Development of a Three Step Cascade Synthesis of 2,4-Dihydro-1H-benzo[f]isochromenes

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Development of a Three Step Cascade Synthesis of 2,4-dihydro-1H-
benzo[f]isochromenes

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Master of Science

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Approved by the Committee, December 2014

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ABSTRACT

A short linear synthesis providing a monocyclic substrate containing a propargylic and homopropargylic alcohol was developed. This diol was then reacted with a variety of aldehydes in the presence of a number of Lewis acids to provide tricyclic 2,4-dihydro-1H-benzo[f]isochromenes. This two component reaction provided the target molecules in moderate yields through a novel alkynyl-Prins/Friedel–Crafts/dehydration cascade.
TABLE OF CONTENTS

Acknowledgements ii
Dedication iii
List of Tables iv
List of Figures v
List of Schemes vi
Chapter 1. Background 1
Chapter 2. Results and Discussion 13
Chapter 3. Conclusion 34
Chapter 4. Experimental 35
Appendix A 60
Appendix B 143
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For my grandmother, Flossie Morgan, and my mother, Karen Forrest.
LIST OF TABLES

2.1 Screen of Potential Lewis Acid Mediators 23
2.2 Yield Data for Synthesis of Benzo[f]isochromenes 24
B.1 Crystal data and structure refinement 145
B.2 Atomic coordinates and equivalent isotropic displacement parameters 146
B.3 Bond lengths and angles 147
B.4 Anisotropic displacement parameters 150
B.5 Hydrogen coordinates and isotropic displacement parameters 151
LIST OF FIGURES

1.1 Examples of Pyran-containing Natural Products 1
1.2 Natural Products Containing Fused Heterotricycles 7
B.1 ORTEP of Lactone 19 144
LIST OF SCHEMES

1.1 Generalized Prins Reaction 2
1.2 Key Component of the Prins Cyclization 3
1.3 Alkynyl-Prins Cyclization to Alkenyl Cation 4
1.4 Diastereoselectivity of the Prins Cyclization 4
1.5 Silyl-Prins Cyclization 5
1.6 Loss of Regiospecific Control in the Traditional Prins Cyclization. 6
1.7 Prins Cyclization Utilized Towards Populene D Analogs 7
1.8 Oxa-Pictet–Spengler Reaction to Isochromenes 10
2.1 Proposed Pathway for 4-Diiodotetrahydropyran Products 14
2.2 Reddy’s 4-Aryldihydropyran Synthesis 15
2.3 Retrosynthetic Analysis of Target Benzo[f]isochromene-5-ols 16
2.4 Alternative Retrosynthetic Analysis of Alkynediol 16
2.5 Synthetic Pathway for Benzo[f]isochromene-5-ols 18
2.6 Modified Pathway to TBDPS-Protected Propargylic Alcohol 19
2.7 Proposed Mechanism for Tandem Prins/Friedel–Crafts/dehydration Reaction Affording 2,4-Dihydro-1H-benzo[f]isochromenes 21
2.8 Possible Side Reaction Involving Oxocarbenium Ion Formation with Propargylic Alcohol 26
2.9 Possible Side Reaction Involving 5-exo-dig Cyclization 27
2.10 Chavre’s Approach to Exocyclic Prins Reactions 28
2.11 Intermediate Cations Formed from 5-exo-dig and 6-endo-dig Cyclizations 29
2.12 Synthetic Pathway for Methoxyphenyl Based Starting Material 30
2.13 Regiochemistry of Alternative Cyclization 32
2.14 Synthetic Pathways to Alternative Heterotricycles
I. Background

A. Introduction

The prevalence of cyclic ethers in natural products has led to a search for simple and adaptive methods of synthesis. The pyran ring, a simple 6 membered cyclic ether, and its derivatives are of particular importance, appearing in a multitude of biologically active compounds including kendomycin\(^1\), (-)-centrolobine\(^2\), and the aspergillides (Figure 1.1).\(^3\) The high variety of substitution patterns has led to a wealth of research attempting to create stereoselective reactions and then incorporate these methods into total syntheses.

There have been a number of methods applied to creating these useful scaffolds. Prior work in the Hinkle lab has focused primarily on the Prins

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cyclization,\textsuperscript{4} reductive etherification, and tandem cyclization-addition methods.\textsuperscript{5} Additional synthetic pathways leading to pyran derivatives include ring closing metathesis\textsuperscript{6} and Diels-Alder cyclizations, among others.\textsuperscript{7}

B. The Prins Reaction and Cyclization

Originally reported in 1919, the Prins reaction is an acid-catalyzed reaction involving an alkene and aldehyde.\textsuperscript{8} In its simplest form, shown in Scheme 1.1, a proton or Lewis acid coordinates with the aldehyde to create an oxonium ion, and the \(\pi\)-electrons of the alkene act as a nucleophile and attack the carbonyl carbon. This results in an alcohol intermediate with a \(\beta\)-cation. This intermediate can then be further reacted with an aldehyde to afford a 1,3-dioxane, nucleophile to afford a simple alcohol, or basic reagent to afford an allylic alcohol.

![Scheme 1.1: Generalized Prins Reaction.](image)

\textsuperscript{5} Hinkle, R. J.; Rahman, A. A.; \textit{Unpublished Results}.
The Prins cyclization has recently become a popular tool for creating a variety of pyran-containing compounds.\textsuperscript{9} Studies on this intramolecular variant of the Prins reaction have shown it to be a highly versatile transformation. The portion of the Prins cyclization shown in Scheme 1.2 is directly analogous to the creation of the $\beta$-cationic alcohol in the Prins reaction and differs only by being an intramolecular process. Similarly to the addition in Scheme 1.1, the initial oxocarbenium ion is formed through an addition step in which an oxygen nucleophile, often a homoallylic alcohol, first attacks an activated carbonyl-containing compound. The hemiacetal formed then undergoes a proton transfer followed by the formation of a new carbon-oxygen double bond and the leaving of either water or the Lewis acid coordinated alcohol. The resulting oxocarbenium ion then undergoes cyclization, in which the alkene moiety attacks the oxocarbenium ion to create the heterocyclic cation. This cation, analogous to the $\beta$-cation from Scheme 1.1, can then be trapped in a number of ways. Often, halides from the Lewis acid activator are incorporated at the $\beta$ position.

\begin{center}
\textbf{Scheme 1.2:} Key Component of the Prins Cyclization.
\end{center}

\textsuperscript{9} For a comprehensive review on both the Prins reaction and Prins cyclization, see Pastor, I. M.; Yus, M. \textit{Curr. Org. Chem.} 2012, 16, 1277-1312.
The alkynyl-Prins cyclization is a similar reaction differing only in use of a triple bond in place of the double bond. As depicted in Scheme 1.3, addition of a homopropargylic alcohol to an activated carbonyl-containing compound followed by rearrangement gives the oxocarbenium ion analogous to that shown in Scheme 1.2. Attack of the carbonyl carbon by a pair of π electrons from the triple bond creates a vinyl cation, which can then be trapped in similar fashion to the alkenyl-Prins cyclization.

Scheme 1.3: Alkynyl-Prins Cyclization to Alkenyl Cation.

One of the most significant aspects of the Prins cyclization is the generation and control of multiple stereocenters. Arguably the most important control is the prevalence for cis diastereoselectivity of the substituents in the 2- and 6- positions detailed in Scheme 1.4.

Scheme 1.4: Diastereoselectivity of the Prins Cyclization.

---

The preferred orientation for $R_1$ is the energetically favorable pseudo-equatorial position as the alkene begins to attack the oxocarbenium ion. As the ring forms, $R_2$ favors the pseudo-equatorial position as well, creating the cis configuration with high selectivity. Literature reports often show diastereoselectivity of 99:1.\textsuperscript{11} When the starting allylic alcohol is enantiomerically pure, this phenomenon allows for high enantioselectivity in products as well, and has been used to great effect in syntheses of natural products.\textsuperscript{12,13}

More recently, a variation on the Prins cyclization has seen wide use (Scheme 1.5).\textsuperscript{14,15} By incorporating a trimethylsilyl group on the terminal alkene, the double bond present in the starting material is effectively retained, providing a dihydropyran without the need for an added base. This reaction, called the silyl-Prins cyclization, also has the benefit of being quick, efficient, and highly diastereoselective. 6-, 2,6-, and 2,3,6- substituted dihydropyrans have been reported, showing that the modification was also highly versatile.

\begin{center}
\begin{align*}
\text{TMS} & \quad \text{OH} & \quad + & \quad \text{O} \\
\text{CH}_2\text{Cl}_2 & \quad \text{Lewis Acid} \\
\text{R} & \quad \text{H} \\
\text{S} & \quad \text{TM} \\
\text{S} & \quad \text{TM} \\
\text{O} & \quad \text{R} \\
\text{O} & \quad \text{R} \\
\end{align*}
\end{center}

Scheme 1.5: Silyl-Prins Cyclization.

\textsuperscript{13} Corminboeuf, O.; Overman, L. E.; Pennington, L. D. \textit{J. Am. Chem. Soc.} 2003, 125, 6650-6652.
In silyl-Prins, the intermediate cation is stabilized by the \( \beta \)-silicon effect.\(^{16}\) A counterion then attacks the silicon in the hyperconjugated TMS group, affording the dihydropyran product. This pathway also allows for region-control of the double bond, unlike the traditional Prins cyclization, where an added base can remove either of two protons, creating two distinct dihydropyrans, as shown in Scheme 1.6.

![Scheme 1.6: Loss of Regiospecific Control in Traditional Prins Cyclization](image)

C. Polycyclic Pyran Derivatives

A fair number of benzoisochromenes and other fused polycyclic pyran derivatives exist. Populene D is a recently discovered natural product with many reported therapeutic properties.\(^{17}\) While a total synthesis has not yet been reported for this compound, a number of analogs were recently synthesized\(^{18}\) using the iodine catalyzed Prins cyclization originally reported by Silva and Quintiliano (Scheme 1.7).\(^{19}\) Many of these compounds showed biological activity and this study also demonstrated some connection between substitution patterns on the aromatic ring and relative usefulness in therapy.

\(^{16}\) Lambert, J. B. Tetrahedron 1990, 46, 2677-2689.
Scheme 1.7: Prins Cyclization Utilized Towards Populene D Analogs.

Other natural products containing fused oxygen heterotricycles include cichorin A,\textsuperscript{20} curcumanggoside,\textsuperscript{21} and dehydroherbarin\textsuperscript{22} (Figure 1.2). The tricyclic cores for each of these molecules could easily be imagined to be formed through a Prins cyclization as well.

Figure 1.2: Natural Products Containing Fused Heterotricycles.

In addition to the previously mentioned iodine catalyzed Prins cyclization, other methods of ring closure to afford heterotricycles have been reported. The interesting approach of both creating a carbonyl and subsequent ring closure was reported by Pillay et al. by incorporating a Wacker oxidation to produce the

precursor of dehydroherbarin (eq 1.1). The same molecule was also synthesized utilizing a tandem base-promoted dehydrohalogenation and electrocyclization (eq 1.2). In 2001, Morley and Pincock reported a [2+2] photocycloaddition of a naphthalene-tethered benzoate (eq 1.3). Jana et al. created a series of tri- and tetracycles using a Heck cyclization (eq 1.4).

![Chemical Structures]

Syntheses of isochromenes and their related compounds are more numerous than their benzo-fused relatives. Several metal-catalyzed cyclizations have been reported. One, utilizing tungsten, incorporates an electrocyclization of the vinylidene shown in eq 1.5 to afford an alkenyltungsten compound which can

---

undergo further substitution.\textsuperscript{27} A gold catalyzed annulation produced an oxocarbenium ion from the interaction of a carbonyl lone pair and the gold-coordinated triple bond (eq 1.6).\textsuperscript{28} Leng et al. created two heterocycles and a fused cyclopropane ring by reacting a diyne substrate with a copper catalyst followed by addition of catalytic PtCl\textsubscript{2} (eq 1.7).\textsuperscript{29} An S\textsubscript{N}2' reaction between a benzylic alcohol and allyl bromide followed by a palladium catalyzed Heck cyclization similar to eq 1.4 affords the compound shown in eq 1.8 where the double bond formed in the cyclization can be inside or outside of the newly formed pyran ring.\textsuperscript{30}

\begin{align*}
\text{R} & \xrightarrow{\text{W(CO)}_5 \cdot \text{THF}, \text{rt}} \text{R} \\
& \xrightarrow{\text{H}} \text{[Au] (5 mol%)} \xrightarrow{\text{[Au]}} \text{R} \\
& \xrightarrow{\text{1) Dimethyl malonate, Cu(MeCN)}_4 \text{PF}_6 \text{ (10 mol%), ClICH}_2\text{CH}_2\text{Cl, rt}} \xrightarrow{\text{2) PtCl}_2 \text{ (10 mol%), 80° C}} \text{MeOOC}^\text{O} \xrightarrow{\text{COOMe}} \text{R} \\
\end{align*}


Guiso et al. have published examples of isochroman formation via an oxa-Pictet–Spengler reaction, which has a mechanism similar to that of the Prins cyclization.\textsuperscript{31,32,33} Both reactions begin with the addition of an oxygen nucleophile to an activated aldehyde to form an oxocarbenium ion. At that point, the oxa-Pictet–Spengler reaction varies from the Prins cyclization by using a π bond from an aromatic system as the nucleophile that attacks the oxocarbenium ion. Deprotonation of the resultant cation then affords the final product and restores the aromaticity of the ring (Scheme 1.8). Similar compounds have shown to have antioxidant and antiplatelet activity.\textsuperscript{34,35,36}

Scheme 1.8: Oxa-Pictet–Spengler Reaction to Isochromenes.

One important consistency in nearly all of these syntheses is the extant aromatic ring system in the substrate. Prior to the beginning of this work, no syntheses of fused heterocycles where both rings in the isochromene core were formed in one step could be found. Shortly after the start of our investigations, Reddy et al. published a series of papers describing tandem Prins/Friedel–Crafts reactions creating heterotricycles in a similar vein to our method, but did so using alkenes instead of alkynes.\textsuperscript{37,38,39} To the best of our knowledge, these were the first examples of synthesizing both rings of an isochromene in one reaction. The most comprehensive of the surveys, outlined in eq 1.9, was carried out with oxygen, nitrogen, and sulfur as the heteroatoms.

\[
\text{XH} + \text{RCHO} \rightarrow \text{H} \text{H} \text{R} \text{X} \quad (1.9)
\]

This synthesis, which uses the traditional alkenyl-Prins cyclization, produced moderate to high yields for the majority of compounds. The group focused on \(\text{Sc(OTf)}_3\) as a catalyst and \(\text{TsOH}\) as a cocatalyst, finding the best results when using 10 mol\% and 30 mol\%, respectively. Choice of cis or trans alkenes in the starting material led in most cases to a high (9:1) selectivity with regards to the hydrogens labeled in eq 1.9 and a single diastereomer in some examples. The major component of reactions performed with cis alkenes was the cis product and the major component of reactions performed with trans

\textsuperscript{37}\textsuperscript{Reddy, B. V. S.; Borkar, P.; Yadav, J. S.; Sridhar, B.; Gree, R. J. Org. Chem. 2011, 76, 7677-7690.}
alkenes was the trans product. In addition to a number of aldehydes, this methodology was successful with cyclohexanone, possibly creating inroads to a multitude of spiro compounds.
II. Results and Discussion

A. Introduction and Retrosynthetic Analysis

Methodology was recently reported by Yadav et al.\textsuperscript{40} (eq 2.1) using stoichiometric iodine to produce silylated 4-iododihydropyrans and Miranda et al.\textsuperscript{41} using catalytic Fe(acac)\textsubscript{3} and trimethylsilyl halides to produce 4-halodihydropyrans (eq 2.2). These reactions follow the general method described in Scheme 1.3. Upon production of the putative vinylic cation, these important intermediates are trapped by iodine and TMS counterions, respectively.

\[
\begin{align*}
\text{HO} & & \text{I} \\
R_1 & & \text{CHO} \\
\text{CH}_2\text{Cl}_2, \text{rt} & & (100 \text{ mol\%}) \\
\longrightarrow & & \\
\text{HO} & & \text{I} \\
R_2 & & \text{TMS} \\
\text{H}_2\text{O} & & (7 \text{ mol\%}) \\
\text{Fe(acac)}_3 & & \text{Me}_3\text{SiX} (150 \text{ mol\%}) \\
& & \text{RCHO, CH}_2\text{Cl}_2, \text{rt} \\
\uparrow & & \\
\text{I} & & \text{TMS} \\
\text{R}_2 & & \text{TMS} \\
\end{align*}
\]

\text{(2.1)}

Ideally, our own bismuth salts could be used in catalytic quantities to perform similar reactions. Initial investigations into these alkynyl-Prins cyclizations were based on substrate produced for a previous project investigated by the Hinkle lab.\textsuperscript{42} A Barbier reaction with valeraldehyde and (3-bromoprop-1-yn-1-yl)trimethylsilane afforded the homoproargylic alcohol 1 shown in eq 2.3.

---


We envisioned that the homopropargylic alcohol would react with bismuth activated aldehydes to produce a cyclic dihydropyranyl cation intermediate that could then be trapped with various trimethylsilyl derivatives, yielding a wide array of 4-substituted dihydropyranS that would retain the TMS moiety at the 5- carbon (eq 2.4).

Results with trimethylsilyl halides, however, provided extremely complex mixtures of compounds. Furthermore, the desired product, was not apparent in crude mixtures, and the only compound isolated from the TMS-I analogue was the diiodotetrahydropyran 2 shown in Scheme 2.1. We believe this compound was formed from protodesilylation of the desired product followed by addition of HI produced in situ to the double bond. Unpurified mixtures from reactions using other TMS-X compounds, including TMS-CN, TMS-OTf, and TMS-H provided intractable mixtures.

Scheme 2.1: Proposed Pathway for 4-Diiodotetrahydropyran Products.
Due to the difficulties in these intermolecular trapping experiments, we turned our attention to intramolecular reactions. Reddy et al. published two papers that formed the basis for the development of this new methodology.\textsuperscript{43,44} Using homoallylic and homopropargylic alcohols and an aromatic solvent, the group was successfully able to manufacture a variety of 4-aryltetrahydropyrans and 4-aryldihydropyrans upon reaction with aldehydes and BF\textsubscript{3}·Et\textsubscript{2}O. These reactions follow the normal Prins cyclization mechanism until the aromatic solvent undergoes a Friedel–Crafts reaction with the key cationic intermediate to afford the final products (Scheme 2.2).

![Scheme 2.2: Reddy's 4-Aryldihydropyran Synthesis.](image)

Based on this approach, we hypothesized that tethering the aromatic ring to the alkyne substrate with an appropriate length chain would allow us to utilize this chemistry to create highly functionalized fused heterotricyclic compounds. Retrosynthetic analysis of the target compound suggested a simple sequence for the synthesis (Scheme 2.3). The desired product could be formed by a tandem

alkynyl-Prins/Friedel–Crafts reaction with a starting protected alkynediol and aldehyde. The protected alkynediol could be produced by a simple nucleophilic addition to phenylacetaldehyde followed by an epoxide opening. An alternative one-step synthesis using 3-butyn-1-ol and phenylacetaldehyde was also considered (Scheme 2.4), but this was ultimately rejected as the multistep synthesis provided for a wider variability of substituents at only a minor increase in time and materials.4 5

**Scheme 2.3:** Retrosynthetic Analysis of Target Benzo[f]isochromene-5-ols.

**Scheme 2.4:** Alternative Retrosynthetic Analysis of Alkynediol.

**B. Initial Substrate Production and Preliminary Results**

With a synthetic road map conceived, the initial specific synthetic strategy, shown in Scheme 2.5, was devised. Production of compound 3 proceeded

unremarkably by a standard procedure in 66% yield. Base promoted desilylation of 3 led to 4 in 83% yield. After introduction of the TES protecting group (91% yield), 5 was deprotonated and used to ring-open isobutylene oxide in the presence of BF$_3$·Et$_2$O, but this sequence did not afford compound 6. Instead, deprotected alkynediol 8 was isolated in 77% yield (eq 2.5). Removal of silyl-protecting groups with BF$_3$·Et$_2$O is well documented, but we had hoped that conducting the ring-opening at low temperature would prevent this side reaction. Isobutylene oxide was chosen to avoid the introduction of a new stereocenter into the resultant alkynediol as well as to take advantage of its ease of handling as a non-volatile liquid in comparison to the simpler oxirane, a gas. Compound 8 was then subjected to reaction with various simple aldehydes and catalytic Bi(OTf)$_3$. TLC and NMR spectroscopic analysis of the resultant products showed large amounts of starting material.

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47 It was discovered that this deprotection was time sensitive and thus required quenching as soon as all starting material was consumed as evidenced by TLC. Allowing the reaction mixture to stir for longer led to significant loss of product.
Scheme 2.5: Synthetic Pathway for Benzo[\(f\)isochromene-5-ols.

Our first instinct was to replace the protecting group on the propargyl alcohol with something more robust. To that end, we chose the tert-butylidiphenylsilyl group primarily because of its resistance to BF\(_3\cdot\)Et\(_2\)O mediated cleavage.\(^{52}\) After introduction of the TBDPS group onto 4 using TBDPSCI and imidazole in DMF (78% yield), compound 9 was subjected to the epoxide opening conditions mentioned earlier to afford 10 in 87% yield (Scheme 2.6).\(^{53}\)

This compound was subjected to a variety of simple aldehydes and catalytic Bi(OTf)\(_3\) in an attempt to cyclize to the desired heterotricycles, but again, TLC and NMR spectroscopic analysis showed large amounts of starting material.


Additionally, a number of other common Lewis acids were tried in catalytic quantities, including BF$_3$·Et$_2$O, TiCl$_4$, and BiBr$_3$, as well as the Brønsted acid HOTf. NMR spectroscopic analysis pointed to no reactions in these cases either.

![Scheme 2.6: Modified Pathway to TBDPS-Protected Propargylic Alcohol.](image)

When this approach failed, we switched to a stoichiometric amount of BF$_3$·Et$_2$O, the approach originally used by Reddy’s group in the intermolecular reactions. Again, this failed, as did stoichiometric amounts of BiBr$_3$ and Bi(OTf)$_3$.

Upon closer review of the NMR spectra, it was found that there were specific aromatic peaks in the reactions performed with 8 that did not appear in any reactions performed with 10. We then hypothesized that these peaks were the result of stoichiometric conversion based on the amount of Lewis acid added. This was confirmed when 1.2 equivalents of BF$_3$·Et$_2$O were used and NMR spectra of crude reaction mixtures showed no remaining starting material and strong signals indicative of a naphthalene system. Due to reactions with 10 not producing desired product, we concluded that the steric bulk of the TBDPS protecting group inhibited addition to the Lewis acid activated aldehydes.
C. Synthesis of 2,4-Dihydro-1H-benzo[\textit{f}]isochromenes

The realization that reactions of the unprotected alkynediol 8 with aldehydes and stoichiometric quantities of Lewis acid produced a naphthalenic product led us to investigate this transformation further. This reaction was shown to produce a relatively novel class of tricyclic compounds called 2,4-dihydro-1H-benzo[\textit{f}]isochromenes (eq 2.5). This represented an additional dehydration reaction in addition to the Prins cyclization and Friedel–Crafts reaction. While unexpected, the subsequent dehydration was not surprising given the energy gained due to the aromatization of the central ring of the heterotricycle and the acidic conditions required to promote cyclization.54

![Chemical structure](image)

The proposed mechanism, shown in Scheme 2.7, proceeds quickly at room temperature through a series of several steps. First, the homopropargylic alcohol of 8 adds to the Lewis acid activated aldehyde, producing acetal 12. Proton transfer between the two oxygens of the acetal creates compound 13, making a good leaving group for oxocarbenium ion formation. Collapse of an oxygen lone pair to create a new π bond facilitates removal of the aforementioned leaving group and produces the key oxocarbenium ion 14. Attack of the carbonyl carbon by one of the π bonds of the alkyne completes the Prins cyclization and produces the high-energy vinyl cation 15. At this point, a π

bond from the pendant phenyl ring breaks and attacks the vinyl cation to form the Friedel–Crafts intermediate 16. Then a base, likely the hydroxy-BF$_3$ complex created previously, removes the proton adjacent to the carbocation, restoring aromaticity of the upper ring in compound 17 and liberating one molecule of water. The remaining hydroxyl then coordinates with BF$_3$ and dehydrates to afford final product 11.
Initial efforts to isolate the final compound proved highly difficult. When the crude reaction mixture was viewed on TLC plates in common solvent systems, large streaks of material extending from the baseline to the solvent front were visible under UV light and using KMnO₄ stain. This apparently polymeric byproduct only proved separable when the polar phase was changed from an oxygenated solvent (EtOAc, Et₂O, MeOH) to methylene chloride. Solvent systems of methylene chloride in hexanes left the polymer at the baseline on TLC plates and thus allowed the purifications to proceed with relative ease. NMR spectroscopic analysis of the baseline byproduct, however, showed nothing that could be attributed to any specific functional groups.

A brief screening of potential Lewis acids was performed and the results are shown in Table 2.1. While the reaction did proceed with all Lewis acids used, the superiority of BF₃·Et₂O quickly became apparent. The high molecular weight of bismuth compounds meant that for each 50 mg of 8 used, the reaction required 113 mg of BiBr₃ or 165 mg of Bi(OTf)₃ compared to 36 mg (32 µL) of BF₃·Et₂O. In addition, the considerably higher cost of bismuth salts compounded their inability to be practical reagents in stoichiometric quantities. TiCl₄ and AlCl₃ were also tested, but crude reaction mixtures appeared much more complex than reactions performed with BF₃·Et₂O and bismuth salts, so these were eliminated from further consideration. Reactions shown in entries 1-5 were conducted at approximately 0.25 M in alkynediol whereas entry 6 was conducted at approximately 0.125 M. Entry 2 was also conducted with bis-TES protected.
alkynediol 18, which was produced by reacting 8 with two equivalents of TESCl and imidazole. (eq 2.6).

**Table 2.1: Screen of Potential Lewis Acid Mediators.**

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>product</th>
<th>Lewis acid</th>
<th>yield (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>11a</td>
<td>BF₃·Et₂O</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>11a</td>
<td>Bi(OTf)₃</td>
<td>19&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td>11b</td>
<td>BF₃·Et₂O</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>11b</td>
<td>Bi(OTf)₃</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>CH₃</td>
<td>11b</td>
<td>BiBr₃</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>11b</td>
<td>BF₃·Et₂O</td>
<td>47&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions run under argon at ~0.25 M in 8 using 1.2 equiv of aldehyde and 1.1 equiv of corresponding Lewis acid. <sup>b</sup> Isolated yields of compounds after silica gel chromatography. <sup>c</sup> The *bis*-TES protected analog 18 was used. <sup>d</sup> Reaction conducted at ~0.125 M.
Target compounds 11a-11j were then synthesized using alkynediol 8, various alkyl and aromatic aldehydes, and 10 mol% excess of BF$_3$-Et$_2$O. These highly viscous, foaming oils were isolated by column chromatography and their structures confirmed by IR, $^1$H, $^{13}$C APT, and $^{13}$C DEPT NMR spectroscopy and either combustion or HRMS analysis. Yields, shown in Table 2.2, were moderate and showed only minor variability. Reactions with pivaldehyde and methyl ethyl ketone showed no reaction, salicylaldehyde and acrolein provided very small amounts of product, and phthalaldehyde provided what appeared to be an amount of product comparable to 11a-11j, but could not be separated from unidentified byproducts.

Table 2.2: Yield Data for Synthesis of Benzo[f]isochromenes.

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>aldehyde (R)</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>Et-</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>i-Pr-</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>11c</td>
<td>sec-Bu-</td>
<td>52$^b$</td>
</tr>
<tr>
<td>4</td>
<td>11d</td>
<td>pentan-3-yl-</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>11e</td>
<td>PhCH$_2$CH$_2$-</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>11f</td>
<td>Ph-</td>
<td>58</td>
</tr>
<tr>
<td>7</td>
<td>11g</td>
<td>p-Br-Ph-</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>11h</td>
<td>p-CF$_3$-Ph-</td>
<td>43</td>
</tr>
<tr>
<td>9</td>
<td>11i</td>
<td>p-NO$_2$-Ph-</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>11j</td>
<td>p-MeO-Ph-</td>
<td>58</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields of compounds after silica gel column chromatography.

$^b$ 11c isolated as a 7:3 mixture of diastereomers.
Compounds 11f-11j, produced from aryl aldehydes, are highly stable with refrigeration for periods of time exceeding 1 year. In contrast, compounds 11a-11e, produced from alkyl aldehydes, are highly unstable and oxidize to lactone 19 even with refrigeration as confirmed by X-ray diffraction experiments (eq 2.7). The mechanism of oxidation is not entirely clear, but previous experiments with similar substrates show that oxidation occurs under relatively mild conditions. GC-MS analysis of the ten products showed that the molecular ion peaks of 11f-11j were much more prevalent than the molecular ion peaks of 11a-11e, a pattern that is further evidence of the increased instability of 11a-11e.

In comparison to work with homoallylic alcohols performed by Reddy et al. (eq 1.9), the cascade we developed with alkyne substrates affords products in lower overall yields. We believe there are three side-reactions possibly responsible for this difference.

The first potential pathway to byproducts is likely due to the propargylic alcohol present in our substrate. In contrast, Reddy's substrate did not contain an allylic alcohol in the analogous position. We believe that this secondary alcohol has the potential to undergo similar addition/oxocarbenium ion formation as shown in Scheme 2.8. At this point, however, formation of the vinyl cation

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55 See Appendix B for X-ray crystallographic data.
through the expected Prins mechanism is highly unlikely given the significantly high energy barrier associated with this strained species.\textsuperscript{57} Thus, we believe that decomposition through this undesired pathway would occur through the oxocarbenium ion intermediate instead of the vinyl cation, but due to the uncertainty in structure of the byproducts, we cannot discount some formation of the cyclopentenyl cation.

\textbf{Scheme 2.8:} Possible Side Reaction Involving Oxocarbenium Ion Formation Through Propargylic Alcohol.

The second pathway involves 5-\textit{exo-dig} cyclization instead of the observed 6-\textit{endo-dig} cyclization in the primary mechanism (Scheme 2.9). After formation of the oxocarbenium ion 14, attack of the carbonyl carbon by the triple bond might afford vinyl cation 20. An intramolecular Friedel–Crafts reaction would then provide inden-2-ol 21. This vinyl cation, again being very high

energy, would be very reactive, and could lead to potential degradation of the reaction. This pathway could be another possible contributor to the polymeric byproduct.

Scheme 2.9: Possible Side Reaction Involving 5-exo-dig Cyclization.

These two options, both favored by Baldwin’s rules, seem to vary based on substituents adjacent to the triple bond. Chavre et al. reported exocyclic tetrahydrofuran products using an internal alkyne (Scheme 2.10).\textsuperscript{58} In this work, the group investigated products formed when the group attached to the triple bond, $R_1$, is a terminal methyl or phenyl group and returned yields solely consisting of 5-exo-dig compounds.

Scheme 2.10: Chavre's Approach to Exocyclic Prins Reactions.

Additionally, Xu et al. reported the use of an alkynyl diethyl acetal which, when combined with FeCl₃ or FeBr₃, produced exocyclic 5 membered rings (eq 2.8).⁵⁹ Again, these compounds have an internal alkyne with a methyl, phenyl, or substituted phenyl ring on the carbon bonded to the intermediate alkenyl cation. These cyclizations are in direct contrast to the Yadav, Miranda, and Reddy papers, referenced in eqs 2.2, 2.3, and Scheme 2.2 respectively. In the latter three reports, the alkyne was either terminal or bonded to a trimethylsilane group.

We believe this research, as well as our own, indicates a preference to have an electron-donating group bonded to the alkyne in order for it to stabilize the vinyl cation formed through 5-exo-dig cyclization (Scheme 2.11). In our case, the cation formed, 20, would have an alcohol moiety on the neighboring carbon, causing a further reduction of electron density, creating additional instability.

This leads to the conclusion that the 6-endo-dig reaction requires the propargylic alcohol present in 8. This has been supported by other work performed in the Hinkle lab where no desired products are formed from reactions with the analog of 8 that is missing the propargylic alcohol (eq 2.9).  

\[ \text{Scheme 2.11: Intermediate Cations Formed from 5-exo-dig and 6-endo-dig Cyclizations.} \]

The final degradation pathway is based on the possibility of oxonia-Cope rearrangement (eq 2.10). [3,3] rearrangements are well known in Prins cyclizations. In the alkenyl Prins cyclization, this often leads only to replacement of side chains and racemization of products. In the alkynyl-Prins cyclization, however, these transformations produce allene intermediates that isomerize to acyclic byproducts.

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60 Chen, Y.; Lewis, S. E.; Hinkle, R. J. Unpublished Results.
D. Future Work

As previously mentioned, in devising the original synthetic scheme, we desired a pathway that would allow us to easily create starting materials with various substitution patterns. The first of these varied materials is the methoxyphenyl based substrate 28, originally developed in tandem with 8, as shown in Scheme 2.12.

Scheme 2.12: Synthetic Pathway for Methoxyphenyl Based Starting Material
An $S_N2'$ reaction between 3-methoxyphenylmagnesium bromide and allyl bromide afforded 22 in 79% yield.oz. Ozonolysis of 22 led to unstable aldehyde 23 which was utilized as a crude material. Deprotonation of trimethylsilylacetylene followed by addition of 23 afforded 24 in 50% yield over two steps. $K_2CO_3$ deprotection of the alkyne led to 25 (71% yield), and introduction of the TBDPS protecting group proceeded to give 26 in 78% yield. Deprotonation and $BF_3\cdot Et_2O$ promoted opening of isobutylene oxide afforded 27 in 76% yield. After attempts at cyclizing 27 failed, 28 was produced by TBAF promoted deprotection of the TBDPS group (87% yield). At this time, production of 28 directly from 25, analogous to the production of 8 from 4, has not been attempted, but is likely to proceed smoothly (eq 2.11).

This substitution pattern was chosen due to the electron donating properties of methoxy groups in Friedel–Crafts reactions. As shown in Scheme 2.13, carbons ortho and para to the methoxy group can participate in attack of the dihydropyranyl cation. This creates a pair of regioisomeric compounds which are likely to have very different chemical properties. In addition to the activating character of the methoxy group, the aliphatic chain also attached to the aromatic ring donates electron density through induction, as both reactive sites are ortho to the chain.

\[ \text{MeO} \quad \text{H} \quad \text{OH} \quad 1. n\text{-BuLi}, -78 \degree C \\
2. \text{isobutylene oxide,} \\
3. \text{NH}_4\text{Cl} \quad \text{MeO} \quad \text{H} \quad \text{OH} \quad (2.11) \]

---

Based on GC-MS NMR spectroscopic analysis of crude reaction mixtures, reactions of 28 with aldehydes and stoichiometric BF₃·Et₂O afford mixtures of the corresponding 8- and 10-methoxybenzo[f]isochromenes. At this time, however, the regioisomers are inseparable from both each other and byproducts of the reactions. Further experiments with these and similar compounds will be conducted in the future.

In addition to this work, modifications to the starting material to produce heterotricycles with inner rings of differing sizes have begun. By modifying Scheme 2.5 to use benzaldehyde and phenylpropionaldehyde, potential products shown in Scheme 2.14 might be made.
Currently, the alkynediols necessary for both of these pathways have been produced using non-optimized procedures. Investigations into both cyclizations have begun, but preliminary results do not look promising.
III. Conclusion

Research providing a short linear sequence to an alkynediol substrate which can be cyclized to a tricyclic product has been conducted. The ultimate mechanism consists of a three reaction cascade that proceeds in rapid fashion to produce novel 2,4-dihydro-1H-benzo[f]isochromenes. Initial investigations into effective catalysts have shown that BF₃·Et₂O has significant benefits over others used. Aldehydes incorporated include both aliphatic and aromatic compounds and show only slight variability in yield (38%-58%), and only a few of the aldehydes tested were not compatible with this methodology.

Additionally, ground work for more highly-substituted benzo[f]isochromene compounds has begun, as well as research potentially leading to heterotricycles with central rings of varying sizes. These syntheses follow the general pathway of the original substrate preparation, demonstrating the adaptability of the procedure in creating new substrates for testing. Research is underway to investigate and improve these new opportunities.
IV. Experimental

A. General Information

All reagents and substrates were purchased from commercial sources and used as received unless otherwise noted. Dichloromethane was distilled from CaH₂ and THF was purified using a Solv-Tek® alumina drying column. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Mercury FTNMR spectrometer (400, and 125 MHz, respectively) using CDCl₃ as solvent and referenced to internal standard (tetramethylsilane) or residual protonated chloroform at 7.27 ppm (¹H) or 77.23 ppm (¹³C). ¹³C NMR spectra were obtained with the aid of a DEPT experiment in which quaternary carbons are absent, methine (CH) carbons are listed as (t), methylene carbons (CH₂) are listed as (s), and methyl carbons (CH₃) are listed as (p). Additional carbon data, including quaternary carbons (q) were gleaned from an APT experiment in which quaternary (0 H) and methylene (2 H) carbons are even (e) and methine (1 H) as well as methyl (3 H) carbons are odd (o). Coupling constants were determined by the method outlined by Hoye, et al. Thin layer chromatography was performed on Sorbent Technologies general-purpose silica gel on glass. Flash column chromatography was performed using Sorbent Technologies chromatographic silica gel (200-475 MESH) or through the use of Biotage – Isolera One™ chromatographic purification system. Unless otherwise noted, all experiments were conducted under argon atmosphere. All HRMS analyses were completed by the COSMIC laboratory of Old Dominion University through positive electrospray ionization on a Bruker 12 Tesla APEX –Qe FTICR-MS with and Apollo II ion source. GC-MS

analyses were conducted on an Agilent 6890 GC equipped with a 5973 mass-selective detector, and using a Rxi®-1ms capillary column. Combustion analyses were performed by Atlantic Microlabs, of Norcross, GA. All compounds were judged to be >95% homogeneous by $^1$H NMR spectroscopy and GC MS.
B. Synthesis of Starting Material

1-phenyl-4-(trimethylsilyl)but-3-yn-2-ol (3):

To a cooled (-78 °C) solution of TMS-acetylene (200 mmol) in 400 mL of THF was added n-butyl lithium (2.5 M in hexanes, 200 mmol) dropwise with stirring under Ar gas. The reaction was then stirred for 30 minutes, after which phenylacetaldehyde (220 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched with NH₄Cl. The reaction mixture was then extracted with Et₂O, dried (MgSO₄), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-30% EtOAc in hexanes) to afford 132 mmol (66%) of a yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ = 7.16-7.06 (m, 5H), 4.37 (q, J=6.3 Hz, 1H), 2.87-2.77 (overlapping dd, J=13.7, 6.6, 6.3 Hz, 2H), 2.00 (broad s, 1H), 0.00 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ = 136.6 (q), 130.1 (t), 128.5 (t), 127.1 (t), 106.1 (q), 90.7 (q), 63.7 (t), 44.1 (s), 0 (p); HRMS (Cl): HRMS (Cl): m/z [M + Na]⁺ calcd for (C₁₃H₁₈OŚi)Na (M+Na)⁺ 241.1019, found 241.1021.
1-phenylbut-3-yn-2-ol (4):

To a solution of 3 (130 mmol) in 260 mL of a 1:1 mixture of THF and methanol was added K$_2$CO$_3$ (260 mmol) with stirring. 13 mL of DI H$_2$O was added to the mixture and the reaction was stirred under Ar gas for 3-4 h until completion as indicated by TLC. The reaction mixture was diluted with water, extracted with Et$_2$O, dried (MgSO$_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-20% EtOAc in hexanes) to afford 95 mmol (73%) of a yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.33-7.23 (m, 5H), 5.05 (qd, $J$= 6.3, 2.0 Hz, 1H), 3.00 (overlapping dd, $J$=13.7, 6.6, 6.3 Hz, 2H), 2.46 (d, $J$=2.3 Hz, 1H), 2.19 (dd, $J$= 3.9 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 136.5 (q), 129.9 (t), 128.6 (t), 127.1 (t), 74.0 (t), 63.1 (t), 44.0 (s).

Triethyl((1-phenylbut-3-yn-2-yl)oxy)silane (5):

To a cooled (0°C) solution of 4 (5.8 mmol) in 25 mL of CH$_2$Cl$_2$ was added imidazole (9.9 mmol) under Ar gas. Upon dissolution of the imidazole, chlorotriethylsilane (8.7 mmol) was added dropwise and the reaction was monitored by TLC. Upon completion of the reaction, the mixture was quenched with NaHCO$_3$, extracted with CH$_2$Cl$_2$ (3 x 10 mL), dried (MgSO$_4$), and concentrated in vacuo. The crude product was then purified by
column chromatography using 10% EtOAc in hexanes to afford 5.3 mmol (91%) of a yellow liquid. \( R_t = 0.68 \) (10% EtOAc in hexanes). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.30-7.20 \) (m, 5 H), 4.483 (dt, \( J = 6.6, 1.9 \) Hz, 1 H), 2.97 (d, \( J = 6.6 \) Hz, 2 H), 2.39 (d, \( J = 1.9 \) Hz, 1 H), 0.89 (t, \( J = 7.8 \) Hz, 9 H), 0.55 (dec, \( J = 7.8 \) Hz, 3 H). \(^{13}\)C (100 MHz, CDCl\(_3\)): \( \delta = 137.5 \) (q), 130.0 (t), 128.3 (t), 126.8 (t), 85.2 (q), 73.0 (t), 64.0 (t), 45.4 (s), 6.9 (p), 4.8 (s). HRMS (Cl): \( m/z \) [M + Na]\(^{+}\) calcd for C\(_{16}\)H\(_{24}\)O\(_2\)SiNa: 283.1489; found: 283.1488.

6-methyl-1-phenylhept-3-yne-2,6-diol (8):

To a cooled (-78 °C) solution of 4 (5.0 mmol) in 10 mL of THF was added n-butyl lithium (1.8 M in hexanes, 10 mmol) dropwise under Ar gas. After stirring for 30 minutes, BF\(_3\)·Et\(_2\)O (7.5 mmol) was added. After stirring for 15 minutes, isobutylene oxide (5.5 mmol) was added dropwise and the mixture was left to stir for 1 h. The reaction was then quenched with NH\(_4\)Cl, extracted with Et\(_2\)O, dried (MgSO\(_4\)), and concentrated in vacuo. The crude product was then purified by column chromatography using 7%-60% EtOAc in hexanes to afford 3.85 mmol (77%) of a viscous yellow oil. \( R_t = 0.07 \) (30% CH\(_2\)Cl\(_2\) in hexanes). IR (neat): 3427, 3030, 2977, 2932, 1496, 1456, 1375, 1152, 1035 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.31-7.20 \) (m, 5 H), 4.55 (t, \( J = 6.6 \) Hz, 1 H), 3.56 (broad s, 1 H), 2.97 (overlapping dd, \( J = 13.7, 6.6, 6.3 \) Hz, 2 H), 2.70 (broad s, 1 H), 2.31 (s, 2 H), 1.22 (s, 6 H). \(^{13}\)C (100 MHz, CDCl\(_3\)): \( \delta = \)}
137.2 (q), 129.8 (t), 128.3 (t), 126.7 (t), 83.6 (q), 82.8 (q), 70.1 (q), 63.3 (t), 44.4 (s), 34.2 (s), 28.62 (p), 28.56 (p). HRMS (Cl): m/z [M + Na]⁺ calcd for C₁₄H₁₈O₂Na: 241.1199; found: 241.1198.

tert-Butyldiphenyl((1-phenylbut-3-yn-2-yl)oxy)silane (9):

To a cooled (0 °C) solution of 4 (25 mmol) in 150 mL of DMF was added imidazole (27.5 mmol) under Ar gas. Upon dissolution of the imidazole, tert-butyldiphenylsilyl chloride was added slowly and the reaction was allowed to stir overnight and gradually warm to room temperature. Upon completion of the reaction, Et₂O and water were added and the organic layer was extracted. The organic layer was then washed with water, dried (MgSO₄) and concentrated in vacuo. The crude product was then purified by column chromatography using 10% EtOAc in hexanes to afford 19.5 mmol (78%) of a viscous, light pink oil. Rᵣ = 0.73 (10% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.76 (dd, J = 7.0, 1.2 Hz, 2 H), 7.64 (d, J = 7.8 Hz, 2 H), 7.49-7.38 (m, 6 H), 7.28-7.24 (m, 3 H), 7.14 (d, J = 7.4 Hz, 2 H), 4.55 (t, J = 6.3 Hz, 1 H), 3.01 (overlapping dd, J = 13.3, 7.0, 6.3 Hz, 2 H), 2.33-2.32 (m, 1 H), 1.11 (s, 9 H). ¹³C (100 MHz, CDCl₃): δ = 137.0 (q), 136.3 (t), 136.1 (t), 133.5 (q), 133.4 (q), 130.1 (t), 130.0 (t), 129.9 (t), 128.2 (t), 127.8 (t), 127.6 (t), 126.8 (t), 84.6 (q), 73.8 (t), 65.1 (t), 45.0 (s), 27.0 (p), 19.4 (q).
6-((tert-butyldiphenylsilyloxy)-2-methyl-7-phenylhept-4-yn-2-ol (10):

To a cooled (-78 °C) solution of 9 (2.6 mmol) in 10 mL of THF was added n-butyl lithium (2.5 M in hexanes, 2.7 mmol) dropwise under Ar gas. After stirring for 30 minutes, BF₃·Et₂O (3.9 mmol) was added. After stirring for 15 minutes, isobutylene oxide (2.9 mmol) was added dropwise and the mixture was left to stir for 1h. The reaction was then quenched with NH₄Cl, extracted with Et₂O, dried (MgSO₄), and concentrated in vacuo. The crude product was then purified by column chromatography using 2%-20% EtOAc in hexanes to afford 2.3 mmol (87%) of a viscous pink oil. Rf = 0.23 (10% EtOAc in hexanes). IR (neat): 3085, 2969, 2935, 2858, 1472, 1430, 1365, 1112, 1081, 860, 825, 742, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.68 (dd, J = 6.6, 1.2 Hz, 2 H), 7.59 (dd, J = 6.6, 1.2 Hz, 2 H), 7.40-7.31 (m, 6 H), 7.24-7.18 (m, 3 H), 7.10 (d, J = 7.0 Hz, 2 H), 4.56 (t, J = 6.3 Hz, 1 H), 2.94 (overlapping dd, J = 13.7, 6.6, 6.2 Hz, 2 H), 2.13 (s, 2 H), 1.4 (s, 1 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 9 H). ¹³C (100 MHz, CDCl₃): δ = 137.6 (q), 136.2 (t), 136.0 (t), 133.9 (q), 133.6 (q), 130.1 (t), 129.9 (t), 129.8 (t), 128.3 (t), 127.8 (t), 127.6 (t), 126.8 (t), 84.1 (q), 82.8 (q), 69.6 (q), 65.3 (t), 45.3 (s), 34.5 (s), 28.6 (p), 27.0 (p), 19.4 (q). HRMS (Cl): m/z [M + Na]⁺ calcd for C₃₀H₃₆O₂SiNa: 479.2377; found: 479.2370.
To a cooled (0°C) solution of 2a (0.92 mmol) in 10 mL of CH₂Cl₂ was added imidazole (3.1 mmol) under Ar gas. Upon dissolution of the imidazole, chlorotriethylsilane (2.7 mmol) was added dropwise and the reaction was monitored by TLC. Upon completion of the reaction, the mixture was quenched with NaHCO₃, extracted with CH₂Cl₂ (3 x 10 mL), dried (MgSO₄), and concentrated in vacuo. The crude product was then purified by column chromatography using 5% EtOAc in hexanes to afford 0.52 mmol (57%) of a yellow oil. Rf = 0.64 (5% EtOAc in hexanes). IR (neat): 3032, 2959, 2879, 1496, 1459, 1417, 1365, 1238, 1075, 1015, 966, 737, 608 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.28-7.18 (m, 5 H), 4.45 (tt, J = 6.7, 1.8 Hz, 1 H), 2.94 (d, J = 6.7 Hz, 2 H), 2.33 (d, J = 1.8 Hz, 2 H), 1.26 (s, 3 H), 1.24 (s, 3 H), 0.94 (t, J = 7.9 Hz, 9 H), 0.89 (t, J = 7.9 Hz, 9 H), 0.61-0.46 (m, 12 H). ¹³C (100 MHz, CDCl₃): δ = 138.1 (q), 130.1 (t), 128.2 (t), 126.6 (t), 83.2 (q), 83.0 (q), 73.4 (q), 64.4 (t), 45.9 (s), 35.7 (s), 29.55 (p), 29.50 (p), 7.3 (p), 6.92 (p), 6.86 (s), 4.9 (s). HRMS (Cl): m/z [M + Na]^+ calcd for C₂₆H₄₆O₂Si₂Na: 469.2929; found: 469.2924.
C. Synthesis of Target Compounds

General Procedure for Synthesis of Benzof[\]isochromenes:

To a stirred solution of 6-methyl-1-phenylhept-3-yne-2,6-diol (8, ~0.25 mmol) and appropriate aldehyde (~0.30 mmol) in 1 mL dry CH\textsubscript{2}Cl\textsubscript{2} was added BF\textsubscript{3}·Et\textsubscript{2}O (~0.275 mmol) dropwise under Ar gas. The reaction was stirred at room temperature for 12 h. The reaction mixture was then quenched with aqueous NaHCO\textsubscript{3}, extracted with Et\textsubscript{2}O, and the organic layer washed with water and brine. The organic layer was dried (MgSO\textsubscript{4}) and concentrated in vacuo to afford the crude product, which was purified by column chromatography to afford the product.
4-ethyl-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11a):

The title compound was prepared according to the general procedure and purified by column chromatography using 10%-40% CH$_2$Cl$_2$ in hexanes to afford 0.15 mmol (36%) of a viscous yellow oil. $R_f = 0.37$ (20% CH$_2$Cl$_2$ in hexanes). IR (neat): 3055, 2968, 2935, 2851, 1602, 1512, 1464, 1448, 1377, 1366, 1183, 1134, 1107, 1058, 1018, 1002 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 7.93 (d, $J =$ 8.2 Hz, 1 H), 7.82 (d, $J =$ 8.2 Hz, 1 H), 7.69 (d, $J =$ 8.6 Hz, 1 H), 7.54-7.44 (m, 2 H), 7.24 (d, $J =$ 8.6 Hz, 1 H), 4.94 (br m, $J =$ 1.56 Hz, 1 H), 3.05, (d, $J =$ 16.0 Hz, 1 H), 2.97 (d, $J =$ 16.0 Hz, 1 H), 2.12-2.02 (m, 1 H), 1.95-1.81 (m, 1 H), 1.50 (s, 3 H), 1.19 (s, 3 H), 0.83 (t, $J =$ 7.03 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 134.3 (q), 132.3 (q), 132.2 (q), 129.2 (q), 128.7 (t), 126.2 (t), 125.4 (t), 123.0 (t), 122.9 (t), 72.4 (t), 70.5 (q), 36.7 (s), 31.1 (p), 29.1 (s), 23.5 (p), 8.7 (p). Anal. calcd for C$_{17}$H$_{20}$O: C, 84.96; H, 8.39. Found: C, 85.10; H, 8.54.
4-isopropyl-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11b):

The title compound was prepared according to the general procedure and purified by column chromatography using 20% CH₂Cl₂ in hexanes to afford 0.12 mmol (47%) of a viscous yellow oil. \( R_f = 0.36 \) (20% CH₂Cl₂ in hexanes). IR (neat): 3059, 2932, 2822, 1602, 1512, 1469, 1379, 1367, 1303, 1263, 1227, 1205, 1177, 1049, 810, 763 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): \( \delta = 7.93 \) (d, \( J = 8.2 \) Hz, 1 H), 7.82 (d, \( J = 7.8 \) Hz, 1 H), 7.67 (d, \( J = 8.6 \) Hz, 1 H), 7.53-7.44 (m, 2 H), 7.24 (d, \( J = 8.6 \) Hz, 1 H), 4.78 (s, 1 H), 3.03 (d, \( J = 15.6 \) Hz, 1 H), 2.89 (d, \( J = 16.0 \) Hz, 1 H), 2.30 (sept., \( J = 7.0, 2.3 \) Hz, 1 H), 1.47 (s, 3 H), 1.16 (d, \( J = 7.0 \), 3 H), 1.12 (s, 3 H), 0.60 (d, \( J = 6.6 \), 3 H). \(^{13}\)C NMR (100 MHz, CDCl₃): \( \delta = 134.6 \) (q), 132.3 (q), 132.2 (q), 129.5 (q), 128.7 (t), 126.1 (t), 125.3 (t), 123.1 (t), 122.9 (t), 76.0 (t), 70.2 (q), 36.7 (s), 34.0 (t), 31.0 (p), 23.5 (p), 20.2 (p), 15.1 (p). Anal. calcd for C₁₈H₂₂O: C, 84.99; H, 8.72. Found: C, 84.87; H, 8.85.
4-(sec-butyl)-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11c):

The title compound was prepared according to the general procedure and purified by column chromatography using 10% CH₂Cl₂ in hexanes to afford 0.13 mmol (52%) of a viscous yellow oil as a 7:3 mixture of diastereomers. Rf = 0.33 (10% CH₂Cl₂ in hexanes). IR (neat): 3060, 2978, 2930, 2875, 2832, 1602, 1512, 1457, 1396, 1378, 1366, 1188, 1132, 1053, 1027, 809, 760 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 8.2 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.54-7.44 (m, 2 H), 7.24 (d, J = 8.5 Hz, 1 H), 4.90 (s, 1 H), 3.03 (d, J = 16.1 Hz, 1 H), 2.90 (d, J = 15.8 Hz, 1 H), 2.03-1.96 (m, 1 H), 1.74-1.61 (m, 1 H), 1.55-1.45 (m, 1 H), 1.45 (s, 3 H), 1.13 (s, 3 H), 1.03 (t, J = 7.3 Hz, 3 H), 0.57 (d, J = 6.74, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 134.8 (q), 132.2 (q), 129.5 (q), 128.6 (t), 126.13 (t), 126.12 (t), 125.3 (t), 123.0 (t), 122.9 (t), 73.8 (t), 70.0 (q), 40.8 (t), 36.6 (s), 31.0 (p), 27.1 (s), 23.4 (p), 12.9 (p), 12.7 (p). Anal. Calcd for C₁₉H₂₄O: C, 85.03; H, 9.01; O, 5.96. Found: C, 84.79; H, 9.15.
2,2-dimethyl-4-(pentan-3-yl)-2,4-dihydro-1H-benzo[f]isochromene (11d):

The title compound was prepared according to the general procedure and purified by column chromatography using 10% CH$_2$Cl$_2$ in hexanes to afford 0.11 mmol (44%) of a viscous yellow oil. $R_f = 0.34$ (10% CH$_2$Cl$_2$ in hexanes). IR (neat): 3058, 2972, 2925, 2874, 2834, 1601, 1511, 1464, 1378, 1366, 1187, 1133, 1061, 818, 803, 756 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.93 (d, $J$ = 8.2 Hz, 1 H), 7.82 (d, $J$ = 7.8 Hz, 1 H), 7.67 (d, $J$ = 8.6 Hz, 1 H), 7.53-7.43 (m, 2 H), 7.24 (d, $J$ = 8.6 Hz, 1 H), 4.98 (d, $J$ = 1.6 Hz), 3.03 (d, $J$ = 15.2 Hz, 1 H), 2.90 (d, $J$ = 16.02, 1 H), 1.80-1.73 (m, 1 H), 1.64-1.56 (m, 2 H), 1.44 (s, 3 H), 1.12 (s, 3 H), 1.07 (t, $J$ = 7.4 Hz, 3 H), 1.18-1.00 (m, 2 H), 0.68 (t, $J$ = 7.4 Hz, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 135.0 (q), 132.3 (q), 132.2 (q), 129.7 (q), 128.6 (t), 126.13 (t), 126.05 (t), 125.2 (t), 123.0 (t), 122.9 (t), 72.5 (t), 70.1 (q), 47.4 (t), 36.6 (s), 31.1 (p), 23.26 (s), 23.25 (p), 21.6 (s), 12.8 (p), 12.7 (p). Anal. Calcd for C$_{20}$H$_{26}$O: C, 85.06; H, 9.28. Found: C, 84.81; H, 9.26.
2,2-dimethyl-4-phenethyl-2,4-dihydro-1H-benzo[f]isochromene (11e):

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH$_2$Cl$_2$ in hexanes to afford 0.16 mmol (43%) of a viscous yellow oil. $R_t$ = 0.39 (40% CH$_2$Cl$_2$ in hexanes). IR (neat): 3068, 3030, 2989, 2870, 1604, 1512, 1496, 1457, 1380, 1274, 1185, 1132, 1100, 1068, 1029, 983, 816, 746 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.94 (d, $J$ = 8.6 Hz, 1 H), 7.82 (d, $J$ = 8.0 Hz, 1 H), 7.68 (d, $J$ = 8.6 Hz, 1 H), 7.55-7.45 (m, 2 H), 7.31-7.13 (m, 6 H), 4.96 (br m, 1 H), 3.06 (d, $J$ = 15.4 Hz, 1 H), 3.01 (d, $J$ = 15.2 Hz, 1 H), 2.79 (ddd, $J$ = 13.7, 10.6, 6.6 Hz, 1 H), 2.54 (ddd, $J$ = 14.5, 10.6, 4.3 Hz, 1 H), 2.34 (dddd, $J$ = 13.7, 10.6, 6.3, 3.1 Hz, 1 H), 2.13 (ddddd, $J$ = 13.7, 10.6, 6.6, 4.7 Hz, 1 H), 1.53 (s, 3 H), 1.19 (s, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 142.9 (q), 134.2 (q), 132.31 (q), 132.27 (q), 129.0 (q), 128.8 (t), 128.7 (t), 128.4 (t), 126.34 (t), 126.31 (t), 125.8 (t), 125.5 (t), 122.9 (t), 122.8 (t), 70.8 (t), 70.7 (q), 38.2 (s), 36.7 (s), 31.1 (p), 30.8 (s), 23.5 (p). GC-MS (El 70 eV): [M$^+$–CH$_2$CH$_2$Ph] = 211 (100%), [M$^+$–HOCH$_2$CH$_2$Ph] = 193 *32%).
2,2-dimethyl-4-phenyl-2,4-dihydro-1H-benzo[f]isochromene (11f):

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH$_2$Cl$_2$ in hexanes to afford 0.14 mmol (58%) of a viscous yellow oil. $R_f = 0.34$ (40% CH$_2$Cl$_2$ in hexanes). IR (neat): 3073, 2991, 2839, 1601, 1512, 1495, 1454, 1366, 1301, 1273, 1180, 1057, 1027, 816, 759, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.00$ (d, $J = 8.6$ Hz, 1 H), 7.78 (d, $J = 8.2$ Hz, 1 H), 7.57-7.46 (m, 3 H), 7.34-7.27 (m, 5 H), 6.87 (d, $J = 8.6$ Hz, 1 H), 5.85 (s, 1 H), 3.22 (d, $J = 16.4$ Hz, 1 H), 3.16 (d, $J = 16.4$ Hz, 1 H), 1.55 (s, 3 H), 1.36 (s, 3 H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 143.0$ (q), 134.1 (q), 132.4 (q), 132.1 (q), 129.2 (t), 128.7 (t), 128.3 (q), 128.2 (t), 126.4 (t), 126.1 (t), 125.7 (t), 124.7 (t), 123.0 (t), 76.2 (t), 71.9 (q), 36.6 (s), 31.2 (p), 23.6 (p). HRMS (Cl): $m/z$ [M + Na]$^+$ calcld for C$_{21}$H$_{20}$ONa: 311.1406; found: 311.1405.
4-(4-bromophenyl)-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11g):

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH$_2$Cl$_2$ in hexanes to afford 0.16 mmol (58%) of a viscous yellow oil. $R_t = 0.44$ (40% CH$_2$Cl$_2$ in hexanes). IR (neat): 3058, 2978, 2935, 2849, 1720, 1588, 1486, 1397, 1275, 1180, 1071, 1011, 814, 752 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.01$ (d, $J = 8.6$ Hz, 1 H), 7.82 (d, $J = 7.8$ Hz, 1 H), 7.58-7.47 (m, 5 H), 7.23 (d, $J = 8.2$ Hz, 2 H), 6.85 (d, $J = 8.6$ Hz, 1 H), 5.84 (s, 1 H), 3.20 (overlapping d, $J = 19.5$, 16.8 Hz, 2 H), 1.57 (s, 3 H), 1.38 (s, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 142.2$ (q), 133.5 (q), 132.6 (q), 132.2 (q), 131.9 (t), 130.9 (t), 128.5 (q), 126.5 (q), 126.6 (t), 126.3 (t), 125.9 (t), 124.5 (t), 123.0 (t), 122.2 (q), 75.7 (t), 72.1 (q), 36.7 (s), 31.2 (p), 23.6 (p). HRMS (Cl): $m/z$ [M + Na]$^+$ calcd for C$_{21}$H$_{19}$BrONa: 389.0511; found: 389.0508.
2,2-dimethyl-4-(4-(trifluoromethyl)phenyl)-2,4-dihydro-1H-
benzo[f]isochromene (11h):

The title compound was prepared according to
the general procedure and purified by column
chromatography using 20%-40% CH₂Cl₂ in
hexanes to afford 0.11 mmol (43%) of a viscous
yellow oil. \( R_t = 0.47 \) (40% CH₂Cl₂ in hexanes). IR
(neat): 3055, 2975, 2925, 1620, 1512, 1419,
1369, 1326, 1160, 1133, 1067, 1019, 915, 841,
814, 766 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): \( \delta = \\
8.00 \) (d, \( J = 8.5 \) Hz, 1 H), 7.79 (d, \( J = 7.9 \) Hz, 1 H), 7.60-7.45 (m, 7 H), 6.82 (d, \( J = \\
8.5 \) Hz, 1 H), 5.91 (s, 1 H), 3.23 (d, \( J = 16.7 \) Hz, 1 H), 3.18 (d, \( J = 16.1 \) Hz, 1 H),
1.55 (s, 3 H), 1.37 (s, 3 H). \(^13\)C NMR (100 MHz, CDCl₃): \( \delta = 146.9 \) (q), 133.0 (q),
132.6 (q), 132.1 (q), 130.6 (CF₂, \( J = 32.4 \) Hz), 129.6 (t), 128.8 (t), 128.5 (q),
126.6 (t), 126.4 (t), 126.0 (t), 125.8 (t), 125.7 (t), 124.3 (t), 123.0 (t), 75.7 (t), 72.2
(q), 36.5 (s), 31.1 (p), 23.6 (p). HRMS (Cl): \( m/z \ [M + Na]^+ \) calcd for C₂₂H₁₉F₃OH:
379.1280; found: 379.1287.
2,2-dimethyl-4-(4-nitrophenyl)-2,4-dihydro-1H-benzo[f]isochromene (11i):

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH₂Cl₂ in hexanes to afford 0.11 mmol (46%) of a viscous yellow oil. *R*₂ = 0.19 (40% CH₂Cl₂ in hexanes). IR (neat):

3060, 2980, 2930, 2854, 1603, 1521, 1353, 1275, 1183, 1079, 1064, 916, 854, 812, 765 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.18 (d, *J* = 8.6 Hz, 2 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.60-7.49 (m, 5 H), 6.79 (d, *J* = 8.6 Hz, 1 H), 5.96 (s, 1 H), 3.21 (overlapping d, *J* = 18.0, 16.8 Hz, 2 H), 1.56 (s, 3H), 1.37 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ = 150.2 (q), 148.0 (q), 132.7 (q), 132.5 (q), 132.2 (q), 130.0 (t), 128.9 (t), 128.7 (q), 126.8 (t), 126.6 (t), 126.1 (t), 124.0 (t), 123.0 (t), 75.4 (t), 72.4 (q), 36.6 (s), 31.1 (p), 23.6 (p). HRMS (Cl): *m/z* [M + Na]⁺ calcd for C₂₁H₁₉NO₃Na: 356.1257; found: 356.1255.
4-(4-methoxyphenyl)-2,2-dimethyl-2,4-dihydro-1H-benzo[f]isochromene (11) :

The title compound was prepared according to the general procedure and purified by column chromatography using 40% CH$_2$Cl$_2$ in hexanes to afford 0.14 mmol (58%) of a viscous yellow oil. $R_f = 0.16$ (40% CH$_2$Cl$_2$ in hexanes). IR (neat): 3061, 3006, 2827, 1599, 1586, 1508, 1456, 1366, 1302, 1241, 1170, 1027, 963, 912, 816, 768, 733 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.99$ (d, $J = 8.6$ Hz, 1 H), 7.78 (d, $J = 7.8$ Hz, 1 H), 7.56-7.52 (m, 2 H), 7.45 (dd, $J = 7.8$, 7.0 Hz, 1 H), 7.24 (d, $J = 8.6$ Hz, 2 H), 6.86 (overlapping d, $J = 9.0$, 8.2 Hz, 3 H), 5.82 (s, 1 H), 3.77 (s, 3 H), 3.20 (d, $J = 16.4$ Hz, 1 H), 3.14 (d, $J = 16.0$ Hz, 1 H), 1.54 (s, 3 H), 1.35 (s, 3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 159.7$ (q), 134.5 (q), 132.6 (q), 132.2 (q), 130.4 (t), 128.8 (t), 128.4 (t), 126.4 (t), 126.1 (t), 125.6 (t), 124.9 (t), 123.0 (t), 114.2 (t), 75.7 (t), 71.8 (q), 55.5 (p), 36.7 (s), 31.3 (p), 23.6 (p). HRMS (Cl): $m/z$ [M + Na]$^+$ calcd for C$_{22}$H$_{22}$O$_2$Na: 341.1512; found: 341.1510.
D. Synthesis of Alternative Starting Material

1-allyl-3-methoxybenzene (22):

To a solution of 1-bromoprop-2-ene (12.4 mmol, 1.05 equiv.) in THF (25 mL), 3-methoxyphenylmagnesium bromide (1.0M in THF, 11.8 mmol, 1 equiv.) was added dropwise with stirring. The reaction was stirred for 4h at 0 °C. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated NH₄Cl (25 mL) and extracted with Et₂O (2x25 mL). The organic layer was dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes to afford 9.34 mmol (79.1%) of a yellow oil. Spectra agree with previously published spectral data.⁶⁶

2-(3-methoxyphenyl)acetaldehyde (23):

To a cooled (-78 °C) solution of 22 (17.6 mmol) in 100 ml of CH₂Cl₂ and 20 mL of MeOH was added a large excess of NaHCO₃. Ozone gas was bubbled through the reaction flask until the mixture turned blue. Oxygen gas was then bubbled through the reaction flask until the mixture was colorless. Dimethylsulfide (88.0 mmol) was added and the reaction was allowed to warm to room temperature.

and stir overnight under Ar gas. The reaction mixture was diluted with water, extracted with \( \text{Et}_2\text{O} \), dried (MgSO\(_4\)), and concentrated in vacuo. The crude product was then used without further purification. Spectra agree with previously published spectral data.\(^{67}\)

\[ \text{1-(3-methoxyphenyl)-4-(trimethylsilyl)but-3-yn-2-ol (24):} \]

\[ \begin{align*}
\text{To a cooled (-78 °C) solution of TMS-acetylene (17.5 mmol) in 100 mL of THF was added n-butyl lithium (2.5 M in hexanes, 18.4 mmol) dropwise with stirring under Ar gas. The reaction was then stirred for 30 minutes, after which 23 (18.4 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched with NH}_4\text{Cl. The reaction mixture was then extracted with Et}_2\text{O, dried (MgSO}_4\text{), and concentrated in vacuo. The crude product was then purified by column chromatography (10%-30% EtOAc in hexanes) to afford 8.8 mmol (50% over two steps) of a yellow liquid. } \]  

\[ \text{\[\text{R}_f = 0.14 (10\% \text{ EtOAc in hexanes).} \] }\]

\[ \text{\[\text{\[\text{\[\text{1H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.24 (t, } J = 7.8 \text{ Hz, 1 H), 6.89-6.81 (m, 3 H), 4.58 (t, } J = 6.7 \text{ Hz, 1 H), 3.82 (s, 3 H), 3.00, (overlapping dd, } J = 13.7, 7, 5.9 \text{ Hz, 2 H), 2.21 (s, 1 H), 0.18 (s, 9 H) 13C (100 MHz, CDCl}_3\text{):} \delta = 159.6 (q), 138.2 (q), 129.3 (t), 122.3 (t),} \] }\]

\[ \text{\[\text{Chemical Formula: } C_{14}H_{20}O_2Si \] \]

\[ \text{Exact Mass: 248.12} \]

\[ \text{Molar Weight: 248.40} \]

\[ m/z: 248.12 (100.0\%), 249.13 (15.4\%), 249.12 (5.1\%), 250.12 (3.3\%), 250.13 (2.3\%) \]

\[ \text{Elemental Analysis: C, 67.70; H, 8.12; O, 12.88; Si, 11.31} \]

115.6 (t), 112.4 (t), 106.2 (q), 90.3 (q), 63.5 (t), 55.2 (p), 44.1 (s), 0 (p). HRMS (Cl): m/z [M + Na]^+ calcd for C_{14}H_{20}O_{2}SiNa: 271.1125; found: 271.1122.

1-(3-methoxyphenyl)but-3-yn-2-ol (25):

To a solution of 24 (8.8 mmol) in 50 mL of a 1:1 mixture of THF and methanol was added K_{2}CO_{3} (17.5 mmol) with stirring. 2 mL of DI H_{2}O was added to the mixture and the reaction was stirred under Ar gas for 3-4 h until completion as indicated by TLC. The reaction mixture was diluted with water, extracted with Et_{2}O, dried (MgSO_{4}), and concentrated in vacuo. The crude product was then purified by column chromatography (10% EtOAc in hexanes) to afford 6.2 mmol (71%) of pure product. Liquid; \( R_f = 0.19 \) (10% EtOAc in hexanes). \(^1\)H NMR (400 MHz, CDCl_{3}) \( \delta = 7.22 \) (t, \( J = 7.8 \) Hz, 1 H), 6.87-6.78 (m, 3 H), 4.56 (d, \( J = 3.9 \) Hz, 1 H), 3.78 (s, 3 H), 2.97 (overlapping dd, \( J = 13.7, 6.6, 6.3 \) Hz, 2 H), 2.48 (d, \( J = 1.9 \) Hz, 1 H), 2.33 (s, 1 H). \(^{13}\)C (100 MHz, CDCl_{3}): \( \delta = 159.7 \) (q), 138.0 (q), 129.5 (t), 122.2 (t), 115.6 (t), 112.5 (t), 84.3 (q), 73.9 (t), 63.0 (t), 55.3 (p), 44.0 (s).
Tert-butyl(1-(3-methoxyphenyl)but-3-yn-2-yl)oxy)diphenylsilane (26):

To a cooled (0 °C) solution of 25 (25 mmol) in 150 mL of DMF was added imidazole (27.5 mmol) under Ar gas. Upon dissolution of the imidazole, tert-butyldiphenylsilyl chloride was added slowly and the reaction was allowed to stir overnight and gradually warm to room temperature. Upon completion of the reaction, Et₂O and water were added and the organic layer was extracted. The organic layer was then washed with water, dried (MgSO₄) and concentrated in vacuo. The crude product was then purified by column chromatography using 10% EtOAc in hexanes to afford 19.5 mmol (78%) of a viscous, light pink oil. Rₜ = 0.73 (10% EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃): δ = 7.69 (dd, J = 6.2, 1.6 Hz, 2 H), 7.59 (dd, J = 6.2 1.6 Hz, 2 H), 7.44-7.32 (m, 6 H), 7.12 (t, J = 7.8 Hz, 1 H), 6.74 (dd, J = 8.2, 2.0 Hz, 1 H), 6.67 (d, J = 7.4 Hz, 1 H), 6.61 (t, J = 2.0 Hz, 1 H), 4.48 (td, J = 6.3, 2.0 Hz, 1 H), 3.71 (s, 3 H), 2.92 (overlapping dd, J = 13.3, 6.3 Hz, 2 H), 2.3 (d, J = 2.0 Hz, 1 H), 1.05 (s, 9 H). ¹³C (100 MHz, CDCl₃): δ = 159.5 (q), 138.5 (q), 136.3 (t), 136.1 (t), 133.5 (q), 133.4 (q), 130.0 (t), 129.9 (t), 129.2 (t), 127.8 (t), 127.6 (t), 122.5 (t), 115.4 (t), 112.5 (t), 84.6 (q), 73.8 (t), 65.1 (t), 55.3 (p), 45.2 (s), 27.1 (p), 19.4 (q).
6-((tert-butyldiphenylsilyl)oxy)-7-(3-methoxyphenyl)-2-methylhept-4-yn-2-ol (27):

To a cooled (-78 °C) solution of 26 (5.2 mmol) in 20 mL of THF was added n-butyl lithium (2.5 M in hexanes, 5.5 mmol) dropwise under Ar gas. After stirring for 30 minutes, BF$_3$·Et$_2$O (7.8 mmol) was added. After stirring for 15 minutes, isobutylene oxide (5.7 mmol) was added dropwise and the mixture was left to stir for 1 h. The reaction was then quenched with NH$_4$Cl, extracted with Et$_2$O, dried (MgSO$_4$), and concentrated in vacuo. The crude product was then purified by column chromatography using 2%-20% EtOAc in hexanes to afford 4.0 mmol (76%) of a viscous pink oil. $R_f = 0.19$ (10% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.71$ (dd, $J = 6.2$, 1.6 Hz, 2 H), 7.61 (dd, $J = 6.3$, 1.5 Hz, 2 H), 7.44-7.33 (m, 6H), 7.15 (t, $J = 7.8$ Hz, 1 H), 6.76-6.71 (m, 2 H), 6.66 (t, $J = 1.9$ Hz, 1 H), 4.57 (tt, $J = 6.7$, 1.9 Hz, 1 H), 3.73 (s, 3 H), 2.94 (overlapping dd, $J = 13.3$, 6.2 Hz, 2 H), 2.17 (d, $J = 2.0$ Hz, 2 H), 1.47 (s, 1 H), 1.09 (s, 3 H), 1.08 (s, 3 H), 1.04 (s, 9 H). $^{13}$C (100 MHz, CDCl$_3$): $\delta = 159.6$ (q), 139.1 (q), 136.2 (t), 136.1 (t), 133.9 (q), 133.6 (q), 130.0 (t), 129.8 (t), 129.2 (t), 127.8 (t), 127.6 (t), 122.4 (t), 115.5 (t), 112.4 (t), 84.2 (q), 82.7 (q), 69.8 (q), 55.3 (p), 45.4 (s), 34.5 (s), 28.6 (p), 27.0 (p), 19.4 (q). HRMS (Cl): m/z [M + Na]$^+$ calcd for C$_{31}$H$_{38}$O$_3$SiNa: 271.1125; found: 271.1122.
1-(3-methoxyphenyl)-6-methylhept-3-yne-2,6-diol (28):

To a solution of 27 (3.5 mmol) in 60 mL of THF was added tetrabutylammonium fluoride (1 M in THF, 10.5 mmol) under Ar gas. The mixture was allowed to stir overnight at room temperature. The reaction was then quenched with potassium sodium tartrate (40 mL), extracted with EtOAc, dried (MgSO₄), and concentrated in vacuo. The crude product was then purified by column chromatography using 7%-70% EtOAc in hexanes to afford 3.0 mmol (87%) of a viscous yellow oil. $R_f = 0.07$ (30% EtOAc in hexanes). $^1$H NMR (400 MHz, CDCl₃): $\delta = 7.22$ (t, $J = 7.8$ Hz, 1 H), 6.86-6.77 (m, 3 H), 4.59 (s, 1 H), 3.79 (s, 3 H), 2.97-2.95 (m, 3 H), 2.34 (d, $J = 1.6$ Hz, 3 H), 1.24 (s, 6 H). $^{13}$C (100 MHz, CDCl₃): $\delta = 159.7$ (q), 138.7 (q), 129.5 (t), 122.2 (t), 115.7 (t), 112.3 (t), 83.6 (q), 82.9 (q), 70.1 (q), 63.4 (t), 55.3 (p), 44.5 (s), 34.4 (s), 28.8 (p) 28.7 (p). HRMS (Cl): m/z [M + Na]$^+$ calcd for C₁₅H₂₀O₃Na: 271.1305; found: 271.1302.
Appendix A

NMR and GCMS Data
all protonated carbons
OTBDPS

9

CH3 carbons

CH2 carbons

CH carbons

all protonated carbons

200 180 160 140 120 100 80 60 40 20 0 ppm
all protonated carbons
11b protonated carbons

CH2 carbons

CH carbons

all protonated carbons
Mixture of Diastereomers
11c
Mixture of Diastereomers
Major Diastereomer
Major Diastereomer

11c

O

Major Diastereomer

O

all protonated carbons
**File**: C:\GC-MS Data\rjhink\SEL-415.D

**Operator**: 

**Acquired**: 15 Apr 2013 16:22 using AcqMethod RJHSAM_LONG (260).M

**Instrument**: Instrument #1

**Sample Name**: SEL-415

**Misc Info**: cyclization with methylbuteradehyde

**Vial Number**: 1

---

**Major Diastereomer**

![Diagram of molecular structure]

**Abundance**

```
Abundance
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000

Time-> 5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Scan 8065 (49.968 min): SEL-415.D\data.ms
```

---

**m/z**

```
m/z -> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270

43.2 45.2 65.1 76.1 89.1 101.1 115.2 127.1 141.2 152.1 165.2 178.2 211.2

221.2 223.2 235.2 251.2 221.2

93
```
File: C:\GC-MS Data\rjhimk\SEL-415.D
Operator: 
Instrument: Instrument #1
Sample Name: SEL-415
Misc Info: Cyclisation with methylbuteraldehyde
Vial Number: 1

Minor Diastereomer

Abundance

TIC: SEL-415.D\data.ms

Scan 8016 (49.680 min): SEL-415.D\data.ms

m/z:

30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270

5000000 4500000 4000000 3500000 3000000 2500000 2000000 1500000 1000000 500000 0

Time-> 5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance

211.2 193.2 178.2 165.1 152.1 141 137 123 115.1 107.1 94
CH3 carbons

CH2 carbons

CH carbons

all protonated carbons
File: C:\GC-MS Data\rjhin\SEL-417.D
Operator:
Acquired: 17 Apr 2013 18:34 using AcqMethod RJSAN_LONG (260).M
Instrument: Instrument #1
Sample Name: SEL-417
Misc Info: cyclization with bromobenzaldehyde
Vial Number: 1

Abundance
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1.3e+07
1.2e+07
1.1e+07
to0000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0

Time -> Scan 11566 (70.538 min): SEL-417_D\data.ms

Abundance
2000000
1800000
1600000
1400000
1200000
1000000
8000000
6000000
4000000
2000000
0

m/z -> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370

110
File: C:\GC-MS Data\rjhink\SEL-384.D
Operator: 
Acquired: 17 Apr 2013 15:08 using AcqMethod RJHSAAM_LONG (260).M
Instrument: Instrument #1
Sample Name: SEL-384
Misc Info: cyclization with trifluorotolualdehyde
Vial Number: 1

Abundance

TIC: SEL-384.D\data.ms

Scan 9948 (61.032 min): SEL-384.D\data.ms

m/z -> 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360

114
all protonated carbons

all protonated carbons
C r - MS D a t a in h A S E L - 3 1 9 . D
u s i n g A c q M e t h o d R J H S A M _ L O N G ( 2 6 0 ) . M
TIC: S E L - 3 1 9 D \ data.m s
F i l e
O p e r a t o r : 
A c q u i r e d : 1 1 A p r 2 0 1 3 1 9 : 5 4 u s i n g A c q M e t h o d R J H S A M _ L O N G ( 2 6 0 ) . M
I n s t r u m e n t : I n s t r u m e n t # 1
S a m p l e N a m e : S E L - 3 1 9
M i s c I n f o : P h O M e i s o c h r o m e n e
V i a l N u m b e r : 1

Abundance

6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0

Time (~)

5.00 10.00 15.00 20.00 25.00 30.00 35.00 40.00 45.00 50.00 55.00 60.00 65.00 70.00 75.00 80.00

Abundance

262.1
229.1
77.1
30 40 50 60 70 80

m / z ~

30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320

275.1 287.1 301.1

262.1
229.1
77.1
30 40 50 60 70

m / z ~

30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300 310 320

275.1 287.1 301.1
Appendix B

Crystallographic Data
Crystallographic Data for 2,2-dimethyl-1,2-dihydro-4H-benzo[\]isochromen-4-one:

![ORTEP of Lactone 19](image)

**Figure B.1:** ORTEP of Lactone 19
Table B.1. Crystal data and structure refinement for p21onc.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>p21onc</th>
</tr>
</thead>
<tbody>
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<td>Empirical formula</td>
<td>C15 H14 O2</td>
</tr>
<tr>
<td>Formula weight</td>
<td>226.26</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.06000(10) Å, ( \alpha = 90^\circ ).</td>
</tr>
<tr>
<td></td>
<td>b = 16.5507(2) Å, ( \beta = 105.7830(10)^\circ ).</td>
</tr>
<tr>
<td></td>
<td>c = 7.08520(10) Å, ( \gamma = 90^\circ ).</td>
</tr>
<tr>
<td>Volume</td>
<td>1135.21(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.324 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.693 mm⁻¹</td>
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<tr>
<td>F(000)</td>
<td>480</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.33 x 0.25 x 0.11 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>4.57 to 66.89°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-11&lt;=h&lt;=11, -19&lt;=k&lt;=16, -7&lt;=l&lt;=8</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>11695</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1959 [R(int) = 0.0341]</td>
</tr>
<tr>
<td>Completeness to theta = 66.89°</td>
<td>96.8 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Numerical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9290 and 0.8032</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1959 / 0 / 210</td>
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<tr>
<td>Goodness-of-fit on F²</td>
<td>1.034</td>
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<tr>
<td>Final R indices [l&gt;2sigma(l)]</td>
<td>R1 = 0.0330, wR2 = 0.0842</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0377, wR2 = 0.0877</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.163 and -0.202 e Å⁻³</td>
</tr>
</tbody>
</table>
Table B.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å² x 10^3) for p21onc. U(eq) is defined as one third of the trace of the orthogonalized U^ii tensor.

<table>
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<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
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<tbody>
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<td>3649(1)</td>
<td>850(1)</td>
<td>23(1)</td>
</tr>
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<td>O(2)</td>
<td>9343(1)</td>
<td>3940(1)</td>
<td>-1471(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(1)</td>
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<td>C(4)</td>
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<td>C(11)</td>
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Table B.3. Bond lengths [Å] and angles [°] for p21onc.

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<tr>
<td>Bond</td>
<td>Angle (°)</td>
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<td>------</td>
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<td>C(8)-C(9)-H(9)</td>
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\begin{align*}
\text{C(9)}-\text{C(10)}-\text{H(10)} & \quad 119.5(9) \\
\text{C(10)}-\text{C(11)}-\text{C(12)} & \quad 121.04(12) \\
\text{C(10)}-\text{C(11)}-\text{H(11)} & \quad 119.7(9) \\
\text{C(12)}-\text{C(11)}-\text{H(11)} & \quad 119.2(9) \\
\text{C(11)}-\text{C(12)}-\text{C(7)} & \quad 118.43(11) \\
\text{C(11)}-\text{C(12)}-\text{C(13)} & \quad 122.80(11) \\
\text{C(7)}-\text{C(12)}-\text{C(13)} & \quad 118.77(11) \\
\text{C(4)}-\text{C(13)}-\text{C(12)} & \quad 119.61(11) \\
\text{C(4)}-\text{C(13)}-\text{C(1)} & \quad 118.27(11) \\
\text{C(12)}-\text{C(13)}-\text{C(1)} & \quad 122.09(11) \\
\text{C(2)}-\text{C(14)}-\text{H(14A)} & \quad 112.1(8) \\
\text{C(2)}-\text{C(14)}-\text{H(14B)} & \quad 110.1(9) \\
\text{H(14A)}-\text{C(14)}-\text{H(14B)} & \quad 109.0(11) \\
\text{C(2)}-\text{C(14)}-\text{H(14C)} & \quad 110.3(8) \\
\text{H(14A)}-\text{C(14)}-\text{H(14C)} & \quad 107.6(11) \\
\text{H(14B)}-\text{C(14)}-\text{H(14C)} & \quad 107.6(12) \\
\text{C(2)}-\text{C(15)}-\text{H(15A)} & \quad 110.3(9) \\
\text{C(2)}-\text{C(15)}-\text{H(15B)} & \quad 108.0(9) \\
\text{H(15A)}-\text{C(15)}-\text{H(15B)} & \quad 108.6(12) \\
\text{C(2)}-\text{C(15)}-\text{H(15C)} & \quad 110.7(9) \\
\text{H(15A)}-\text{C(15)}-\text{H(15C)} & \quad 110.3(13) \\
\text{H(15B)}-\text{C(15)}-\text{H(15C)} & \quad 108.9(12)
\end{align*}

Symmetry transformations used to generate equivalent atoms:
Table B.4. Anisotropic displacement parameters (Å² x 10^3) for p21onc. The anisotropic displacement factor exponent takes the form:

\[-2\pi^2 \left( h^2 a^* a^* U^{11} + \ldots + 2hk a^* b^* U^{12} \right)\]

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Table B.5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for p21onc.

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