2$ 248.1776, found 247.1704 $(M-H)^-$.

4-Benzylbenzoic acid (18d) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 12.3-11.2 (br, 1H), 8.05 (d, *J* = 7 Hz, 2H), 7.40-7.21 (m, 7H), 4.06 (s, 2H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 172.5, 147.8, 140.2, 129.2, 129.1, 128.8, 128.3, 127.5, 126.7, 42.3; HRMS (QTOF) m/z exact mass calculated for $C_{14}H_{12}O_2$ 212.0837, found 211.0765 $(M-H)^-$.

4-(Phenoxymethyl)benzoic acid (18e) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 9.94 (br, 1H), 7.36-7.25 (m, 6H), 7.12-6.80 (m, 6H), 5.16 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): ∂ 172.0, 152.6, 141.0, 130.5, 130.0, 129.7, 127.6, 121.1, 115.6, 69.3; HRMS (QTOF) m/z exact mass calculated for $C_{14}H_{12}O_3$ 228.0789, found 227.0714 $(M-H)^-$.

4-((Heptyloxy)methyl)benzoic acid (18f) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 9.93 (br, 1H), 8.05 (d, J = 7 Hz, 2H), 7.43 (d, J = 7 Hz, 2H), 4.56 (s, 2H), 3.63 (d, J = 7 Hz, 2H), 1,64-1.15 (m, 10 H), 0.87 (t, J = 7 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 171.9, 145.1, 128.8, 128.0, 127.5, 71.5, 71.1, 32.1, 29.9, 29.4, 26.5, 22.9, 14.3; HRMS (QTOF) m/z exact mass calculated for $C_{15}H_{22}O_3$ 250.1569, found 250.1576.

4-(8-Methoxy-8-oxooctyl)benzoic acid (18g) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 7.98 (d, J = 7 Hz, 2H), 7.23 (d, J = 7 Hz, 2H), 3.63 (s, 3H), 2.63 (t, J = 7 Hz, 2H), 2.24 (t, J = 7 Hz, 2H), 1.59-1.20 (m, 10H);^{13}C NMR (100 MHz, $CDCl_3$): ∂ 174.5, 172.3, 149.5, 130.4, 128.7, 127.1, 51.7, 36.2, 34.2, 31.2, 29.4, 29.2, 29.0, 25.0; HRMS (QTOF) m/z exact mass calculated for $C_{16}H_{22}O_4$ 278.1518, found 278.1517.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)benzoic acid (18h) - ^{1}H NMR (300 MHz, $CDCl_3$): ∂ 12.76-11.76 (br, 1H), 8.05-7.95 (m, 2H), 7.32-7.26 (m, 2H), 6.90-6.74 (m, 3H), 6.02 (s, 2H), 3.96 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): ∂ 172.5, 147.7, 147.4, 147.2, 136.2, 132.4, 130.7, 127.9, 122.6, 109.7, 108.5, 101.4, 20.8; HRMS (ESI) m/z exact mass calculated for $C_{15}H_{12}O_4$ 257.0808, found 257.0808.

Reaction of methyl coumalate with propene

In a high-pressure autoclave aparatus, methyl coumalate (501 g, 3.3 mmol) and 10% Pd/C (127 mg, 0.25 w/w relative to methyl coumalate) were mixed in ca. 50 mL of toluene. The reaction vessel was sealed, charged several times with propene gas until the solution became saturated (3.3 bar). A nitrogen head was placed on the reaction (32.1 bar), where the mixture was heated to 200 ºC along with mechanical stirring. After 5 hours of heating, the reaction vessel was cooled to room temperature and depressurized. The solution was then filtered through a pad of Celite to remove the catalyst, washing thoroughly with ethyl acetate. The filtrate was concentrated under reduced pressure and purified via flash silica gel chromatography (4:1 hexanes/ethyl acetate) to yield pure methyl *p*-toluate **19** as an off-white powder (389 g, 79%) with no recovered starting material remaining. The spectra of **19** all match those of the commercially available compound.

Reaction of coumalic acid with propene

Coumalic acid (525 mg, 3.7 mmol) and 10% Pd/C catalyst (137 mg, 0.25 w/w relative to coumalic acid) were mixed in ca. 50 mL toluene in a high-presure reactor vessel. The vessel was sealed and charged several times with propene gas (3.0 bar). A nitrogen head was placed on the solution (32.0 bar), and the reaction was heated to 200 ºC along with mechanical stirring. After 5 hours of heating, the reaction vessel was cooled to room temperature and depressurized. The solution was filtered through a pad of celite in order to remove the suspended palladium catalyst, washing thoroughly with

ethyl acetate. The filtrate was concentrated in vacuo, and the crude material was analyzed by GCMS, which indicated the prescence of the desired product **20** (8.561 min) and <5% of isopropyl 4-methylbenzoate **21** (8.665 min). The product was purified via flash silica gel chromatography (1:1 hexanes/ethyl acetate) to yield pure **20** as a white power (386 mg, 76%). The spectra of the product matches that of the commercially-available compound.

The reaction was scaled-up using 2.014 g coumalic acid (14.4 mmol) and 10% Pd/C (510 mg), following the exact same procedure as previous experiments. Again, GCMS analysis detected the prescence of impurity **21**. Pure **20** was produced as a white power (1.414 g, 72%).

Reaction of methyl coumale with methyl acrylate

In a sealable, high-pressure autoclave aparatus, methyl coumalate (999 mg, 6.6 mmol), 10% Pd/C catalyst (256 mg, 0.25 w/w equivalents relative to methyl coumalate), and methyl acrylate (6.6 mL, 73 mmol, 10 equiv.) were mixed in ca. 50 mL toluene. The reaction vessel was sealed, charged with a nitrogen atmosphere (32.1 bar) and heated to 200 ºC along with mechanical stirring. After 5 hours, the reaction vessel was cooled to room temperature, and the solution was filtered through a pad of Celite to remove the catalyst, washing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo and the crude compound was purified by flash silica gel chromatography (2:1 hexanes/ethyl acetate) to give a 55:45 ratio mixture of *para* and *meta* dimethyl terephthalates **22** and **23** as a pale yellow solid (1.173 g, 92% overall yield). The ratio of

isomers is based on both ^{1}H NMR peak integration, as well as GCMS peak ratios (**22** and **23** elute at 9.379 min and 9.418 min, respectively). The spectra for each of the compounds produced match those of the commercially-available compounds.

The above reaction was scaled up to a higher scale of coumalic acid (2.015 g, 13.2 mmol), following a similar procedure, again using 10% Pd/C catalyst (503 mg, 0.25 w/w relative to methyl coumalate), and methyl acrylate (12.8 mL, 142 mmol). After purification, the reaction produced a roughly 1:1 mixture of isomers **22** and **23** based on ^{1}H NMR integration and GCMS analysis (2.475 g, 96% yield overall).

Reaction of methyl coumale with ethyl acrylate

In a sealable, high-pressure autoclave aparatus, methyl coumalate (513 mg, 3.4 mmol), 10% Pd/C catalyst (131 mg, 0.25 w/w equivalents relative to methyl coumalate), and ethyl acrylate (4.2 mL, 39 mmol, 10 equiv.) were mixed in ca. 50 mL toluene. The reaction vessel was sealed, charged with a nitrogen atmosphere (32.1 bar) and heated to 200 ºC along with mechanical stirring. After 5 hours, the reaction vessel was cooled to room temperature, and the solution was filtered through a pad of Celite to remove the catalyst, washing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo and the crude compound was purified by flash silica gel chromatography (2:1 hexanes/ethyl acetate) to give a 55:45 ratio mixture of *para* and *meta* isomers **26** and **27** as a yellow liquid (656 mg, 93% overall yield). The ratio of isomers is based on both ^{1}H NMR peak integration, as well as GCMS peak ratios. The spectra for each of the compounds produced match those of found in the literature.[19]

Reaction of methyl coumalate and methyl acrylate, using LiCl catalyst

In a sealable, high-pressure autoclave aparatus, methyl coumalate (504 mg, 3.3 mmol), 10% Pd/C catalyst (127 mg, 0.25 w/w equivalents relative to methyl coumalate), methyl acrylate (4 mL, 44 mmol, 10 equiv.), and lithium chloride (25 mg, 0.06 mmol, 10% loading) were mixed in ca. 50 mL toluene. The reaction vessel was sealed, charged with a nitrogen atmosphere (32.1 bar) and heated to 200 ºC along with mechanical stirring. After 5 hours, the reaction vessel was cooled to room temperature, and the solution was filtered through a pad of Celite to remove the catalyst, washing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo and the crude compound was purified by flash silica gel chromatography (2:1 hexanes/ethyl acetate) to give a roughly a 1:1 ratio of a mixture of *para* and *meta* dimethyl terephthalates **22** and **23** as a pale yellow solid (591 mg, 92% overall yield). The ratio of isomers is based on both ^{1}H NMR peak integration, as well as GCMS peak ratios (**22** and **23** elute at 9.379 min and 9.418 min, respectively). The spectra for each of the compounds produced match those of the commercially-available compounds.

Reaction of methyl coumalate and methyl acrylate, using $AlCl_3$ catalyst

In a sealable, high-pressure autoclave aparatus, methyl coumalate (542 mg, 3.6 mmol), 10% Pd/C catalyst (150 mg, 0.25 w/w equivalents relative to methyl coumalate), methyl acrylate (4 mL, 44 mmol, 10 equiv.), and aluminum trichloride (48 mg, 0.36 mmol, 10% loading) were mixed in ca. 50 mL toluene. The reaction vessel was sealed, charged with a nitrogen atmosphere (32.1 bar) and heated to 200 ºC along with

mechanical stirring. After 5 hours, the reaction vessel was cooled to room temperature, and the solution was filtered through a pad of Celite to remove the catalyst, washing thoroughly with ethyl acetate. The filtrate was concentrated in vacuo and the crude compound was purified by flash silica gel chromatography (2:1 hexanes/ethyl acetate) to give a roughly a 1:4 ratio of a mixture of *para* and *meta* dimethyl terephthalates **22** and **23** as a white solid (102 mg, 15% overall yield). The ratio of isomers is based on both ^{1}H NMR peak integration, as well as GCMS peak ratios (**22** and **23** elute at 9.379 min and 9.418 min, respectively). The spectra for each of the compounds produced match those of the commercially-available compounds.

Reference

1. Marko, I. E.; Evans, G. R.; Seres, P.; Chelle, I.; Janousek, Z. *Pure Appl. Chem*. **1996**, *68*, 113.
2. For a review, see Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H.; *Tetrahedron*, **1992**, *48*, 9111.
3. Wiley, R. H.; Smith, N. R.; Allen, C. F. H.; Reynolds, G. A. *Organic Syntheses, Coll. Vol. 4,* **1963**, 201.
4. Matsushita, Y.; Sakamoto, K.; Murakami, T.; Matsui, T. *Synth. Comm.* **1994**, *24*, 3307.
5. Dylewski, S. W. *Organic Chemical Manufacturing, Volume 7: Selected Processes*, U.S. Environmental Protection Agency, Research Triangle Park, NC, January 1981.

6. Ashworth, I. W.; Bowden, M. C.; Dembofsky, B.; Levin, D.; Moss, W.; Robinson, E.; Szczur, N.; Virica, J. *Org. Process R & D.* **2003**, *71*, 74.

7. Asanuma, N.; Yamakawa, K. Preparation of aromatic carboxylic acids *Jpn. Kokai Tokkyo Koho*, 2000256252, Sep 19 2000.

8. Nakai, T.; Iwai, T.; Mihara, M.; Ito, T.; Mizuno, T. *Tetrahedron Lett*. **2010**, 51, 2225.

9. Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.*, **1980**, *102*, 7816.

10. Zimmerman, H. E.; Grunewald, G. L.; Paufler, R. M. *Org. Synth. Coll. Vol. 5* **1973**, 982.

11. Jones, R. A.; Krische, M. J. *J. Org. Chem*. **2009**, *11*, 1849.

12. Kotretsou, S. I.; Georgiadis, M. P. *Org. Prep. and Proc. Int*. **2000**, *32*, 161.

13. van Dam, M. J. D.; Koegl, F. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 39.

14. Izumi, T.; Kasahara, A. *Bull. Chem. Soc. of Jpn.* **1975**, *48*, 1673.

15. Cyr, T. D.; Poulton, G. A. *Can. J. Chem.* **1978**, *56*, 1796.

16. (a) Gooßen, L. J.; Rodriguez, N. *Chem. Comm.* **2004**, 724; (b) Miller, J. A.; Nelson, J. A.; Byrne, M. P. *J. Org. Chem.* **1993**, *58*, 18.

17. Wadsworth, A. D.; Sperry, J.; Brimble, M. A. *Synthesis*. **2010**, *15*, 2604.

18. Tam, T. F.; Coles, P. *Synthesis*. **1988**, *5*, 383.

19. (a) Shang, R.; Fu, Y.; Li, J-B.; Zhang, S-L.; Guo, Q-X.; Liu, L. *J. Am. Chem. Soc*. **2009**, *131*, 5738; (b) Carbaugh, A. D.; Vosburg, W.; Scherer, T. J.; Castillo, C. E.; Christianson, M. A.; Kostarellas, J.; Gosai, S. J.; Leonard, M. S. *ARKIVOC.* **2007**, *12*, 43.

20. Amatorea, M.; Gosmin, C. *Chem. Comm.* **2008**, *40*, 5019.

GENERAL CONCLUSIONS

This thesis covers both the chemical synthesis of natural products and natural product analogues, as well as the new preparation of chemicals from biobased sources.

Chapter 1 shows the synthesis of two new analogues of a psychoactive natural product, salvinorin A. These new compounds are structurally similar to salvinorin A, containing the required functional groups of the natural product but without the molecular complexity.

Chapter 2 describes the first synthesis of a naturally-occuring antimicrobial compound. Additionally, two analogues were prepared, both of which have higher antimicrobial activity than the corresponding natural product.

Chapter 3 describes the large scale preparation of alpha olefins from naturally occuring fatty acids via a decarbonylation procedure utilizing homogeneous palladium catalysts. The reaction has been proven to work well on a wide variety of carboxylic acid substrates, including primary, secondary, and tertiary acids.

Finally, chapter 4 involves the preparation of *para*-substituted benzoic acid derivatives from coumalic acid. This chemistry is one of the few methods of generating aromatic rings from a biobased starting material and could be used as a preparation of intermediates towards terephthalic acid.

ACKNOWLEDGEMENTS

I would first like to give sincere thanks to my major professor, Dr. George A. Kraus for his guidance and encouragement on all of my graduate work.

I would also like to thank the members of my program of study committee, Drs. William Jenks, Gregory Phillips, Klaus Schmidt-Rohr, and Arthur Winter for all their help and guidance during my course of study at Iowa State University.

Thanks go out to the Center for Biorenewable Chemicals for their funding and support for both my projects with alpha olefins and pyrones. In particular I would like to thank Dr. Brent Shanks and Adam Okerlund in Chemical Engineering for allowing me the use of their autoclave apparatus for high pressure reactions.

Next, I would like to thank all the past and present members of the Kraus' group for helping me keep my sanity thoroughout my life in the laboratory though many helpful and interesting discussions.

I am grateful to my family, especially my parents for their continual support, love, and understanding during the pursuit of my PhD.

Finally, I'd like to give a special thanks to my wife, Heather, for her unwavering love and encouragement during even the most difficult times, and for helping me realize that sometimes there is more to life than research.