Progress Towards the Total Synthesis of Hydroxybrazilin

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I would also like to thank my parents and sister for their encouragement and support.
Abstract

This thesis outlines the development and optimization of the synthesis of an analog to a common nucleophile used in the Interrupted Fesit-Bénary reaction. This nucleophile is proposed to be more stable under acidic conditions, while still allowing further functionalization after the IFB reaction. The nucleophile was then utilized in an attempted total synthesis of the natural product hydroxybrazilin, which has a myriad of interesting therapeutic activities and industrial applications. The new analog proved to be lower yielding comparatively, and unfortunately did not provide the extra stability under acidic conditions that was desired. This did provide mechanistic insight, and the shorter sidechain was easier to work with in some of the later stages of the synthesis. We are also able to use this information to propose future routes and strategies that may lead to the total synthesis of hydroxybrazilin from the same starting materials.

The synthesis of the electrophile was also optimized, along with some alterations to the synthetic steps following the IFB reaction due to the differences between our new nucleophile and the old one.
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoyl</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>Diasteromeric ratio</td>
</tr>
<tr>
<td>DTBB</td>
<td>4,4′-Di-tert-butylbiphenyl</td>
</tr>
<tr>
<td>Ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatograph</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple Bond Correlation</td>
</tr>
<tr>
<td>HSQC</td>
<td>Heteronuclear Single Bond Correlation</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IBX</td>
<td>Iodoxybenzoic acid</td>
</tr>
<tr>
<td>IFB</td>
<td>Interrupted-Feist-Bénary</td>
</tr>
<tr>
<td>In vacou</td>
<td>Under reduced pressure</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Min.</td>
<td>Minutes</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliters</td>
</tr>
<tr>
<td>Mmol</td>
<td>Millimoles</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>PTC</td>
<td>Phase transfer catalyst</td>
</tr>
<tr>
<td>QD</td>
<td>Quinidine</td>
</tr>
<tr>
<td>QN</td>
<td>Quinine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Rfx</td>
<td>Reflux</td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Sat.</td>
<td>Saturated</td>
</tr>
<tr>
<td>TBDMS</td>
<td>Tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Tert-butyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
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</tbody>
</table>
# Table of Contents

Acknowledgements i  
Abstract ii  
List of Abbreviations iii  

1. Introduction  
   1.1 Natural Product Synthesis 1  
   1.2 Cinchona Alkaloids and the Interrupted Feist-Bénary Reaction 2  
   1.3 Hydroxybrazilin 7  
   1.4 Previous Attempted Synthesis 14  

References 18  

2. Results and Discussion  
   2.1 Retrosynthesis 24  
   2.2 Proposed Synthesis 25  
   2.3 Synthesis of nucleophile and comparative methodology 28  
   2.4 Synthesis of Electrophile 34  
   2.5 IFB and Later Functionalization 37  

References 54
3. Future Studies

3.1 Oxidizing Aldehyde  56

3.2 Alternate Protecting Groups  56

3.3 Protecting Primary Alcohol  59

3.4 Dearylation  60

3.5 Hydrogenation  63

References  65

Conclusions  66

Methods  67

NMR Spectra  76

References  86
1. Introduction

1.1 Natural Product Synthesis

Nature has developed a multitude of unique compounds that provide a variety of beneficial effects for the organism in which they are produced in. These natural products can also provide negative effects to other organisms that could potentially cause harm to the organism, in a type of defensive mechanism\textsuperscript{1}. Due to the variety of different resources available and problems organisms face, nature provides a vast array of compounds with a plethora of activities. Some organisms can even develop a different solution to the same problem.

While these compounds are created to benefit the organism, many can be repurposed to provide similar effects in humans, such as paclitaxel and galanthamine, which are used to treat cancer and Alzheimer’s respectively\textsuperscript{2}. Even compounds that themselves do not have beneficial side effects can be used as starting points or scaffolds in creating and designing targets for medicinal purposes, such as aspirin\textsuperscript{3}. Most natural products have long been used in local or herbal medicines for up to thousands of years. Unfortunately, extracting large amounts of these products from a rare species, or species that contain a multitude of other compounds, is costly and time intensive\textsuperscript{4}. The responsibility of solving this problem, and the task of utilizing natural product scaffolds for drug design, is largely taken up by organic chemists.

Perhaps the largest hurdle to overcome for organic chemists in designing synthetic routes to natural products is that of stereoselectivity. Almost all natural
products that are used as drugs have at least one chiral center\(^5\), even molecules like the simple sugars and amino acids in our bodies. Utilizing a racemic mixture or the wrong enantiomer can lead to, at best a loss in activity, and at worse disastrous side effects. While the most infamous case of this is with the drug Thalidomide, numerous other examples exist, such as D-Ethambutol being used to treat tuberculosis, while the L enantiomer causes blindness (Figure 1-1)\(^6\). Thus, it is paramount that natural product syntheses are enantioselective, as unlike diastereomers, all physical properties of enantiomers are identical, except for optical rotation, making it extremely difficult to cost effectively separate them on a large scale.

**Figure 1-1. Structure of Ethambutol**

\[ \text{D-Ethambutol} \quad \text{L-Ethambutol} \]

**1.2 Cinchona Alkaloids and the Interrupted Feist-Bénary Reaction**

Cinchona alkaloids are a class of natural products that are isolated from a variety of trees and shrubs. The most well-known of this class of compounds is quinine, best known for its antimalarial and antipyretic activity, and its pseudoenantiomer quinidine\(^7\). Other common cinchona alkaloids include cinchonine and cinchonidine, again pseudoenantiomers of each other, where the methoxy group is replaced with a
proton, and dihydroquinine and dihydroquinidine, where the vinyl group is reduced and fully saturated (Figure 1-2).

**Figure 1-2. Structure of Quinine and Quinidine Derivatives**

While largely isolated from the bark of various plants, the growing demand of these compounds for their uses in medicine led to an increase in efforts to be able to make them synthetically. This desire was only exacerbated by the shortage that occurred during World War II, in which the Allies were cut off from their supply\(^7\). With these driving forces, the first synthesis of quinine was reported in 1944 by Woodward\(^8\), however the synthesis is suspected to be for d-quinotoxine, which had previously been shown to be easily converted to quinine by Rabe\(^9\).

Since then the usage of cinchona alkaloids has broadened to be utilized as chiral catalysts in various synthetic pathways. Their versatility as catalysts comes mainly from the secondary alcohol and quinuclidine nitrogen in close proximity to each other. This arrangement provides a base, a weak acid, and hydrogen bonding sites, as well as the ability to further functionalize the alcohol. This coupled with the
steric hinderance of the isoquinoline creates a pocket that enables it to be utilized to great effect as a chiral catalyst which can be highlighted by the following examples.

The first use of a cinchona derived catalyst in a nitroaldol, or Henry reaction, was conducted by Shibasaki and coworkers\textsuperscript{10}. They were able to utilize a cinchona derived phase transfer catalyst (PTC) in their synthesis of Propranolol, a beta blocker (Scheme 1-1). While these catalysts did not initially achieve high enantiomeric excess, 23\%, it is useful to show their scope in catalysis.

**Scheme 1-1**

Corey and coworkers then built upon this by again utilizing a cinchona catalyst as a phase transfer catalyst in a Henry reaction towards the synthesis of Amprenavir, a HIV-protease inhibitor (Scheme 1-2)\textsuperscript{11}. While not enantioselective, this reaction did yield the desired diastereomer in a 17:1 ratio.
An extremely interesting use of cinchona derived catalysts in asymmetric synthesis was reported by Wynberg and coworkers\textsuperscript{12}. The cinchona catalyst was utilized as a base to promote the cycloaddition of chloral and a ketene in high yield and with high enantiomeric excess, 98\%. This application was utilized to synthesize a β-lactone intermediate on the way to the synthesis of malic acid (Scheme 1-3).

The flexibility of cinchona derived catalysts makes them ideal for use in the natural product syntheses in our work. Therefore, the Feist-Bénary reaction was modified by the Calter group by Ryan Phillips to allow the synthesis of stereospecific hydroxydihydrofurans\textsuperscript{13}, a common moiety in many natural products. The Feist-Bénary reaction yields a furan, through an aldol reaction followed by O-alkylation (Scheme 1-4). An acidic work up then yields the furan after elimination. If this last
step is omitted, the hydroxydihydrofuran can be isolated, and with the proper catalyst, yield products with high enantiomeric excess.

**Scheme 1-4**

As previously mentioned, the amines that we utilize for our catalysts are quinine or quinidine derived. The general structure includes a pyrimidine center (Figure 1-3) which is either mono or bis substituted with quinine or quinidine, as they give preference for opposite enantiomers. The “back” R group, or \( R_2 \), is typically a phenyl and the “front”, \( R_1 \), is what is varied in order to optimize enantiomeric excess. \( R_1 \) ranges anywhere from being unsubstituted, phenyl, naphthyl, anthracene, or pyridine derived groups.

**Figure 1-3.** General Structure for Chiral Catalysts in the Calter Group
The initial work done by Phillips on the Interrupted Feist-Bénary reaction utilized α-bromo derived electrophiles, with the bromine acting as the leaving group. Since then, the scope of this reaction has been expanded to include α-tosyloxyacetophenones and α, β-unsaturated carbonyls with an electron withdrawing group at the β position, as electrophiles (Scheme 1-5).

Scheme 1-5

The IFB reaction has been utilized to synthesize many complicated ring systems that are intermediates towards natural products. This has resulted in the total synthesis of (-) Glycinol and (-)-Variabilin.
1.3 Hydroxybrazilin

Isolated from the legume family of trees, specifically *haematoxylum campechianum*, more commonly known as the logwood tree, hydroxybrazilin (Figure 1-4) is a natural product with vast medicinal and industrial applications. Hydroxybrazilin is a member of the brazilin family of natural products, all of which are isolated from varying species of legumes. It was originally discovered in the early 1500s by Spanish explores in the Yucatan. It was noticed for the red color that it dyed fabrics, and from there was shipped back to Europe where it was used as a clothing dye for centuries. During this time, it was cultivated as a vigorous trade had developed. In the middle of the 19th century it was discovered that hydroxybrazilin was also a great component for staining cell nuclei for histology. It is still one of the main components used to this day. However, during the 1970s and in 2008, a large shortage of hydroxybrazilin occurred, due to the interruption of its exaction from the logwood tree, leading to a large price spike. While there are potential alternatives to some specific uses in histology, no current alternatives can entirely replace it, although a synthetic route to hydroxybrazilin could help alleviate any future shortages.
This family of compounds has also been utilized in local and herbal medicines for centuries. They are known mainly for their cardiotonic and immunosuppressive properties, which is suspected to come from the main metabolite of hydroxybrazilin, brazilein\textsuperscript{19}. The cardiotonic effects may come from one of, or the combination of, two pathways. One pathway is by decreasing atherogenesis, a disorder of the artery wall in which an adhesion of lipids to the endothelial cell surface thickens the vascular wall thus decreasing blood flow, by decreasing lipid adhesion\textsuperscript{20}. This pathway involves targeting NF-kB gene expression, thus reducing VCAM-1 mRNA expression and protein synthesis. Another pathway comes from increasing nitric oxide production, which causes vasorelaxation, a decrease in tension in blood vessel walls\textsuperscript{21}. In addition to these main properties, hydroxybrazilin has been shown to be an antioxidant\textsuperscript{22}, by increasing ARE-mediated gene expression, and have anti-inflammatory activity\textsuperscript{23} by down regulating the mRNA expression in iNOS, COX-2, and TNF-\(\alpha\) genes. It is also suspected that it increases fibroblast migration, which improves the wound healing process.

Two other closely related compounds in the brazilin family are brazilin and brazelein. They are isolated from \textit{caesalpinia sappan}, a species of legume found in
Asia. Similarly, to hydroxybrazilin, they have also been utilized as herbal medicines and have shown to have extensive medicinal properties. These include brazilin having anti-inflammatory\(^{24}\), anti-influenza\(^{25}\), and anti-allergic properties\(^{26}\). The anti-inflammatory properties come from the decreased expression of IRAK4 protein and the anti-allergic properties from inhibited mRNA and protein expression of interleukin IL-4 and IL-5. Extracts of *caesalpinia sappan* have been shown to possess antibacterial activity towards strains of MRSA\(^{27}\) and have cytotoxicity towards a few tumor cell lines including skin, lung, throat, and prostate cancer\(^{28}\).

As mentioned previously brazilein is the major metabolite of hyrdroxybrazilin. Thus, these three members of the brazilin family are suspected to be related through the following pathways. Hydroxybrazilin can be converted to brazilein through elimination, and brazilein and brazilin can be interconverted through oxidation and reduction (Scheme 1-6)\(^{29}\).

**Scheme 1-6**

There are a few reports of syntheses of brazilin and related compounds, however there are no reported syntheses of hydroxybrazilin. Two noteworthy
syntheses of brazilin, and in one case brazilein, include the work done by Pettus and co-workers$^{30}$, and Pan and co-workers$^{31}$. The synthesis of brazilin by Pettus utilized a regioselective dirhodium-catalyzed aryl C-H insertion to make an indanone intermediate (Scheme 1-7). The other highlight of this synthesis was the use of a regioselective phenol oxidation, using IBX, to an o-quinone and a tautomerization of the o-quinone to a p-quinone methide. This synthesis was a racemic one however.
The synthesis by Pan and co-workers also synthesized brazilein from brazilin and was enantioselective for the positive enantiomer. This synthesis utilized a chiral auxiliary, in the form of AD-mix-β, to use a Sharpless dihydroxylation to synthesis the syn addition intermediate (Scheme 1-8). From here they then used a stereocontrolled Friedel-Crafts cyclization to furnish the tetracyclic core of brazilin. After deprotection they were able to synthesize brazilin with a 99% ee. From here they then oxidized brazilin to brazilein. It should be noted that no catalytic asymmetric syntheses of compounds in the brazilin family have been reported to date however.
Scheme 1-8

\[
\text{Scheme 1-8}
\]

\[
\text{Scheme 1-8}
\]
1.4 Previous Attempted Synthesis

Hydroxybrazilin has been a target in the Calter group previously, with Alexander Korotkov laying the groundwork for the synthesis\textsuperscript{32}. Korotkov’s synthesis utilized a common nucleophile optimized by Na Li\textsuperscript{33}, another member of the Calter group. This nucleophile is made by activating propylene glycol, and then protecting the ketone of commercially available diethyl 1,3-acetonedicarboxylate. The protected bis-ester can then be converted to a methyl ketone with the use of a Grignard reaction and cyclized to the nucleophile for an IFB reaction (Scheme 1-9).

Scheme 1-9

The electrophile for the IFB reaction started with the commercially available indane, which was dibrominated\textsuperscript{34}, and then oxidized with potassium permanganate\textsuperscript{35}. The synthesis of the electrophile is finished with the tosylation at the α position of the ketone (Scheme 1-10).
Having both in hand, Korotkov submitted nucleophile and electrophile to an IFB reaction, achieving a yield of 73% and 88 % ee after optimization (Scheme 1-11).

The IFB product was then reduced, initially attempting to achieve the 1, 4-reduction\textsuperscript{36}, however it actually yielded diastereomers of an allylic alcohol. Upon treatment of a weak acid, PPTS, this alcohol rearranged and aromatized. Continuing with a common method developed in the Calter lab to cleave the sidechain, the primary alcohol was oxidized under various conditions, also attempting to oxidize the secondary alcohol in one step. These oxidation conditions including DMP, Swern, and PCC. Unfortunately, no oxidation was observed at either the primary or secondary alcohol, and only decomposition products were observed. These decomposition products arise due to the multitude of alcohols present, primarily the phenol.
To further explore the mechanism of the core structure, an analog was synthesized utilizing dimedone as the nucleophile, to observe what rearrangement would occur without the protected ketone present\(^{32}\). Upon acidic rearrangement with PPTS, aromatization cannot occur, and therefore yielded the “open” unsaturated ketone (Figure 1-5). Another analog, was also developed with 1,3-cyclohexanedione, which followed the same pathway as the dimedone analog (Figure 1-5)\(^{37}\). The secondary alcohol in this analog was then able to be oxidized without the presence of the free phenol and primary alcohol complicating things.

**Figure 1-5.** Dimedone and 1,3-cyclohexanedione Analogs
With this in mind, we turned towards trying to replicate a rearrangement similar to these two analogs, while still keeping functionalization on the ring in order to furnish the phenol on hydroxybrazilin. The simplest way to do this would be to change the protecting group of the ketone, towards something more stable under acidic conditions. Again, the simplest protecting group to change to would be to change to a dioxolane from a dioxane, shortening the protecting group by one carbon. This change in protecting group has been shown to be about thirty times more stable under acidic conditions (Figure 1-6)\textsuperscript{38}.

**Figure 1-6. Relative Rates of Hydrolysis of Protected Cyclohexanone**
References


31. Wang, X.; Zhang, H.; Yang, X.; Zhao, J.; Pan, C., Enantioselective total synthesis of (+)-brazilin, (-)-brazilein and (+)-brazilide A. Chemical Communications 2013, 49 (47), 5405-5407.


34. Kim, S.-H.; Bajji, A.; Tangallapally, R.; Markovitz, B.; Trovato, R.; Shenderovich, M.; Baichwal, V.; Bartel, P.; Cimbora, D.; McKinnon, R.; Robinson,


2. Results and Discussion

2.1 Retrosynthesis

While most of the groundwork for the initial steps in the synthesis of hydroxybrazilin were worked out by a combination of Korotkov\textsuperscript{1} and Li\textsuperscript{2}, the changing of the protecting group does lead to some changes in the synthetic route. We can start from target 1, hydroxybrazilin, and utilize a Buckwald-Hartwig coupling to exchange the bromines for the two phenols to form 2, which can be prepared by the selective opening of epoxide 3 (Scheme 2-1). This epoxide can be formed by methylenating ketone 4 and then making the epoxide. Ketone 4 would be prepared from IFB product 5 through reducing the unsaturated ketone, acidic rearrangement, oxidation of primary and secondary alcohol, cleavage of sidechain and aromatization. This IFB product would utilize the same electrophile prepared by Korotkov and a similar nucleophile as well, 6 and 13 respectively.
2.2 Proposed Synthesis

With the new synthetic route attempting to take advantage of the added stability of dioxolane over dioxane to acid, we will need to alter the original synthetic route that Korotkov proposed\(^1\). While most of this is only a rearrangement in the order of synthetic steps, some reactions will need to be changed. The main reaction that will
require a different procedure is cleaving the side chain. The propyl sidechain can easily be eliminated once the primary alcohol is oxidized to an aldehyde.

Unfortunately, this will not be possible with an ethyl sidechain, instead we must go through a ketyl intermediate (Figure 2-1). We propose that this would be able to be accomplished with the use of tributyltin hydride, due to its nature as a radical reducing agent (Scheme 2-2)\(^3\).

**Figure 2-1. Ketyl Intermediate**
Scheme 2-2

Hydroxybrazillin


2.3 Synthesis of nucleophile and comparative methodology

We start our synthesis of compound 13, our nucleophile for the IFB reaction, with commercially available ethylene glycol. Similar to propylene glycol, we activate with TMSCl to yield 8, which is then used to protect commercially available diethyl 1,3-acetonedicarboxylate (Scheme 2-3). No real differences were observed between the synthesis of either compound 8 or 9 compared to the propyl variant2.

Scheme 2-3

From here we then utilize a Grignard reaction to form methyl ketone 10 (Scheme 2-4). Compared to the propyl version, it is evident that the ethyl version is much slower to react, as evidenced by the longer reaction time and a larger excess of reagent (Table 2-1)2. It is also seemingly less stable in the ketone intermediate as a larger percentage of desired product is converted to the double addition byproduct of tertiary alcohol 11, than is observed with the propyl variant. Interestingly another byproduct is observed with the dioxolane protected intermediate, where a proton is
abstracted and the ring opens to yield 12. Luckily this byproduct is observed in fairly low quantities, and is observed mainly on larger scale reactions (greater than 5 g). Unfortunately, it is difficult to separate from the desired methyl ketone without being chromatographed again with toluene/acetone.

Scheme 2-4

Table 2-1. Percent conversion of Grignard reaction by NMR

<table>
<thead>
<tr>
<th>Time (Hrs.)</th>
<th>Eq. MeMgBr (mol)</th>
<th>9 (%)</th>
<th>10 (%)</th>
<th>11 (%)</th>
<th>12 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>1.15</td>
<td>66</td>
<td>25</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>1.3</td>
<td>63</td>
<td>25</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>1.3</td>
<td>28</td>
<td>34</td>
<td>33</td>
<td>5</td>
</tr>
<tr>
<td>48</td>
<td>1.3</td>
<td>5</td>
<td>18</td>
<td>71</td>
<td>6</td>
</tr>
</tbody>
</table>
While unable to quite match the yield of the dioxane variant, we are able to obtain methyl ketone 10 in a decent yield. From here a Dieckmann condensation with LDA is used to form cyclized 13 (Scheme 2-5). Utilizing the same conditions optimized for the dioxane nucleophile gave no conversion (Table 2-2). Upon longer reaction times we were able to obtain modest conversion to product 13. Thinking that the kinetics may be different, we attempted to increase conversion by further lengthening the reaction, however this unfortunately lead to decomposition of the reaction. We also screened other conditions that Li used including higher temperatures with DME as the solvent, and changing our base to LiHMDS, a more sterically hindered, less nucleophilic base (Table 2-3). Even at optimized conditions the reaction does not go to completion and starting material 10 is recovered. This slower reactivity and lower yield, coupled with the physical instability of the product (oil) compared to the dioxane variant (solid) lead us to conduct ab initio calculations in an attempt to discern the reason for this drastic difference. It should be noted that protected bis-ester 9 is also recovered as byproduct 12 from the previous step can be recyclized under the basic reaction conditions.
Scheme 2-5

\[
\begin{align*}
\text{10} & \xrightarrow{\text{Base}} \text{13} \\
\text{10} & \xrightarrow{\text{Base}} \text{13}
\end{align*}
\]

Table 2-2. Dieckmann Condensation of Dioxolane Protected Ketone

<table>
<thead>
<tr>
<th>Time (Hrs.)</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>THF</td>
<td>LDA</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>LDA</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
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<td>LDA</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>THF</td>
<td>LDA</td>
<td>Decomposition</td>
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Table 2-3. Dieckmann Condensation of Dioxane Protected Ketone

<table>
<thead>
<tr>
<th>Time (Hrs.)</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>THF</td>
<td>LDA</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>LiHMDS</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>DME</td>
<td>LDA</td>
<td>48</td>
</tr>
</tbody>
</table>
Due to the vast differences in yield, reaction rate, and physical properties between the synthesis of our nucleophile, 13, compared to the dioxane protected analog, rough free energy calculations for the both reaction pathways (Scheme 2-6) were conducted utilizing the Gaussian 09 suite of programs\textsuperscript{4}, with assistance from David Cabanero. All calculations were done utilizing B3LYP/6-31g level of theory, in a PCM solvated model for THF. Transition state energies were calculated using structures optimized by TS(berny).

**Scheme 2-6**
From these calculations we were able to observe differences between each step in this reaction. The initial formation of the enol is seen to go through transition states with slightly different \( \Delta G^\ddagger \) values, in which the dioxane (n=1) is more favored than the dioxolane (n=0). However, the enololate intermediate is almost identical (Figure 2-2) in relative free energy. Differences in the \( \Delta G \)'s of the next intermediate occur due to the larger bond angle of the dioxolane protected ketone over the dioxane, thus allowing more freedom of bond rotation for the enol to attack the ester. The relative rate of this step is 1.016 s\(^{-1}\) in favor of the dioxane analog. The final step of collapsing the tetrahedral intermediate to form the cyclized nucleophile shows that this same reason is then detrimental to the dioxolane analog, as it has greater ring strain caused by this larger bond angle from the [5.6] spiro ring system compared to the [6.6] ring system.

**Figure 2-2.** Relative \( \Delta G \) for Dioxane/Dioxolane Analog Dieckmann Condensations

![Graph showing relative ΔG for Dioxane/Dioxolane Analog Dieckmann Condensations](image)
For the entire reaction the $\Delta G$ difference is 2.79 kcal/mol in favor of the dioxane protecting group. Although this does show that the dioxane analog is more favorable, as seen in the experimental results, this does not seem to be a large enough difference to explain the substantial differences observed experimentally. It is also possible that there is a large difference that was not accounted for by not utilizing polarization or diffuse functions due to the additional computational time required as well as the diisopropylamine from LDA not being considered in the calculations.

**2.4 Synthesis of Electrophile**

We start the synthesis of our electrophile with commercially available indane, by dibrominating it to yield a mixture of bromine additions in an excellent 99% yield (Scheme 2-6)$^5$. While high yielding, we do also have the presence of alternate bromination biproducts. While these have not been isolated, as they are difficult to separate by chromatography, we suspect the presence of two biproducts. One of these byproducts is suspected to be where the bromines again add ortho to each other, $^{15}$, as observed by the coupling constant of 7 Hz, and one where they add meta to each other, $^{16}$. Estimating off of NMR, it can be stated that our desired addition, $^{14}$, is 85% of this mixture, while both biproducts combine for the remaining 15%.
Compound 14 was then oxidized following the same procedure utilized by Korotkov to yield 17 (Scheme 2-7). We have been unable to match the yields that were reported however, and attempted to optimize these conditions. Initially the reaction didn’t proceed to completion with potassium permanganate and iron(III) chloride hexahydrate (Table 2-4). We then utilized a different solid support, copper(II) sulfate, however this only exacerbated the problem except when run in DCM. Fortunately, we were able to achieve complete conversion with the use of chromium(VI) trioxide, with a modest yield of 39%. It should be noted that this yield assumes the use of pure 14, if the NMR estimates are taken into account the yield increases to 46%.
Scheme 2-7

![Scheme 2-7]

**Table 2-4. Optimization of Oxidation of 14 to 17**

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Eq. of Oxidant</th>
<th>Time (Hrs.)</th>
<th>Solvent</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>KMnO₄, FeCl₃, 6 H₂O</td>
<td>10</td>
<td>16</td>
<td>Acetone</td>
<td>37.5</td>
<td>5.8</td>
</tr>
<tr>
<td>KMnO₄, CuSO₄, 5. H₂O</td>
<td>6</td>
<td>16</td>
<td>Neat</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>KMnO₄, CuSO₄, 5. H₂O</td>
<td>6</td>
<td>16</td>
<td>Acetone</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>KMnO₄, CuSO₄, 5. H₂O</td>
<td>6</td>
<td>16</td>
<td>Acetonitrile</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>KMnO₄, CuSO₄, 5. H₂O</td>
<td>6</td>
<td>72</td>
<td>DCM</td>
<td>57</td>
<td>13.7</td>
</tr>
<tr>
<td>KMnO₄, FeCl₃, 6 H₂O</td>
<td>10</td>
<td>2</td>
<td>Acetone</td>
<td>23</td>
<td>8.7</td>
</tr>
<tr>
<td>KMnO₄, FeCl₃, 6 H₂O</td>
<td>6</td>
<td>16</td>
<td>Acetone</td>
<td>17</td>
<td>6.1</td>
</tr>
<tr>
<td>CrO₃</td>
<td>3</td>
<td>2</td>
<td>Acetic Acid</td>
<td>85</td>
<td>28</td>
</tr>
<tr>
<td>CrO₃</td>
<td>4</td>
<td>16</td>
<td>Acetic Acid</td>
<td>100</td>
<td>39</td>
</tr>
</tbody>
</table>

The last step in preparing our electrophile is to tosylate 17 to yield 6. This reaction proceeds smoothly with a 57% yield (Scheme 2-8).
While working with the dioxane protected analog, Korotkov optimized the reaction conditions for an Interrupted Fiest-Bénary reaction involving 6 as the electrophile (Scheme 2-9). He was able to achieve 73% yield with DABCO as catalyst, and 88% ee with the use of a mono-QN catalyst (Figure 2-3) in toluene.

While it would be intriguing to see if we are able to match the enantioselective results with the dioxolane protected analog, the main purpose of acid stability must be proven first. Moreover, this functionalization is quite far from the active site of an IFB reaction, and would probably do little to affect the enantioselectivity. This is backed by the minor difference in % ee that Korotkov observed between the dioxane and dimedone analogs of 88% ee and 84% ee respectively when using the same catalyst.

Figure 2-3. Optimal Catalyst for IFB of Korotkov’s Synthesis
Utilizing the same conditions, we submit 6 and 13 to an IFB reaction (Scheme 2-9). As with the dioxane protected analog, we found that the reaction proceeds better in DCM than toluene (Table 2-4), although it should be noted that the best enantioselective results observed for the dioxane analog were achieved in toluene. This is suspected to be due to the slower reaction rate.

Scheme 2-9

![Scheme 2-9]({"file_url":null,"file_type":null,"width":null,"height":null,"alt":null})

**Table 2-4. Reaction Conditions for IFB**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Time (Hrs.)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>72</td>
<td>5%</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>72</td>
<td>34%</td>
</tr>
<tr>
<td>DCM</td>
<td>72</td>
<td>63%</td>
</tr>
</tbody>
</table>

Similar to what was observed by Kortokov, we do get a minor amount of O-alkylation and C-alkylation products, 18 and 19, in addition to the IFB product (Figure 2-4). While this was typically observed when he utilized K₂CO₃ as the base,
potassium bicarbonate can decompose to potassium carbonate, thus causing the minor appearance of these byproducts.

**Figure 2-4.** Biproducts of IFB Reaction

Continuing our synthetic plan, we utilize DIBAL in order to reduce the unsaturated ketone of IFB product 5, to allylic alcohol 20 (Scheme 2-10). This reaction initially proved troublesome, as we were unable to get complete conversion. This becomes an issue when attempting to purify the reaction mixture as our reduced product will aromatize on the acidic silica gel, hinting that our change in protecting group might not be stable enough. We have been able to overcome this challenge with two solutions though.

**Scheme 2-10**
First, we were able to separate the IFB product, 5, and both of the diastereomers of allylic alcohol, 20, if we neutralized the silica gel with triethylamine before, and while running the column. With this we were able to confirm that the reaction is not diastereoselective, and produces a 50:50 ratio of the two diastereomers of 20. Second, we optimized the reaction conditions so that we were eventually able to achieve complete conversion. We started our optimization by increasing the amount of DIBAL and the reaction length, however this had little effect (Table 2-5). Fortunately, we were able to achieve complete conversion with the use of DIBAL stored in a different solvent, toluene as opposed to THF. This increased reactivity comes from the fact that THF is a more coordinating solvent than toluene is, and hinders the progress of the reaction.

**Table 2-5. Optimization of Reduction of 5 to 20**

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Time (Hrs.)</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIBAL 1 M in THF</td>
<td>2</td>
<td>60%</td>
<td>47%</td>
</tr>
<tr>
<td>DIBAL 1 M in THF</td>
<td>5</td>
<td>55%</td>
<td>40%</td>
</tr>
<tr>
<td>DIBAL 1 M in THF</td>
<td>16</td>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>DIBAL 1.5 M in toluene</td>
<td>4</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td>DIBAL 1.5 M in toluene</td>
<td>6</td>
<td>100%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Although our experience with the acidity of silica gel and compound 20 rearranging to the aromatized 21 suggesting that the protecting group may not be
stable under acidic conditions, we proceeded to attempt to obtain the rearranged product 22 utilizing catalytic PPTS (Scheme 2-11). Regrettably, the same product was observed as with the dioxane analog.

**Scheme 2-11**

We persisted and attempted to isolate our desired product, 22, by lowering the temperature, however no reaction at all occurs until the reaction is brought to 0 °C, where it aromatizes (Table 2-6). As mentioned above, we were able to separate the diastereomers of 20, and we postulated that they may have different rates or stability undergoing the rearrangement. Again, our efforts were fruitless and we only obtained the aromatized product. This was also the case when we attempted to change the
solvent in order to change the acidity of the solution with THF and acetonitrile. We also attempted to run the reaction with a stronger acid, tosic acid, hoping that the reaction may proceed to our desired product, albeit at a lower temperature. While a reaction did occur at a lower temperature, -10 °C, it again yielded the aromatized version. Although unfortunate that we obtain the aromatized version, the rearrangement does proceed with high yields, thus leaving the potential for further functional changes leading to hydroxybrazilin.

Table 2-6. Screening of Rearrangement Conditions

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>-78</td>
<td>PPTS</td>
<td>No reaction</td>
</tr>
<tr>
<td>-42</td>
<td>PPTS</td>
<td>No reaction</td>
</tr>
<tr>
<td>-22</td>
<td>PPTS</td>
<td>No reaction</td>
</tr>
<tr>
<td>-10</td>
<td>PPTS</td>
<td>No reaction</td>
</tr>
<tr>
<td>0</td>
<td>PPTS</td>
<td>21</td>
</tr>
<tr>
<td>-10</td>
<td>TsOH*</td>
<td>21</td>
</tr>
</tbody>
</table>

*same range of temperatures run for TsOH as with PPTS, no reaction until -10 °C

Although quite certain that we were obtaining the aromatized “open” product 21, we wished to confirm that we were not getting the aromatized “closed” product 23 (Figure 2-5) before continuing forward with our synthesis. This might also provide insight to the mechanism of the reaction as well.
As telling these apart by NMR would be tricky, we utilized GC mass spectrometry. This quickly showed that we were indeed getting the “open” form of the aromatized product due to the molecular ion peak of 414 m/z (Figure 2-6). This corresponds to the loss of the sidechain from the “open” form (Figure 2-7). While the calculated mass is 412, the isotopes of bromine lead to the distinctive pattern yielding 414 as the molecular ion, as there are two bromines present.
**Figure 2-6.** Mass Spectrum of

**Figure 2-7.** Molecular Ion of 21

Chemical Formula: C_{13}H_{11}Br_2O_4^+
Calculated Mass: 412.90
With the structure of the aromatized product confirmed, we then turned towards trying to understand why the dioxolane protecting group, more stable to acid hydrolysis, cleaved just as easily as the dioxane protecting group. We first must consider that the model that we used for this, cyclohexanone, is quite different from our product, 20. To provide a closer analog we utilized IFB product 5 to test if the protecting group would hydrolyze (Scheme 2-12). Even upon warming to room temperature the IFB product did not hydrolyze. This indicates that the presence of the allylic alcohol is key in the rearrangement, and thus aromatization of compound 20 (Scheme 2-13).

Scheme 2-12

![Scheme 2-12](image)

Scheme 2-13

![Scheme 2-13](image)

We then propose that the compound rearranges from this intermediate, which can form a dienol ether, instead of simply hydrolyzing the protecting group first. It is
interesting to note that the tertiary alcohol, luckily, is never observed to leave, thus yielding the elimination product 24 (Figure 2-8) or any similar elimination products. It would be suspected that this tertiary and benzylic carbocation would be much more stable than the secondary allylic one that we propose. This becomes more intriguing when the aromatized product is formed, as the tertiary alcohol is now doubly benzylic. Regardless, as these eliminated furans would be quite unwanted byproducts, as we lose the enantioselectivity we installed through the IFB reaction, and instead revert to a Fiest-Bénary product, we have not investigated the reasoning for this thoroughly.

**Figure 2-8. Potential Elimination Product**

![Potential Elimination Product](image)

Returning to our synthesis, we then attempted to again follow Kortokov’s plan, and oxidize both the primary and secondary alcohols with DMP. The DMP was prepared utilizing oxone to make precursor IBX, which was then acetylated with acetic anhydride to yield DMP, as opposed to being acquired commercially (Scheme 2-14)⁹.
Unfortunately, we had issues that arose from the free phenol, leading to quinone 25 instead of our desired product 26 (Scheme 2-15). It is curious to note that the secondary alcohol was oxidized before the primary alcohol was in this case. This may simply be due to the phenol actually reacting first, and thus providing some steric hindrance or hydrogen bonding to the primary alcohol through the acetate arms of DMP.

Free phenols are known to react with hypervalent iodine species to produce quinones (Scheme 2-16), typically with IBX, the precursor to DMP\textsuperscript{10}. DMP can easily be hydrolyzed to IBX in the presence of moisture however.
This type of reaction is only observed when an electron donating group is present anywhere on the aromatic ring, which we have in the form of the ether of the sidechain. The reaction will proceed to form a quinone on the most nucleophilic and least sterically hindered ortho position of the ring (Scheme 2-17).
Scheme 2-17

Since we only have one available ortho position, the quinone will form there. In order to prevent this quinone formation we must protect the free phenol. We chose to benzyl protect the phenol due to its relative ease to deprotect later on when compared to a methyl protected phenol (Scheme 2-18). This reaction proceeds slowly at room temperature, and does not go to conversion even after three days. Upon refluxing we have had mixed results of the reaction going to completion and even some bis protection of the primary alcohol with excess benzyl bromide. If we only
add the benzyl bromide in a stoichiometric amount, we are unable to achieve complete conversion before the reaction decomposes (Table 2-7).

**Scheme 2-18**

![Scheme 2-18](image)

**Table 2-7. Optimization of Protecting Conditions for 21 to 27**

<table>
<thead>
<tr>
<th>Eq of BnBr</th>
<th>Temperature</th>
<th>Time (Hrs.)</th>
<th>% Conversion</th>
<th>28 Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>RT</td>
<td>72</td>
<td>15%</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Reflux</td>
<td>48</td>
<td>100%</td>
<td>Yes</td>
</tr>
<tr>
<td>2.5</td>
<td>Reflux</td>
<td>72</td>
<td>100%</td>
<td>No</td>
</tr>
<tr>
<td>1</td>
<td>Reflux</td>
<td>96</td>
<td>Incomplete*</td>
<td>No</td>
</tr>
<tr>
<td>1.1</td>
<td>Reflux</td>
<td>16</td>
<td>18%</td>
<td>No</td>
</tr>
</tbody>
</table>

*-reaction decomposed, conversion was only monitored by TLC

With the presence of the potential double protection, we wanted to ensure that we were in fact getting the first addition at the phenol, at not one of the other three alcohols before proceeding forward. As the phenol is the most acidic of them, it
should be the first to react, with the primary alcohol being the second most acidic.

With this in mind, we utilized a combination of gradient Heteronuclear Single Quantum Coherence (gHSQC) and gradient Heteronuclear Multiple Quantum Coherence (gHMBC) NMR experiments to prove the location of the mono protection. HSQC is used to show the heteronuclear $J_1$ coupling between proton and carbon nuclei. This experiment was used to assign the carbon peaks (Figure 2-9). From this we can assign the carbons on the ethyl sidechain to be at 60.92 (C1) and 71.70 ppm (C2). The carbon ortho to the phenol will be the most likely to show coupling in the HMBC if the phenol is protected, and it can be assigned to the peak at 95.97 ppm (C3) (Figure 2-10).

**Figure 2-9. gHSQC of 27**
Figure 2-10. Labeling of Compound 27

The HMBC is used to show long range ($J_2$-$J_5$) coupling between proton and carbon nuclei. Utilizing this spectrum (Figure 2-11) we are able to see the $J_4$ coupling of the methylene protons on the benzyl protecting group to the aromatic carbon at 95.97 ppm that was assigned to the ortho position of the phenol through the HSQC. This confirms that we get protected 27 as our mono addition, as there are no interactions from the benzyl protons to the sidechain carbons.
With protected 27 in hand we again attempted to oxidize both the primary and secondary alcohols with DMP (Scheme 2-19). We have also screened PDC conditions for this oxidation. Unfortunately, both with DMP and PDC this has only led to a low conversion of 29, where the aldehyde is formed but the secondary alcohol is not oxidized, even with excess oxidant.
Scheme 2-19

\[ \text{Br} \quad \text{HO} \quad \text{BnO} \quad \text{O}\text{-}\text{CH}_2\text{OH} \quad \text{Br} \]

\[ \text{Br} \quad \text{HO} \quad \text{BnO} \quad \text{O}\text{-}\text{CO}_2 \]

2 eq. DMP
DCM, 3 hours

27

29
References


3. Future Studies

3.1 Oxidizing Aldehyde

The simplest route forward would be to isolate aldehyde 29 and attempt to resubmit it to an oxidation (Scheme 3-1), as there would only be the secondary alcohol left to oxidize. Once 30 is isolated we would then be able to continue our original synthetic plan. This will require further conversion of the initial oxidation to 29 to make this route viable.

Scheme 3-1

3.2 Alternate Protecting Groups

As our plan to stabilize the rearrangement of compound 20 by changing the protecting group to the most similar analog failed to yield the desired result, we could pursue further protecting group changes. Another similar group is a dithiane group (Figure 3-1), which is more stable under acidic conditions than both the dioxane or dioxolane groups.
Luckily the methodology for this change has already been worked out by Ryan Phillips\(^2\) (Scheme 3-2), as he initially utilized this protecting group before Li opted to change to the dioxane protected ketone due to the easier synthesis early on, and the greater ease of converting the final functionality to the desired phenol (Scheme 3-3)\(^3\).

**Scheme 3-2**
While this added stability may solve this issue, it does seemingly follow the same reasoning that we employed for the change to a dioxolane group. This coupled with our mechanistic insight, may prove to be a fruitless endeavor, as the protecting group itself is probably not where the acid instability is coming from. It is instead coming from the mechanism of the rearrangement itself, after the allylic alcohol leaves. With this in mind, we could change to a group that would be easier to convert to our desired phenol at the end of our synthesis, such as a dimethoxy group (Figure 3-2). This could either be installed from the beginning of the synthesis, or simply utilize the conversion utilized by Li from the dithiane\(^3\).

**Figure 3-2. Dimethoxy Protected Ketone**

If our product of the rearrangement still aromatizes we would no longer have to worry about oxidizing both the primary and secondary alcohols, and thus be able to focus only on the secondary. This would also eliminate the need to cleave the sidechain at the end of the synthesis, although we would still have to deprotect the methyl protected phenol with the general procedure (Scheme 3-4)\(^4\).
We could still have issues arise from the other unprotected phenol and hypervalent iodine reagents, but this could easily be avoided by methyl protecting the other phenol as well, since the first one will need to be deprotected regardless (Scheme 3-5)\(^5\).

### Scheme 3-5

\[
\begin{align*}
\text{OH} & \quad \text{Base, Me}_2\text{SO}_4 & \quad \text{OMe} \\
\text{苯} & \quad \rightarrow & \quad \text{苯}
\end{align*}
\]

3-3 Protecting Primary Alcohol

As we have been able to protect the phenol, but have had issues when attempting to oxidize both the secondary and primary alcohol at the same time, we could attempt to protect the primary alcohol selectively. This would allow us to focus on the secondary alcohol, and later come back to oxidizing the primary alcohol when it is the only one left. This could be achieved from an intermediate such as 31 (Scheme 3-6) to yield 30/32.
The simplest and probably most effective group to selectively protect the primary alcohol over the secondary one, would be with a TBDMS group (Scheme 3-7), which could easily be removed after the functionalization of the secondary alcohol.

**Scheme 3-7**

3-4 Dearylation

Alternatively, we could attempt to target the primary alcohol first by following a common pathway utilized in our lab optimized by Li\(^3\). This pathway involves a base initiated aromatization of the IFB product. This path may still have issues with the free phenol, but we could protect the phenol, oxidize the primary alcohol, and cleave the sidechain (Scheme 3-8).
This would mean we would then have to dearylate and open up the dihydrobenzofuran moiety. There are few literature precedents in this area, but Yus and coworkers have developed a similar procedure utilizing a reductive lithiation (Scheme 3-9)\(^7\).

**Scheme 3-9**
Unfortunately, there are complications that arise, the most pertinent being the selectivity of dearylation over dealkylation. When \( n=1 \), they achieve a 2:1 ratio of dearylation to dealkylation. However, when \( n=0 \) they observed only the dealkylation product, which would not be helpful to our synthesis. They do note that it is a very sensitive system to steric and electronic factors, and with the addition of the two phenols we may be able to achieve a modest yield of the dearlylation product (Figure 3-3). If this proves unsuccessful the phenols will give us a handle to vary these steric and electronic influences.

**Figure 3-3. Potential Dearylation Product**

![Potential Dearylation Product](image.png)

The other main issue that may arise is the potential metal halogen exchange that could occur with the bromines, which would cause the loss of functionality that we need to install the phenols on this aromatic ring. This could be overcome by converting the bromines to benzyl protected phenols with a Buchwald-Hartwig coupling, as we originally planned in our initial synthesis (Scheme 3-10).
From the dearylated product we would then be able to oxidize the secondary alcohol, methylenate, and form the epoxide like in our initial synthetic plan.

3-5 Hydrogenation

From our attempts to oxidize unprotected phenol, 21, we were able to synthesize the ortho quinone 25. While this is detrimental to our synthesis of hydroxybrazilin, it could be a useful way to implement functionality into our molecule at a later stage in the synthesis. This would be extremely useful for the synthesis of any analogs of the brazilin family, as we wouldn’t have to develop a new nucleophile to include a handle on the molecule from the start. In addition, any unsymmetrical nucleophile could lead to two different IFB products (Figure 3-4), depending upon the steric and electronic effects any functionality would have on the IFB mechanism.

Figure 3-4. Potential IFB Products
To pursue any analogs, we would first need to reduce the quinone though. We have attempted this with a hydrogenation and acylation of the resulting phenols (Scheme 3-11)\(^8\). However, we have so far been unsuccessful in this endeavor, and only recover the quinone. Thus, this reaction will require further optimization, potentially increasing the pressure and the equivalents of base, as only 2.1 equivalents were added. The additional base will probably be needed in order to both buffer the acetic anhydride, and to deprotonate the phenols after the reduction occurs.

**Scheme 3-11**
References


Conclusions

In conclusion, we have optimized the synthesis of a new nucleophile (dioxolane protected cyclohexanetrione) to be utilized in an IFB reaction. The driving force for synthesizing this nucleophile was to better withstand an acid catalyzed rearrangement in a synthesis towards the natural product hydroxybrazilin. This proved to be futile, however it does give further insight into the mechanism of this rearrangement. This insight can be utilized to plan future changes that may better withstand the acidic conditions, and yield a derivative of our desired 22. Although initial plans of this synthesis resulted in the same result as with previous nucleophiles (dioxane protected), we were able to continue and alter the planned synthesis. We have also found a potential pathway to synthesizing analogs of hydroxybrazilin, and explored alternative synthetic routes towards our target.
Methods

All commercial reagents were used as directly received. DMF, toluene, DCM, diethyl ether, pyridine, THF, and DME were filtered through an activated alumina column in a solvent purification system. When they were needed, anhydrous diisopropyl amine and DCM were distilled over calcium hydride. Flash column chromatography used in the purification of the compounds was performed on Dynamic Adsorbents 60 Å, 32-63 μm silica gel. Thin-layer chromatography (TLC) was accomplished using SiliCycle 0.25 mm thickness, 60 Å pore size silica gel plates. The TLC plates were visualized using a UV/Vis lamp or a ceric ammonium molybdate stain. All $^1$H, $^{13}$C, HSQC, and HMBC NMR were all taken on Varian-300 (300 Hz and 75 Hz), 400 (400 Hz and 100 Hz), and 500 (500 Hz and 125 Hz), spectrometers. Mass spectra were taken on an Agilent Technologies 6890 GC System with 5797 Network mass selective detector.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \quad \overset{2.5 \text{ eq. TMSCl}}{\text{DCM}} \quad \overset{3 \text{ eq. NEt}_3}{\text{16 Hours}} \quad \text{TMSO} \quad \text{OTMS} \\
\end{align*}
\]

1,2-Bis-(tirmethylsiloxy)ethane (8): TMSCl (6.35 mL, 50.0 mmol) was added slowly to a solution of ethylene glycol (1.12 mL, 20.0 mmol) and NEt$_3$ (8.36 mL, 60.0 mmol) in 80 mL CH$_2$Cl$_2$ at 0 °C. The reaction was warmed to room temperature overnight and then washed with saturated NaHCO$_3$ (80 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 80 mL). The
combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was filtered through a plug of silica gel (hexanes/EtOAC 1:1) to give 8 (3.98 g, 97%) as a yellow oil. This compound has been characterized before$^1$.

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.64 (s, 4H), 0.13 (s, 18H).

**Diethyl 3-(1,3-dioxolane)pentanedioate (9):** To a solution of diethyl 1,3-acetonedicarboxylate (8.83 g, 43.7 mmol) and 8 (11.7 g, 56.8 mmol) in 200 mL of CH$_2$Cl$_2$ was added 1.97 mL TMS-OTf (10.9 mmol) at -42 °C. The reaction was then warmed to RT and held there for 24 hours. Pyridine (40 mL) was added and the solution was quenched with saturated NaCO$_3$ (100 mL). The organic phase was then washed with alternating saturated NaCO$_3$ (3 x 100 mL) and 1 M NaSO$_4$ (3 x 100 mL) and extracted with CH$_2$Cl$_2$. The combined organic phase was dried over NaSO$_4$ and concentrated in vacuo. The crude product was taken on without any further purification (10.4 g, 97%) as a yellow oil. This compound has been characterized before$^2$. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.12 (q, J=7.2 Hz, 4H), 3.99 (s, 4H), 2.91 (s, 4H), 1.23 (t, J=7.2 Hz, 6H).
**Ethyl 2-(2-(2-oxopropyl)-1,3-dioxolan-2-yl)acetate (10):** Methylmagnesium bromide (3 M in diethyl ether, 22.5 mL, 66.3 mmol) was added dropwise to a solution of 9 (12.6 g, 51.0 mmol) in CH₂Cl₂ (510 mL) at -78 °C. After 36 hours at -78 °C, 100 mL of saturated NH₄Cl was added to quench the reaction. The mixture was allowed to warm to room temperature and was then extracted with CH₂Cl₂ (3 x 250 mL). The organic layer was dried with Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography (hexanes/isopropanol, 9:1) to give 10 (2.76 g, 27%) as a yellow oil. An additional 34% of starting material 9 was recovered. ¹H NMR (CDCl₃, 300 MHz) δ 4.12 (q, J=7.2 Hz, 2H), 3.99 (s, 4H), 3.06 (s, 2H), 2.84 (s, 2H), 2.21 (s, 2H) 1.23 (t, J=7.2 Hz, 3H). ¹³C (CDCl₃ 100 MHz) 205.13, 169.12, 112.48, 64.07, 60.44, 59.54, 49.97, 42.08, 14.14.

**5-(1,3-Dioxolane)-1,3-cyclohexadione (13):** 5.95 mL of nBuLi (9.52 mmol) was added to a solution of diisopropylamine (0.96 mL, 9.52 mmol) in 10 mL of THF at -78 °C. The reaction mixture was allowed to warm to room temperature and after 30 minutes was added to a solution of 10 (1.96 g, 9.07 mmol) in 90 mL of THF via cannula at -78 °C. After warming to room temperature, the solution was heated at reflux for 6 h. The solvent was removed *in vacuo* and the residue was diluted with CH₂Cl₂ (40 mL) and water (40 mL). The aqueous layer was extracted with CH₂Cl₂.
(3 x 40mL) at pH 12, 7, and 1. The pH was adjusted with 1 M HCl. The organic layers were dried separately over Na₂SO₄ and concentrated in vacuo. The basic pH yielded a mixture of 9 and 10. The neutral and acidic washes were combined to give 13 (0.37 g, 24%) as a brown oil. ¹H NMR (CDCl₃, 300 MHz) δ 4.02 (s, 4H), 3.44 (s, 2H), 2.89 (s, 4H). ¹³C (CDCl₃ 100 MHz) 197.12, 170.92, 124.13, 107.94, 64.46, 53.40, 48.44.

5,6-dibromo-indane (14): Bromine (1.83 mL, 35.7 mmol) was added to a solution of indane (2.08 mL, 17.0 mmol), iron powder (0.28 g, 5.1 mmol), and I₂ (0.22 g, 0.86 mmol) in 100 mL CH₂Cl₂ at 0 °C. After 2 hours aq. Na₂S₂O₃ (75 mL) was added to quench the reaction and was extracted with CH₂Cl₂ (3 x 75 mL). The organic layer was dried with Na₂SO₄ and concentrated in vacuo. The resulting brown solid (4.65 g, 85%) was taken on without any further purification. This compound has been characterized before. ¹H NMR (CDCl₃, 300 MHz) δ 7.46 (s, 2H), 2.85 (t, 4H), 2.08 (m, 2H).

5,6-dibromoindan-1-one (17): CrO₃ (12.5 g, 125.2 mmol) was added portion wise to a solution of acetic acid (150 mL) and 6 (8.64 g, 31.3 mmol) at 0 °C (caution should
be advised as the reaction is exothermic). The reaction was allowed to warm to room temperature overnight and water (75 mL) was added. The resulting precipitate was collected through vacuum filtration and washed with water to afford 14 (1.8 g). A further 1.7 g can be isolated from extracting the filtrate with CH₂Cl₂ (3 x 75 mL). The organic layer was dried with Na₂SO₄ and concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography (hexanes/EtOAC 9:1). Total yield 3.5 g, 39% as white-yellow powder. This compound has been characterized before⁴. ¹H NMR (CDCl₃, 300 MHz) δ 7.98 (s, 1H), 7.80 (s, 1H), 3.08 (t, 2H), 2.71 (t, 2H).

5,6-dibromo-1-oxo-2,3-dihydro-1H-inden-2-yl 4-methylbenzenesulfonate (6):
Tosic acid monohydrate (0.89 g, 4.71 mmol) was added to a solution of 14 (1.05 g, 3.62 mmol) and iodosobenzene (1.04 g, 4.71 mmol) in acetonitrile (25 mL) at room temperature. The reaction was then heated to reflux for 3 h. The reaction was then cooled and the solvent removed in vacuo. The resulting residue was then diluted in CH₂Cl₂ (50 mL) and water (50 mL) and extracted with CH₂Cl₂ (3 x 50mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude product was then recrystallized with toluene/hexanes (1:1) to yield 6 (0.95 g, 57%) as a white-yellow powder. ¹H NMR (CDCl₃, 300 MHz) δ 7.96 (s, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.76 (s,1H), 7.39 (d, J=8.1 Hz, 2H), 5.12 (m, 1H), 3.60 (m, 1H), 3.19 (m, 1H),
2.47 (s, 3H). $^{13}$C (CDCl$_3$ 100 MHz) 195.28, 149.17, 145.41, 134.24, 134.10, 133.99, 133.88, 133.00, 131.95, 129.93, 129.19, 128.19, 125.55, 123.81, 77.71, 33.17, 21.70.

$^{13}$C (CDCl$_3$ 100 MHz) 190.63, 176.60, 169.10, 144.22, 140.49, 130.36, 125.21, 123.82, 108.75, 97.06, 80.66, 64.90, 43.37, 40.61, 37.23, 29.64.

8,9-dibromo-10b-hydroxy-4,5a,6,10b-tetrahydrospiro[indeno[2,1-b]benzofuran-3,2'-[1,3]dioxolan]-1(2H)-one (5): To a solution of 6 (0.45 g, 0.97 mmol) and DABCO (0.01 g, 0.097 mmol) at room temperature in CH$_2$Cl$_2$ (20 mL), was added 13 (0.17 g, 0.97 mmol) and KHCO$_3$ (0.19 g, 1.94 mmol). After 72 hours the reaction was quenched with sat. NaCO$_3$ (25 mL) and extracted with CH$_2$Cl$_2$ (3 x 25 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude solid was purified by silica gel flash column chromatography (hexanes/EtOAc 4:1) to afford 5 (0.28 g, 63%) as a brown powder. $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.05 (s, 1H), 7.46 (s, 1H), 5.39 (m, 1H), 4.00 (m, 4H), 3.61 (m, 1H), 3.35 (bs, 1H), 3.05 (m, 1H), 2.74 (m, 2H), 2.64 (m, 2H). $^{13}$C (CDCl$_3$ 100 MHz) 190.63, 176.60, 169.10, 144.22, 140.49, 130.36, 125.21, 123.82, 108.75, 97.06, 80.66, 64.90, 43.37, 40.61, 37.23, 29.64.
8,9-dibromo-1,4,5a,6-tetrahydrospiro[indeno[2,1-b]benzofuran-3,2'-[1,3]dioxolane]-1,10b(2H)-dial (20): To a solution of 5 (0.43 g, 0.93 mmol) and diethyl ether (40 mL) at 0 °C was added DIBAL (1.5 M in toluene, 4.95 mL, 7.42 mmol). After 6 hours the reaction was diluted with diethyl ether (30 mL) andaq. KNaC₄H₆O₆·4H₂O (40 mL) was added. The solution was extracted with diethyl ether (3 x 30 mL) and the organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude solid can be taken on without further purification (0.38 g, 90%). If purification is needed, it can be purified by silica gel flash column chromatography (hexanes/EtOAc 4:1, 0.1% NEt₃). ¹H NMR (CDCl₃, 300 MHz) δ 7.73 (s, 1H), 7.44 (s, 1H), 5.35 (m, 1H), 5.16 (m, 1H), 4.56, (bs, 1H), 4.00 (m, 4H), 3.58 (m, 1H), 2.84 (m, 1H), 2.44 (s, 2H), 1.99 (m, 2H). ¹³C (CDCl₃ 100 MHz) 154.24, 142.56, 137.92, 128.88, 125.48, 112.80, 108.88, 90.80, 73.02, 52.15, 44.07, 44.78, 33.74.

5,6-dibromo-1-(2-hydroxy-4-(2-hydroxyethoxy)phenyl)-2,3-dihydro-1H-indene-1,2-dial (21): To a solution of 20 (0.05 g, 0.11 mmol) and CH₂Cl₂ (3 mL) was added
PPTS (3 mg, 0.01 mmol) at room temperature. After 30 minutes the reaction was washed with sat. NaHCO₃ (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude solid was purified by silica gel flash column chromatography (hexanes/EtOAc 4:1) to afford 21 (0.05 g, 99%) as brown powder. ¹H NMR (CDCl₃, 300 MHz) δ 7.83 (s, 1H), 7.47 (s, 1H), 7.34 (d, J=8.1 Hz, 1H), 6.54 (d, J=8.1 Hz, 1H), 6.41, (s, 1H), 5.33 (m, 1H), 4.03 (m, 2H), 3.94 (m, 2H), 3.59 (m, 1H), 2.94 (m, 1H). ¹³C (CDCl₃ 100 MHz) 161.35, 161.05, 144.55, 141.31, 141.11, 130.19, 129.34, 123.67, 121.60, 108.72, 97.45, 95.20, 90.17, 69.58, 61.22, 37.60.

1-(2-(benzyloxy)-4-(2-hydroxyethoxy)phenyl)-5,6-dibromo-2,3-dihydro-1H-indene-1,2-diol (27): To a solution of 21 (0.10 g, 0.22 mmol) and acetonitrile (2 mL) was added K₂CO₃ (0.42 g, 0.25 mmol) and benzyl bromide (30 μL, 0.25 mmol). The solution was heated to reflux for 16 hours, after which it was concentrated in vacuo. The crude was dissolved in ether and 5% aq. KOH, and washed with ether (3 x 10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude solid was purified by silica gel flash column chromatography (hexanes/EtOAc 1:1) to afford 27 (17 mg, 14%) as brown powder. ¹H NMR (CDCl₃, 500 MHz) δ 7.83 (s, 1H), 7.49 (s, 1H), 7.28–7.40 (m, 6H), 6.55 (d, J=8.1 Hz, 1H),
6.42 (d, J=8.1 Hz, 1H), 5.54, (m, 1H), 4.35 (m, 2H), 4.17 (m, 2H), 3.91 (m, 2H), 3.59 (m, 1H), 2.94 (m, 1H).

3-(5,6-dibromo-1-hydroxy-2-oxo-2,3-dihydro-1H-inden-1-yl)-6-(2-hydroxyethoxy)cyclohexa-3,5-diene-1,2-dione (25): To a solution of 21 (0.1 g, 0.21 mmol) in CH₂Cl₂ (10 mL), was added Na₂CO₃ (0.18 g, 2.1 mmol) and DMP (0.36 g, 0.84 mmol) at room temperature. After 3 hours it was quenched with aq. Na₂SO₃ (5 mL) and aq. Na₂CO₃ (5 mL) and extracted with CH₂Cl₂ (3x10 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude solid was purified by silica gel flash column chromatography (hexanes/EtOAc 2:1) to yield 25 (0.01 g, 10%). ¹H NMR (CDCl₃, 300 MHz) δ 8.03 (d, J=7.5 Hz, 1H) 7.60 (s, 1H), 7.55 (s, 1H), 7.42 (d, J=7.5 Hz, 1H), 4.50 (m, 2H), 3.89 (m, 2H), 3.42 (m, 1H), 3.05 (m, 1H).

2-Iodoxybenzoic acid: To a solution of oxone (18.00 g, 60.0 mmol) and 50 mL H₂O was added 2-iodobenzoic acid (4.00 g, 16.1 mmol) and the reaction was heated to an internal temperature of 70 °C for 3 hours. The solution was then cooled to 0 °C for 2 hours. The solid was then filtered and washed with H₂O (20 mL) and acetone (10 mL) to yield IBX (4.05 g, 89%) as white powder. This compound has been characterized.
before\textsuperscript{5}. \textsuperscript{1}H NMR (DMSO, 300 MHz) $\delta$ 8.12 (d, $J=7.5$ Hz, 1H), 8.01 (m, 2H), 7.84 (d, $J=7.2$ Hz, 1H).

**Dess-Martin Periodinane:** To a solution of acetic anhydride (18 mL) and TsOH.H$_2$O (0.3 g, 1.5 mmol) was added IBX (4.05 g, 14.5 mmol). The reaction was heated to 80 $^\circ$C for 3 hours. It was then cooled to 0 $^\circ$C for 2 hours after which the solid was filtered and washed with ether to yield DMP (3.90 g, 66%) as a white powder. It should be noted that the reaction was run in the dark. This compound has been characterized before\textsuperscript{5}. \textsuperscript{1}H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.30 (m, 2H), 8.02 (m, 2H), 2.10 (s, 6H), 2.22 (s, 3H).

**Iodosobenzene:** This compound was prepared by the same method as utilized by Saltzman and Sharefkin\textsuperscript{6}. 

1
References


