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Studies Toward the Total Synthesis of Eletefine

Kyle Rugg

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Studies Toward the Total Synthesis of Eletefine

Kyle William Rugg

Submitted in Partial Fulfillment of the Requirements for the Degree Master of Science in Chemistry

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September 3, 2013
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Abstract

Eletefine is a natural product of the stephaoxocane family of alkaloids. It possesses an isoquinoline moiety functionalized with three methoxy groups forming an electron rich aromatic system. Eletefine also possesses a ten-membered ring with a novel bridged vinyl ether functionality, and a remote chiral alcohol, making it a conspicuous and desirable target for the synthetic organic chemist. The plant from which eletefine was first isolated (*Cissampelos glaberrima*) has been used in traditional medicine for the relief of symptoms from urinary tract infections and asthma. The proposed synthesis of eletefine is a convergent route which features a Sonogashira coupling and a novel alkyne hydration. Herein, methods towards the synthesis of the model system *des*-hydroxyeletefine are described, in particular attempts towards formation of the AB ring system of *des*-hydroxyeletefine, as well as C₈-C₉ bond formation methodology via acylation and Sonogashira coupling.
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<td>µ</td>
<td>micro</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
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<td>aq.</td>
<td>aqueous</td>
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<td>Ar</td>
<td>aryl</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
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<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
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<td>BPO</td>
<td>benzoyl peroxide</td>
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<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
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<td>cat.</td>
<td>catalytic</td>
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<td>DCC</td>
<td>$N,N'$-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
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<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropylethyl amine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>DPEPhos</td>
<td>(oxydi-2,1-phenylene)bis(diphenylphosphine)</td>
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<tr>
<td>dppb</td>
<td>1,4-bis(diphenylphosphino)butane</td>
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<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
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<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
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<td>Et</td>
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<td>glyme</td>
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<td>$^{1}$H-NMR</td>
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<tr>
<td>IC$_{50}$</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram(s)</td>
</tr>
<tr>
<td>L</td>
<td>liter(s) or ligand</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>LiDBB</td>
<td>lithium 4,4’-di(tert-butyl)biphenylide</td>
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<td>m</td>
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<td>MAD</td>
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<td>methyl</td>
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<td>n-butyllithium</td>
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<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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<tr>
<td>NHK</td>
<td>Nozaki-Hiyama-Kishi reaction</td>
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<td>NMO</td>
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<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
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<td>R</td>
<td>substituent</td>
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<td>s-BuLi</td>
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<td>tert-butyllithium</td>
</tr>
<tr>
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</table>
Tf  
trifluoromethanesulfonyl

THF  
tetrahydrofuran

TLC  
thin layer chromatography

TMEDA  
$N,N,N',N'$-tetramethylethylenediamine

TMS  
trimethylsilyl

Ts  
$p$-toluenesulfonyl

UV  
ultraviolet

X  
halide, pseudohalogen, or hydrogen substituent

Xantphos  
4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
I. The Natural Product Eletefine

Eletefine (1) is a natural product of the stephaoxocane family of alkaloids. This alkaloid possesses an isoquinoline moiety, which in addition to three methoxy groups, forms an electron rich aromatic system. Eletefine also possesses a ten-membered ring with a novel bridged vinyl ether functionality, and a chiral alcohol, making it a conspicuous and desirable target for the synthetic organic chemist. It is the aim of the Cody group to complete the total synthesis of 1, which has not previously been achieved. Natural products and their derivatives are important sources (and inspirations) for new pharmaceutical candidates, as a vast number of current drugs to treat life-threatening diseases stem from natural product structures.\textsuperscript{1} Additionally, the total syntheses of natural products often serve as the most practical means of producing sufficient quantities of a compound; isolation processes from natural sources may be low yielding, and the process both time-consuming and destructive to the natural resource. The synthesis of natural products also provides the impetus for new synthetic methodologies: the target or synthetic intermediate may present a novel moiety or challenge that warrants new chemistry to be developed. Herein, the current progress towards the total synthesis of eletefine within the Cody group is reported.

\begin{center}
\includegraphics[width=0.3\textwidth]{eletefine.png}
\end{center}

\textbf{Figure 1:} Eletefine (1).

a. Isolation

i. \textit{Cissampelos glaberrima}

Eletefine (1) was first isolated from \textit{Cissampelos glaberrima} (aka “jarrinha”) in 1998 by the da-Cunha group.\textsuperscript{2} \textit{C. glaberrima} is a plant of the Menispermaceae family found in northeastern Brazil. This
family of plants has yielded several different alkaloids. One example is milonine, an opioid derivative. Extractions with ethanol and chloroform on 1 kg of dried root afforded 97 mg of eletifene. The physical appearance is described as a reddish-brown wax which fluoresces under 360 nm UV irradiation. The structure of eletifene was elucidated by FT-IR, MS (EI), $^1$H-NMR, $^{13}$C-NMR, and NOE spectroscopy.

### ii. Stephania longa

An isolation procedure by the Yue group on the species *Stephania longa* afforded three new stephaoxocane alkaloids, in addition to eletifene. These new alkaloids were identified as stephalonganines A-C (2, 3, and 4, Figure 3).

### b. The Stephaoxocanes

Excentricine (5) was the first stephaoxocene to be isolated. The stephaoxocene skeleton (6) has a characteristic ABCD heterocyclic ring system, as well as a divinyl ether bridge (Figure 2). To date, all stephaoxocanes discovered have at least two methoxy groups at the 6 and 7 positions, and have a chiral alcohol at carbon 12 (Figure 3).

![Figure 2: Stephaoxocene skeleton (6).](image-url)
c. Biological Significance of Eletefine

The plant from which eletefine was initially isolated (C. glaberrima) has been used in folk medicine for the relief of symptoms from urinary tract infections and asthma.\(^2\) Other plants from the *Stephania* genus (aka Menispermaceae family of plants) have been used in southern China for treatment against fever, inflammation, and dysentery.\(^4\) Other plants in the *Cissampelos* genus have been used against heart and genital diseases. As reported by Kaufman, *et al.*,\(^8\) simplified analogs of stephaoxocanes (Figure 4) have shown inhibitory activities against acetylcholinesterase (IC\(_{50}\) values: 19.6 µM (10); 46 µM (11)).
This biological activity has the potential to enhance cognitive function in humans and animals, which may be effective against Alzheimer’s disease. Biological testing on a true stephaoxocane has not been performed to date. The synthesis of eletefine would also be beneficial in this regard. A completed total synthesis of eletefine would be a logical gateway to the synthesis of the entire stephaoxocane family.

II. Previous Work toward Stephaoxocanes

a. Stephaoxocanidine – T. S. Kaufman

The group of Teodoro S. Kaufman has recently commenced the synthesis of stephaoxocanidine. The Kaufman group begins with a conversion of ester 12 to acetal 13. Tosylation of amine 13 and ring-closing affords lactone 14. A Jackson cyclization of lactone 14 gives tetrahydroisoquinoline 15 with high relative stereoselectivity. This selectivity is attributed to the steric implications of the nucleophilic attack by the aryl system on the intermediate oxygen stabilized carbocation. Addition of triethylamine provides elimination of the tosylate and ether, affording isoquinoline 10 in 45 % overall yield from 12. Subsequent bromination with N-bromosuccinimide gives bromo lactone 11 in 47 % yield. (Scheme 1).
Scheme 1: Kaufman’s work toward stephaoxocanidine (7).

Kaufman’s work toward analogs of stephaoxocanidine is continued by conversion of lactone 10 to hemiacetal 17 via a Grignard reaction with allylmagnesium bromide 16. Oxidation of the alkene with osmium tetroxide gives 1,2,4-triol 18 (Scheme 2).8 This is Kaufman’s last reported progress toward stephaoxocanidine. The group has since focused on constructing the ten-membered ring (Scheme 3).

Scheme 2: Kaufman’s work toward stephaoxocanidine (7), continued.

Kaufman’s new target, simplified excentricine analogue 19, is prepared by first converting aldehyde 20 to amine 21, then performing a reduction and amide formation to afford diene 22. A Grubbs-mediated ring closing metathesis and hydrogenation gives the 14-membered ring compound 23. A Bischler-Napieralski reaction closes the 6-membered ring to give tetrahydroisoquinoline 19 possessing the 10-membered ring.10
Scheme 3: Kaufmann’s synthesis of ABC tricyclic ring system 19 of excentrine (5).

While Kaufmann’s work is rather linear in nature, the Cody group approach utilizes convergent strategies. In order to improve the efficiency of a multi-step process, a convergent synthesis is often employed in the total synthesis of complex molecules. In a synthetic process that is linear in nature, the overall yield for the process decreases as following steps are employed. For example, a four step linear process (A → B → C → D → E) that gives a 75% yield for each step provides only a 32% overall yield. However, in a convergent process, individually assembled fragments are then combined. In a convergent process (A → B, D → E, C + E → F) comprising the same number of steps that gives 75% for each step provides an improved 42% overall yield.

b. Eletefine – J. A. Cody

i. Retrosynthetic Analysis

Eletefine is envisioned to be synthesized by two possible convergent routes, A or B (Scheme 4). Both of these approaches have common intermediates. The two routes differ in the order of the acylation and Sonogashira reactions. Synthetic route A is first simplified to alkyne 24 via a novel alkyne hydration. This alkyne is further simplified to lactone 25 or 26, which is constructed from two fragments; an isoquinoline moiety 28 or 29 and chiral lactone 30. The key transformations are Sonogashira addition of lactone 30 followed by either anion chemistry or Lewis acid mediated catalysis to close the 10-membered ring. Synthetic route B differs in the order of the anion chemistry and Sonogashira steps. In route B,
alkyne 24 is simplified to the branched terminal alkyne 27 via Sonogashira coupling. Alkyne 27 is simplified to the isoquinoline and lactone moieties (28 or 29, 30) using anion chemistry; the same fragments as in route A.

**Scheme 4:** Retrosynthetic analysis for the target eletefine (1).

### ii. Attempted Synthesis of Racemic Lactone 30

While the synthesis of (R)-30 is known,\(^1\) it was decided that racemic lactone 30 would be employed. The synthesis of racemic lactone 30 was envisioned to begin with iodination of alkene 31 to form iodolactone 32 (Scheme 5). To date, the product resulting from the reaction of iodolactone 32 with sodium methoxide forms a product (presumably epoxide 33) which is unstable in our hands. In order to develop the end-game chemistry of the synthesis, the Cody group has circumvented the use of racemic lactone 30 and will implement a model alkyne.
c. des-Hydroxyeletefine – J.A. Cody

i. Model System: des-Hydroxyeletefine

A simplified target for the Cody research group is des-hydroxyeletefine 35 (Figure 5), which is being used as a model system so that methodology may be resolved before precious chiral material is utilized. It is possible that des-hydroxyeletefine could have interesting biological activity.

Figure 5: des-Hydroxyeletefine (35).

The retrosynthetic analysis of des-hydroxyeletefine 35 (Scheme 6) differs in the alkyne moiety. Rather than utilizing lactone \((R)-30\) (or racemic lactone 30), a variety of terminal alkynes (40, 41, 42) are utilized in the synthesis.
Scheme 6: Retrosynthetic analysis for the formation of des-hydroxyeletefine (35).

ii. Preparation of Model Alkyne Fragments

Because des-hydroxyeletefine 35 does not have a chiral center, a chiral alkyne is not utilized in its synthesis. Exploratory synthesis of des-hydroxyeletefine 35 requires several different functionalities due to the anion chemistry being performed. A variety of carbonyl functionalities have been prepared (Scheme 7) from commercially available carboxylic acid 43. Ester 42 is prepared by reaction of carboxylic acid 43 with methyl iodide under basic conditions. Three other derivatives have been prepared. LAH reduction of carboxylic acid 43 forms primary alcohol 44, which is subsequently oxidized with pyridinium chlorochromate to form aldehyde 41, with a typical 68% yield over the two steps. Acid chloride 40 is prepared from carboxylic acid 43 via refluxing in thionyl chloride. All derivitization steps afford products in moderate to high yields.12–14
Scheme 7: Preparation of terminal alkynes for model route.

With the preparation of terminal alkynes 40-42, the other fragment required to explore routes A and B is triflate 28.

iii. Preparation of Triflate 28

In addition to alkyne fragments 40-42, isoquinolone 45 is a key intermediate in the synthesis of eletefine (1) and des-hydroxyeletefine (35). Isoquinolone 45 is retained in the synthesis of des-hydroxyeletefine (35); it does not require modification for the change in targets. To begin the synthesis of isoquinolone 45, the commercially available 3,4,5-trimethoxybenzoyl chloride 46 undergoes a Schotten-Baumann transformation with (commercially available) aminoacetaldehyde dimethyl acetal 47. Acetal 48 is used without further purification to produce isoquinolone 45 via a modified Pomeranz-Fritsch type reaction.12 (Scheme 8).

Scheme 8: Preparation of isoquinolone fragment 45.
With isoquinolone fragment 45 prepared, triflation is performed so that a future Sonogashira reaction may be performed. The triflation of crude isoquinolone 45 yielded the desired O-trflate product 28 and one side product; N-trflate 49 (Scheme 9). O-trflate 28 is presumed to be the kinetic product, with N-trflate 49 as the thermodynamic product. As a testament to this theory, ratios and overall yield of O-/N-trflate were observed to vary based on temperature (Table 1). Lower temperatures and shorter reaction time yielded a higher ratio of O-trflate 28 to N-trflate 49. These mixtures may be separated by careful column chromatography.

Scheme 9: Triflation of isoquinolone 45 to produce O- and N-trflates 28 and 49.

The mixture of products was confirmed by work done by Douglas Tusch, a former undergraduate in the Cody research group, via TLC, GC-MS, IR, and \(^1\)H/\(^{19}\)F-NMR experiments.\(^{12}\) Ratio variance data was confirmed by Russell Burkhardt.\(^ {15}\)

Table 1: Overview of temperature dependence on triflation product ratios.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Temp. (°C)</th>
<th>Reaction Time (h)</th>
<th>Ratio O-Tf (28) to N-Tf (49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>25</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>-3</td>
<td>23.5</td>
<td>6:1</td>
</tr>
<tr>
<td>3</td>
<td>-13</td>
<td>24</td>
<td>8:1</td>
</tr>
<tr>
<td>4</td>
<td>-25</td>
<td>1</td>
<td>38:1</td>
</tr>
<tr>
<td>5</td>
<td>-78</td>
<td>5</td>
<td>34:1</td>
</tr>
</tbody>
</table>
iv. Sonogashira Reactions with Triflate 28

Once O-triflate 28 is prepared, a Sonogashira reaction may be performed with a model alkyne to continue route A. The Sonogashira coupling reaction performed between O-triflate 28 and methyl 6-heptynoate 42 was observed in high yields to afford isoquinoline 37. A similar reaction was performed with the N-triflate substrate – no reaction was observed by TLC (Scheme 10). Both of these Sonogashira reactions were performed with ester 42 and 7 mol % of dichlorobis(triphenylphosphine)palladium(II) catalyst, 8 mol % of copper(I) iodide, under basic conditions (diethylamine) and reflux in tetrahydrofuran.12–14

Scheme 10: Sonogashira reactions between O- and N-triflates 28 and 49 and alkyne 42.

v. Friedel-Crafts Acylations

In order to attempt to close the ten-membered ring to pursue the des-hydroxyeletefine (35) end-game, a variety of Friedel-Crafts acylations were attempted. With isoquinoline 37 containing an internal alkyne, protic Friedel-Crafts conditions were attempted with a solution of 80 % v/v sulfuric acid. Under these conditions, only hydrolysis of the ester functionality was observed to afford carboxylic acid 50. Under Lewis acidic conditions (aluminum trichloride), no ring closing was observed, and thus ketone 36 was not formed.13,14
Scheme 11: Friedel-Crafts acylations attempted with isoquinolines 37 and 51.

It is believed that the presence of three sp\(^2\) carbons and two sp carbons in a ten-membered ring accounts for the difficulty in the cyclization of ester 37. Ester 37 was therefore reduced using hydrogen and palladium on carbon, and Friedel-Crafts acylations were then attempted with resulting saturated ester 51. When Friedel-Craft acylations (both protic and aprotic) were performed, similar results to attempted cyclization of 37 were observed: under protic conditions, hydrolysis of ester 51 to give acid 52 was observed. Under Lewis acidic conditions, no cyclization to give ketone 53 was observed. It is believed that in the case of saturated ester 51, the cyclization is contending mainly with entropy.\(^{12,13,16}\)

vi. Bromination Attempts with Isoquinoline 37

In order to close the ten-membered ring via route A conditions, it was clear to the Cody group\(^{12,15}\) that methods other than Friedel-Crafts acylation would have to be performed. Anion chemistry is an alternative that was previously explored by the group (Scheme 12). Shindo, et al. have reported the ability to close a seven-membered ring under anionic acylation conditions.\(^{17}\) In order to explore anion chemistry, a halide had to be incorporated. Attempts to brominate alkyne 37 with DBDMH to afford bromide 38 gave inconclusive results. To circumvent this, hydrogenation of the alkyne was performed to produce the reduced compound 51, which with subsequent DBDMH conditions afforded brominated
isoquinoline 38 in moderate yields.\textsuperscript{13,14} Attempts to perform a lithium-halogen exchange on bromide 38 in order to close the ten-membered ring were unsuccessful; the \textit{tert}-butyl anion added in a 1,2-fashion into the ester functionality to produce ketone 54.

\begin{center}
\textbf{Scheme 12:} Bromination attempts with internal alkyne 37 and reduced compound 51.
\end{center}

Experimenting with anion chemistry under different conditions could prove to be beneficial in the future. One such experiment is a Grignard-exchange reaction in which a higher energy organomagnesium reagent is exchanged with that of lower energy.\textsuperscript{18} In our case, an organomagnesium reagent (for example, isopropylmagnesium bromide), could be reacted with brominated isoquinoline 51 to give the corresponding organomagnesium intermediate 55. This anion could then in turn react with the electrophilic carbonyl, closing the ten-membered ring (Scheme 13).
Scheme 13: Proposed Grignard exchange reaction between reduced brominated isoquinoline 51 and an isopropylmagnesium halide.

At lower temperatures, the magnesium-halogen exchange is favored over the attack of the carbonyl electrophile. Additionally, only one equivalent of the Grignard reagent is used, in contrast with the lithium-halogen exchange in which multiple equivalents are often needed. A Grignard exchange reaction would therefore lessen the formation of byproducts. In the event that the rate of the exchange reaction is too slow, an alternate experiment could be attempted in which a lithium trialkylmagnesium ate complex is used. These complexes exhibit reactivity greater than that of a typical Grignard reagent, but lesser reactivity than an organolithium (Scheme 14). Alternatively, lithium chloride may be used as an additive in standard magnesium-halogen exchange conditions in order to aid in reducing aggregate formation.

Scheme 14: Proposed Grignard exchange reaction between reduced brominated isoquinoline 51 and a lithium trialkylmagnesium ate complex.
vii. **Preparation of Bromo Triflate 29**

In order to pursue route B, bromination of triflate 28 was performed to form bromo triflate 29. A variety of brominating reagents were tested (Scheme 15). *N*-bromosuccinimide afforded bromo triflate 29 in low yields, and bromine in acetic acid also afforded the compound in very low yields. The reagent of choice was DBDMH, which gave the desired bromo triflate 29 in moderate yields of up to 61% (Scheme 15).\(^{12,13}\)

![Scheme 15: Bromination of triflate 28 with various reagents.](image)

When the DBDMH reaction was investigated in more detail, it was found that a mixture of bromo triflate 29 and dibrominated compound 55 was formed (Scheme 16). The ratio was determined to be 52% to 9%, respectively, by \(^{19}\)F-NMR and GC-MS. Separation of the 29/55 mixture via flash chromatography proved formidable, but it was determined (by 2D-TLC) that dibrominated compound 55 degraded on silica gel. In order to ensure selectivity for subsequent steps, isolation of pure bromo triflate 29 is paramount.\(^{12-14}\)

![Scheme 16: DBDMH bromination of triflate 28 to afford mixture.](image)
viii. Route A attempts with Bromo Triflate 29

It was thought that the crude mixture of bromo triflate 29 and dibrominated isoquinolone 55 may be effective in the Sonogashira reaction, giving regioselectivity to the position alpha to the nitrogen. As hypothesized, attempting the Sonogashira reaction with the crude mixture of bromo triflate 29 and dibrominated isoquinolone 55 afforded only the alkyne alpha to the isoquinolinic nitrogen (Scheme 17).12

![Scheme 17: Sonogashira reaction with triflate mixture.](image)

Despite the presence of two brominated sites on isoquinoline 55, oxidative addition by the palladium catalyst occurred at the carbon-halogen bond alpha to the nitrogen atom of the isoquinoline moiety; regioisomers 56 and 57 were not observed. This observation is consistent with reports by Stoltz, et al. in which pyrazine 59 with two brominated sites is subjected to a palladium catalyzed reaction with pyrrole 58 – only oxidative addition of the carbon-halide bond on the pyrazine ring of 59 is observed to give pyrrole 60 (Scheme 18).21

![Scheme 18: Oxidative addition is observed alpha to a nitrogen atom by Stoltz, et al.](image)
While this precedence gives promise for the route A Sonogashira coupling, difficulties may be faced with reacting the mixture of bromo triflate 29 and dibrominated species 55 under anion conditions for route B. This is due to the possibility of forming an anion at the bromide alpha to the nitrogen on dibrominated isoquinoline 55. It is expected, however, that exchange at the bromide alpha to the methoxy group will be favored.22–24

ix. Summary: Proposed Completion of des-Hydroxyeletefine 35

Previous efforts undertaken in the Cody research group have focused largely on the completion of des-hydroxyeletefine 35 via route A. Both the isoquinolone and alkyne fragments have been successfully synthesized in high yields. However, route A is no longer viable for the preparation of des-hydroxyeletefine 35 due to difficulties in forming the ten-membered ring. Therefore, route B is the preferred route for completing des-hydroxyeletefine 35. In order to pursue route B conditions to complete des-hydroxyeletefine, the alkyne must be added under anion conditions (Scheme 19). The anion addition reaction may be tested with any of the carboxylic acid derivatives 40-42.

Scheme 19: Proposed anion additions of bromo triflate 29 into carboxylic acid derivatives 40-42.

In order to test this, Ijaz Ahmed – a previous graduate student in the Cody Research Group – attempted a reaction of purified bromo triflate 29 with benzaldehyde (Scheme 20).12
Scheme 20: Addition of bromo triflate 29 into benzaldehyde.

Reaction of bromo triflate 29 under t-butyllithium conditions with benzaldehyde afforded corresponding benzyl alcohol 63 in minimal yield. This reaction with the alkyne derivatives (40-42, Scheme 19) must be performed in order to test route B conditions. Once terminal alkyne 61 has successfully been prepared, it is envisioned that a Sonogashira ring closing reaction would be performed under previously attempted conditions in order to form the ten-membered ring of compound 36. Finally, a subsequent alkyne hydration may be performed in order to form the bridged vinyl ether of des-hydroxyeletefine 35 (Scheme 21).25–30

Scheme 21: Proposed completion of des-hydroxyeletefine (35).

To summarize, an analogue of eletefine (1), des-hydroxyeletefine (35), is being targeted by the Cody group in order to resolve the end-game chemistry. Isoquinolone 45 has been prepared in high yields, and triflation of this compound has proved successful. However, when bromination of triflate 28 is attempted, a mixture of compounds is obtained – dibrominated compound 55 and bromo triflate 29. This mixture is acceptable for route A, as Sonogashira coupling is selective to the desired site. However, for route B conditions, the anion may form at either bromo position on dibrominated compound 55. This issue must be circumvented. With successful purification (or an alternate preparation) of bromo triflate 29, anion
addition of a carboxylic acid derivative may be performed and subsequent Sonogashira conditions are proposed to close the ten-membered ring. Alkyne hydration would then form the novel bridged vinyl ether, thereby completing des-hydroxyeletefine (35). Once this analogue has been synthesized and conditions have been resolved, focus may be turned towards formation of chiral lactone \((R)-30\) in order to complete the synthesis of eletefine (1).

### III. Results and Discussion

One difficulty encountered in the aforementioned work is the low efficiency in production of pure bromo triflate \(29\). It was determined that bromo triflate \(29\) had to be be synthesized by alternate means, or bypassed entirely. Two distinct retrosyntheses were devised in order to circumvent the issue and form the C\(_8\)-C\(_9\) bond of des-hydroxyeletefine (35): acylation of ring A before forming ring B (Scheme 22, avoids bromination step), and incorporation of bromine in the formation of bromo-isoquinolone \(65\) (which can subsequently undergo triflation; Scheme 23).

![Scheme 22: Acylation of ring A prior to ring B closure would avoid bromo triflate 29.](image1)

![Scheme 23: Brominated isoquinolone 65 may subsequently be triflated to afford bromo triflate 29.](image2)
a. Alternate Routes to form AB Ring System

Three methods were explored to synthesize bromo isoquinolone 65: a Mizoroki-Heck reaction route, a Suzuki/palladium catalyzed cyclization method, and an annulation with norbornadiene.

i. Mizoroki-Heck Reaction

It was anticipated that mono-brominated isoquinolone could be prepared via a Heck reaction with the terminal enamide 66 (Scheme 24).

\[
\begin{align*}
\text{NH} & \quad \text{Br} \\
\text{O} & \quad \text{Br} \quad \text{OCH}_3 \\
\text{H}_3\text{CO} & \quad \text{H}_3\text{CO} \\
66 & \quad 65 \\
\end{align*}
\]

Scheme 24: Proposed formation of mono-brominated isoquinolone 65 from enamide 66 via a palladium-catalyzed Mizoroki-Heck reaction.

In order to investigate this route, a model system was used consisting of a 2-bromobenzamide core. Preparation of enamide 68 was attempted via acid-catalyzed addition of acetaldehyde to primary amide 67 (Scheme 25), however no enamide or imine were detected (only the presence of starting material 67), likely attributed to the volatility of the aldehyde and instability of the terminal enamide. In the literature, this reaction proves successful with larger aldehydes giving a more substituted, and therefore stable, enamide.\textsuperscript{31}

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br} \\
\text{O} & \quad \text{NH} \quad \text{O} \\
\text{TsOH, PhMe, reflux} & \quad \text{H}_3\text{CO} \\
67 & \quad 68 \\
\end{align*}
\]

Scheme 25: Attempted formation of enamide 68 via condensation with acetaldehyde.
To synthesize enamide 68, an analogous route previously employed by Fleming was utilized.\textsuperscript{32} Oxazolidinone 69 is prepared in high yield (91\%) from commercially available 2-oxazolidinone (70). By treatment with \textit{n}-butyllithium followed by 2-bromobenzoyl chloride (71, prepared in quantitative yield from the commercially available 2-bromobenzoic acid) (Scheme 26).\textsuperscript{32} Subsequent decarboxylation using lithium diisopropylamide gave enamide 68 in low yield (35\%).

\textbf{Scheme 26:} Preparation of model enamide 68.

Once enamide 68 was prepared, Heck cyclizations were attempted (Scheme 27), screening bidentate phosphine ligands 73-77 (Figure 6), as precedence for using this class of ligand exists with electron-rich olefins such as that in enamide 68.\textsuperscript{33} However, likely due to the instability of the enamide, the only reaction that was observed was degradation of starting material to give primary amide 67 (Table 2).

\textbf{Scheme 27:} Attempted Heck reactions to give isoquinolone 27.
Table 2: Heck reaction product ratios (Pd(OAc)$_2$ precatalyst): primary amide formation.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Ratio (1 h)</th>
<th>Ratio (12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5 mol %)</td>
<td>SM 68 : 1° amide 67</td>
<td>SM 68: 1° amide 67</td>
</tr>
<tr>
<td>dppe</td>
<td>5:1</td>
<td>1:1</td>
</tr>
<tr>
<td>dppp</td>
<td>5:1</td>
<td>1:1</td>
</tr>
<tr>
<td>dppb</td>
<td>5:1</td>
<td>1:1</td>
</tr>
<tr>
<td>xantphos</td>
<td>5:1</td>
<td>1:1</td>
</tr>
<tr>
<td>DPEPhos</td>
<td>5:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

Figure 6: Ligands used in Heck reactions.

Since the Heck reaction did not produce the desired isoquinoline 72 from enamide 68, two systems were used to test the reaction conditions: ethyl ester 78 with butyl acrylate 79 (Scheme 28), and diethylamide 81 with butyl acrylate 79 (Scheme 29).

Scheme 28: Attempted Heck reactions with ester 78 and butyl acrylate 79.
Scheme 29: Attempted Heck reactions with amide 81 and butyl acrylate 79.

Both of these test reactions afforded product (80, 82 respectively) in roughly a 1:1 ratio with starting aryl bromide (78, 81 respectively). These results demonstrate the inability of the enamide to react, and that an issue with oxidative addition is not the cause of unreactivity with the enamide system. With these findings in consideration, it was decided that enamide 68 should be protected. When protections of enamide 68 were attempted with TESOTf and TBSCl (Scheme 30), only starting material 68 and primary amide 67 were observed. However, Boc protection of the enamide was successful (Scheme 31), but the attempted Heck reaction was unsuccessful, giving again only a mixture of starting material and primary amide.

Scheme 30: Attempted O-protection reactions of enamide 68.

Scheme 31: Boc-protection of enamide 68 and attempted Heck cyclization.

Due to the difficulties in preparing model isoquinolone 81 via a Heck reaction, an alternate method was sought.
ii. Annulation with Norbornadiene

A convenient method for synthesizing isoquinolones from corresponding halobenzamides was described by Lautens, et al.\textsuperscript{34} (Scheme 32). The reaction involves an annulation reaction between a halobenzamide \textsuperscript{82} and norbornadiene \textsuperscript{83} serving as an acetylene synthon. While the reaction primarily gives isoquinolone \textsuperscript{84}, a variety of byproducts were observed (\textsuperscript{85}, \textsuperscript{86}, and \textsuperscript{87}).

\begin{scheme}
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{82} & \quad \text{83} \\
\text{Pd(OAc)}_2 (10 \text{ mol \%}) & \quad \text{PtBu}_3\text{HBF}_4 (22 \text{ mol \%}) \\
\text{Cs}_2\text{CO}_3 & \\
\text{toluene, 130 \text{ \degree}C, 16 h}
\end{align*}
\end{scheme}

\textbf{Scheme 32:} Annulation of halobenzamide \textsuperscript{82} with norbornadiene \textsuperscript{83} producing a variety of adducts.

Lautens observed that with a chloride, yields were favorable. Bromides tended to give low yielding and difficult to separate mixtures. When Lautens tested the scope of the reaction, relatively electronically neutral substituents (-F, -CH\textsubscript{3}, -H) gave high yields, while more electron rich (-OCH\textsubscript{3}) and electron deficient (-NO\textsubscript{2}) rings gave much lower yields.

We envisioned that with our dibrominated system, annulation of dibromide \textsuperscript{88}/\textsuperscript{89} with norbornadiene \textsuperscript{83} would be a convenient method for production of our desired bromo-isoquinolone \textsuperscript{65}/\textsuperscript{84} (Scheme 33).

\begin{scheme}
\begin{align*}
\text{H}_3\text{CO} & \quad \text{OCH}_3 \\
\text{H}_3\text{CO} & \quad \text{Br} \\
\text{88, R} & = \text{H} \\
\text{89, R} & = \text{Bn} \\
\text{NHR} & \quad \text{O} \\
\text{83} & \quad \text{83} \\
\text{Pd(OAc)}_2 (10 \text{ mol \%}) & \quad \text{PtBu}_3\text{HBF}_4 (22 \text{ mol \%}) \\
\text{Cs}_2\text{CO}_3 & \\
\text{toluene, 130 \text{ \degree}C, 16 h}
\end{align*}
\end{scheme}

\textbf{Scheme 33:} Annulation of dibrominated amide \textsuperscript{88}/\textsuperscript{89} with norbornadiene \textsuperscript{83} would ideally give mono-brominated isoquinolone \textsuperscript{65}/\textsuperscript{84}.
A model system (Scheme 34) was employed to test the methodology. When annulation with \( N \)-benzyl-2-bromobenzamide 82 and norbornadiene 83 was attempted, isoquinolone 84 and adduct 86 were observed, each with roughly a 10% crude yield.

![Scheme 34: Attempted annulation of \( N \)-benzyl-2-bromobenzamide (82) with norbornadiene 83.](image)

In our hands, we were unable to reproduce Lautens’ observations. With the inability to directly install the olefin directly, it was proposed that the isoquinolone could be formed via a Wacker-type oxidation.

### iii. Suzuki Coupling and Wacker-type Oxidation

Izumi et al. reported that derivatives of isoquinolone 72 could be prepared from the corresponding derivatives of styrene 88 by a palladium-catalyzed Wacker oxidation and cyclization (Scheme 35).35

![Scheme 35: Izumi’s reported palladium-catalyzed oxidation/cyclization reaction to synthesize isoquinolones.](image)

We envisioned that with our system, cyclization of olefin 89 under Wacker oxidation/cyclization conditions would give bromo-isoquinolone 65 (Scheme 36).
Scheme 36: Proposed cyclization of styrene derivative 89 to give bromo isoquinolone 65.

In order to test our methodology, a model system was once again employed (Scheme 37). N-Benzyl-2-bromobenzamide 82 was initially reacted under Suzuki conditions\textsuperscript{36} to give styrene derivative 90 in 87% crude yield. The crude reaction mixture was then subjected to palladium-catalyzed oxidation and cyclization gave benzyl protected isoquinolone 84 in moderate yield.

Scheme 37: Synthesis of model isoquinolone 84 via palladium-catalyzed cyclization.

With the model system being a success, the system for eletefine was employed. Beginning with the commercially available 3,4,5-trimethoxybenzoyl chloride 46, amidation with ammonium acetate\textsuperscript{37} gave 3,4,5-trimethoxybenzamide 92 in moderate yield after recrystallization. Bromination with DBDMH\textsuperscript{38} provided dibromide 93 in low yield (Scheme 38).

Scheme 38: Preparation of dibromide 93 from commercially available acid chloride 46.

With dibromide 93 prepared, Suzuki couplings were attempted in an effort to synthesize the Wacker precursor, styrene 89 (Scheme 39). Initially, no product was observed when the reaction was run under
reflux conditions. In order to drive the reaction to completion, the reaction was set up in a high-pressure vessel and heated to 190 °C. While styrene 89 could not be isolated (due to instability to silica as determined by 2D TLC) or properly characterized, the crude reaction mixture was carried forward.

![Scheme 39](image)

**Scheme 39:** Attempted preparation of styrene 89.

A Wacker oxidation reaction with presumed styrene 89 was attempted (Scheme 40). The reaction was initially performed using 10 mol % of palladium(II) chloride and one equivalent of copper(I) chloride. Only the suspected styrene 89 was recovered. Increasing the catalyst loading to 30 mol % of palladium(II) chloride and three equivalents of copper(I) chloride again did not yield any product 65; only styrene 89 was recovered.

![Scheme 40](image)

**Scheme 40:** Attempted Wacker oxidation to yield bromo isoquinolone 65.

With styrene 89 proving difficult to prepare and a lack of success with the Wacker oxidation, it was decided that alternative methods should be sought.

b. **C₈-C₉ Bond Formation prior to Ring B Formation**

The C₈-C₉ bond of *des*-hydroxyeletefine 35 and eletefine 1 has been the crux of the total synthesis since preliminary reactions with isoquinolone 45 and its derivatives were performed. The bond’s formation is paramount to completion of the synthesis. However, difficulties have been encountered in our attempts to
form the bond with various derivatives of isoquinolone 45. In order to facilitate its formation, it was envisioned that the C₈-C₉ bond could be formed on a simpler system – that of ring A. This would circumvent several reactivity and functionalization issues faced with the AB ring system (isoquinolone 45). Several methods were devised by the Cody group in an effort to form the pivotal bond, including Friedel-Crafts acylation, *ortho*-Fries rearrangement, Nozaki-Hiyama-Kishi coupling, and Sonogashira coupling.

i. Acylation of Ring A

1. *Ortho*-Fries type Rearrangement of a Mixed Anhydride

It was initially envisioned that mixed anhydride 94 could undergo a Fries-type rearrangement³⁹,⁴⁰ to give acylated ring A 95 (Scheme 41). The Fries-type rearrangement would commence *via* intermolecular nucleophilic attack of Ring A on a carbonyl of the anhydride (it is presumed that the carbonyl of the alkyl moiety would be attacked, as the electron donating nature of the aromatic system would decrease the electrophilicity of the aryl carbonyl). The aliphatic chain would then liberate, giving the acylated aromatic system 95.

![Scheme 41: Proposed Fries-type rearrangement to afford acylated aryl system 95.](image)

However, when the synthesis of mixed anhydride 94 was attempted (both in the presence and absence of triethylamine), only starting materials were observed. Upon increasing the reaction temperature to reflux, a complex mixture was formed, comprising mostly of starting material with no product 94 observed (Scheme 42).
Scheme 42: Attempted formation of mixed anhydride 94.

With the inability to synthesize mixed anhydride 94, an alternate route to acylated aromatic system 95 was conceived: the direct acylation of the A ring with a toluene system.

2. Toluene system

It was envisioned that ring A of 3,4,5-trimethoxytoluene 96 could readily undergo Friedel-Crafts acylation, and subsequently be oxidized to carboxylic acid 95 (Scheme 43).

Scheme 43: Proposed Friedel-Crafts acylation and benzylic oxidation to provide aryl system 95.

Initial experiments using benzoyl chloride 98 as a model acyl chloride were performed by screening various Lewis acids (Scheme 44).

Scheme 44: Toluene compound 96 acylated with benzoyl chloride 98 to afford ketone 99.

It was evident from the screen (Table 3) that milder Lewis acids were most effective, with triethylsilyl trifluoromethanesulfonate (TESOTf) being the most effective, followed by zinc dichloride. It should be noted that in addition to starting material and product being recovered, the TESOTf reaction afforded a
large amount of triethylsilanol (attributing to high crude yields) which may be readily removed by flash chromatography to give a 61 % isolated yield of acylated compound 99.\textsuperscript{41}

**Table 3:** Lewis acid screen for toluyl ring A acylation.

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Crude Yield</th>
<th>\textsuperscript{1}H-NMR ratio SM:pdt (96:99)</th>
</tr>
</thead>
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<tr>
<td>AlCl\textsubscript{3}</td>
<td>83 %</td>
<td>1.7 : 1</td>
</tr>
<tr>
<td>BF\textsubscript{3}-THF</td>
<td>83 %</td>
<td>3.9 : 1</td>
</tr>
<tr>
<td>FeCl\textsubscript{3}</td>
<td>64 %</td>
<td>n/a (no SM or product recovered)</td>
</tr>
<tr>
<td>ZnCl\textsubscript{2}</td>
<td>95 %</td>
<td>1 : 1.5</td>
</tr>
<tr>
<td>polyphosphoric acid</td>
<td>70 %</td>
<td>4.9 : 1</td>
</tr>
<tr>
<td>TESOTf</td>
<td>&gt;99 %</td>
<td>1 : 8.9</td>
</tr>
</tbody>
</table>

With conditions resolved for the acylation of 3,4,5-trimethoxytoluene 96, a series of oxidations were attempted (Scheme 45).

![Scheme 45: Attempted oxidation of acylated ring A.](image)

The oxidants employed were 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)\textsuperscript{42}, potassium permanganate/copper sulfate pentahydrate\textsuperscript{43}, and Jones reagent\textsuperscript{44}. None of these conditions gave desired acid 100, but rather starting material 99 (or degradation in the case of Jones reagent). In the future, benzylic oxidation may be more effective if a benzylic alcohol is installed prior to oxidation (Scheme 46).\textsuperscript{45}
Scheme 46: Possible formation of benzyl alcohol 101 and subsequent oxidation.

In lieu of installation of a benzylic alcohol, it was thought that acylation could be performed on the readily available 3,4,5-trimethoxybenzyl alcohol 102.

3. Benzyl alcohol system

It was thought that using benzyl alcohol 102 (or protected benzyl alcohol 103) instead of toluene 96 would enable ease of oxidation, and allow an appropriate reactive system for the key C₈-C₉ bond to be formed (Scheme 47).

Scheme 47: Direct acylation of trimethoxybenzyl alcohol species.

An initial experiment involving Friedel-Crafts acylation of benzyl alcohol 102 was performed under Brønsted acidic conditions (Scheme 48). With no starting material 102 or desired product 101 observed, the structure of C₂₅ symmetric dimer 106 was elucidated by ¹H-NMR and GC-MS.

Scheme 48: Attempted acylation of benzyl alcohol 102 with benzoyl chloride 98.
With the aim of avoiding formation of dimer 106, protected alcohol 107 was prepared from commercially available 3,4,5-trimethoxybenzyl alcohol 102 (Scheme 49).

Scheme 49: Preparation of benzoyl protected alcohol 107.

Initially, an ortho-Fries type rearrangement was attempted with benzoyl protected alcohol 107 under Lewis acidic conditions, however the result was only cleavage of the protecting group to give 3,4,5-trimethoxybenzyl alcohol 102 by GC-MS (Scheme 50).

Scheme 50: Attempted ortho-Fries rearrangement of benzoyl protected alcohol 107.

With the ortho-Fries type rearrangement being unsuccessful, a Friedel-Crafts acylation of ester 107 was attempted (Scheme 51). While no desired product was observed, a mixture of benzoic acid, benzoyl chloride 98, and dimer 106 was observed by GC-MS.

Scheme 51: Attempted acylation of benzoyl protected alcohol 107.
In order to avoid formation of dimer 106, it was thought that incorporation of a bulky and relatively acid-resistant silyl ether could be incorporated. TESOTf was initially chosen (Scheme 52), however when the protection was performed, dimer 106 was observed, likely due to the presence of triflic acid.

**Scheme 52:** Attempted triethylsilyl protection of benzyl alcohol 102.

It was evident to the Cody group that a different silylating reagent had to be selected. A bulkier and more acid-resistant silyl chloride, tert-butyldiphenylsilyl (TBDPS) chloride, was chosen and protection proceeded in high yield (Scheme 53).

**Scheme 53:** TBDPS protection of benzyl alcohol 102 to afford silyl ether 110.

To test the ability to acylate TBDPS protected alcohol 110, a Friedel-Crafts acylation was performed using the conditions developed for the toluyl case (Scheme 54). Starting materials were observed to be consumed by TLC, however no product 111, starting material 110, or dimer 106 was observed, and no byproducts were isolated by column chromatography.

**Scheme 54:** Attempted acylation of TBDPS protected alcohol 110 using TESOTf.
Performing the reaction at 0 °C also gave a complex mixture, and use of other Lewis acids (AlCl₃, BF₃·THF, ZnCl₂, polyphosphoric acid) afforded complex mixtures consisting of dimer 106 and possible trace product 111, as observed by ¹H-NMR and LC-MS. Subjection of an aforementioned mixture to column chromatography gave dimer 106 and benzoic acid. An additional experiment using 5.0 equivalents of benzoyl chloride was run with the notion that increased concentration of the coupling partner would decrease the likelihood of dimerization, however, starting materials were consumed (¹H-NMR) with no dimer 106 or product observed 111. Other acylation conditions were then sought.

It was reported by Frost, et al. that Friedel-Crafts acylation could be performed using the mild Lewis acid indium(III) trifluoromethanesulfonate in catalytic (1 mol %) quantities with lithium perchlorate as an additive (Scheme 55).⁴⁷

![Scheme 55: Acylation using indium(III) triflate as reported by Frost, et al.](image_url)

Using our system at room temperature with 100 mol % loading of In(OTf)₃, it was observed that starting materials were consumed; however no product 111 or dimer 106 was recovered (Scheme 56). It was suspected that the material was degrading. When the reaction was run at 0 °C with a 10 mol % loading, similar results were obtained.

![Scheme 56: Attempted acylation using indium(III) triflate under model conditions.](image_url)
Due to the high number of Lewis basic sites on protected benzyl alcohol 110, it was considered a possibility that the Lewis acid was reacting not with the desired benzoyl chloride 98, but a site on trimethoxy species 110. In order to reverse this, a milder and more selective Lewis acid was thought to be needed. One such Lewis acid is methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide), or MAD (114, Figure 7).48–50

![Figure 7: MAD catalyst (114).](image)

It was envisioned by the Cody group that MAD 114 could be used to control the selectivity of the acylation reaction, avoiding degradation pathways suspected to have occurred with other Lewis acids (Scheme 57).

![Scheme 57: Proposed use of MAD (114) to acylate protected benzyl alcohol 110.](image)

MAD was prepared48,49 by reaction of two equivalents of butylated hydroxytoluene (BHT, 117) with one equivalent of trimethylaluminum 116 (Scheme 58). It is then typically used in situ.

![Scheme 58: Preparation of MAD (114).](image)
The first experiment attempted was a model acylation using benzoyl chloride (98) as the coupling partner (Scheme 59).

Scheme 59: MAD (114) acylation attempt with benzoyl chloride (98).

After work-up, only starting material 110, BHT (116), and acetophenone (117) were recovered. The origin of the acetophenone (117) is from the equivalent of a methyl anion which MAD is able to provide. It was therefore inferred that MAD (114) was methylating the benzoyl chloride before it could act as a classical Lewis acid and perform a Friedel-Crafts. Three experiments were devised to help the Friedel-Crafts proceed.

The first experiment provided an additional equivalent of benzoyl chloride (98), with the aim that the first equivalent would be methylated to give acetophenone (117), and the second equivalent would be available for a Friedel-Crafts acylation (Scheme 60).

Scheme 60: MAD (114) acylation attempt with two equivalents of benzoyl chloride (98).

When the experiment was performed, starting material 110 was consumed, but only a complex mixture was obtained. Similar results were seen when toluene was used as solvent.
The second experiment avoided use of an acid chloride altogether, replacing the functionality with a carboxylic acid. The notion behind this is that the methyl anion would initially deprotonate the carboxylic acid, then allow the carboxylate to coordinate to the available site on the aluminum. This would idyllically promote attack of the carbonyl in a Friedel-Crafts fashion (Scheme 61).

Scheme 61: Postulated MAD acylation pathway using benzoic acid (118).

When the reaction was performed, only starting material 110 and BHT 116 were recovered; benzoic acid 118 was not. This may indicate that the benzoic acid 118 was deprotonated by MAD catalyst 114, but the resulting carboxylate did not coordinate to the MAD catalyst 114 as desired (Scheme 62).

Scheme 62: MAD (114) acylation attempt with benzoic acid (118).

The third experiment was designed to avoid methylation/deprotonation by the catalyst altogether. This experiment involved aluminum triphenoxide system 121 which was intended to have similar selectivity to MAD (Scheme 63). The catalyst was prepared by the same method as MAD 114, except using three equivalents of BHT 116.
Scheme 63: Acylation attempt with Al(OAr)$_3$ catalyst (121).

The reaction afforded consumption of starting material 110, presence of BHT 116 and an unknown side product, with no desired ketone 111 observed.

Future experiments that may be performed involve a Lewis acid whose reactivity, to the best of the author’s knowledge, has not been extensively studied; chloroaluminum bis(2,6-di-tert-butyl-4-methylphenoxide), or CAD (122, Figure 8).

Figure 8: CAD catalyst (122).

It is reasoned by the Cody group that the proposed CAD catalyst 122 will function similarly to that of aluminum trichloride, with enhanced selectivity (Scheme 64).

Scheme 64: Proposed use of CAD (122) to acylate protected benzyl alcohol 110.
The CAD catalyst 122 could be prepared using a method similar to that of the MAD 114 preparation (Scheme 58), except using diethylaluminum chloride as the aluminum-based starting material.

In order to form the C₈-C₉ bond of des-hydroxyeletefine (35), Friedel-Crafts acylation involving a carboxylate system was attempted.

4. Carboxylic acid system

Trimethoxybenzoyl species 123/124 was envisioned to be acylated under Friedel-Crafts conditions using 6-heptynoic acid 43 or the corresponding acid chloride 40 (Scheme 65).

\[
\text{Acid} + 123, R = \text{OH} \quad 124, R = \text{OCH}_3 \\
\xrightarrow{\text{X = OH}} 43, X = \text{OH} \quad 40, X = \text{Cl} \\
\xrightarrow{\text{Acid}} 95, R = \text{OH} \quad 125, R = \text{OCH}_3
\]

Scheme 65: Direct acylation of trimethoxybenzoyl species 123/124.

Acylations were attempted under Lewis acidic conditions, primarily between methyl 3,4,5-trimethoxybenzoate 124 and 6-heptynoyl chloride 40. Under mild reflux with a catalytic amount of Lewis acid, only starting material was observed. In a pressure vessel with stoichiometric quantities of Lewis acid (aluminum(III) chloride, iron(III) chloride, and pyridinium para-toluenesulfonate were tried), a complex mixture primarily comprised of starting material was observed by TLC. (Scheme 66). It was later determined by GC-MS that the product formed in the acylation reaction was dimer 126 of starting material 124 (Figure 9).
Scheme 66: Attempted acylation of methyl 3,4,5-trimethoxybenzoate 124.

Figure 9: Trimethoxybenzoate dimer 126.

Anthraquinone 126 is suspected to form by intermolecular Friedel-Crafts dimerization of the starting material. This is likely attributed to a combination of the high electron-donating ability of the aryl ring and the reactivity of the carbonyl. Based on the results compiled in this methodology, it was recognized that Friedel-Crafts acylation of ring A was not serving as the most facile and forthright route to the C₈-C₉ bond of des-hydroxyeletefine 35.

5. Nozaki-Hiyama-Kishi Reaction

One alternate route to the C₈-C₉ bond of des-hydroxyeletefine 35 conceived by the Cody group was a Nozaki-Hiyama-Kishi (NHK) coupling⁵³–⁵⁵ reaction between methyl 2-iodo-3,4,5-trimethoxybenzoate 127 and 6-heptynal 41 (Scheme 67). Resultant benzyl alcohol 128 would then be oxidized to give desired ketone 125. Advantages of the NHK reaction include high functional group compatibility as well as chemoselectivity towards aldehydes.
**Scheme 67:** Proposed Nozaki-Hiyama-Kishi coupling to form C₈-C₉ bond and subsequent oxidation.

Preliminary results for the NHK coupling route showed little success, with model aldehyde 129 consumed and no product 130 present (Scheme 68). Ring-closed byproduct 131 was also not observed. The lack of success was surmised to be attributed to difficulty in solubilizing the nickel(II) chloride. In the future, use of a more soluble precatalyst such as NiCl₂·glyme may be beneficial in this regard.

**Scheme 68:** Preliminary NHK reaction with isovaleraldehyde 129.

It was decided that the NHK route would be held in abeyance in order to give attention to successes in other chemistry.

**ii. Sonogashira Coupling to Ring A**

The unsuccessful formation of bromo isoquinolone 65 as well as the C₈-C₉ bond by acylation led to the conception of a new route towards the synthesis of des-hydroxyeletefine 35, a Sonogashira coupling to ring A in order to form the paramount C₈-C₉ bond.
1. Formation of Phthalide Intermediate 132

In the modified retrosynthesis, route B is adapted to make acetal 133 the key intermediate. It is envisioned to be formed from ring opening of phthalide 132, which is formed via *trans*-addition across the internal alkyne formed in the Sonogashira reaction between an aryl iodide (an ester 127 or an acid 134) and diyne 135 (Scheme 69).

![Scheme 69: Retrosynthetic analysis of route involving phthalide 132.](image)

The formation of phthalide 132 has two main advantages: it installs the carbonyl after the carbon-carbon bond is formed, thus enabling the C8-C9 bond to be formed *via* cross-coupling. Secondly, it provides a favorable site for the formation of amide 133, which is speculated to be thermodynamically favored due to the formation of a ketone. Kundu, et al. demonstrated that phthalides 136 and isocoumarins 137 may be formed *in situ* from a Sonogashira coupling between 2-iodobenzoic acid 138 and a variety of alkynes (Scheme 70), and therefore the method reported by Kundu, et al. was first tried.56

![Scheme 70: Formation of phthalides 136 and isocoumarins 137 as demonstrated by Kundu, et al.](image)
To begin investigation of the formation of phthalide 132, iodo-acid 134 was first prepared from a method described by Molander, et al.\textsuperscript{57} (Scheme 71).

Scheme 71: Iodination to give iodo acid 134.

After recrystallization, iodo acid 134 was reacted under Sonogashira reactions with a model alkyne, methyl 6-heptynoate 42 (Scheme 72). The reaction proceeded to form the carbon-carbon bond of interest, and subsequent 6-endo-dig cyclization gave coumarin 139 in low yields, with the 5-exo-dig target 140 not observed.

Scheme 72: Formation of coumarin 139 by Sonogashira reaction.

As the formation of coumarin 139 versus phthalide 140 may be cumbersome to control, it was decided that the initial focus of the investigation should be on the formation of the C$_8$-C$_9$ bond, rather than the formation of phthalide 140. This would be employed by use of iodo ester 127, thus removing the ability of the molecule to ring close. This two-step process would involve reaction between iodo ester 127 and alkyne 135 to give internal alkyne 141, which could then later be deprotected to give desired phthalide 132 (Scheme 73).
Scheme 73: Proposed two-step formation of phthalide 132.

To synthesize iodo ester 127, methods similar to those used in the formation of iodo acid 134 were employed (Scheme 74). While the method employed by the Cody group uses expensive silver trifluoroacetate as the Lewis acid, methods using iodine in periodic acid have been described by Li, et al. and could be a cost effective alternative for the synthesis of iodo ester 127. 58

Scheme 74: Iodination to give iodo ester 127.

Initial model Sonogashira experiments using iodo ester 127 and methyl 6-heptynoate 42 under conditions utilized previously by the Cody group 12,13 led to long reaction times and low conversion (Scheme 75). A mixture of starting material (aryl iodide 127), product 142, and hydrodehalogenation product 124 was observed in a 3.1 : 2.8 : 1 ratio, respectively (by crude 1H-NMR).

Scheme 75: Preliminary Sonogashira reaction between iodo ester 127 and alkyne 42.
It is believed that formation of hydrodehalogenation product 124 is caused by $\beta$-hydride elimination of the solvent/base piperidine after its coordination to the initial palladium(II) complex 143. The resulting palladium(II) hydride complex 147 undergoes reductive elimination to give byproduct 124 (Scheme 76).  

**Scheme 76:** Proposed hydrodehalogenation mechanism to give byproduct 124.

It was reported by Li, et al. that use of piperidine as a solvent in the Sonogashira reaction between iodo ester 127 and propargyl alcohol 150 afforded internal alkyne 151 in high yields (Scheme 77).  

**Scheme 77:** Sonogashira reaction performed with piperidine as solvent/base by Li, et al.

Using conditions adapted from Li, et al., it was observed that model internal alkyne 142 could be obtained in 83 % yield (Scheme 78).
Scheme 78: Sonogashira reaction performed with piperidine as solvent/base using model alkyne 42.

With success in formation of the C₈-C₉ bond using model alkyne 42, the reaction was then performed using the actual substrate, 1,6-heptadiyne 135 (Scheme 79). The product 141 was obtained in a 48% yield.

Scheme 79: Sonogashira reaction performed with piperidine as solvent/base using diyne 135.

With success in forming the C₈-C₉ bond for the des-hydroxyeletefine 35 case, the mixture was carried forward in an effort to functionalize the material and complete the synthesis of des-hydroxyeletefine 35.

2. Functionalization of Alkyne Intermediate 141

Preliminary success in synthesis of diyne 141 meant that methods towards its functionalization and subsequent completion of des-hydroxyeletefine 35 could be sought. In general, the completion of the synthesis may be envisioned by first hydrolysis of ester 141 to form acid 152, then formation of amide 153 by N,N'-dicyclohexylcarbodiimide (DCC) coupling with acid 152 and amine 47 (Scheme 80).
Two possible methods can be perceived to form isoquinoline 154. One possibility is use of standard Bronsted acid conditions to both close ring B and perform an alkyne hydration (Method A), with another possibility being mild ring closure conditions to give dihydroisoquinoline 155, and then harsher conditions to hydrolyze the methoxy group and perform the alkyne hydration (Method B, Scheme 81).

Once isoquinoline 154 is formed, des-hydroxyeletefine 35 may be completed by triflation of isoquinoline 154, intramolecular Sonogashira coupling of alkyne 61, and finally alkyne hydration of ketone 36 (Scheme 82).
Scheme 82: Proposed completion of des-hydroxyeletefine (35) using Sonogashira methodology.

IV. Conclusions

Synthetic methodologies have resulted in successful formation of advanced intermediates of des-hydroxyeletefine 35. Formation of the pivotal C₈-C₉ bond by a Sonogashira coupling on ring A afforded diyne intermediate 141 which provides an opportunity to complete the synthesis of des-hydroxyeletefine 35. Furthermore, future methodologies involving CAD catalyst 122 to perform a selective Friedel-Crafts acylation resulting in the formation of the C₈-C₉ bond may sprout an alternate synthesis of the target. In-depth study of the Nozaki-Hiyama-Kishi reaction may additionally present itself useful. Successful formation of the AB ring system (i.e. bromo-triflate 29) via Heck reaction, Suzuki coupling/Wacker oxidation, or norbornadiene annulation would have allowed for additional study of the original synthetic routes A and B, however the aforementioned methodologies may prove fruitful in completion of the synthesis of des-hydroxyeletefine 35.
References


(14) Tusch, D. J. *Unpublished results* **2010**.


General Procedures

All non-aqueous reactions were performed in flame- or oven-dried (125 °C) glassware under an atmosphere of argon, and stirred magnetically unless otherwise specified. Pyrophoric and other air- and water-sensitive reagents were transferred to reactions via the appropriate syringe or cannula through a rubber septum. Reaction temperatures other than room temperature were performed in baths: dry ice/acetone slush for -78 °C, icewater for 0 °C, and a heating mantle regulated by a variable autotransformer for temperatures greater than room temperature. The phrases “concentrated in vacuo”, “concentrated under reduced pressure”, or “concentrated” refer to removal of solvent via Büchi R-110 or IKA RV-10 rotary-evaporator followed by pumping to constant mass using an oil pump (< 1 mmHg). Distillations were performed under argon atmosphere if at room pressure, and under vacuum using a water aspirator (> 15 mmHg) or an oil pump (< 1 mmHg) if below room pressure.

Reagents and Solvents

Deionized water was used for all aqueous reactions, work-up procedures, and for the preparation of aqueous solutions. All commercially available reagents and solvents were used as obtained from the supplier without further purification except those stated below, which were purified as follows:

Distilled from sodium benzophenone ketyl: tetrahydrofuran
Distilled under argon from calcium hydride: dichloromethane, triethylamine
Dried over 4Å molecular sieves: toluene, acetonitrile, diethyl ether, ethyl acetate, ethanol, 1,2-dichloroethane

Organolithium reagents were titrated using diphenylacetic acid as titrant in the intended reaction solvent at 0 °C.
Chromatography

The phrases “column chromatography” or “chromatography” refer to flash column chromatography using 230-400 mesh silica gel (SiliCycle) and standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plastic plates (EMD). Visualization was effected by short-wave (254 nm) UV illumination, and/or placing the plate in an iodine chamber for 15-30 seconds and then using a heat-gun to remove the iodine, and/or by dipping the plate in a stain solution and heating with a heat-gun for 10-15 seconds when appropriate. Stain solutions were prepared as follows:

Potassium permanganate: 3 g potassium permanganate, 20 g potassium carbonate, and 5 mL of 5 % w/w sodium hydroxide in 300 mL water

p-Anisaldehyde: 15 mL p-anisaldehyde and 2.5 mL conc. sulfuric acid in 250 mL ethanol

Ceric ammonium molybdate: 0.5 g ceric ammonium sulfate, 12 g ammonium molybdate, and 15 mL conc. sulfuric acid in 235 mL of water

Physical Data

Melting point ranges were determined on an Electrothermal Mel-Temp® capillary melting point apparatus and are uncorrected.

Proton nuclear magnetic resonance (\textsuperscript{1}H-NMR) spectra were obtained on a Bruker DRX-300 (300.13 MHz) or Avance III 500 (500.13 MHz) nuclear magnetic resonance spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane and are internally referenced using CDCl\textsubscript{3} as solvent (7.26 ppm), unless otherwise specified. \textsuperscript{1}H-NMR data are reported as follows: chemical shift (multiplicity, coupling constants in Hz, number of protons). Multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of
doublets), ddd (doublet of doublets of doublets), m (multiplet and/or multiple resonances), br s (broad singlet), br d (broad doublet).

Carbon nuclear magnetic resonance (13C-NMR) spectra were obtained on a Bruker DRX-300 (75.48 MHz) or Avance III 500 (125.77 MHz) nuclear magnetic resonance spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane and are internally referenced using CDCl3 as solvent (77.16 ppm), unless otherwise specified.

Fourier-transform infrared (FT-IR) spectra were recorded using ATR on a Shimadzu IRAffinity-1 FT-IR and are reported in wavenumbers (cm\(^{-1}\)).

Low-resolution mass spectra were obtained using a Hewlett Packard 6890 Series gas chromatograph with a 5973 Mass Selective Detector using electron impact (EI) methods and dichloromethane, ethyl acetate, or diethyl ether as the sample solvent.
## Compound Index

Tabulated below are page numbers for experimental and spectral data for compounds of relevance.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Experimental</th>
<th>$^1$H-NMR</th>
<th>$^{13}$C-NMR</th>
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Experiments

5,6,7-Trimethoxyisoquinolin-1-yl trifluoromethanesulfonate (28)

To a stirred solution of isoquinolone 45 (1.74 g, 7.37 mmol) in CH₂Cl₂ (53 mL) at -20 °C was added trifluoromethanesulfonic anhydride (1.49 mL, 8.56 mmol) over 10 min. followed by diisopropylethylamine (2.19 mL, 12.5 mmol) over 20 min. The reaction was stirred at that temperature for 1 h until TLC indicated completion, followed by quenching with saturated sodium bicarbonate (55 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organics were washed with water (100 mL), dried over MgSO₄, filtered through Celite, and concentrated in vacuo. The crude mixture was purified via flash chromatography (2 % EtOAc/hexanes → 15 % EtOAc/hexanes) to give 28 as a yellow solid (2.11 g, 78 % yield).

¹H-NMR (300 MHz, CDCl₃): δ 8.06 (d, J = 5.7 Hz, 1H); 7.87 (d, J = 5.7 Hz, 1H); 7.11 (s, 1H); 4.08 (s, 3H); 4.05 (s, 6H).

MS (EI): Calcd. for C₁₃H₁₂F₃NO₆S [M⁺] = 367, found = 367.
2-Bromobenzoyl chloride (71)

To a solution of 2-bromobenzoic acid (6.00 g, 29.8 mmol) in THF (65 mL) was added DMF (1 drop) followed by oxalyl chloride (4.62 g, 36.4 mmol). The resulting solution was stirred until gas evolution ceased (approx. 5 min) after which the solution was refluxed for 30 min. The solution was concentrated *in vacuo* to give 71 as a golden oil (6.46 g, 99 % yield) in accordance with the literature.

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 8.11-8.03 (m, 1H); 7.75-7.69 (m, 1H); 7.51-7.39 (m, 2H).
2-Bromo-N-vinylbenzamide (68)

To a stirred solution of 2-oxazolidinone 70 (2.88 g, 33.1 mmol) and triphenylmethane (indicator, approx. 1 mg) in THF (70 mL) at -78 °C was added n-butyllithium in hexanes (2.38 M, 14.5 mL, 34.5 mmol) dropwise until a pink color persisted. The reaction was stirred and allowed to warm to rt over 1 h, after which 2-bromobenzoyl chloride 71 (10.9 g, 49.7 mmol) was added dropwise over 5 min. The reaction was stirred for 30 min before being quenched with saturated sodium bicarbonate (60 mL). The resulting mixture was extracted with CH$_2$Cl$_2$ (4 x 100 mL) and the combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The resulting crude material (8.18 g, 91 % crude yield) was used directly in the following reaction. To a solution of diisopropylamine (3.63 g, 35.8 mmol) in THF (20 mL) at -78 °C was added n-butyllithium in hexanes (2.38 M, 13.7 mL, 32.6 mmol) dropwise via syringe. The solution was stirred at that temperature for 45 min before being allowed to warm to rt. After stirring at rt for 10 min, the reaction was cooled to -78 °C upon which a yellow color persisted. 3-(2-Bromobenzoyl)oxazolidin-2-one 69 (8.00 g, 29.6 mmol) in THF (10 mL) was added dropwise to the reaction over 10 min, and the reaction was stirred for 2 h at -78 °C, upon which time the reaction was quenched with saturated ammonium chloride (30 mL). The resulting mixture was extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined organics were dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The crude material was purified \textit{via} flash chromatography (30 % EtOAc/hexanes $\rightarrow$ 100 % EtOAc) to give 68 as a yellow solid (2.34 g, 35 % yield).
$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.82 (br s, 1H); 7.50 (qd, $J = 16.0$, 7.77, 1.70 Hz, 2H); 7.33-7.19 (m, 2H); 7.11-6.97 (ddd, 1H); 4.71 (d, $J = 15.8$ Hz, 1H); 4.49 (d, $J = 8.65$ Hz, 1H).

$^{13}$C-NMR (126 MHz, CDCl$_3$): $\delta$ 164.7; 136.7; 133.7; 132.0; 130.2; 128.5; 127.8; 119.4; 97.1.

MS (EI): Calcd. for C$_9$H$_8$BrNO [M$^+$] = 225, found = 225.

FTIR (neat, cm$^{-1}$): 3264; 2174; 2158; 2012; 1630; 1499; 1381; 1296; 1198.
tert-Butyl (2-bromobenzoyl)(vinyl)carbamate (80)

To a stirred solution of enamide 68 (500 mg, 2.21 mmol) in CH$_3$CN (20 mL) was added di-tert-butyl dicarbonate (965 mg, 4.42 mmol) followed by 4-(dimethylamino)pyridine (27 mg, 0.22 mmol). The reaction was stirred at rt for 24 h before concentration in vacuo. The crude product was purified via flash chromatography (25 % EtOAc/hexanes $\rightarrow$ 35 % EtOAc/hexanes) to give 80 as a yellow oil (558 mg, 77 % yield).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.49 (d, $J$ = 7.98 Hz, 1H); 7.31-7.17 (m, 3H); 6.71 (dd, $J$ = 16.0 Hz, 9.3 Hz, 1H); 5.33 (d, $J$ = 16.1 Hz, 1H); 4.95 (d, $J$ = 9.1 Hz, 1H); 1.09 (s, 9H).

$^{13}$C-NMR (126 MHz, CDCl$_3$): $\delta$ 169.1; 151.1; 139.3; 133.0; 131.1; 129.5; 128.5; 127.3; 119.3; 106.4; 84.3; 27.3.

MS (EI): Calcd. for C$_{14}$H$_{16}$BrNO$_3$ [M$^+$] = 325, found = 325.

FTIR (neat, cm$^{-1}$): 2980; 1746; 1682; 1636; 1348; 1244; 1130; 743.
\[ \text{O}_2, \text{PdCl}_2, \text{CuCl}, 1,3\text{-propanediol, THF, 60} \, \text{oC} \rightarrow \text{48} \, \% \, \text{yield (two steps)} \]

\[ \text{O} \]

\[ \text{NBn} \]

\[ \text{PdCl}_2(\text{PPh}_3)_2, \text{Na}_2\text{CO}_3, \text{THF, H}_2\text{O, reflux} \]

\[ \text{O} \]

\[ \text{NBn} \]

\[ \text{OBu} \]

\[ \text{OBu} \]

\[ \text{82} \]

\[ \text{81} \]

\[ \text{91} \]

\[ \text{80} \]

\[ \text{90} \]

\[ \text{89} \]

\[ \text{84} \]

\[ \text{N-Benzylisoquinolin-1(2H)-one (84)} \]

To a solution of \(N\)-benzyl-2-bromobenzamide 82 (500 mg, 1.72 mmol), vinylboronic acid dibutyl ester 91 (476 mg, 2.58 mmol), and sodium carbonate (1.28 g, 12.1 mmol) in THF/H\(_2\)O (9 mL/3 mL) was added dichlorobis(triphenylphosphine)palladium(II) (61 mg, 86.2 µmol). The reaction was heated at 70 °C for 24 h until TLC indicated completion, after which the reaction was poured into saturated ammonium chloride (50 mL). The resulting mixture was filtered thru Celite, washing with EtOAc (20 mL). The filtrate was extracted with EtOAc (3 x 20 mL), and the combined organics were washed with saturated brine (75 mL) and concentrated \textit{in vacuo}. The resulting crude material 90 (343 mg, 84 % crude yield) was used directly in the next step. To a flask charged with palladium(II) chloride (4 mg, 0.02 mmol) and copper(I) chloride (21 mg, 0.21 mmol) under oxygen atmosphere was added a solution of \(N\)-benzyl-2-vinylbenzamide 90 (50 mg, 0.21 mmol) and 1,3-propanediol (16 mg, 0.21 mmol) in THF (0.5 mL). The reaction was heated at 50 °C for 30 h until TLC indicated completion, at which time the reaction was diluted with Et\(_2\)O (5 mL). The resulting mixture was filtered thru Celite, washing with Et\(_2\)O (15 mL). The filtrate was concentrated \textit{in vacuo}, and the crude material was purified \textit{via} flash chromatography (15 % EtOAc/hexanes \(\rightarrow\) 30 % EtOAc/hexanes) to give 84 as a yellow solid (28 mg, 55 % yield) in accordance with the literature.

\[ ^1\text{H-NMR (300 MHz, CDCl}_3\):} \delta 8.47 (d, \(J = 8.14 \text{ Hz, 1H); 7.68-7.60} \, (m, \, 1H); \, 7.54-7.45 \, (m, \, 2H); \, 7.39-7.24 \, (m, \, 5H); \, 7.09 \, (d, \, J = 7.38 \text{ Hz, 1H); 6.49} \, (d, \, J = 7.42 \text{ Hz, 1H); 5.23} \, (s, \, 2H). \]

\[ \text{MS (EI):} \, \text{Calcd. for C}_{16}\text{H}_{13}\text{NO }[\text{M}^+] = 235, \, \text{found} = 235. \]
To a solution of 3,4,5-trimethoxybenzamide 92 (2.50 g, 11.8 mmol) in chloroform (120 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (8.46 g, 29.6 mmol). The reaction was stirred at rt overnight before diluting with EtOAc (150 mL), to which 1 M sodium hydroxide (60 mL) was added and the mixture vigorously stirred for 5 min. The phases were separated and the aqueous phase extracted with EtOAc (3 x 60 mL). The combined organics were washed with water (2 x 100 mL) and saturated brine (100 mL). The organics were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified via flash chromatography (5 % EtOAc/hexanes → 100 % EtOAc) to give 93 as a yellow solid (1.05 g, 24 % yield).

\[ \text{H-NMR (400 MHz, DMSO-d6): } \delta 7.93 \text{ (br s, 1H); 7.70 (br s, 1H); 3.87 (s, 3H); 3.82 (s, 6H).} \]

\[ \text{C-NMR (126 MHz, DMSO-d6): } \delta 166.8; 150.3; 147.1; 136.9; 109.4; 61.3; 60.8. \]

MS (EI): Calcd. for C₁₀H₁₁Br₂NO₄ [M⁺] = 367, found = 367.

FTIR (neat, cm⁻¹): 2980; 2453; 2361; 2160; 1997; 1375.
**tert-Butyldiphenyl((3,4,5-trimethoxybenzyl)oxy)silane (110)**

To a solution of 3,4,5-trimethoxybenzyl alcohol **102** (991 mg, 5.00 mmol) in DMF (4 mL) was added imidazole (1.02 g, 15.0 mmol). The reaction was stirred for 5 min at rt before *tert*-butyldiphenylsilyl chloride (1.79 g, 6.50 mmol) was added. The reaction was stirred at rt overnight before the reaction mixture was diluted with Et₂O (20 mL), and the resulting mixture washed with 10 % ammonium chloride (20 mL) and water (20 mL). The combined aqueous phases were extracted with Et₂O (3 x 20 mL), and the combined organics were dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting crude material was purified *via* flash chromatography (2 % EtOAc/hexanes → 20 % EtOAc/hexanes) to give **110** as a slightly yellow oil (1.87 g, 86 % yield).

^1^H-NMR (300 MHz, CDCl₃): δ 7.74-7.66 (m, 4H); 7.47-7.34 (m, 6H); 6.57 (s, 2H); 4.73 (s, 2H); 3.84 (s, 3H); 3.82 (s, 6H); 1.11 (s, 9H).

MS (EI): Caled. for C₂₆H₃₂O₄Si [M⁺] = 436, found = 436.
Methyl 2-iodo-3,4,5-trimethoxybenzoate (127)

To a solution of methyl 3,4,5-trimethoxybenzoate **124** (10.00 g, 44.2 mmol) in chloroform (70 mL) was added silver trifluoroacetate (10.25 g, 46.4 mmol) followed by iodine (11.78 g, 46.4 mmol) in several portions. The reaction was heated at reflux for 2 d before filtering to remove AgI, washing with chloroform (80 mL). The filtrate was washed with 20 % sodium thiosulfate (2 x 50 mL) followed by 50 % brine (50 mL). The organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo* to give **127** as a golden oil (15.15 g, 97 % yield).

**1H-NMR** (300 MHz, CDCl₃): δ 7.14 (s, 1H); 3.89 (s, 3H); 3.87 (s, 3H); 3.85 (s, 3H); 3.83 (s, 3H).

**13C-NMR** (126 MHz, CDCl₃): δ 166.9; 153.9; 153.4; 144.9; 131.1; 110.5; 83.8; 61.2; 60.8; 56.3; 52.5.

**MS (EI):** Calcd. for C₁₁H₁₃IO₅ [M⁺] = 352, found = 352.

**FTIR** (neat, cm⁻¹): 2999; 2940; 2845; 2187; 2010; 1719; 1329; 1213; 1099; 999; 731.
2-Benzoyl-3,4,5-trimethoxytoluene (99)

To a solution of benzoyl chloride 98 (155 mg, 1.1 mmol) and 3,4,5-trimethoxytoluene 96 (182 mg, 1.0 mmol) in 1,2-dichloroethane (3 mL) in a round bottom flask equipped with a reflux condenser, heating mantle, and magnetic stirring was added triethylsilyl trifluoromethanesulfonate (793 mg, 3.0 mmol) under an atmosphere of argon. The reaction was heated at 60 °C for 6 h. Upon cooling to room temperature, the reaction was quenched with water (15 mL) and the mixture was sonicated for 1 min. The resulting suspension was extracted with Et₂O (3 x 15 mL) and the combined organics were washed with saturated sodium bicarbonate (15 mL) and brine (15 mL), dried over sodium sulfate, decanted, and concentrated in vacuo. The biphasic crude product was separated to remove triethylsilanol and purified by flash chromatography (2 % EtOAc/hexanes → 100 % EtOAc) to give 99 as a yellow solid (174 mg, 61 % yield) in accordance with the literature.

\[ \text{1H-NMR (500 MHz, CDCl}_3\text{): } \delta 7.82-7.79 \text{ (m, 2H); 7.57-7.53 (m, 1H); 7.46-7.42 (m, 2H); 6.55 (s, 1H); 3.89 (s, 3H); 3.85 (s, 3H); 3.68 (s, 3H); 2.12 (s, 3H).} \]

\[ \text{13C-NMR (126 MHz, CDCl}_3\text{): } \delta 197.4; 154.2; 151.0; 139.8; 138.2; 133.4; 131.1; 129.5; 128.6; 126.8; 109.4; 61.4; 61.0; 56.2; 19.3. \]

MS (EI): Calcd. for C\textsubscript{17}H\textsubscript{18}O\textsubscript{4} [M\textsuperscript{+}] = 286, found = 286.

FTIR (neat, cm\textsuperscript{-1}): 2939, 2924, 2149, 2037, 1665, 1593, 1580, 1450, 1334, 1273, 1236, 1115.
Methyl 5-(5,6,7-trimethoxy-1-oxo-1H-isochromen-3-yl)pentanoate (139)

To a solution of 2-iodo-3,4,5-trimethoxybenzoic acid 134 (200 mg, 0.59 mmol), methyl 6-heptynoate 42 (124 mg, 0.89 mmol), and diethylamine (469 mg, 6.51 mmol) in THF (4 mL) was added copper(I) iodide (17 mg, 0.09 mmol) followed by dichlorobis(triphenylphosphine)palladium(II) (42 mg, 0.06 mmol). The resulting solution was heated at 60 °C overnight before dilution with EtOAc (10 mL). The organics were washed with saturated brine (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated \textit{in vacuo}. The crude material was purified via flash chromatography (5 % EtOAc/hexanes $\rightarrow$ 34 % EtOAc/hexanes) to give 139 as a yellow solid (25 mg, 12 % yield).

$^1$H-NMR (500 MHz, CDCl₃): \( \delta \) 7.49 (s, 1H); 6.49 (s, 1H); 3.98 (s, 3H); 3.942 (s, 3H); 3.936 (s, 3H); 3.67 (s, 3H); 2.55 (t, \( J = 7.0 \) Hz, 2H); 2.36 (t, \( J = 7.1 \) Hz, 2H); 1.79-1.67 (m, 4H).

$^{13}$C-NMR (126 MHz, CDCl₃): \( \delta \) 173.8; 162.8; 155.9; 153.3; 147.8; 147.1; 127.0; 115.6; 106.1; 97.5; 61.5; 61.1; 56.3; 51.6; 33.7; 33.3; 26.5; 24.3.


FTIR (neat, cm⁻¹): 2953; 2932; 2855; 2361; 2158; 1734; 1721; 1651; 1595; 1462; 1433; 1416; 1364; 1258; 1096; 1018; 790.
Methyl 3,4,5-trimethoxy-2-(7-methoxy-7-oxohept-1-yn-1-yl)benzoate (142)

To a stirred solution of aryl iodide 127 (2.00 g, 5.68 mmol) and alkyne 42 (1.19 g, 8.52 mmol) in piperidine (43 mL) under argon was added copper(I) iodide (162 mg, 0.85 mmol) and dichlorobis(triphenylphosphine)palladium(II) (399 mg, 0.57 mmol). The reaction was heated at 40 °C for 24 h until the reaction was determined to be complete by GC-MS. The reaction was then cooled to rt, filtered through Celite with diethyl ether as the wash solvent, and concentrated in vacuo. The crude product was purified via flash chromatography (5 % EtOAc/hexanes → 100 % EtOAc) to give 142 as a brown oil (1.72 g, 83 % yield).

$^1$H-NMR (500 MHz, CDCl$_3$): δ 7.23 (s, 1H); 3.915 (s, 3H); 3.914 (s, 3H); 3.90 (s, 3H); 3.89 (s, 3H); 3.67 (s, 3H); 2.55 (t, $J$ = 7.3 Hz; 2H); 2.38 (t, $J$ = 7.5 Hz, 2H); 1.85 (m, 2H); 1.69 (m, 2H).

$^{13}$C-NMR (126 MHz, CDCl$_3$): δ 174.0; 166.7; 155.6; 152.5; 145.8; 128.0; 113.0; 109.5; 98.2; 74.7; 61.3; 56.3; 52.3; 51.6; 33.8; 28.3; 24.3; 19.9.

MS (El): Calcd. for C$_{19}$H$_{24}$O$_7$ [M$^+$] = 364, found = 364.

FTIR (neat, cm$^{-1}$): 2947, 2421, 2156, 1732, 1709, 1587, 1491, 1431, 1402, 1337, 1124, 1082, 750.
Methyl 2-(hepta-1,6-diyn-1-yl)-3,4,5-trimethoxybenzoate (141)

To a stirred solution of aryl iodide 127 (2.82 g, 8.00 mmol) and alkyne 135 (1.11 g, 12.0 mmol) in piperidine (60 mL) under argon was added copper(I) iodide (122 mg, 0.64 mmol) and dichlorobis(triphenylphosphine)palladium(II) (393 mg, 0.56 mmol). The reaction was stirred at rt for 24 h until the reaction was determined to be complete by GC-MS. The reaction was then cooled to rt, filtered through Celite with diethyl ether as the wash solvent. The filtrate was washed with saturated sodium bicarbonate (3 x 100 mL) and saturated brine (100 mL). The organics were dried over MgSO₄, filtered thru Celite, and concentrated *in vacuo*. The crude product was purified *via* flash chromatography (4 % EtOAc/hexanes → 100 % EtOAc) to give 141 as a brown oil (2.14 g, 84 % yield).

**¹H-NMR (500 MHz, CDCl₃):** δ 7.23 (s, 1H); 3.92 (s, 6H); 3.90 (s, 3H); 3.89 (s, 3H); 2.66 (t, *J* = 6.9 Hz, 2H); 2.45 (td, *J* = 7.2, 2.6 Hz, 2H); 1.97 (t, *J* = 2.8 Hz, 1H); 1.87 (quintet, *J* = 13.9, 7.0 Hz, 2H).

**¹³C-NMR (126 MHz, CDCl₃):** δ 166.5; 155.5; 152.4; 145.7; 127.8; 112.7; 109.4; 97.4; 83.7; 74.9; 68.8; 61.11; 61.08; 56.1; 52.2.

MS (EI): Calcd. for C₁₈H₂₀O₅ [M⁺] = 316, found = 316.

FTIR (neat, cm⁻¹): 3277; 2936; 2847; 2160; 1730; 1490; 1431.
Appendix: $^1$H-NMR, $^{13}$C-NMR, and FT-IR Spectra

[Diagram of chemical structures and spectral data]

ppm

N
OCH$_3$
H$_3$CO
H$_3$CO
OTf

EtOAc

9.23
0.96
0.99
1.00
28