One-pot Tandem Diels-Alder/Nazarov Reactions to Generate Advanced Tricyclic Intermediates

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**Abstract**

One-pot multi-component reactions represent efficacious strategies to rapidly obtain complex intermediates applicable in the synthesis of therapeutically germane compounds. Nazarov reactions of aryl vinyl ketones are viewed as important steps in total synthesis and contribute to expanding the chemist’s synthetic toolbox. Currently, activated substrates or photochemical means are necessary to effect this transformation because the energy barrier is predicted to be relatively high. The stabilizing effect of silyl substituents beta to a carbocation intermediate has been well documented. a) We hypothesized that incorporation of a silyl group into the ynone starting materials may stabilize the reactive intermediates, enabling the aryl Nazarov reaction to proceed even with unactivated substrates. The use of aryl silyl ynones proved successful and as a consequence our group developed a tandem process utilizing the Diels-Alder and Nazarov reactions of aryl ynones to generate carbo- and heterocyclic fused ring systems in good yields. The tandem reactions proceed under Lewis acidic conditions to generate three new carbon-carbon bonds, a quaternary carbon and two stereogenic centers. In order to access a wider range of pharmaceutically important compounds through concise routes, a more versatile technology is needed.

The use of diynones as relatively high energy starting materials facilitates multiple carbon-carbon bond formations in a one-pot reaction. With respect to unsymmetrical diynones, regiocontrol of the double bond is accomplished through silane elimination rather than loss of hydrogen, ensuring the formation of one major product. Furthermore, the Diels-Alder cycloaddition occurs preferentially on the silyl substituted
alkyne at low temperatures, allowing for a “timed” double Diels-Alder reaction in which two different dienes can be added, generating a highly asymmetric product. Such molecular control permits a significant amount of versatility within the method. b) Our lab has designed and successfully executed a highly modifiable multicomponent reaction, initiating from a double Diels-Alder cycloaddition followed by a Nazarov reaction to furnish the [6-5-6] backbone. This method produces three fused rings evolving from the construction of five new carbon-carbon bonds, quaternary or vicinal quaternary carbons, and stereogenic centers in a one-pot reaction. A diverse array of drug-like scaffolds can be rapidly synthesized through these tandem processes providing a high level of stereo- and regiocontrol in the products.

\[\text{SiR}_3 = \text{TMS or TES} \]
\[R = \text{alkyl, aryl, TMS, TES} \]
\[R_1 = H, \text{ CH}_3; R_2 = H, \text{ CH}_3 \]
Dedication

I dedicate this dissertation to Michael R. King

for his steadfast love and support
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1 Introduction

1.1 Pericyclic Reactions in Synthetic Methodology

Pharmaceutical endeavors toward biologically important molecules rely heavily on cost-effective and economical synthetic methodologies.\(^1\) It is in our best interest to more effectively manage the synthetic design of societally important compounds as this can greatly reduce or eliminate hazardous waste. Building a biologically important molecule often involves a significant number of steps.\(^2\) Each step typically necessitates a purification aspect which is very expensive and generates a considerable amount of waste. Strategic synthetic methodology employs sustainable chemistry to target ubiquitous molecular frameworks. Such techniques minimize the number of steps in an overall synthesis which serves to reduce waste and lower cost.

Five- and six-membered rings are highly prevalent in biologically active compounds and therefore routes towards these polycyclic structures receive considerable attention.\(^3-5\)

Oftentimes, cost effective and environmentally pragmatic syntheses for biologically germane molecules have yet to be realized. Pericyclic reactions tend to be the predominante route by which five- and six-membered rings are constructed. Pericyclic reactions constitute a cyclic array of atoms and therefore orbitals which are interacting in the transition state in a concerted process. The \([4 + 2]\) cycloaddition is perhaps one of the most innovative and influential pericyclic reactions for synthesizing desirable cyclic target molecules.\(^6\) The Nazarov cyclization has also been an important contribution to the field of organic synthesis. There has been an increased effort to incorporate pericyclic
reactions such as these into tandem or cascade reactions to maximize bond formation efficiency. 1,7

1.2 The Diels-Alder Cycloaddition

Discovered in 1928 by Otto Diels and Kurt Alder, the pericyclic reaction between dienophile 1.1 and diene 1.2 to form a six-membered ring 1.3 containing an alkene was first known as the diene synthesis 6 (Figure 1-1). It was not until 1950 that Otto Diels and Kurt Alder received the Nobel Prize in Chemistry for their work on the [4 + 2] cycloaddition. 8 Due to the importance of the method, research in the area of Diels-Alder cycloadditions is still ongoing. 9

![Figure 1-1: [4+2] cycloaddition between 1.1 and 1.2 to form 1.3.](image)

The Diels-Alder cycloaddition has strict orbital symmetry requirements that result in a concerted mechanism. As a result, the reaction has a significant amount of stereo-control in the product outcome. Considering the reaction between 1.4 and 1.5, the two possible products are diastereomers 1.6 (the endo product) and 1.7 (the exo product) (Scheme 1-1). 10 The formation of the endo product is favored due to secondary orbital overlap; this is known as the Alder “endo rule”. Due to the orbital symmetry requirements of the cycloaddition mechanism, the reaction is highly efficient with respect to stereospecificity.
Since its discovery, the Diels-Alder reaction has been modified to meet current needs in chemistry, particularly by increasing functionality in the products. Essentially, a functionalized compound can participate in a number of different reaction pathways while an analogous non-functionalized derivative tends to be lower in energy and therefore less useful. An important adaptation to the Diels-Alder reaction has been the introduction of ynones \( \text{1.8} \) as the dienophile which reacts with a diene \( \text{1.2} \) yielding conjugated adduct \( \text{1.9} \) and the enone moiety (in red) (Scheme 1-2).\(^{11}\) The utilization of alkynes as dienophiles in cycloaddition reactions with dienes has many attractive features, such as greater functionality over traditionally used alkene dienophiles. For example, \( \text{1.10} \) undergoes cyclization with \( \text{1.2} \) generating the less functionalized adduct \( \text{1.11} \). The use of alkynes as dienophiles generates cyclo-\( 1,4 \)-hexadienes \( \text{1.9} \), which are otherwise produced by harsh dissolved metal reduction of arenes.\(^{12}\) Such reduction reactions often require conditions intolerant to sensitive functional groups. Ynones are inherently valuable dienophiles because of their ability to transfer useful functionality to the Diels-Alder product. While a few examples of ynone \( [4 + 2] \) cyclizations have been reported in the literature, ynone pericyclic routes remain largely unexplored.\(^{11,13}\) While the Diels-Alder reaction is the most direct route for the synthesis of six-membered rings,
the Nazarov cyclization represents the most accessible method for the general synthesis of cyclopentanones or five-membered rings.

Scheme 1-2: Diels-Alder cyclization employing an ynone 1.8 as the dienophile to generate a skipped diene product 1.9,11,13

1.3 The Nazarov Reaction

The Nazarov cyclization is a stereospecific reaction involving 4π electrons in the construction of a cyclopentadiene and was discovered in 1941 by Ivan Nazarov.14 The proposed mechanism for the Nazarov cyclization typically initiates with 1.11 complexing to a Lewis acid. The pentadienyl cation 1.12 then cyclizes to give oxyallyl cation 1.13 which undergoes deprotonation to form intermediate 1.14. Finally, aqueous workup provides cyclopentadiene 1.15.

Scheme 1-3: Proposed mechanism for the Nazarov cyclization.

Due to orbital symmetry requirements, the Nazarov proceeds in a conrotatory electrocyclization resulting in a stereospecific relationship between the two R groups 1.16 (circled in red, Scheme 1-4). In the example shown, the cis configuration would arise from disrotatory ring closure which is electronically forbidden according to orbital
symmetry as described by the Woodward-Hoffmann rules. The stereospecific control obtained from the concerted mechanism is highly valuable in synthetic organic chemistry.

Scheme 1-4: The Nazarov cyclization proceeds in a conrotatory fashion resulting in a trans-relationship between the two R groups.

Significant advancements have been made in the area of Nazarov cyclizations by a number of groups endeavoring to improve the synthetic utility of the reaction. Although an important discovery, in its early days the Nazarov method suffered from several drawbacks. One disadvantage to the reaction was the potential for regioisomers in unsymmetrical substrates due to unbiased proton elimination. Divinyl ketone 1.17 can participate in a Nazarov reaction to give intermediate 1.18, which upon deprotonation can ultimately form 1.19 or 1.20 (Scheme 1-5).

Scheme 1-5: In an unsymmetrical substrate, the Nazarov cyclization can generate a mixture of regioisomers.

In order to amend this limitation, a strategically placed silyl substituent can replace the proton in the elimination step, ensuring a consistent regiochemical outcome (Scheme 1-6). Silane substituted divinyl ketone 1.20 will cyclize to afford 1.21 as the
exclusive product. The formation of 1.22 was not observed. This feat is possible because of the \( \beta \)-silyl effect which stabilizes the reactive intermediate 1.23, the silyl group therefore becomes more susceptible to elimination. In this way, only one product is formed even though it is the less thermodynamically favored product.

![Scheme 1-6: Incorporation of silyl group which undergoes elimination during the reaction, ensuring regiocontrol of the double bond in the product.](image)

Additionally, stoichiometric or super stoichiometric amounts of Lewis or Brønsted acid are necessary to initiate the Nazarov cyclization which is uneconomical. To address this problem a polarized divinyl ketone 1.24 was developed comprising an electron-donating group and an electron-withdrawing group.\(^{18}\) Due to the regio-location of these groups a push-pull system was established (see 1.25) whereas a “vinyl nucleophile” would react with a “vinyl electrophile”. These substrates did not necessitate harsh promoters and were found to undergo the Nazarov reaction to give 1.26 with a mild catalyst (2 mol% of Cu(OTf)$_2$). An additional advantage is that more reactive dienes can be used in such a system whereas with a harsh catalyst the use of functionalized dienes is often limited. Other innovative approaches to method development have used pericyclic reactions such as the Nazarov and Diels-Alder cycloaddition in one-pot in an effort to conduct more economical syntheses.
1.4 Tandem or Cascade Reactions

The utilization of the Diels-Alder and Nazarov reactions in tandem or cascade methodologies constitutes a particularly robust approach towards effective bond formations. Recently a tandem Diels-Alder and retro-ene reaction was reported for the synthesis of cyclohexene derivatives (Scheme 1-8). A sulfur substituted diene 1.27 reacts with an electron deficient dienophile 1.28 to generate intermediate 1.29. Oxidation of the sulfur moiety on 1.29 followed by acidification initiates a retro-ene reaction, extrusion of sulfur dioxide results in 1.30 as the final product. This two component pericyclic reaction is an innovative way to access regiospecific six-membered rings not attainable through standard [4+2] cycloadditions.

Scheme 1-8: An efficient route towards cyclohexenes from a tandem Diels-Alder and retro-ene reaction.
Another notable example of tandem pericyclic reactions is demonstrated in the synthesis of complex polycyclic lactams (Scheme 1-9). The pyridinium salt \(1.31\) and secondary amine \(1.32\) form the Zincke aldehyde starting material \(1.33\). Upon heating to 200 °C, Zincke aldehyde \(1.33\) participates in a series of pericyclic reactions to ultimately generate lactam \(1.34\). The cascade sequence involves an impressive number of bond formations that begin from simple starting materials \(1.31\) and \(1.32\). This method can be used to produce a variety of lactam scaffolds having application in total synthesis and pharmaceuticals. The design of synthetic methodology which targets a common structural core prevalent in biologically active compounds, has extensive application to the synthesis of the target class of compounds as well as derivatization of those compounds.

Scheme 1-9: Pericyclic cascade reaction starting from \(1.31\) and \(1.32\) to rapidly form polycyclic lactams. \(^{24}\)

1.5 Conclusion

The incorporation of pericyclic reactions into tandem processes is a powerful tool for the synthesis of advanced polycyclic systems. \(^{25}\) The use of inexpensive, high energy starting materials to accomplish multiple carbon-carbon bond formations in a single reaction flask is not only a resourceful approach to solving complex synthesis problems, but can also drastically reduce chemical waste production in our society. The design of
efficient synthetic methodology is integral to pharmaceutical development as well as expanding the frontiers of synthetic organic chemistry.²⁶

1.6 References


(17) Grant, T. N.; Rieder, C. J.; West, F. G. Chem. Commun. 2009, 0 (38), 5676.


2 β-Silyl-Assisted Tandem Diels–Alder/Nazarov Reaction of 1-Aryl-3-(trimethylsilyl) Ynones

2.1 Introduction

Terpenoids and related structures have a rich history for piquing the interest of synthetic research groups, primarily due to the interesting biological activities inherent in many of these compounds.\(^1\) Fused five and six-membered polycyclic ring systems comprise the basic structure for a large number of important biologically active molecules.\(^2\)–\(^9\) New and efficient methods for the rapid construction of polycyclic substructures are highly sought after as a means to achieve more economical syntheses of naturally occurring or derivatized compounds of interest.\(^10\) One can achieve this through the use of multicomponent and/or tandem reaction processes, and in the case of polycyclic compound synthesis this would likely involve an annulation step.

The Nazarov cyclization is a synthetically valuable reaction toward cyclopentenones, and while a general catalytic asymmetric strategy has not yet been developed,\(^11\) significant advancements have been made in regard to the Nazarov reaction.\(^12\)–\(^23\) There has been considerable interest in an aryl Nazarov cyclization as this bond formation is viewed by some as an essential step in the syntheses of several biologically important naturally occurring compounds.\(^19,24\)–\(^26\) However, the formation of the five-membered rings through a Nazarov cyclization involving aryl substrates is a synthetically challenging feat, requiring either dication intermediates via superacids\(^27\) or highly activated substrates.\(^28\)–\(^30\) The Frontier group has conducted impressive studies on an Ir(III)-catalyzed Nazarov cyclization of polarized aryl vinyl ketone substrates (Figure
Photolysis has been successfully used by Smith and Agosta with aryl vinyl ketones to form a new five-membered ring embedded within a [6–5–6] polycyclic framework. The Gao group has expanded the substrate scope of the photo-Nazarov reaction to a variety of substituted arenes and heteroaromatics (Figure 2-1b). In many cases, the aryl vinyl ketone substrate for the Nazarov reaction must be synthesized with a heavy bias toward reactivity (an electron-rich aryl paired with an electron-poor alkene, Figure 2-1a); otherwise, the Nazarov cyclization is unlikely to be the favored pathway. A more general method that can tolerate a variety of aryl vinyl ketone substrates, and additionally can be coupled with a multicomponent and/or tandem reaction event starting from relatively simple substrates, would be highly attractive for arriving at these useful synthetic scaffolds.

**Figure 2-1:** a) Nazarov cyclizations of polarized aryl vinyl ketones through an iridium catalyst. b) Photocatalyzed Nazarov cyclization of diversified aryl vinyl ketones.

### 2.2 Nazarov Cyclization of Aryl Substituted and Terminal Ynones

Our research endeavors are directed toward method development for rapidly accessing biologically interesting polycyclic frameworks, via multicomponent and tandem reaction sequences, that starts from alkyne-containing substrates. The use of
high-energy alkyne- and polyyne-containing substrates provides the thermodynamic driving force for arriving at complex polycyclic products by way of multicomponent/tandem reaction sequences. We were curious as to whether aryl-substituted ynones would undergo a tandem Diels−Alder/Nazarov reaction. This would arrive at a [6−5−6]-tricyclic scaffold containing an aryl moiety, a structural characteristic present in the taiwaniaquinol family of biologically active natural products.2,19,24,38–42

Ynone starting materials such as 2.1 were of particular interest to us as they readily undergo Diels–Alder cycloadditions with 2.2a to form a skipped diene intermediate 2.3. We noted that compound 2.3 contains the necessary functionality to participate in a Nazarov cyclization (shown in red) (Scheme 2-1) and wondered if we could effect this transformation to give 2.4. The proposed schematic would yield biologically relevant precursors such as 2.4 in an economical one-pot reaction using inexpensive starting materials.

Scheme 2-1: Proposed pathway for tandem Diels–Alder/Nazarov reaction of ynone 2.1 forming intermediate 2.3 and then ultimately yielding desired product 2.4.

The method could be applied to the synthesis of biologically pertinent compounds bearing a [6-5-6] framework, particularly those having an aromatic component. Several members of the taiwaniaquinoid family exhibit antitumor activity and are in fact characterized by a [6-5-6] structure containing an aryl moiety (Figure 2-2).40
Our initial intent was to perform the reaction step by step, first forming the Diels-Alder adduct 2.3. Once 2.3 had been synthesized and characterized then it would be used as our advanced starting material to screen different Lewis acids for the Nazarov step. Preliminary reactions used terminal ynone 2.1a with 2.2a. We found that 2.3a could be generated in high yield using microwave irradiation (Scheme 2-2). We isolated enough 2.3a to screen multiple Lewis acids for the Nazarov cyclization.

![Scheme 2-2: Microwave synthesis using ynone 2.1a and diene 2.2a to generate 2.3a in excellent yield.](image)

In addition to Lewis acids, we also explored using amine catalysts to generate an iminium ion from the Diels-Alder adduct 2.3a. We hypothesized that an iminium ion intermediate 2.5 would be more reactive, and therefore more likely to participate in the Nazarov step. Additionally, a number of chiral amines could be used to effect an enantioselective transformation. Pyrrole 2.6 was used in the presence of trifluoroacetic acid at room temperature under nitrogen, although the desired product X was not obtained (Scheme 2-3a). L-proline 2.7 was tried under refluxing conditions and the
starting material 2.3a began to oxidize to 2.8 after an extended period of time. (Scheme 2-3b). The reactions did not proceed as expected; starting material remained along with a small amount of oxidized product 2.8.

Scheme 2-3: Attempted formation of iminium ion from 2.3a to give intermediate 2.5 in an effort to initiate Nazarov reaction. a) Pyrrole was used in strongly acidic conditions at room temperature. b) L-proline was used under refluxing conditions.

In addition to screening directly from 2.3a to initiate the Nazarov cyclization (Scheme 2-3), we also looked at trying the one-pot reaction using ynone 2.1a and diene 2.2a. Having gained experience with the synthesis and identification of 2.3a, we wanted to expand our efforts by incorporating a catalyst screen that focused on the one-pot Diels-Alder/Nazarov reaction as well. Common catalysts were screened with ynone 2.1a and 2.2a (Table 2-1). In some cases, only a small amount of 2.3a formed, streaking towards the top of the TLC plate was observed and suggests diene polymerization from BF₃•O(Et)₂ (entry 1). A considerable amount of starting material 2.1a remained with FeCl₃ in addition to a small amount of 2.3a and oxidized 2.8 (entry 2). A greater amount of 2.1a was converted with AlCl₃ then FeCl₃, however, oxidized 2.8 was present as well.
(entry 3). A small amount of **2.1a** was converted to the **2.3a** using In(OTf)₃ although diene polymerization was also apparent in this reaction (entry 4). At room temperature **2.3a** formed cleanly using Al(CH₃)₂Cl but failed to undergo the Nazarov reaction upon refluxing (entry 5). The intermediate **2.3a** was generated rapidly with BCl₃, although no change was observed and after several hours a small amount of decomposition became evident. Lewis acids BF₃•O(Et)₂ and In(OTf)₃ appear to not be compatible with diene **2.2a** as diene polymerization is considerably faster than the Diels-Alder cycloaddition with **2.1a**.

**Table 2-1**: Preliminary screening of oxophilic Lewis acids for the tandem Diels-Alder/Nazarov reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃•O(Et)₂</td>
<td>C₂H₄Cl₂, r.t. to reflux</td>
<td>Mixture <strong>2.3a</strong> and <strong>2.8</strong></td>
</tr>
<tr>
<td>2</td>
<td>Fe(Cl)₃</td>
<td>C₂H₄Cl₂, r.t. to reflux</td>
<td>Mixture <strong>2.3a</strong> and <strong>2.8</strong></td>
</tr>
<tr>
<td>3</td>
<td>Al(Cl)₃</td>
<td>C₂H₄Cl₂, r.t. to reflux</td>
<td>Mixture <strong>2.3a</strong> and <strong>2.8</strong></td>
</tr>
<tr>
<td>4</td>
<td>In(OTf)₃</td>
<td>C₂H₄Cl₂, r.t. to reflux</td>
<td>Mixture <strong>2.3a</strong> and <strong>2.8</strong></td>
</tr>
<tr>
<td>5</td>
<td>Al(CH₃)₂Cl</td>
<td>C₂H₄Cl₂, r.t. to reflux</td>
<td><strong>2.3a</strong></td>
</tr>
<tr>
<td>6</td>
<td>BCl₃</td>
<td>-78 °C to r.t., CH₂Cl₂</td>
<td><strong>2.3a</strong> and <strong>2.8</strong></td>
</tr>
</tbody>
</table>

Upon examining our substrate, we considered that the aryl moiety may not be electron-rich enough for a pericyclic reaction to occur. Resonance contributor **2.3b** places a positive charge on the “nucleophilic” carbon (as shown) (Figure 2-3). We hypothesized
that adding electron-donating groups such as methoxy substituents to the ynone 2.1 would enhance the electron density present in the aromatic ring, making it more suitable for a Nazarov reaction. Typically, for the Nazarov cyclization to occur, an electron-rich aryl needs to be paired with an electron-poor alkene.31

![Figure 2-3: Diels-Alder adduct may not be electron-rich enough for the pericyclic reaction to occur, adding electron-donating groups increases the “nucleophilic” character of the ring.]

Proline catalysis was not successful (via an iminium intermediate) with 2.3b for the Nazarov reaction (Scheme 2-4). No formation of the desired product 2.4b was observed. The use of a secondary amine to form the iminium ion may be difficult on a more congested ketone. Furthermore, we wanted to prevent the oxidation pathway from being so accessible. One route to accomplishing this would be to pursue acyclic dienes as well as dienes that were more substituted, so that oxidation of 2.3b would not be possible. In addition to amine catalysis, we screened several more Lewis acids with 2.3b in an attempt to initiate the Nazarov reaction; however, we continued to observe the formation of oxidized product 2.9 in small amounts.
We noticed that oxidation primarily became an issue under longer reaction times and when harsher conditions were employed. To remove oxidation as a potential reaction pathway cyclopentadiene 2.2b was used instead of 2.2a (Scheme 2-5). The intermediate 2.3c will be unable to oxidize due to Bredt’s rule.45,46

Scheme 2-5: Use of cyclic diene 2.2b would prevent oxidation of 2.3c since a double bond at the bridgehead would not be feasible.

An aluminum Lewis acid, Al(CH₃)₂Cl, was used with 2.1b and 2.2b and the reaction monitored until starting material had been fully converted, analysis by ¹H NMR of the crude mixture showed 2.3c as the major product (Scheme 2-6a). Intermediate 2.3c was also synthesized using microwave irradiation to give similar results in terms of yield.
The formation of 2.3c provided us with additional material for a series of small scale screening reactions.

**Scheme 2-6b:** a) Formation of 2.3c in modest yield using Al(CH$_3$)$_2$Cl. b) Formation of 2.3c in modest yield using a microwave.

Since the formation of an iminium ion through a secondary amine was unsuccessful, we suspected that the bulkier amine may have difficulty reacting with 2.3b due to sterics. To minimize this issue, we selected methylbenzylamine to try next, as a primary amine it is less sterically hindered. Additionally, we were interested in trying to form the iminium ion intermediate using 2.1b as the smaller substrate may be able to more easily react with an amine. The reactions were conducted using trifluoroacetic acid (TFA) and methylbenzylamine at room temperature (**Table 2-2**). Protonation of 2.1b results in an activated substrate that will be more susceptible towards nucleophilic attack from the amine. Three different solvents were screened, CH$_2$Cl$_2$, acetonitrile, and toluene, and all contained methylbenzylamine, the formation of 2.3c was observed in all of the reactions (entries 1-3). A fourth reaction was run that used TFA but excluded the amine, we found that in this reaction 2.3c was present as well (entry 4). Since TFA is likely to initiate the Diels-Alder cycloaddition, the reaction without the amine was used to determine the likelihood that the iminium ion was actually forming. Based on the results it seems that TFA may have been responsible for the cycloaddition and that the iminium
ion was not forming. While some $2.1b$ remained in all of the reactions, no other product was observed aside from $2.3c$. Since room temperature conditions had not been able to push $2.3c$ into a Nazarov cyclization we turned to refluxing the reaction. The reaction ran for several days while being monitored by TLC, however, no further reaction occurred.

**Table 2-2:** Screening with trifluoroacetic acid and methylbenzylamine using $2.1b$ and $2.2b$ to form $2.3c$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Methylbenzylamine</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>Yes</td>
<td>Formation of $2.3c$</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>Yes</td>
<td>Formation of $2.3c$</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>Yes</td>
<td>Formation of $2.3c$</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$Cl$_2$</td>
<td>No</td>
<td>Formation of $2.3c$</td>
</tr>
</tbody>
</table>

A screening table of suitable Lewis acids was put together to be used with $2.3c$ in an attempt to force the Nazarov cyclization to occur (**Table 2-3**). The starting material $2.3c$ was reacted with Ti[OCH(CH$_3$)$_2$)$_4$ beginning at room temperature and then refluxed, no conversion of $2.3c$ was seen (entry 1). The stronger Lewis acid, AlCl$_3$ and $2.3c$ were reacted at lower temperatures. Over the course of the reaction a considerable amount of $2.3c$ was converted to what appeared to be an HCl addition product $2.10$ (entry 2). A second reaction was attempted using AlCl$_3$ in the presence of Hunig's base in an effort to minimize the amount of HCl present in the reaction; however, no reaction occurred (entry 3). Reactions that used Yb(OTf)$_3$, TMS(OTf), Bi(OTf)$_3$, and BF$_3$O(Et)$_2$, gave no reaction of the $2.3c$ (entries 4-7). A small amount of $2.10$ appeared to be present in the reaction mixture from FeCl$_3$ (entry 8). Both reactions with In(OTf)$_3$ and Sc(OTf)$_3$ showed no
conversion of 2.3c to give 2.4c (entries 9 and 10). While Al(CH₃)₂Cl in toluene gave no reaction, a trace amount of HCl addition product 2.10 was present in the ¹H NMR spectrum after several days (entries 11 and 12). Formation of the HCl addition product 2.10 occurred readily when 2.3c was used with an appropriate Lewis acid. Additional screening was conducted using common Lewis acids; however, no formation of 2.4c was observed.

**Table 2-3:** Lewis acid screening using 2.3c as starting material to form Nazarov product 2.4c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ti[OCH(CH₃)₂]₄</td>
<td>C₂H₄Cl₂, r.t. to 80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>CH₂Cl₂, -78 °C to -40 °C</td>
<td>2.10</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃ with Hunigs</td>
<td>CH₂Cl₂, -78 °C to r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Yb(Otf)₃</td>
<td>CH₂Cl₂, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>TMS(Otf)</td>
<td>CH₂Cl₂, -78 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>Bi(Otf)₃</td>
<td>CH₂Cl₂, -78 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>BF₃O(Et)₂</td>
<td>C₂H₆Cl₂, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>Fe(Cl)₃</td>
<td>C₂H₆Cl₂, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>In(Otf)₃</td>
<td>C₂H₆Cl₂, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>Sc(Otf)₃</td>
<td>toluene, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>Al(CH₃)₂Cl</td>
<td>toluene, r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>Al(CH₃)₂Cl</td>
<td>CH₂Cl₂, r.t. 2 days</td>
<td>Trace 2.10</td>
</tr>
</tbody>
</table>

Since we strongly suspected HCl addition was occurring to 2.3c, we wanted to run a reaction using 2.3c and a solution of HCl to be certain of the product outcome (Scheme 2-7). The reaction was run at -78 °C and when 2.3c was reacted with HCl, the expected addition product 2.10 was formed. The HCl addition to intermediate 2.3c
proved to be a difficult problem because many reactive and effective Lewis acids produce HCl as a side product. It was clearly a more favorable reaction pathway than the Nazarov reaction. While the addition of base to remove HCl had proved ineffective, we were still interested in trying different bases with certain Lewis acids. If the Lewis acid reacted preferentially with the ynone substrate instead of the base, it could be a viable pathway.

Scheme 2-7: Test reaction using 2.3c and a solution of HCl to be certain of the HCl addition product 2.10.

We continued screening reaction conditions to promote the Nazarov cyclization of 2.3c. We were pleased to find that AlCl₃ and 2,6-lutidine in toluene formed a new product in 30 minutes (entry 1). No reaction occurred when Al(CH₃)₂Cl and ZnEt₂ were run in toluene and heated gently (entries 2 and 3). Due to HCl addition problems, SnCl₄ was also tried in the presence of 2,6-lutidine; however, no reaction was observed (entry 4). No desired product 2.4c formed under AuCl₃/Ag(OTf) conditions (Entry 5). For Lewis acids Zn(Et)₂, Zn(Cl)₂, and EtAlCl₂ no reaction of 2.3c was observed by TLC or ¹H NMR analysis (entries 6-8). Multiple products were formed resulting from the addition of BF₃·O(Et)₂ to the reaction but none of them appeared to be the desired Nazarov product 2.4c (entry 9). Bronsted acids were used in ¹H NMR reactions so that any conversion of 2.3c could be monitored closely; however, a number of products formed and 2.3c essentially decomposed (entries 10-12).

Table 2-4: Further screening for 2.3c to undergo Nazarov cyclization giving 2.4c.
2.2.1 Unexpected Formation of Mystery Product

Analysis of the crude mixture from the AlCl3/2,6-lutidine reaction (entry 1, Table 2-4) by 1H NMR showed only one proton in the aromatic region, a preliminary indicator for a successful Nazarov reaction (Ha). However, the expected methine proton (Hb) was absent, instead there appeared to be several methine protons (Scheme 2-8). After fully characterizing the isolated mystery product 2.11 we believe that 2.3c underwent a Nazarov cyclization to give 2.4c which reacted further to form the final product 2.11. We were intrigued by the formation of 2.11, particularly by the short, mild reaction conditions that resulted in a three-membered ring in a bicyclic system.
Scheme 2-8: Reaction of $2.3c$ with AlCl$_3$ and 2,6-lutidine in toluene to give $2.11$, which, is believed to occur after formation of Nazarov product $2.4c$.

The proposed mechanism for the formation of mystery $2.11$ is thought to initiate from a Nazarov cyclization of $2.3c$ giving intermediate $2.4c$ (Figure 2-4). Protonation of the double bond in $2.4c$, due to the adventitious presence of acid in the reaction, generating $2.4c'$ could then result in Lewis acid bound $2.11$. Upon quenching the reaction and aqueous workup the final product $2.11$ could then be isolated. We were intrigued by the formation of mystery product $2.11$ and speculated that if the conditions were reproducible, it might be possible for us to stop the mystery product reaction at the desired Nazarov product $2.4c$. Unfortunately, after further studies it was determined that the conditions for the mystery product $2.4c$ were not reproducible.

Figure 2-4: Proposed mechanism for the formation of mystery product $2.11$. 
A Lewis acid screening survey was conducted using ynone 2.1b and 2.2c to generate 2.3d (Table 2-5). No reaction of ynone 2.1b with 2.2c occurred when EtAlCl2 was used (entry 1). The BF3·O(Et)2 reaction showed minor product spots by TLC, however, it was unclear whether these “products” were of interest or not and isolation was unsuccessful (entry 2). Rapid formation of one major product was observed when TiCl4 reacted with 2.1b and 2.2c in CH2Cl2 (entry 3). Upon characterization, it was found that 2.3d had not been formed using TiCl4, instead the sole product 2.12 was the result of furan addition to ynone 2.1b (entry 3). Interestingly, when the TiCl4 reaction was run in toluene no reaction occurred (entry 4). The TLC from the AlCl3 reaction also showed spots of interest although isolation was not successful (entry 5). Over the course of other reactions utilizing 2.2c the addition product 2.12 was observed as a side product.

Table 2-5: A predominately Lewis acid based screening survey was conducted using ynone 2.1b and 2.2c to generate 2.3d. Over the course of some reactions the addition product 2.12 was observed as a side product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtAlCl2</td>
<td>CH2Cl2, -78 °C to r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>BF3·O(Et)2</td>
<td>CH2Cl2, -78 °C</td>
<td>TLC showed spots</td>
</tr>
<tr>
<td>3</td>
<td>TiCl4</td>
<td>CH2Cl2, -78 °C to r.t.</td>
<td>2.12</td>
</tr>
<tr>
<td>4</td>
<td>TiCl4</td>
<td>toluene, -78 °C to r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>AlCl3</td>
<td>CH2Cl2, -78 °C</td>
<td>TLC showed two spots</td>
</tr>
</tbody>
</table>

A Diels-Alder cycloaddition of 2.1b and 2.2d to generate 2.3e was conducted using aluminum Lewis acids. The gem-dimethyl moiety present in diene 2.2d would
prevent oxidation of the skipped diene intermediate 2.3e. Additionally, the gem-dimethyl group is present in several interesting biologically active compounds (outlined in red, Scheme 2-9). TLC monitoring indicated immediate product formation of 2.3e when AlCl₃ was added at room temperature (Scheme 2-9a). The Al(CH₃)₂Cl reaction also generated 2.3e rapidly as evidenced by TLC and ¹H NMR analysis (Scheme 2-9b). Although, for both Lewis acids it was found that the reaction was most efficient when more than one equivalent of Lewis acid was used. The gem-dimethyl diene 2.2d is highly reactive in the Diels-Alder cycloaddition and as such we found Al(CH₃)₂Cl to be more suitable than AlCl₃ for yielding 2.3e.

Although, for both Lewis acids it was found that the reaction was most efficient when more than one equivalent of Lewis acid was used. The gem-dimethyl diene 2.2d is highly reactive in the Diels-Alder cycloaddition and as such we found Al(CH₃)₂Cl to be more suitable than AlCl₃ for yielding 2.3e.

Scheme 2-9: a) Synthesis of 2.3e from 2.1b and 2.2d using Al(CH₃)₂Cl. b) Synthesis of 2.3e from 2.1b and 2.2d using AlCl₃.

Next, we conducted screening reactions for the gem-dimethyl 2.3e in the Nazarov cyclization using Lewis and Bronsted acids to form 2.4e. Due to the vast differences in reactivity of the acids it was necessary to have varying temperatures for each specific reaction. As a relatively strong Lewis acid, the BF₃·O(Et)₂ reaction was started at -78 °C
and warmed to room temperature when no reaction occurred (entry 1). \(\text{In(OTf)}_3\) was refluxed gently when no conversion of \(\text{2.3e}\) was seen at room temperature, although even with heating \(\text{2.4e}\) did not form (entry 2). Both \(\text{SnCl}_4\) and \(\text{TiCl}_4\) reactions were kept at lower temperatures to prevent decomposition; however, a small amount HCl addition on adduct \(\text{2.3e}\) was observed for both reactions (entries 3 and 4). The milder Lewis acids, \(\text{ZnCl}_2\) and \(\text{Al(CH}_3)_2\text{Cl}\) gave no reaction at room temperature (entries 5 and 6). The flask containing \(\text{Al(CH}_3)_2\text{Cl}\) was heated to reflux with no evidence of \(\text{2.4e}\) forming (entry 6). \(\text{H}_3\text{PO}_4\) was used in \(\text{C}_2\text{H}_4\text{Cl}_2\) and toluene, both reactions were refluxed, although no product \(\text{2.4e}\) formation was observed by TLC or \(^1\text{H} \text{NMR}\) (entries 7 and 8). Finally, \(\text{H}_2\text{SO}_4\) was reacted with \(\text{2.3e}\), the temperature was initially kept low but after no reaction occurred it was increased to room temperature, after which decomposition resulted (entry 9).

**Table 2-6:** Screening for gem-dimethyl \(\text{2.3e}\) in the Nazarov cyclization using Lewis and Bronsted acids to form \(\text{2.4e}\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis/Bronsted acid</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{BF}_3\text{O(Et)}_2)</td>
<td>(\text{CH}_2\text{Cl}_2), -78 °C to r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>(\text{In(OTf)}_3)</td>
<td>(\text{CH}_2\text{Cl}_2), r.t. to 30 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>(\text{SnCl}_4)</td>
<td>(\text{CH}_2\text{Cl}_2), -78 to -68 °C</td>
<td>HCl addition</td>
</tr>
<tr>
<td>4</td>
<td>(\text{TiCl}_4)</td>
<td>(\text{CH}_2\text{Cl}_2), -78 to -54 °C</td>
<td>HCl addition</td>
</tr>
<tr>
<td>5</td>
<td>(\text{ZnCl}_2)</td>
<td>(\text{CH}_2\text{Cl}_2), r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Al(CH}_3)_2\text{Cl})</td>
<td>(\text{CH}_2\text{Cl}_2), r.t. to reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>(\text{H}_3\text{PO}_4)</td>
<td>(\text{CH}_2\text{Cl}_2), r.t. to reflux in (\text{C}_2\text{H}_4\text{Cl}_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>(\text{H}_3\text{PO}_4)</td>
<td>Toluene, reflux</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>(\text{H}_2\text{SO}_4)</td>
<td>(\text{CH}_2\text{Cl}_2), variable</td>
<td>decomposition</td>
</tr>
</tbody>
</table>
Lewis Acid catalysts were 25 mol%.

2.3 Tandem Diels-Alder/Nazarov Reaction of Silyl-substituted Ynones

In a previous study, we observed that silyl-substituted diynones demonstrated increased reactivity in both the Diels–Alder and Nazarov reaction.\textsuperscript{34,36} Since silyl substitution can have a strong stabilizing effect on the oxyallyl cation intermediate via the $\beta$-silyl effect,\textsuperscript{47–50} we wondered whether silyl group incorporation onto the terminus of the ynone would sufficiently stabilize the reaction intermediates, enabling the Nazarov reaction to proceed under more mild conditions. For the preliminary reaction, silyl-substituted phenyl ynone 2.1c was allowed to react with 2.2a in the presence of BCl\textsubscript{3}. We observed rapid formation of intermediate 2.3f, which, subsequently underwent the Nazarov cyclization to generate what appeared to be 2.4f by TLC (Scheme 2-10).

Examination of the crude mixture by $^1$H NMR showed only four aromatic peaks and an aliphatic peak that was likely due to a methine proton.

Scheme 2-10: Trimethyl-silyl substituted ynone 2.1c reacted with 2.2a successfully to first form 2.3f, which, rapidly underwent the Nazarov cyclization to give desired product 2.4f.

We had expected to see four peaks in the aromatic region indicating cyclization had occurred in addition to a methine proton in the aliphatic region and this was evident
in the $^1$H NMR (Figure 2-5). Further NMR studies and mass spectrometry characterization showed that 2.4f had been formed.

![Figure 2-5: $^1$H NMR of isolated Nazarov product 2.4f showing four expected peaks in the aromatic region and a methine hydrogen in the aliphatic region.](image)

Interestingly, we have observed that the Diels–Alder product 2.3a formed rapidly with both aluminum and BCl$_3$. However, we did not observe any formation of the desired product 2.4a and more forcing conditions resulted in decomposition of 2.3a (Scheme 2-11a). $^1$H NMR analysis of the crude reaction mixture showed considerable decomposition and no amount of desired 2.4a was detected by GC-MS. Pleased with the successful formation of 2.4f using silyl substituted ynone 2.1c, the reaction was rerun on a larger scale to obtain the yield and ensure reproducibility. Indeed, silyl-substituted
ynone 2.1c underwent the tandem Diels−Alder/Nazarov reaction rapidly to generate the desired product 2.4f in good yield (56%) and excellent diastereoselectivity (>20:1, based on GC−MS analysis), presumably via the oxyallyl cation intermediate 2.13 (Scheme 2-11b). The syn relationship between the methine hydrogen and the TMS group was confirmed by 2D NOESY NMR spectroscopic analysis. Although desilylation is typical in other Nazarov reactions resulting in excellent regiocontrol of the resulting double bond,34,36,47–50 rearomatization via loss of a proton is preferred in this case, leaving the TMS group intact. A stoichiometric amount of Lewis acid was necessary for full conversion of the starting material, a requirement that has often been reported for Nazarov cyclizations.11,34,36

![Scheme 2-11: Attempted tandem Diels-Alder/Nazarov cyclization with terminal ynone yielding 2.3a as the product instead of the desired Nazarov product 2.4a. b) Successful cyclization using a silane substituted ynone 2.1c that is believed to proceed through intermediate 2.13 to yield 2.4f as the major diastereomer in >20:1 ratio by GC-MS. Syn stereochemistry of 2.4f was established through 2D NOESY NMR.](image)

To make the trimethylsilyl ynone starting material 2.1c involves simple chemistry, is inexpensive, and can be completed in one step. Therefore, the synthesis of 2.1c is very economical and a large number of derivatives of 2.1c can be made in the
same way. The synthesis of 2.1c is accomplished by the reaction of acid chloride 2.14 and bis(trimethylsilyl)acetylene 2.15 (Scheme 2-12).

\[
\begin{array}{c}
\text{O} \\
\text{Cl} \\
2.14 \quad \text{TMS} \quad \text{TMS} \\
\text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \\
\text{AlCl}_3 \\
\text{O} \\
\text{2.1c 38\%} \\
\end{array}
\]

Scheme 2-12: Synthesis of ynone 2.1c from acid chloride 2.14 and bis(trimethylsilyl)acetylene 2.15.

A silyl substituent is advantageous since it can be converted into other functional groups or cleaved, providing the potential for a broader scope. A small-scale reaction was conducted with Nazarov 2.4f and tetrabutylammonium fluoride (TBAF) at 0 °C. We found that the silyl group was readily cleaved to give 2.16 (Scheme 2-13). Additionally, literature precedence shows several conditions for transformation of silyl group, enabling it to participate in other reaction pathways.\(^{51}\)

\[
\begin{array}{c}
\text{O} \\
\text{2.4f} \\
\text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \\
\text{TBAF} \\
\text{O} \\
\text{2.16} \\
\end{array}
\]

Scheme 2-13: Removal of silyl substituent is easily accomplished with tetrabutylammonium fluoride (TBAF).

The \textit{para}-substituted amino ynone 2.1d successfully formed 2.3g but failed to generate the desired product 2.4g (Scheme 2-14). Based on the \(^1\text{H}\) NMR spectrum of the crude mixture, it is unclear exactly what happened after intermediate 2.3g was formed but decomposition may have resulted. With respect to 2.4g not forming, the Lewis acid may have preferentially bound to the amine group instead of the carbonyl oxygen.
Scheme 2-14: The para-substituted amino ynone 2.1d successfully formed 2.3g but failed to generate the desired product 2.4g.

Having established the proof of concept, we began looking at the scope of this reaction (Table 2-7). We first looked at electron-rich aryls, and although the o-methoxy-substituted ynone 2.1e had rapidly formed the Diels–Alder adduct and then was demethylated\(^\text{19}\) we felt that it was important for the scope to include a successful example of 2.1e undergoing the Nazarov reaction. Another graduate student in the Chalifoux lab, Punyanuch Sophanpanichkul, synthesized an ynone having a slightly bulkier ethyl group (2.1f, entry 3) in an attempt to minimize dealkylation, but this pathway was still faster than the Nazarov step, resulting only in the formation of 2.16. Punyanuch next used AlBr\(_3\) with 2.1f, she did obtain desired product 2.4h, albeit in poor yield (entry 3). The p-methoxy-substituted ynone 2.1g successfully underwent the Diels–Alder/Nazarov reaction to generate 2.4i in modest yield (entry 4). It is not surprising that electron-donating groups (EDG) in the ortho and para positions (2.1f–g) perform poorly as they are less reactive dienophiles for the Diels–Alder cycloaddition and they inductively deactivate the aryl carbon undergoing the rate-determining Nazarov cyclization. We were pleased that bromine-substituted ynones 2.1h and 2.1i both reacted to give compounds 2.4j and 2.4k in 51% and 63% yield, respectively, as these products will be suitable for subsequent transition-metal-catalyzed coupling reactions (entries 5 and 6).
Having an electron-withdrawing group (EWG) in the ortho position (2.1j) resulted in significant decomposition of 2.4l and while preliminary results with 2.1j were not promising, Punyanuch was successful in obtaining a 26% yield of 2.4l (entry 7). However, the electron-poor para-substituted ynone 2.1k successfully gave 2.4m in very good yield (entry 8). Fluorinated compounds have considerable importance in biologically active molecules, and as such, we were pleased to observe that substrate 2.1l underwent the tandem Diels–Alder/Nazarov reaction quickly to form 2.4n in excellent yield (entry 9). The naphthyl-substituted ynone 2.1m was also tolerated and rapidly generated 2.4o in 57% yield (entry 10).

Table 2-7: Substrate scope of ynone 2.1 for the tandem Diels-Alder/Nazarov cyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product</th>
<th>Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1c</td>
<td>H</td>
<td><img src="image1.png" alt="Diagram" /></td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>2.1e</td>
<td>o-MeO</td>
<td><img src="image2.png" alt="Diagram" /></td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>2.1f</td>
<td>(\alpha\text{-EtO} )</td>
<td><img src="image" alt="Chemical Structure 2.4h" /></td>
<td>17</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>2.1g</td>
<td>(p\text{-MeO} )</td>
<td><img src="image" alt="Chemical Structure 2.4i" /></td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>2.1h</td>
<td>(\alpha\text{-Br} )</td>
<td><img src="image" alt="Chemical Structure 2.4j" /></td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>2.1i</td>
<td>(p\text{-Br} )</td>
<td><img src="image" alt="Chemical Structure 2.4k" /></td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>2.1j</td>
<td>(\alpha\text{-CF}_3 )</td>
<td><img src="image" alt="Chemical Structure 2.4l" /></td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>2.1k</td>
<td>(p\text{-CF}_3 )</td>
<td><img src="image" alt="Chemical Structure 2.4m" /></td>
<td>63</td>
</tr>
</tbody>
</table>
We also decided to look at meta-substituted aryl ynones in order to gain insight into the regioselectivity of the Nazarov step with regard to these substrates. Punyanuch investigated these reactions and performed the work necessary to complete the regioselective studies (Table 2-8). Using AlBr$_3$ produced the desired product 2.4p in excellent yield with excellent regioselectivity (entry 1). Both the trifluoromethyl- and methyl-substituted ynones, 2.1o and 2.1p, reacted to generate the Nazarov products 2.4q and 2.4r, in modest yields 47%, and 41%, respectively (entries 2 and 3). Chloro-substituted ynone 2.1q provided product 2.4s in modest yield as an inseparable 3:1 mixture of regioisomers (entry 4). This decrease in regioselectivity can possibly be attributed to a steric effect as cyclization at C-2 of the aryl would be relatively easier in 5n on account of the smaller chlorine substituent at C-3. Based on Punyanuch’s results it appears that having an EDG para to the carbon that is making the C–C bond during the rate-determining Nazarov cyclization (and meta to the carbonyl) increases the rate of the reaction and the yield.
Table 2-8: Substrate scope for regioisomeric investigations.

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Products</th>
<th>Yield [%][a]</th>
<th>2.4:2.4′ ratio[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1n</td>
<td>MeO</td>
<td>2.4p:2.4p′</td>
<td>72</td>
<td>15:1</td>
</tr>
<tr>
<td>2</td>
<td>2.1o</td>
<td>CF₃</td>
<td>2.4q:2.4q′</td>
<td>47[b]</td>
<td>45:1</td>
</tr>
<tr>
<td>3</td>
<td>2.1p</td>
<td>CH₃</td>
<td>2.4r:2.4r′</td>
<td>41</td>
<td>10:1</td>
</tr>
<tr>
<td>4</td>
<td>2.1q</td>
<td>Cl</td>
<td>2.4s:2.4s′</td>
<td>44[b]</td>
<td>3:1</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] Isolated yield of both regioisomers (2.4r:2.4r′) in a 10:1 ratio, entry 2, and a 3:1 ratio for 2.4s:2.4s′, entry 4. [c]Crude regioisomeric ratio of products determined by GC-MS analysis and ¹H NMR. Stereochemistry of minor regioisomers was assigned by analogy.

We expanded our heteroaryl-substituted ynone scope to see if other substrates would also participate in the tandem Diels–Alder/Nazarov reaction (Scheme 2-15).

Thiophene-substituted ynone 2.1r rapidly underwent the tandem reaction to give 2.4t in 66\% yield. Punyanuch synthesized the furan-substituted ynone 2.1s which also worked to provide 2.4u in good yield. She also successfully used N-methylpyrrole derivative 2.1s in the tandem reaction to provide 2.4v in good yield. It should be noted that we observed an unexpected minor side product in these reactions, determined to be desilylated products 2.4t–v. While 2.4t was isolated in 7\% yield (relative stereochemistry not determined), Punyanuch detected 2.4u in a trace amount, and she was unable to isolate 2.4v due to its decomposition upon attempted isolation. Nonetheless, we were pleased that the heteroaryl-substituted ynones reacted to generate an interesting class of [5–5–6] heterotricyclic ring systems. A plausible explanation for the formation of desilylated products 2.4t′–v’ is that, due to the less aromatic character of these heteroaryl systems, the rate of desilylation in the oxyallyl cation intermediate 2.17 becomes competitive with
the rate of deprotonation/rearomatization, as seen in analogous systems.\textsuperscript{50} A subsequent [1,5]-hydride shift in 2.18 to re-establish aromaticity followed by protonation of 2.19 during workup would provide product 2.4t′–v′.

Scheme 2-15: five-membered heterocycles underwent the tandem Diels-Alder/Nazarov reactions to give the desired products in very good yields. Desilylated side products were present in both reactions, crude ratios determined by GC-MS or \(^1\)H NMR analysis. Proposed mechanism for desilylation during the tandem Diels-Alder/Nazarov reaction of heteroaromatic yrones.

2.3.1 Catalytic Screening for Tandem Diels-Alder/Nazarov Reaction

Various catalysts were screened for the tandem Diels-Alder/Nazarov reaction. It is of considerable interest for the multi-component reaction to be catalytic as well as enantioselective. Even after refluxing in C\(_2\)H\(_4\)Cl\(_2\) no reaction occurred with 2.1c and 2.2a using Wilkinson’s catalyst (RhCl(PPh\(_3\))\(_3\)). A colorless to light yellow color change was observed upon addition of the catalyst to the reaction mixture. This suggests that the catalyst did bind to the 2.1c as 2.2a was added after the catalyst (entry 1). In order to
form a more reactive catalytic species, Wilkinson’s catalyst and AgSbF\(_6\) were used in the reaction mixture; however, the resulting activated catalyst was not strong enough to promote the reaction of \(2.1c\) and \(2.2a\) (entry 2). A cloudy solution was instantly visible after adding AuCl\(_3\) to AgSbF\(_6\), this indicates removal of a chloride ion from the catalyst to form insoluble AgCl. Even though a more reactive species of Au\(^{3+}\) was present in solution, no reaction occurred (entry 3).

No reaction took place when RuCl\(_2\)(PTA)\(_4\) was added to \(2.1c\) and \(2.2a\) in CH\(_2\)Cl\(_2\) or refluxing in EtOH:H\(_2\)O (entries 4 and 5). A color change was observed only after the addition of diene \(2.2a\), indicating that the catalyst may be binding to \(2.2a\) instead of ynone \(2.1c\) (entry 5). Formation of \(2.3f\) was evident by TLC from Wilkinson’s catalysts reaction, although this may be from heating in toluene. No amount of desired product \(2.4f\) was seen by TLC (entry 6). In the Cu(OTf)\(_2\) reaction \(2.3f\) formed but did not react further to give \(2.4f\). The formation of \(2.4f\) was not observed and \(2.3f\) may have occurred due to heating but it is not entirely clear (entry 7). Given that the rhodium catalyst appeared to bind to \(2.1c\), we intend to spend more time investigating more reactive rhodium catalysts.

**Table 2-9**: Catalytic screening for tandem Diels-Alder/Nazarov reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RhCl(PPh(_3))(_3)</td>
<td>C(_2)H(_4)Cl(_2), Δ</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>RhCl(PPh(_3))(_3)/ AgSbF(_6)</td>
<td>C(_2)H(_4)Cl(_2), r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>AuCl(_3) / AgSbF(_6)</td>
<td>C(_2)H(_4)Cl(_2), r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>RuCl(_2)(PTA)(_4)</td>
<td>CH(_2)Cl(_2)</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>5</td>
<td>RuCl₂(PTA)₄</td>
<td>EtOH:H₂O (4:1) ∆</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>RhCl(PPh₃)₃</td>
<td>toluene ∆</td>
<td>2.3f formation</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)₂</td>
<td>C₂H₄Cl₂, ∆</td>
<td>2.3f formed</td>
</tr>
</tbody>
</table>

### 2.4 Conclusion

In conclusion, we have demonstrated a tandem Diels–Alder/Nazarov reaction of 3-(trimethylsilyl)-1-aryl and 3-(trimethylsilyl)-1-heteroaryl ynone to yield biologically important polycyclic scaffolds in a one-pot reaction. Additionally, we have shown that our method can be applied to a variety of substituted ynones, allowing for extensive modification of the core structure. The one-pot tandem Diels–Alder/Nazarov reaction is highly regio- and diastereoselective, providing concise and efficient access to broad structural diversity while also imparting useful functional handles (arene, alkene, TMS, and ketone) for further chemical elaboration.

### 2.5 Experimental

**General procedures and methods:** Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. CH₂Cl₂ was purified using a PureSolv MD 5 solvent purification system. Evaporation and concentration in vacuo by rotary evaporation. Where appropriate, reactions were performed in standard, dry glassware under an inert atmosphere of N₂. Column chromatography: Silica gel irregular 60 Å (40-60 micron) from VWR International. The bulb-to-bulb distillation was performed using a kugelrohr apparatus, Büchi GKR-51. Thin-layer chromatography (TLC): glass sheets covered with silica gel 60 F₂₅₄ from Millipore a Corporation; visualization by UV light, anisaldehyde stain or KMnO₄ stain.
IR spectra (cm\(^{-1}\)): Thermo Nicolet 6700 FT-IR (diamond ATR), data are reported as cm\(^{-1}\).

\(^1\)H, \(^{19}\)F, and \(^{13}\)C NMR: Varian NMR 400 MHz, 500 MHz at rt in CDCl\(_3\); solvent peaks (7.26 ppm and 77.16 ppm for \(^1\)H and \(^{13}\)C, respectively) or C\(_6\)D\(_6\); solvent peaks (7.16 ppm and 128.06 ppm for \(^1\)H and \(^{13}\)C, respectively) as reference. GCMS (EI): Agilent 7890A with a 5970C mass spectrometer with triple axis detector using a 122-5532UI DB-5MS Ui column (30m x 0.25mm). ESI/APCI-TOF MS: Agilent G6230A instrument with purine and HP-Ø921 as internal calibrants.

\[
\begin{align*}
\text{R'}\text{Cl} + \text{TMS} &= \text{AlCl}_3 \
\text{DCM, 0 ºC} &\rightarrow \text{R} = \text{TMS}
\end{align*}
\]

**General procedure for 1-Aryl-3-(Trimethylsilyl) ynone synthesis:**\(^{52,53}\)

To a solution of acid chloride (1.1 equiv.) in CH\(_2\)Cl\(_2\) at 0 ºC under N\(_2\) atmosphere was added AlCl\(_3\) (1.0 equiv.) followed by bis(trimethylsilyl)acetylene (1.0 equiv.). The reaction was quenched at 0 ºC through the addition of saturated aqueous NH\(_4\)Cl and extracted with Et\(_2\)O. The layers were separated, the organic phase washed with H\(_2\)O, brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo.

\[2.1c\]

**2.1c was synthesized following the general procedure:**\(^{54,55}\) This reaction was performed according to the general procedure, acid chloride (5.135 g, 36.53 mmol) and bis(trimethylsilyl)acetylene (5.50 g, 32.3 mmol) in CH\(_2\)Cl\(_2\) (50 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7
buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$ (17:1)] to yield 2.1c (2.81 g, 43%) as a pale yellow oil. R$_f$ = 0.5 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.17 – 8.09 (m, 2H), 7.64 – 7.56 (m, 1H), 7.51 – 7.43 (m, 2H), 0.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 177.7, 136.5, 134.2, 129.7, 128.6, 100.9, 100.6, -0.6; IR (film): 3066, 2961, 2914, 1647, 1597 cm$^{-1}$; HRMS (ESI-TOF) m/z calcd for [C$_{12}$H$_{14}$OSi+H]$^+$ 203.0887; found 203.0888.

2.1e was synthesized following the general procedure: This reaction was performed according to the general procedure, acid chloride (1.272 g, 7.454 mmol) and bis(trimethylsilyl)acetylene (1.12 g, 6.57 mmol) in CH$_2$Cl$_2$ (12 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$/EtOAc (80:19:1)] to yield 2.1e (1.13 g, 74%) as a pale yellow oil. R$_f$ = 0.5 (EtOAc:hexanes, 1:5); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.98 (d, $J$ = 7.8 Hz, 1H), 7.49 (dd, $J$ = 8.8, 7.3 Hz, 1H), 7.04 – 6.91 (m, 2H), 3.88 (s, 3H), 0.26 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 176.4, 159.9, 135.1, 132.8, 126.4, 120.3, 112.3, 103.0, 98.5, 55.8, -0.6; IR (film): 2958, 2838, 2151, 1647, 1622, 1597 cm$^{-1}$; HRMS (APCI-TOF) m/z calcd for [C$_{13}$H$_{16}$O$_2$Si+H]$^+$ 233.0992; found 233.0981.
2.1g was synthesized following the general procedure:\textsuperscript{53,54} This reaction was performed according to the general procedure, acid chloride (1.10 g, 6.45 mmol) and bis(trimethylsilyl)acetylene (999 mg, 5.86 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; CH\textsubscript{2}Cl\textsubscript{2}/hexanes (1:1)] to yield 2.1g (690 mg, 51\%) as a colorless oil. \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 8.10\) (m, 2H), 6.94 (m, 2H), 3.87 (s, 3H), 0.30 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 176.4, 164.6, 132.1, 130.0, 113.9, 101.1, 99.6, 55.7, -0.5\); IR (film): 2971, 2904, 2841, 2148, 1634, 1591 cm\textsuperscript{-1}; HRMS (APCI-TOF) \(m/z\) calcd for [C\textsubscript{13}H\textsubscript{16}O\textsubscript{2}Si+H]\textsuperscript{+} 233.0992; found 233.0983.

\begin{center}
\includegraphics[width=0.2\textwidth]{2.1h.png}
\end{center}

2.1h was synthesized following the general procedure: This reaction was performed according to the general procedure, acid chloride (1.621 g, 7.388 mmol) and bis(trimethylsilyl)acetylene (1.14 g, 6.69 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH\textsubscript{2}Cl\textsubscript{2}/EtOAc (86:13:1)] to yield 2.1h (1.44 g, 77\%) as a yellow oil. \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 8.03\) (d, \(J \approx 7.6\ \text{Hz}, 1\text{H}\)), 7.66 (d, \(J \approx 7.8\ \text{Hz}, 1\text{H}\)), 7.42 (dd, \(J = 7.4, 7.3\ \text{Hz}, 1\text{H}\)), 7.36 (dd, \(J = 7.5, 7.3\ \text{Hz}, 1\text{H}\)), 0.28 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 177.0, 136.9,\)
135.1, 133.5, 133.3, 127.4, 121.3, 101.7, 101.5, -0.7; IR (film): 2965, 2154, 1647, 1584 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C₁₂H₁₃BrOSi+H]⁺ 280.9992; found 280.9994.

**2.1i was synthesized following the general procedure:** This reaction was performed according to the general procedure, acid chloride (1.58 g, 7.20 mmol) and bis(trimethylsilyl)acetylene (1.12 g, 6.57 mmol) in CH₂Cl₂ (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH₂Cl₂ (60:40)] to yield **2.1i** (568 mg, 31%) as a colorless oil. Rᵣ = 0.6 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 7.98 (m, 2H), 7.62 (m, 2H), 0.31 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 176.6, 135.4, 132.1, 131.1, 129.8, 101.5, 100.5, -0.6; IR (film): 2961, 2901, 2151, 1644 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₂H₁₃BrOSi+H]⁺ 280.9992; found 280.9978.

**2.1j** was synthesized following the general procedure: This reaction was performed according to the general procedure, acid chloride (3.35 g, 16.0 mmol) and bis(trimethylsilyl)acetylene (2.61 g, 15.0 mmol) in CH₂Cl₂ (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [silica gel; hexanes/CH₂Cl₂ (10:1)] to yield **2.1j** (3.42 mg, 84%) as a pale-yellow oil. Rᵣ = 0.5
(hexanes:EtOAc, 10:1); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.08 - 8.03$ (m, 1H), 7.79 – 7.73 (m, 1H), 7.70 – 7.61 (m, 2H), 0.28 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 177.4$, 137.0 (q, $J = 1.6$ Hz), 132.3, 131.9, 131.7, 128.6 (q, $J = 32.9$ Hz), 127.4 (q, $J = 5.7$ Hz), 123.3 (q, $J = 273.7$ Hz), 102.1, 101.7, -0.8; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -58.50$; IR (film): 2966, 2253, 2153 cm$^{-1}$; HRMS (ESI-TOF) m/z calcd for [C$_{13}$H$_{13}$F$_3$SiO+Na]$^+$ 293.0586; found 293.0580.

2.1k was synthesized following the general procedure: This reaction was performed according to the general procedure, acid chloride (1.105 g, 5.298 mmol) and bis(trimethylsilyl)acetylene (821 mg, 4.81 mmol) in CH$_2$Cl$_2$ (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$ (4:1)] to yield 2.1k (774 mg, 60%) as a pale yellow oil. 

R$_f = 0.6$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.24 – 8.19$ (m, 2H), 7.74 – 7.70 (m, 2H), 0.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 176.5$, 139.1, 135.4 (q, $J = 32.7$ Hz), 130.0, 125.8 (q, $J = 3.7$ Hz), 123.7 (q, $J = 272.7$ Hz), 102.4, 100.4, -0.7; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -63.3$; IR (film): 2965, 2911, 2160, 1657 cm$^{-1}$; HRMS (APCI-TOF) m/z calcd for [C$_{13}$H$_{13}$F$_3$OSi+H]$^+$ 271.0761; found 271.0748.
2.1l was synthesized following the general procedure. This reaction was performed according to the general procedure, acid chloride (1.825 g, 11.51 mmol) and bis(trimethylsilyl)acetylene (1.85 g, 10.9 mmol) in CH₂Cl₂ (15 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH₂Cl₂ (4:1)] to yield 2.1l (1.65 g, 69%) as a colorless oil. Rₓ = 0.6 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 8.24 – 8.06 (m, 2H), 7.23 – 7.04 (m, 2H), 0.31 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 176.1, 166.6 (d, J = 256.7 Hz), 133.1 (d, J = 2.8 Hz), 132.4 (d, J = 9.7 Hz), 115.9 (d, J = 22.2 Hz), 101.0, 100.6, -0.6; ¹⁹F NMR (376 MHz, CDCl₃): δ = -103.0 – -103.2 (m); IR (film): 2968, 2908, 2151, 1651, 1594 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₂H₁₃FOSi+H]⁺ 221.0792; found 221.0777.

2.1m was synthesized following the general procedure. This reaction was performed according to the general procedure, acid chloride (1.77 g, 9.29 mmol) and bis(trimethylsilyl)acetylene (1.44 g, 8.45 mmol) in CH₂Cl₂ (15 mL). The solvent was removed in vacuo and the crude product purified by Kugelrohr distillation at 165 °C to yield 2.1m (543 mg, 26%) as a burnt orange oil. Rₓ = 0.6 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 8.70 (s, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 8.1 Hz,
1H), 7.89 – 7.83 (m, 2H), 7.64 – 7.52 (m, 2H), 0.38 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 177.7, 136.2, 134.1, 133.0, 132.4, 130.0, 129.1, 128.6, 128.0, 127.0, 124.0, 101.1, 100.6, -0.5\); IR (film): 3060, 2958, 2904, 2154, 1752, 1638, 1625 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for [C\(_{16}\)H\(_{16}\)OSi+H]\(^+\) 253.1043; found 253.1046.

2.1r was synthesized following the general procedure\(^{55}\). This reaction was performed according to the general procedure, acid chloride (1.281 g, 8.738 mmol) and bis(trimethylsilyl)acetylene (1.20 g, 7.04 mmol) in CH\(_2\)Cl\(_2\) (20 mL). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH\(_2\)Cl\(_2\) (95:5)] to yield 2.1r (927 mg, 63%) as a pale yellow oil. \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.89\) (d, \(J = 3.7\) Hz, 1H), 7.68 (d, \(J = 4.8\) Hz, 1H), 7.13 (dd, \(J = 4.8, 3.7\) Hz 1H), 0.27 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 169.4, 144.6, 135.7, 135.5, 128.4, 100.4, 99.1, -0.7\); IR (film): 3098, 2971, 2898, 2151, 1619 cm\(^{-1}\); HRMS (APCI-TOF) \(m/z\) calcd for [C\(_{10}\)H\(_{12}\)OSSi+H]\(^+\) 209.0451; found 209.0442.
**Compound 2.4f:** To a solution of 2.1c (231 mg, 1.14 mmol) in CH$_2$Cl$_2$ (12 mL) under N$_2$ at 0 °C was added boron trichloride (1.14 mL, 1.14 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (188 mg, 2.28 mmol). The reaction was stirred until complete by TLC (0.5 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$/EtOAc (83:16:1)] to yield 2.4f (182 mg, 56%) as a pale yellow oil. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 180 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). $R_f = 0.6$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.65 – 7.59$ (m, 1H), 7.53 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.24 – 7.16 (m, 1H), 2.68 (dd, $J = 7.1$, 3.7 Hz, 1H), 2.41 (d, $J = 14.7$ Hz, 1H), 2.35 (dd, $J = 14.5$, 3.8 Hz, 1H), 2.29 (d, $J = 14.7$ Hz, 1H), 2.20 (dd, $J = 14.0$, 6.4 Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), -0.06 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 210.1$, 162.3, 137.2, 134.6, 126.9, 126.3, 126.0, 124.4, 123.4, 51.0, 37.2, 36.4, 33.4, 19.8, 19.1, -3.7; IR (film): 2958, 2933, 2838, 1708, 1606 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{18}$H$_{26}$OSi+H]$^+$ 285.1669; found 285.1677.

![Chemical Structure](image)
**Compound 2.16:** To a solution of 2.1e (163 mg, 0.701 mmol) in CH$_2$Cl$_2$ (10 mL) under N$_2$ at 0 °C was added boron trichloride (0.70 mL, 0.70 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (115 mg, 1.40 mmol). The reaction was stirred until complete by TLC (15 min.). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$/EtOAc (90:9:1)] to yield 2.16 (158 mg, 75%) as a pale yellow oil. R$_f$ = 0.8 (EtOAc:hexanes, 1:5); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 12.14 (s, 1H), 7.71 – 7.62 (m, 1H), 7.51 – 7.40 (m, 1H), 7.02 – 6.95 (m, 1H), 6.90 – 6.82 (m, 1H), 2.80 (s, 4H), 1.69 (s, 3H), 1.64 (s, 3H), -0.04 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 207.5, 162.9, 143.2, 136.8, 135.1, 132.9, 123.4, 121.9, 119.3, 119.0, 118.4, 36.6, 36.1, 18.3, 18.3, -1.0; IR (film): 3072, 2955, 2908, 2854, 2810, 1625, 1603 cm$^{-1}$; HRMS (ESI-TOF) m/z calcld for [C$_{18}$H$_{24}$O$_2$Si – C$_3$H$_9$Si]$^+$ 227.1067; found 227.1076.

**Compound 2.4i:** To a solution of 2.1g (125 mg, 0.538 mmol) in CH$_2$Cl$_2$ (12 mL) under N$_2$ at 0 °C was added boron trichloride (0.54 mL, 0.54 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (88.4 mg, 1.08 mmol). The reaction was stirred until complete by TLC (3 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed
with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH₂Cl₂/ EtOAc (60:39:1)] to yield 2.4i (74 mg, 44%) as a colorless oil. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). Rₓ = 0.4 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 7.61 – 7.56 (m, 1H), 6.81 – 6.75 (m, 2H), 3.85 (s, 3H), 2.67 (dd, J = 7.2, 3.8 Hz, 1H), 2.41 (d, J = 15.4 Hz, 1H), 2.37 – 2.31 (m, 1H), 2.27 (d, J = 14.7 Hz, 1H), 2.22 (dd, J = 15.5, 6.5 Hz, 1H), 1.54 (s, 3H), 1.46 (s, 3H), -0.04 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 208.1, 165.3, 165.2, 130.8, 126.8, 126.4, 125.3, 113.5, 108.1, 55.6, 51.3, 37.3, 36.4, 33.5, 20.0, 19.1, -3.7; IR (film): 2949, 2901, 2838, 1698, 1597 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₀H₂₆O₂Si+H]⁺ 315.1775; found 315.1754.

**Compound 2.4j:** To a solution of 2.1h (164 mg, 0.583 mmol) in CH₂Cl₂ (10 mL) under N₂ at 0 °C was added boron trichloride (0.58 mL, 0.58 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (95.8 mg, 1.17 mmol). The reaction was stirred until complete by TLC (4-5 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the
crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH₂Cl₂/EtOAc (70:29:1)] to yield 2.4j (108 mg, 51%) as a pale yellow solid. The diastereomeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 180 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). Rₚ = 0.5 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 7.37 – 7.27 (m, 3H), 2.71 (dd, J = 7.1, 3.8 Hz, 1H), 2.44 – 2.32 (m, 2H), 2.30 – 2.22 (m, 1H), 2.22 – 2.14 (m, 1H), 1.52 (s, 3H), 1.42 (s, 3H), -0.06 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 207.2, 165.5, 134.9, 134.3, 131.1, 126.75, 126.68, 123.5, 119.4, 51.8, 36.63, 36.60, 33.5, 19.9, 19.2, -3.6; IR (film): 2961, 2923, 2866, 2829, 1685 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C₁₈H₂₃BrOSi+H]+ 363.0774; found 363.0775.

Compound 2.4k: To a solution of 2.1i (146 mg, 0.519 mmol) in CH₂Cl₂ (10 mL) under N₂ at 0 °C was added boron trichloride (0.52 mL, 0.52 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (85.3 mg, 1.04 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH₂Cl₂/EtOAc (60:39:1)] to yield 2.4k (120 mg, 63%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be > 20:1 by GC analysis.
(GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). Rf = 0.3 (EtOAc:hexanes, 1:10); 1H NMR (400 MHz, CDCl3): δ = 7.52 – 7.46 (m, 2H), 7.38 – 7.33 (m, 1H), 2.68 (dd, J = 7.2, 3.7 Hz, 1H), 2.41 (d, J = 14.9 Hz, 1H), 2.34 (dd, J = 14.7, 3.8 Hz, 1H), 2.29 – 2.15 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), -0.04 (s, 9H); 13C NMR (100 MHz, CDCl3): δ = 208.9, 164.1, 136.0, 130.1, 129.7, 127.6, 126.8, 126.5, 124.7, 51.1, 37.5, 36.3, 33.3, 19.9, 19.1, -3.7; IR (film): 2952, 2927, 2838, 1708, 1591 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C18H23BrOSi+H]⁺ 363.0774; found 363.0755.

**Compound 2.4m:** To a solution of 2.1k (124 mg, 0.459 mmol) in CH2Cl2 (10 mL) under N2 at 0 °C was added boron trichloride (0.46 mL, 0.46 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (75.4 mg, 0.917 mmol). The reaction was stirred until complete by TLC (0.5-1 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO3 and extracted with Et2O. The layers were separated, the organic phase washed with H2O, brine, and dried over Na2SO4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH2Cl2/EtOAc (70:28:2)] to yield 2.4m (102 mg, 63%) as an off-white solid. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). Rf = 0.6 (EtOAc:hexanes, 1:10); 1H NMR (400 MHz,
CDCl$_3$): $\delta = 7.77 - 7.73$ (m, 1H), 7.64 – 7.61 (m, 1H), 7.53 – 7.49 (m, 1H), 2.78 (dd, $J = 7.2, 3.8$ Hz, 1H), 2.48 (d, $J = 15.0$ Hz, 1H), 2.42 – 2.29 (m, 2H), 2.25 (dd, $J = 14.2, 6.8$ Hz, 1H), 1.55 (s, 3H), 1.45 (s, 3H), -0.02 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 209.4, 162.7, 139.7, 136.0$ (q, $J = 32.0$ Hz), 126.9, 126.6, 124.1, 123.9 (q, $J = 273.2$ Hz), 123.1 (q, $J = 3.6$ Hz), 121.4 (q, $J = 3.8$ Hz), 51.5, 37.9, 36.4, 33.5, 19.9, 19.1, -3.8; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -62.91$; IR (film): 2955, 2899, 2837, 1714, 1622 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{19}$H$_{23}$F$_3$OSi+H]$^+$ 353.1543; found 353.1534.

**Compound 2.4n:** To a solution of 2.1l (144 mg, 0.654 mmol) in CH$_2$Cl$_2$ (10 mL) under N$_2$ at 0 °C was added boron trichloride (0.65 mL, 0.65 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (107 mg, 1.31 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH$_2$Cl$_2$/EtOAc (70:29:1)] to yield 2.4n (141 mg, 71%) as an off-white solid. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 180 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). $R_f = 0.6$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.66 - 7.59$ (m, 1H), 7.03 – 6.96 (m, 1H), 6.95 – 6.87 (m, 1H), 2.70 (dd, $J = 7.2, 3.8$ Hz, 1H), 2.48 (d, $J = 15.0$ Hz, 1H), 2.42 – 2.29 (m, 2H), 2.25 (dd, $J = 14.2, 6.8$ Hz, 1H), 1.55 (s, 3H), 1.45 (s, 3H), -0.02 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 209.4, 162.7, 139.7, 136.0$ (q, $J = 32.0$ Hz), 126.9, 126.6, 124.1, 123.9 (q, $J = 273.2$ Hz), 123.1 (q, $J = 3.6$ Hz), 121.4 (q, $J = 3.8$ Hz), 51.5, 37.9, 36.4, 33.5, 19.9, 19.1, -3.8; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = -62.91$; IR (film): 2955, 2899, 2837, 1714, 1622 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{19}$H$_{23}$F$_3$OSi+H]$^+$ 353.1543; found 353.1534.
7.2, 3.6 Hz, 1H), 2.43 – 2.32 (m, 2H), 2.28 – 2.14 (m, 2H), 1.52 (s, 3H), 1.44 (s, 3H), -0.04 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 208.2, 167.4 (d, $J$ = 255.5 Hz), 165.5 (d, $J$ = 9.2 Hz), 133.7 (d, $J$ = 1.6 Hz), 126.7, 126.5, 125.8 (d, $J$ = 10.7 Hz), 114.4 (d, $J$ = 24.1 Hz), 110.8 (d, $J$ = 22.1 Hz), 51.3, 37.6 (d, $J$ = 2.1 Hz), 36.4, 33.4, 19.9, 19.1, -3.7; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ = -102.81 (m); IR (film): 2958, 2914, 1708, 1603, 1587 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{18}$H$_{23}$FOSi+H]$^+$ 303.1575; found 303.1551.

**Compound 2.4o:** To a solution of 2.1m (158 mg, 0.626 mmol) in CH$_2$Cl$_2$ (12 mL) under N$_2$ at -40 °C was added boron trichloride (0.63 mL, 0.63 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (102 mg, 1.24 mmol). The reaction was stirred until complete by TLC (1 h). The reaction was quenched at -40 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by washing with cold hexanes to yield 2.4o (120 mg, 57%) as a beige solid. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). $R_f$ = 0.5 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.31 – 8.24 (m, 1H), 7.94 – 7.89 (m, 1H), 7.72 (s, 2H), 7.64 – 7.52 (m, 2H), 2.97 – 2.87 (m, 2H), 2.83 (dd, $J$ = 7.8, 6.3 Hz, 1H), 2.39 (dd, $J$ = 14.5, 6.2 Hz, 1H), 2.15 (dd, $J$ = 14.1, 7.8 Hz, 1H), 1.66 (s, 3H), 1.58 (s, 3H), -0.05 (s,
\[ ^{13}\text{C} \text{NMR} \ (100 \text{ MHz, } \text{CDCl}_3): \ \delta = 209.0, 162.4, 138.1, 134.6, 130.7, 129.7, 128.5, 128.1, 127.9, 127.5, 127.0, 125.7, 119.8, 53.2, 40.0, 37.2, 34.6, 19.5, 19.0, -2.0; \ \text{IR (film):} \ \nu = 3056, 2914, 2838, 1689, 1591 \text{ cm}^{-1}; \ \text{HRMS (APCI-TOF)} \ m/z \ \text{calcd for [C}_{22}\text{H}_{26}\text{OSi+H}]^+ \ 335.1826; \ \text{found} \ 335.1808. \]

**Compound 2.4t:** To a solution of 2.1r (203 mg, 0.974 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (12 mL) under N\textsubscript{2} at -78 °C was added boron trichloride (0.97 mL, 0.97 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (160 mg, 1.95 mmol). The reaction was stirred for 30 minutes at -78 °C and then removed from bath and allowed to warm gradually to 0 °C until complete by TLC (1 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO\textsubscript{3} and extracted with Et\textsubscript{2}O. The layers were separated, the organic phase washed with H\textsubscript{2}O, brine, and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH\textsubscript{2}Cl\textsubscript{2}/EtOAc (70:28:2)] to yield 2.4t (188 mg, 66%) as a yellow oil. The diasteromeric ratio of the crude product was determined to be > 20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 180 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). R\textsubscript{f} = 0.5 (EtOAc:hexanes, 1:10); \(^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3): \ \delta = 7.82 \ (d, J = 4.8 \text{ Hz, } 1\text{H}), 6.89 \ (d, J = 4.8, \text{ Hz, } 1\text{H}), 2.93 \ (dd, J = 6.9, 3.1 \text{ Hz, } 1\text{H}), 2.41 \ (dd, J = 14.6, 3.2 \text{ Hz, } 1\text{H}), 2.31 \ (d, J = 15.5 \text{ Hz, } 1\text{H}), 2.21 – 2.10 \ (m, 2\text{H}), 1.56 \ (s, 3\text{H}), 1.42 \ (s, 3\text{H}), -0.03 \ (s, 9\text{H}); \ ^{13}\text{C} \text{NMR} \ (100 \text{ MHz, CDCl}_3): \ \delta = 200.2, 176.0, 140.6,
139.5, 126.2, 126.1, 122.1, 56.0, 36.9, 35.9, 33.4, 19.6, 19.2, -3.7; IR (film): 2942, 2847, 1695 cm\(^{-1}\); HRMS (APCI-TOF) \(m/z\) calcd for \([C_{16}H_{22}OSSi+H]^+\) 291.1233; found 291.1207.

![Structure](image)

The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; hexanes/CH\(_2\)Cl\(_2\)/EtOAc (70:28:2)] to yield \(2.4t’\) (15 mg, 7%) as a colorless oil. \(R_f = 0.4\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.86\) (d, \(J = 4.8\) Hz, 1H), 7.03 (d, \(J = 4.8\) Hz, 1H), 3.55 – 3.48 (m, 1H), 3.17 – 3.10 (m, 1H), 2.48 – 2.34 (m, 2H), 2.33 – 2.24 (m, 1H), 2.11 (dd, \(J = 14.5, 4.3\) Hz, 1H), 1.65 (s, 3H), 1.51 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 199.7, 172.1, 141.7, 140.6, 127.2, 126.0, 122.8, 52.6, 37.0, 35.0, 32.1, 19.5, 19.4\); IR (film): 2920, 2844, 1695 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([C_{13}H_{14}OS+H]^+\) 219.0838; found 219.0821.

2.6 References


(39) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. Phytochemistry 1996, 42 (6), 1657.
(49) Scott E. Denmark, R. C. K. Tetrahedron 1988, 44 (13), 4043.
3 Multicomponent Double Diels-Alder/Nazarov Tandem Cyclization of Symmetric Cross-conjugated Diynones to Generate [6-5-6] Tricyclic Products

3.1 Introduction

There is a demand to expand the repertoire of synthetic methodologies that result in economical routes towards complex and medicinally relevant compounds. Designing new methods for the synthesis of polycyclic products from relatively simple starting materials is vital research due to the inherent challenges involved in total syntheses. Significant work has focused on tandem and domino processes in order to obtain greater complexity in the products using fewer synthetic steps. A tandem cyclization reaction that either initiates from, or incorporates the Nazarov reaction is a very useful way to build complex polycyclic products that contain five-membered rings. Recently, Wender and coworkers reported an excellent example of an efficient tandem [5+2] cycloaddition/Nazarov reaction for the synthesis of [7-5] bicyclic products using a rhodium catalyst (Scheme 3-1a). A one-step Nazarov cascade reaction reported by West and coworkers is another noteworthy method for the sequential formation of five and six-membered rings to produce steroid derivatives (Scheme 3-1b). These methods are an excellent demonstration of progress for the concise construction of important biologically active compounds consisting of fused five-membered ring systems.
Biologically germane molecules that specifically contain a rare [6-5-6] carbotricyclic skeleton are an interesting class of diterpenoid natural products, many of which show promise as therapeutics (Figure 3-1a). For example, the hirsutellones were isolated from the fungus *Hirsutella nivea* BCC 2594 and exhibit potent activity, particularly hirsutellones A and B, against tuberculosis (*Mycobacterium tuberculosis* H₃₇Ra).¹⁵⁻¹⁷ Related pyrrocidines¹⁸ and GKK1032s¹⁹ are antibiotic compounds. The taiwaniaquinoids, many of which show activity as aromatase inhibitors, are another example of attractive synthetic targets containing a [6-5-6] tricyclic system.²⁰⁻²⁴ Gibberellic acid is an essential plant hormone that has interested a number of synthetic groups.²⁵⁻²⁹ Molecules containing a [6-5-6] ring structure clearly represent an important class of biologically relevant compounds. Therefore, strategies that target this uncommon yet interesting [6-5-6] core would enable a number of biologically active natural products and their derivatives to be efficiently synthesized. There has been only limited work on the rapid generation of this core structure.³⁰ An impressive gold-catalyzed tandem heteroenyne/Nazarov cascade reported by Jin and Yamamoto allows for the formation of [6-5-6] and other tricyclic systems (Figure 3-1b).³¹ This methodology results in the
formation of two new rings with the third ring being prebuilt into the starting material.

Post-synthetic transformations of these compounds towards a broad scope of biologically relevant terpenoid products would require challenging redox chemistry. However, this work is inspiring with respect to the idea of generating complex polycyclic compounds in a single reaction via tandem cyclization reactions. We have developed a strategic route towards functionalized [6-5-6] carbotricyclic intermediates from simple diynones where all three rings are built in a single reaction step and the product contains numerous functional handles for post-synthesis modifications (Figure 3-1c).

![Diagrams and structures from the text](image-url)
**Figure 3-1:** Biologically pertinent, naturally occurring compounds bearing a [6-5-6]-carbotricyclic skeleton. Tandem double Diels-Alder/Nazarov reaction to generate [6-5-6] structures.

### 3.2 Reactions of Diynones

Our research in the area of alkyne cycloaddition reactions prompted us to devise concise synthetic routes towards polycyclic intermediates that bear useful functionality for further synthetic manipulations. Valuable substrates such as diynones 3.1 are a relatively untapped resource in the synthetic organic community (Figure 3-2). We believe these relatively high-energy starting materials, under appropriate reaction conditions, are highly suitable for multicomponent and tandem processes to occur for the purpose of targeting complex products. In this regard, we envisioned that a Lewis acid facilitated Diels-Alder reaction between diynone 3.1 and diene 3.2 would first generate the monocyclic ketone intermediate 3.3 followed by a second Diels-Alder reaction to furnish bicyclic intermediate 3.4 (Figure 3-2a). We hypothesized that intermediate 3.4 contained the necessary functionality (shown in red) to further undergo a Nazarov cyclization. Our goal was to employ a single Lewis acid that could, in one-pot, drive this multicomponent/tandem reaction through both the double Diels-Alder reaction and a Nazarov cyclization to ultimately provide [6-5-6] tricyclic products 3.5 or 3.6. A common obstacle in Nazarov cyclizations is regio-control of the double bond that is generated in the product. We envisioned that the incorporation of silicon-based groups ($R^1 = \text{SiMe}_3$) would not only stabilize the diynone precursors$^{32-34}$ but also allow for a regioselective elimination to occur to selectively generate isomer 3.5 (Figure 3-2)$^{35-38}$. When $R^1$ is an alkyl or aryl group, elimination will exclusively form isomer 3.6, producing vicinal quaternary centers.
3.3 Preliminary Results: Double Diels-Alder Proof of Concept

The initial goal was to successfully react a diynone 3.1 in a double Diels-Alder reaction. After the double Diels-Alder was successfully accomplished then work would begin on facilitating the third cyclization, the Nazarov. We chose 3.1a as a model substrate since it is inexpensive to make and can be synthesized in two steps (Scheme 3-2). Upon reacting an aluminum Lewis acid with 3.1a and cyclopentadiene 3.2a we obtained monocyclized 3.3a, which was isolated and reacted further to generate the bis-cyclized 3.4a and 3.4a' in a 1.2:1 ratio. We were pleased with these results since this gave proof of concept for the double Diels-Alder cycloaddition utilizing a hindered substrate 3.1a. The reaction did not go to completion and a significant amount of starting material 3.1a remained; however, 3.3a was isolated in 24% yield. The formation of 3.4a did not go to completion even with additional equivalents of Lewis acid. Nonetheless, the successful double Diels-Alder cycloaddition of bis phenyl diynone 3.1a indicated that a one-pot version was feasible. We next looked at generating bis-cyclized intermediate 3.4 in a one pot reaction.
We synthesized bis(trimethylsilyl) diynone 3.1b as this would be a more reactive dienophile in the cycloaddition (Scheme 3-3). We found that diynone 3.1b reacted rapidly with 3.2a to generate 3.3b which was quickly converted to the bis-cyclized product 3.4b and 3.4b’ in a 1.7:1 diastereomeric ratio. No starting material remained even though 0.20 equivalents of Al(CH₃)₂Cl had been used. We were pleased with this result since this route forms four new carbon-carbon bonds in a one-pot reaction. It was observed that the diastereoselectivity of the reaction was low and in an effort to improve the selectivity we screened a variety of common oxophilic Lewis acids.

We screened various Lewis acids under low temperature conditions and a bulky ligand in an attempt to increase the diastereoselectivity for the Diels-Alder cycloaddition of 3.1b and 3.2a (Table 3-1). Entries 1,3 and 7,8 yielded the highest diastereomeric ratios, between 2.4-2.8. While this was higher than what had been observed in preliminary reactions, it was still a fairly poor ratio. Solubility issues likely prevented formation of 3.4b for (entry 2), using AlCl₃. Neither TiCl₄ (entry 4) or ZnCl₂ (entry 5) increased the
product ratio by a significant amount. The complexation of the BINOL ligand to Lewis acids (entries 6-9) appeared to have little or no influence over the selectivity of the cycloaddition. The zinc Lewis acid reactions (entries 5 and 9) proceeded at a slow rate and upon quenching, a significant amount of starting material 3.1b and monocyclized intermediate 3.3b remained. The reactions were proceeding well but were quenched before they were finished as the primary goal was to determine diastereoselectivity of the bis-cyclized 3.4b:3.4b’. It is interesting to note that the zinc Lewis acid almost completely forms the monocyclized product 3.3b before formation of the 3.4b occurs. More sterically congested ligands may impact selectivity to a greater extent than BINOL. While a higher ratio would have been more useful, we suspected that the bis-cyclized 3.4b would be a challenging substrate for the Nazarov reaction due to its rigid conformation and potential for steric hindrance in the reaction.

Table 3-1: Brief screening table was run to improve diastereoselectivity of bis-cyclized 3.4b:3.4b’.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temp (°C)</th>
<th>3.4b:3.4b’ d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃•O(Et)₂</td>
<td>-78</td>
<td>(2.6:1)</td>
</tr>
<tr>
<td>2</td>
<td>AlCl₃</td>
<td>-78 to r.t.</td>
<td>only 3.1b</td>
</tr>
<tr>
<td>3</td>
<td>SnCl₄</td>
<td>-78</td>
<td>(2.6:1)</td>
</tr>
<tr>
<td>4</td>
<td>TiCl₄</td>
<td>-78</td>
<td>(1.5:1)</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂</td>
<td>-78 to r.t.</td>
<td>(2:1)</td>
</tr>
<tr>
<td>6</td>
<td>Al(CH₃)₂Cl/1 equiv. BINOL</td>
<td>0</td>
<td>(1.9:1)</td>
</tr>
<tr>
<td>7</td>
<td>SnCl₄/ 1 equiv. BINOL</td>
<td>-78</td>
<td>(2.4:1)</td>
</tr>
<tr>
<td>8</td>
<td>SnCl₄/ 2 equiv. BINOL</td>
<td>-78</td>
<td>(2.8:1)</td>
</tr>
</tbody>
</table>
3.4 One-pot Double Diels-Alder/Nazarov Tandem Reaction of Diynones

Based on preliminary experiments conducted with cyclic diene 3.2a, we were interested in investigating the multicomponent reaction with acyclic dienes. When 2,3-dimethyl-1,3-butadiene 3.2b was reacted with 3.1b we found that monocyclized 3.3c rapidly formed and was immediately converted into the Nazarov product 3.5c. Interestingly enough we did not observe the formation of the bis-cyclized intermediate 3.4c. During the course of the reaction we can observe the rapid formation of monocyclic intermediate 3.3c (vide supra). Intermediate 3.3c can be produced and isolated when the reaction is run at −78 °C and then quenched. A second Diels-Alder reaction then occurs in situ to generate bicyclic intermediate 3.4c, which is not isolable. We propose that it rapidly undergoes the Nazarov cyclization resulting in 3.5c (Scheme 3-4).

Scheme 3-4: Reaction of diynone 3.1b with 3.2b to initially form monocyclized 3.3c and then rapid formation of Nazarov product 3.5c.
Based on experimental observations we hypothesize that the energy barrier for the formation of 3.4c is higher than the barrier for the Nazarov reaction, resulting in a non-observable intermediate 3.4c (Figure 3-3). Stabilization of the carbocationic intermediate 3.5c′ via the β-silyl effect weakens the Si–C bond resulting in the regioselective elimination of a TMS group (Figure 3-3).35–38 Compound 3.5c has a number of useful functional handles for further synthetic elaboration including two isolated alkenes and a conjugated enone. The remaining TMS substituent can easily act as a segue towards tertiary alcohols and other functional groups via the Tamao-Fleming oxidation.121

![Figure 3-3: Nazarov cyclization and stabilization of the carbocation intermediate 3.5c′ via the β-silyl effect.](image)

A preliminary catalytic screening (20 mol%) was conducted with Lewis acids that have been shown to work well in activating alkynyl ketones (Table 3-2). AlCl₃ and SnCl₄ reactions were started at -78 °C and slowly warmed to room temperature because both reactions showed partial formation of 3.3c and 3.5c (entries 1 and 2). The ZnCl₂ reaction showed only a small amount of monocyclized 3.3c by TLC. This is unsurprising since ZnCl₂ is a relatively mild Lewis acid and would therefore be unable to sufficiently activate diynone 3.1b towards the tandem reaction sequence (entry 3). EtAlCl₂ performed the best generating a larger amount of 3.3c and 3.5c than the other Lewis acids (entry 4). Since none of the reactions went to completion, six additional equivalents of diene 3.2b were added to each reaction, however, no additional reaction progress was observed. The
lack of reaction progress must be due to an insufficient amount of Lewis acid because after excess diene was added no change was observed in any of the reactions. Based on these results the reaction is not catalytic under these conditions, rather, a full equivalent of Lewis acid is necessary which is common for Nazarov reactions.\textsuperscript{35,39–41}

**Table 3-2:** Most suitable Lewis acids were screening for their catalytic ability for the tandem reaction sequence of \textit{3.1b} and \textit{3.2b}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl(_3)</td>
<td>-78 °C to r.t.</td>
<td>Formation of \textit{3.3c} and \textit{3.5c}</td>
</tr>
<tr>
<td>2</td>
<td>SnCl(_4)</td>
<td>-78 °C to r.t.</td>
<td>Formation of \textit{3.3c} and \textit{3.5c}</td>
</tr>
<tr>
<td>3</td>
<td>ZnCl(_2)</td>
<td>0 °C to r.t.</td>
<td>Barely formation of \textit{3.3c}</td>
</tr>
<tr>
<td>4</td>
<td>EtAlCl(_2)</td>
<td>0 °C to r.t.</td>
<td>Formation of \textit{3.3c} and \textit{3.5c}</td>
</tr>
</tbody>
</table>

Reactions were performed with 20 mol\% Lewis acid. 2 equivalents of diene were used initially.

Next we examined common Lewis acids for the Diels-Alder reaction of bis(trimethylsilyl)diynone \textit{3.1b}\textsuperscript{42} and \textit{3.2b} (**Table 3-3**). We were predominately interested in determining efficacious Lewis acids for the direct conversion of \textit{3.1b} to \textit{3.5c} in a single reaction pot, presumably through intermediates \textit{3.3c} and \textit{3.4c}. Even a full equivalent of zinc chloride gave only trace monocyclic intermediate \textit{3.3c} and was not reactive enough to initiate the second Diels-Alder reaction (entry 1). Stronger Lewis acids rapidly decomposed diene \textit{3.2b} and thus compound \textit{3.1b} remained unreacted (entries 2-5). Aluminum chloride was successful at producing desired product \textit{3.5c} in moderate yield (entry 6). More soluble ethylaluminum dichloride and dimethylaluminum chloride gave clean, fast reactions at room temperature to provide \textit{3.5c} in 64\% and 78\% yields, respectively (entries 7-8). While indium triflate did not give the desired product
(entry 9), boron trichloride rapidly generated $3.5c$ in 58% yield (entry 10). It should be noted that a stoichiometric amount of Lewis acid is necessary for good yield and that using a catalytic amount of Lewis acid catalyst resulted in poor conversion of $3.1b$ to $3.5c$. The likely cause for this is product inhibition of the catalyst, which has also been reported for other Nazarov cyclizations.$^{35,39–41}$

Table 3-3: Lewis acid screen for the double Diels-Alder/Nazarov reaction.$^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>T (°C)</th>
<th>t [h]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZnCl$_2$</td>
<td>23</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BF$_3$·Et$_2$O</td>
<td>-17</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>SnCl$_4$</td>
<td>-78</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>TiCl$_4$</td>
<td>-78</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>FeCl$_3$</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>AlCl$_3$</td>
<td>0</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>EtAlCl$_2$</td>
<td>23</td>
<td>0.5</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>Me$_2$AlCl</td>
<td>23</td>
<td>1.5</td>
<td>78</td>
</tr>
<tr>
<td>9</td>
<td>In(OTf)$_3$</td>
<td>23</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>BCl$_3$</td>
<td>-5</td>
<td>10 min</td>
<td>58</td>
</tr>
</tbody>
</table>

$^{[a]}$ Conditions: $3.1b$ in CH$_2$Cl$_2$ (ca. 0.07 M), $3.2b$ (5 equiv.), Lewis acid (1.2 equiv.). $^{[b]}$ Isolated yield of $3.5c$. Reactions were monitored by TLC and $^1$H NMR analysis.

Upon workup product $3.5c$ is isolated in excellent regio- and diastereoselectivity determined by GC-MS. The major diastereomer of $3.5c$ has a syn relationship between the methine hydrogen (H$_a$) and the TMS substituent which was confirmed by NOESY correlations (Figure 3-4 and Figure 3-5) and single crystal X-ray crystallographic analysis (Figure 3-6).
Figure 3-4: NOESY spectrum of 3.5c showing the methine H ↔ TMS correlation. (line added as a guide to the eye to point out relevant correlations in assigning stereochemistry).

Figure 3-5: Expanded NOESY spectrum of 3.5c.
Figure 3-6: Single crystal X-ray structures of compound 3.5c showing the syn relationship between the methine hydrogen and the TMS group (50% probability).

3.4.1 Double Diels-Alder/Nazarov of Symmetrically Substituted Silyl Diynones

We were highly interested in the successful use of diene 3.2c with 3.1b in the Diels-Alder cycloaddition because the gem-dimethyl moiety is present in a number of biologically active compounds (Table 3-4). Both BF$_3$•O(Et)$_2$ and SnCl$_4$ showed formation of monocyclized 3.3d by TLC (entries 1 and 2). Formation of 3.3d was very slow under AlMe$_3$ conditions (entry 3). While a very mild Lewis acid, ZnCl$_2$ yield monocyclized 3.3d by TLC (entry 4). This is likely due to the fact that 3.2c is a more reactive diene than 3.2b. Based on analysis of the crude reaction mixtures by $^1$H NMR as well as TLC monitoring over the course of the reaction, 3.5d was not observed (entries 1-5). Further studies were conducted with 3.1b and 3.2c, however, no evidence of the Nazarov product 3.5d was observed. It appeared that the rate of polymerization of 3.2c was significantly faster than the rate of the second Diels-Alder cycloaddition. Slow addition of 3.2c was tried to minimize the polymerization although was unsuccessful. Given how readily the first Diels-Alder reaction occurs, we suspect that the difficulty in the second cycloaddition results from steric hindrance between 3.3d and the gem-dimethyl groups of 3.2c.
Table 3-4: Preliminary Lewis acid screening for diynone 3.1b and gem-dimethyl diene 3.2c.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temperature</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₃·O(Et)₂</td>
<td>-78 °C</td>
<td>3.3d</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>-78 °C</td>
<td>3.3d</td>
</tr>
<tr>
<td>3</td>
<td>AlMe₃</td>
<td>0 °C</td>
<td>3.1b and 3.3d</td>
</tr>
<tr>
<td>4</td>
<td>ZnCl₂</td>
<td>0 °C</td>
<td>3.3d</td>
</tr>
<tr>
<td>5</td>
<td>Al(CH₃)₂Cl</td>
<td>23 °C</td>
<td>3.3d</td>
</tr>
</tbody>
</table>

All reactions used CH₂Cl₂ as solvent.

We then examined the reaction of diynone 3.1b with functionalized diene 3.2d (Scheme 3-5). Reaction monitoring by TLC showed rapid conversion of 3.1b to what was possibly monocyclized 3.3e, which immediately begin to disappear and was followed by the formation of a second spot believed to be 3.5e. Indeed, analysis of the crude mixture by ¹H NMR showed what was likely the desired Nazarov 3.5e. We were pleased with this result as it enabled us to use a highly reactive siloxy diene in the tandem reaction sequence that would provide a useful functional handle for further chemical elaborations. Purification was attempted on a neutral silica gel column to avoid decomposition as 3.5e was likely very reactive. However, no amount of 3.5e was recovered from the column and it is believed that the product 3.5e decomposed. The reaction was run a second time and purification was attempted using Kugelrohr distillation to give what appeared to be Nazarov product 3.5e' (Scheme 3-5). While
isolation of 3.5e proved to be difficult we were pleased that a hetero-diene 3.2d was successfully used in the tandem reaction sequence.

Scheme 3-5: Diynone 3.1b appears to have successfully reacted with functionalized diene 3.2d in a double Diels-Alder/Nazarov reaction to give 3.5e.

3.4.2 Double Diels-Alder/Nazarov Scope for Symmetrical Diynones

A concise scope of the symmetrical diynones and acyclic dienes were examined and summarized (Table 3-5). TMS diynone 3.1b rapidly formed 3.5c in excellent yield (entry 1). The reaction of 3.1b with less reactive 1,3-butadiene 3.2e required the use of the more Lewis acidic EtAlCl₂ but nonetheless successfully formed 3.5f in good yield and excellent diastereoselectivity (entry 2). The reaction of 3.1b with isoprene 3.2f also worked well to provide 3.5g in 54% yield as a 7:1.4:1:1 ratio of isomers, presumably made up of regioisomers (from the Diels-Alder step) and diastereomers (epimers at the methine position). Purification of 3.5g by column chromatography only successfully separated one minor isomer, though it was not isolated or detected possibly due to
decomposition on the column. Additional efforts were made to separate the isomers by bulb-to-bulb distillation and other chromatographic means but were unsuccessful. The major isomer of 3.5g was determined to be the one shown in table 2, where R² = H, R³ = Me and the methine hydrogen is syn to the TMS group (entry 3; see supporting information for complete structural assignment). Sterically hindered bis(triethylsilyl) diynone 3.1c resulted in a respectable yield of 3.5h (entry 4).

Table 3-5: Scope for symmetrical diynone 3.1a.
diastereomers) determined by GC-MS analysis of crude product mixture. Isomeric ratio (mixture of regioisomers and diastereomers) determined by GC-MS analysis after purification.

3.4.3 Double Diels-Alder/Nazarov of Symmetrically Substituted Alkyl/Aryl Diynones

After successfully utilizing TMS diynone 3.1b in a double Diels-Alder/Nazarov reaction we next looked at applying the method to alkyl substituted diynone 3.1d. The reaction of the symmetrical dimethyl diynone 3.1d with diene 3.2b resulted in modest yield and excellent selectivity for the formation of the conjugated 1,3-dienone product 3.6i (Scheme 3-6, reaction a). The stereochemical relationship in 3.6i was determined by 2D NMR spectroscopic analysis. We were very pleased to observe that bis(phenyl)diynone 3.1a undergoes the one-pot double Diels-Alder/Nazarov reaction sequence to provide the extremely sterically congested product 3.6j, albeit in modest yield (Scheme 3-6, reaction a). It should be noted that this one-pot reaction to form products 3.6i and 3.6j is generating vicinal quaternary centers, five new carbon-carbon bonds, and three new rings. Conducting these reactions at higher temperatures in an attempt to improve the yields of products 3.6i and 3.6j only led to significant decomposition. The more Lewis acidic boron trichloride was used in an attempt to optimize the yield (Scheme 3-6). It was found that compounds 3.7 and 3.8 were the major products observed in this reaction with only trace amounts of 3.6i and 3.6j detected. This is likely the result of double bond migration in 3.6i and 3.6j, presumably catalyzed by BCl₃, to ultimately afford conjugated products 3.7 and 3.8, respectively.
Scheme 3-6: Formation of Nazarov product 3.6i and 3.6j from EtAlCl$_2$. Observed double bond migration in a BCl$_3$-catalyzed double Diels-Alder/Nazarov reaction to form conjugated products 3.7 and 3.8.

The formation of 3.7 may result from acid induced alkene isomerization of 3.6i (Scheme 3-7). Our proposed mechanism involves protonation of 3.6i to form intermediate 3.9 which then undergoes hydrogen elimination to give 3.10. A second protonation of the newly formed alkene can occur to produce 3.11 which again can undergo hydrogen elimination finally resulting in 3.7. Isomerization of the double bond into conjugation with the ketone is the likely driving force for the preferential formation of 3.7.

Scheme 3-7: Proposed mechanism for the formation of 3.7 from 3.6i.
Upon increasing the reaction temperature in an attempt to optimize the conversion of 3.1a to product 3.6j, we observed decomposition that resulted in a significant amount of intractable material. However, we were able to isolate a trace amount of Wagner-Meerwein rearrangement product 3.13 (Scheme 3-8). We propose that the mechanism involves alkyl migration of the oxyallyl cation intermediate 3.14 to form a stabilized benzylic cation 3.15 followed by 1,2-phenyl migration. This suggests that alternate pathways such as rearrangements\textsuperscript{[19c, 19d, 22]} or oxyallyl cation trapping\textsuperscript{[5a, 5c, 5d, 23]} by excess diene or side products can account for the lower yield of product 3.6, although we were unable to observe or isolate these products. The rearranged product 3.13 is reproducible, however, stopping the reaction at the appropriate time before the product decomposes can be challenging.

Scheme 3-8: Attempted optimization of the yield for product 3.6j by conducting the reaction in refluxing DCE resulted in the formation of product 3.13 in trace amount along with intractable baseline material (TLC).
3.5 Enantioselective Efforts

Having developed a scope for the double Diels-Alder/Nazarov tandem reaction, our goal was to explore potential catalysts for an enantioselective method. The Corey-Bakshi-Shibata oxazaborolidine (CBS) catalyst has been shown to catalyze a number of important transformations including the Diels-Alder cycloaddition.\textsuperscript{43} We tried AlBr\textsubscript{3} with the CBS precatalyst, initially at low temperatures then refluxing in dichloromethane (entries 1-5). Formation of monocyclized 3.3c was observed at 23 °C although the reaction appeared to stall giving a 1:2 ratio of 3.1b:3.3c. The reaction was repeated with excess CBS to be certain the Lewis acid was binding to the precatalyst (entry 3). Under refluxing conditions some Nazarov product 3.5c was generated, although after examining the \textsuperscript{1}H NMR for the crude mixture it was believed that the refluxing conditions resulted in decomposition of the catalyst system. Lastly, we looked at using CBS with triflic acid at -78 °C but diene decomposition occurred quickly giving no reaction (entry 6). While the formation of monocyclized 3.3c (entries 2 and 3) was a promising result, further catalyst studies are necessary to obtain formation of 3.5c.

Table 3-6: Preliminary screening using the Corey-Bakshi-Shibata oxazaborolidine (CBS) pre-catalyst with diynone 3.1b and diene 3.2b to generate Nazarov 3.5c enantioselectively.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst with CBS</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlBr\textsubscript{3}</td>
<td>-45 °C to r.t.</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
We continued our enantioselective investigations with a variety of ligands as well as other modes of activating ketones (Table 3-7). Chiral amines are highly useful in asymmetric transformations and provide a method of forming a more reactive intermediate in comparison with a Lewis activated ketone. We tried L-proline with trifluoroacetic acid but even after refluxing in C$_2$H$_4$Cl$_2$ no reaction occurred (Entry 1).

We also wanted to utilize the pybox ligand with both copper and bismuth triflates since these are known to catalyze cycloaddition reactions although in both cases no conversion of 3.1b was detected (Entries 2 and 3). Leighton’s catalyst has been shown to be very reactive, however, in our case there was no reaction even when AgOTf was added to bind to the chloride (Entries 4 and 5). As a ligand cinchonidine can be used with a number of different Lewis acids and has been shown to work with BCl$_3$. While BCl$_3$ was found to be a very reactive Lewis acid for the tandem double Diels-Alder/Nazarov reaction we found that when complexed with a ligand it gave no reaction (Entry 6). We suspect that once bound to an oxygen bearing ligand BCl$_3$ is much less Lewis acidic and can therefore not sufficiently activate the diynone. While (-)-DIP-chloride is commonly used for asymmetric reductions, we have in the past observed that diynones are more difficult to reduce. As such we wondered if it would sufficiently activate the diynone as a Lewis acid towards the tandem reaction processes. Unfortunately, no reaction was observed with (-)-DIP-chloride (Entry 7).

<table>
<thead>
<tr>
<th></th>
<th>Ligand</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>AlBr$_3$</td>
<td>r.t.</td>
<td>3.1b and 3.3c (1:2)</td>
</tr>
<tr>
<td>3</td>
<td>Excess CBS w/AlBr$_3$</td>
<td>r.t.</td>
<td>3.1b and 3.3c (1:2)</td>
</tr>
<tr>
<td>4</td>
<td>AlBr$_3$</td>
<td>Reflux in C$_2$H$_4$Cl$_2$</td>
<td>Some 3.5c, CBS decomposed</td>
</tr>
<tr>
<td>5</td>
<td>AlBr$_3$</td>
<td>Reflux in C$_2$H$_4$Cl$_2$</td>
<td>3.5c and CBS decomposed</td>
</tr>
<tr>
<td>6</td>
<td>triflic acid</td>
<td>-78 ºC</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Solvent used was DCM unless otherwise noted.
Table 3-7: Preliminary screening with diynone 3.1b and diene 3.2b to generate Nazarov 3.5c enantioselectively. Ligands used in the catalytic screening process.

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L-Proline/TFA</td>
<td>Reflux in C$_2$H$_4$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Pybox with Cu(OTf)$_2$</td>
<td>THF, 23</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>Pybox with Bi(OTf)$_3$</td>
<td>THF, 23</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Leighton’s catalyst</td>
<td>CH$_2$Cl$_2$, 23</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>Leighton’s catalyst, AgOTf</td>
<td>0 to 23, CH$_2$Cl$_2$</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>BCl$_3$ w/ cinchonidine</td>
<td>CH$_2$Cl$_2$, 23</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>(-)-DIP-chloride</td>
<td>CH$_2$Cl$_2$, r.t.</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

BINOL has considerable precedence in the literature as a highly successful multi-use ligand.\textsuperscript{44} We conducted a Lewis acid/BINOL screening towards the synthesis of Nazarov product 3.5c (Table 3-8). An AlCl$_3$/BINOL complex under refluxing conditions gave a small amount of monocyclized product 3.3c but the intermediate did not react further to give the desired product 3.5c (entry 1). The use of TiBr$_4$ with and without AgOTf formed only a small amount of 3.3c with unreacted 3.1b (entries 2 and 3). Diene polymerization was noted during the reaction and although benzene was used as a solvent in an effort to minimize diene decomposition, no reaction occurred (entry 4). Tin Lewis acids, SnCl$_2$ and SnCl$_4$ both yielded no conversion of 3.1b and SnCl$_4$ reacted too quickly with the diene and decomposition ensued (entries 5 and 6). No reaction occurred using...
TiF₃ and it may be that the Lewis acid is not reactive enough (entry 7). As with other strong Lewis acids Bi(OTf)₃ caused the diene to polymerize before the Diels-Alder cycloaddition could occur (entry 8). Reactions run with Dy(OTf)₃, In(OTf)₃, and Yb(OTf)₃ gave no conversion even to the monocyclized 3.3c (entries 9-11). In fact, Yb(OTf)₃ caused the diene to decompose as well. Additionally, neither AlBr₃ or Ti(OCH(CH₃)₂)₄ gave any reaction to 3.3c (entries 12 and 13). It is evident by the reaction outcomes that a fairly strong and likely reactive catalyst is necessary to effect even the first Diels-Alder cycloaddition.

Table 3-8: Preliminary screening using BINOL with diynone 3.1b and diene 3.2b to generate Nazarov 3.5c enantioselectively.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid/R-BINOL</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi and AlCl₃</td>
<td>Reflux in DCE</td>
<td>Some 3.1b and 3.3c</td>
</tr>
<tr>
<td>2</td>
<td>TiBr₄</td>
<td>-60 to 0 °C to r.t.</td>
<td>Some 3.3c</td>
</tr>
<tr>
<td>3</td>
<td>TiBr₄/AgOTf</td>
<td>0 °C to r.t.</td>
<td>trace 3.3c</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi and TiBr₄</td>
<td>benzene, 0 to 23</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>SnCl₂</td>
<td>0 °C to r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄</td>
<td>0 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi and TiF₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi and Bi(OTf)₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>n-BuLi and Dy(OTf)₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>n-BuLi and In(OTf)₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>n-BuLi and Yb(OTf)₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>12</td>
<td>n-BuLi and AlBr₃</td>
<td>23</td>
<td>No reaction</td>
</tr>
<tr>
<td>13</td>
<td>Ti(OCH(CH₃)₂)₄</td>
<td>23</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Solvent used was DCM unless otherwise specified.

The use of chiral brønsted acids in a number of different asymmetric reactions has been widely successful.45,46 Since the bulk of our enantioselective screening has so far
consisted of binding Lewis acids to well-established chiral ligands we were interested in trying a different approach. Lewis acids BCl$_3$ and BBr$_3$ were reacted with a chiral phosphoric acid$^{47}$ since these boron Lewis acids had demonstrated a high level of reactivity with 3.1b in their achiral form (Figure 3-7). The chiral Brønsted acid complex showed some activity, forming a small amount of 3.3c. However, the reaction ceased to progress further with a large amount of 3.1b remaining. The temperature was initially begun at -78 ºC and then increased to room temperature. While enantioselective reactions are temperature dependent we were predominately interested in first obtaining a working catalyst system that can influence stereoselectivity. There are a number of BINOL variations available and it is possible to make the catalyst more reactive by adding electron withdrawing groups to the ligand. While not as successful as we had hoped we are interested in returning to work with chiral Brønsted acids in the future.

Figure 3-7: Preparation and screening of chiral phosphoric acid activated with BCl$_3$ and BBr$_3$. Both catalysts showed minor activity with diynone 3.1b and 3.2b to give a mixture of starting material 3.1b and monocyclized 3.3c.
Throughout our screening process we noticed that once a ligand was bound to the Lewis acid, the Lewis acid would no longer activate our dienophile 3.1b. In order to circumvent this issue, we considered using a diboron Lewis acid which would contain two Lewis acidic cites\(^{48}\), one which could bind to a ligand and the other could bind to the diynone 3.1 (Scheme 3-9). However, the desired diboron compound 3.16 was not commercially available. Literature precedence indicated that the dibromo naphthalene compound could be easily converted to the organomercury intermediate 3.17.\(^{49}\) Once isolated the organomercury product 3.17 could be converted to the diboron Lewis acid 3.16. The organomercury intermediate was characterized by \(^1\)H NMR which showed a symmetric naphthalene system. Analysis of the Lewis acid product 3.16 by \(^1\)H NMR indicated a mixture that appeared to not contain 3.16. The reaction was attempted again with the same results, which, indicated we had not been successful in forming the desired Lewis acid 3.16. We believe the authors may have used BCl\(_3\) in its pure form from a cylinder whereas we used a 1.0 M solution in hexanes. Unfortunately, due to time constraints and the initial cost of the dibromo naphthalene we decided to pursue other enantioselective avenues.

Scheme 3-9: Attempted preparation of diboron Lewis acid 3.16 containing two Lewis acidic cites.
3.6 Investigations into Timed Diene Addition Reactions

Using two different dienes with symmetric diynone 3.1b could result in multiple isomers. However, bulky or strained dienes may influence silyl elimination resulting in one regioisomer as the major product. Monocyclized 3.3c was synthesized in order to determine if it will participate with cyclopentadiene 3.2a in a second Diels-Alder cycloaddition. We were pleased to find that the formation of unsymmetrical bis-cyclized 3.3k was a success (Scheme 3-10). However, no Nazarov cyclization of 3.3k appeared to occur even after heating. The bis-cyclized intermediate 3.3k may be a challenging substrate for the tandem reaction sequence due to steric hindrance.

Scheme 3-10: Successful formation of unsymmetrical bis-cyclized product 3.3k from monocyclized 3.3c.

We were interested in conducting a multi-diene reaction with TMS ketone 3.1b. Theoretically, one would expect two regioisomers with their respective diastereomers for the reaction outcome. Particularly since the dienes are unhindered and may not introduce a silyl elimination bias over the course of the reaction. Diynone 3.1b reacted with 3.2b to give monocyclized 3.3c at -78 °C. After full conversion of 3.3c, diene 3.2e was added to the mixture and the reaction was warmed, generating a mixture of products. The first diene 3.2b was limited to 1.3 equivalents, the second diene 3.2e was used in excess and bubbled into the solution at -78 °C. Examination of the crude mixture by 1H NMR showed multiple products. By GC-MS four different isomers were present in addition to a
small amount of Nazarov product 3.5c (Scheme 3-11). The GC-MS ratio was 26:21:1.4:1, the two major isomers are regioisomers 3.5l and 3.5m in a nearly 1:1 ratio. The two minor ones are possibly their respective diastereomers in a 1.4:1 ratio. Additionally, a 5% impurity of 3.5c was found in the reaction mixture as well. A slight excess of diene was used, 1.3 equivalents, and this would have resulted in a small formation of undesired 3.5c. The small excess was used because full conversion to 3.3c can be difficult with 1 equivalent. As to future mixed diene reactions it is evidently necessary to use as close as possible to 1 equivalent of a reactive diene since more sluggish dienes are unable to compete in terms of rate. Although a mixture of regioisomers was generated this reaction demonstrates that two different dienes can be used in the double Diels-Alder/Nazarov reaction.

Scheme 3-11: Multi-diene reaction of diynone 3.1b with diene 3.2b then addition of diene 3.2e followed by warming and formation of isomers. The four expected isomers from multi-diene addition reaction.
3.7 Scalability of Double Diels-Alder/Nazarov Tandem Reaction

It is very valuable if small scale reactions are scalable under the current reaction conditions to generate the desired product in the expected yield on a gram scale. The TMS diynone 3.1b was run on a 1.05 g scale using Al(CH$_3$)$_2$Cl at room temperature and 1.06 g of desired 3.5c was obtained in 71% yield (Scheme 3-12). It is important to note that the reaction time was 2 hours, which is approximately the same amount of time necessary for a 100 mg scale. These results indicate that the reaction is reproducible on large scales increasing the utility of the method for industrial use.

\[
\text{TMS} \quad 3.1b, \ 1.05 \text{ g} \quad + \quad \begin{array}{c}
\text{TMS}
\end{array} \quad 3.2b \quad \xrightarrow{1.2 \text{ equiv. Al(CH$_3$)$_2$Cl}} \quad \begin{array}{c}
\text{TMS}
\end{array} \quad 3.5c \quad 1.06 \text{ g}, \ 71% \\
2 \text{ h, CH}_2\text{Cl}_2
\]

Scheme 3-12: Diynone 3.1b was found to react well with 3.2b on a gram scale reaction to generate 3.5c in excellent yield.

3.8 Conclusion

Studies have successfully been conducted on a double Diels-Alder proof of concept and then expanded into a one-pot tandem reaction. While considerable work is still necessary, good progress was made on determining suitable enantioselective catalysts for the system. We have determined that the tandem sequence will require a relatively strong/electron deficient binding center that will not become too deactivated through ligand interactions. Importantly, the silyl method in particular is applicable to gram scale reactions. While exploratory efforts have been made into using two different dienes, the results indicate that a symmetrical diynone when reacted with two different
dienes will generate nearly a 1:1 ratio of regioisomers. Additionally, the use of strong catalysts or reagents to activate the diynone pose a challenge when coupled with highly reactive dienes.

In summary, we have demonstrated the first multicomponent double Diels-Alder/Nazarov tandem reaction of cross-conjugated diynones to yield [6-5-6] tricyclic products in a one-pot reaction. This polycyclization method produces five new carbon-carbon bonds, three new rings, and quaternary or vicinal quaternary centers with high regio- and diastereocontrol. This method provides a tool for rapid access to important [6-5-6] tricyclic terpenoid scaffolds while also imparting useful functional handles for further chemical elaboration. Further studies of this reaction and its utility are ongoing in our laboratory.

3.9 Experimental

**General procedures and methods:** Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. CH$_2$Cl$_2$ and THF were purified using a PureSolv MD 5 solvent purification system. Evaporation and concentration in vacuo by rotary evaporation. Where appropriate, reactions were performed in standard, dry glassware under an inert atmosphere of N$_2$. Column chromatography: Silica gel irregular 60 Å (40-60 micron) from VWR International. The bulb-to-bulb distillation was performed using a kugelrohr apparatus, Büchi GKR-51. Thin-layer chromatography (TLC): glass sheets covered with silica gel 60 F$_{254}$ from Millipore a Corporation; visualization by UV light, anisaldehyde stain or KMnO$_4$ stain. Mp: Mel-Temp apparatus; uncorrected. IR spectra (cm$^{-1}$): Thermo Nicolet
6700 FT-IR (diamond ATR), data are reported as cm$^{-1}$. $^1$H and $^{13}$C NMR: Varian NMR 400 MHz, 500 MHz at rt in CDCl$_3$; solvent peaks (7.26 ppm and 77.16 ppm for $^1$H and $^{13}$C, respectively) or C$_6$D$_6$; solvent peaks (7.16 ppm and 128.06 ppm for $^1$H and $^{13}$C, respectively) as reference. GCMS (EI): Agilent 7890A with a 5970C mass spectrometer with triple axis detector using a 122-5532UI DB-5MS Ui column (30m x 0.25mm). ESI-TOF MS: Agilent G6230A instrument with purine and HP-Ø921 as internal calibrants. X-ray crystallographic data was collected at 100 K on a Bruker APEX CCD diffractometer with Mo Kα radiation ($\lambda = 0.71073$ Å) and a detector-to-crystal distance of 4.94 cm. Data collection was optimized utilizing the APEX 2 software with 0.5° rotation between frames. Data integration, correction for Lorentz and polarization effects, and final cell refinement were performed using SAINTPLUS and corrected for absorption using SADABS. The structures were solved by direct methods and refined using SHELXTL, version 6.10. All non-hydrogen atoms were refined anisotropically and hydrogen atoms placed in calculated positions.

Crystallographic data for 5c: C$_{16}$H$_{22}$OSi; $M_r$=258.42; crystal size=0.290 x 0.240 x 0.220 mm$^3$; monoclinic; space group $P2_1/n$; $a=9.3025(7)$, $b=13.9823(11)$, $c=11.2578(9)$ Å; $\alpha$=90°, $\beta$=94.4382(13)°, $\gamma$=90°; $V$=1459.9(2) Å$^3$; $Z$=4, $\rho_{\text{calc}}$=1.176 Mg/m$^3$; $\mu$=0.148 mm$^{-1}$; $\lambda$=0.71073 Å; $T$=100(2) K; 2$\theta$$_{\text{max}}$=30.00°; reflections measured 20019, independent 4257 [$R$(int)=0.0531]; $R$$_{1}$=0.0439, $w$R$_{2}$=0.1047 (I>2$\sigma$(I)); residual electron density=0.461 and −0.261 eÅ$^{-3}$. CCDC 1455860 (5c) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
**S1** was synthesized following a known procedure:\(^{42}\) Ethynyltrimethylsilane was distilled before use: \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 5.07\) (bs, 1H), 2.75 (bs, 1H), 0.15 (s, 18H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 102.0, 89.4, 52.9, -0.2\); IR (film): 3361 (br), 2960, 2173, 1249 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([\text{C}_{11}\text{H}_{20}\text{Si}_{2}\text{O}+\text{Na}]^+\) 247.0945; found 247.0950.

**S2** was synthesized following a known procedure:\(^{54}\) R\(_f\) = 0.5 (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 5.08\) (s, 1H), 2.69 (bs, 1H), 0.96 (t, \(J = 8.0\) Hz, 18H), 0.58 (q, \(J = 7.9\) Hz, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 103.6, 86.7, 52.9, 7.3, 4.2\); IR (film): 3404 (br), 2955, 2872, 2164 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([\text{C}_{17}\text{H}_{32}\text{Si}_{2}\text{O}+\text{Na}]^+\) 331.1884; found 331.1891.

**S3** was synthesized following a known procedure:\(^{42}\) Phenylacetylene was distilled before use: M.p. 62–66 °C (lit.\(^{55}\) 69–70 °C); \(R_f = 0.4\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.55 – 7.50\) (m, 4H), 7.38 – 7.29 (m, 6H), 5.68 (s, 1H), 3.18 (bs, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 131.9, 128.8, 128.3, 122.0, 86.2, 84.6, 53.2\); IR
(film): 3251 (br), 2209, 1485 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([\text{C}_{17}\text{H}_{12}\text{O}+\text{Na}]^+\) 255.0780; found 255.0782.

**S4**

**S4 was synthesized following a known procedure:**\(^{42}\) M.p. 103–105 °C (lit.\(^{56}\) 152–153 °C); \(R_f = 0.4\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 5.05\) (dhept, \(J = 6.8, 2.3\) Hz, 1H), 2.10 (bs, 1H), 1.88 (d, \(J = 2.3\) Hz, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 80.5, 77.1, 52.1, 3.5\); IR (film): 3190 (br), 2292, 2258, 2224, 1479 cm\(^{-1}\).

**3.1b**

**3.1b was synthesized following a known procedure:**\(^{42}\) M.p. 48–50 °C; \(R_f = 0.8\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.22\) (s, 18H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 160.1, 102.6, 99.2, -0.9\); IR (film): 2964, 2154, 1616 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([\text{C}_{11}\text{H}_{18}\text{Si}_{2}\text{O}+\text{H}]^+\) 223.0969; found 223.0963.

**3.1c**

**3.1c was synthesized following a known procedure:**\(^{42}\) \(R_f = 0.8\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.96\) (t, \(J = 8.0\) Hz, 18H), 0.63 (q, \(J = 8.0\) Hz, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 159.7, 104.2, 97.5, 7.1, 3.8\); IR (film): 2958, 2872, 2154,
1631 cm$^{-1}$; HRMS (ESI-TOF) \textit{m/z} calcd for $[\text{C}_{17}\text{H}_{30}\text{Si}_2\text{O}+\text{Na}]^+$ 329.1727; found 329.1728.

3.1d was synthesized following a known procedure: M.p. 78–80 °C (lit. 79.7–80 °C); $R_f = 0.4$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.97$ (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 161.0, 90.5, 81.3, 4.0$; IR (film): 2209, 1619 cm$^{-1}$; HRMS (ESI-TOF) \textit{m/z} calcd for $[\text{C}_{7}\text{H}_{6}\text{O}+\text{H}]^+$ 107.0491; found 107.0495.

3.1a was synthesized following a known procedure: M.p. 59–62 °C (lit. 63.4–64.2 °C); $R_f = 0.4$ (EtOAc:hexanes, 1:10); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.69 – 7.62$ (m, 2H), 7.53 – 7.46 (m, 1H), 7.45 – 7.38 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 160.9, 133.5, 131.3, 128.8, 119.5, 91.8, 89.5$; IR (film): 2209, 2163, 1604, 1583 cm$^{-1}$; HRMS (ESI-TOF) \textit{m/z} calcd for $[\text{C}_{17}\text{H}_{10}\text{O}+\text{Na}]^+$ 253.0624; found 253.0622.

**Compound 3.3c:** To a solution of 3.1b (93 mg, 0.42 mmol) in CH$_2$Cl$_2$ (4 mL) at −78 °C under N$_2$ was added dimethylaluminum chloride (0.50 mL, 0.50 mmol, 1.0 M in hexanes)
followed by 2,3-dimethyl-1,3-butadiene (287 mg, 3.35 mmol). The reaction was stirred until complete by TLC (1-1.5 h). The reaction was quenched at −78 ºC with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The mixture was filtered through a silica gel plug and the solvent was removed in vacuo to yield crude 3.1c (112 mg, 88%) as a colorless oil and was not further purified: Rf = 0.7 (EtOAc:hexanes, 1:10); ¹H NMR (500 MHz, C₆D₆): δ = 3.11 (t, J = 8.0 Hz, 2H), 2.78 (t, J = 8.1 Hz, 2H), 1.54 (s, 3H), 1.47 (s, 3H), 0.31 (s, 9H). 0.05 (s, 9H); ¹³C NMR (125 MHz, C₆D₆): δ = 179.1, 152.8, 142.0, 122.4, 122.4, 103.5, 99.5, 39.9, 35.6, 18.4, 17.9, −0.2, −0.8; IR (film): 2920, 1644 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C₁₇H₂₈Si₂O⁺H]⁺ 305.1751; found 305.1753.

### Compound 3.5c

To a solution of 3.1b (178 mg, 0.800 mmol) in CH₂Cl₂ (6 mL) under N₂ was added dimethylaluminum chloride (0.96 mL, 0.96 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (330 mg, 4.0 mmol). The reaction was stirred until complete by TLC (1-1.5 h). The reaction was quenched at r.t. with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The mixture was filtered and the solvent was removed in vacuo and the crude product purified by kugelrohr distillation under high vacuum to yield 3.5c (196 mg, 78%) as an off-white solid. The isomeric ratio of the crude product was determined to be 21:1 by GC analysis. The isomeric ratio of the purified
product was determined to be 19:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 3 min., ramp at 2 °C/min. to 280 °C and hold for 10 min.): M.p. 91–95 °C; Rf = 0.5 (EtOAc:hexanes, 1:10); 1H NMR (500 MHz, CDCl3): δ = 2.91 – 2.61 (m, 4H), 2.39 (dd, J = 7.1, 3.2 Hz, 1H), 2.26 (dd, J = 14.5, 3.3 Hz, 1H), 2.16 (d, J = 14.9 Hz, 1H), 2.11 – 2.00 (m, 2H), 1.66 (s, 2xCH3, 6H), 1.54 (s, 2xCH3, 6H), 0.00 (s, 9H); 13C NMR (100 MHz, CDCl3): δ = 209.6, 175.8, 136.4, 126.1, 125.1, 123.6, 121.0, 49.3, 40.6, 34.1, 33.1, 32.8, 28.6, 19.4, 18.9, 18.7, 18.5, –3.0; IR (film): 2869, 1690, 1631 cm⁻¹; HRMS (ESI-TOF) m/z calcld for [C20H30SiO+Na]⁺ 337.1958; found 337.1960.

**Compound 3.5h:** To a solution of 3.1c (317 mg, 1.03 mmol) in CH2Cl2 (10 mL) under N2 was added dimethylaluminum chloride (1.24 mL, 1.24 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (425 mg, 5.20 mmol). The reaction was stirred until complete by TLC (3-3.5 h). The reaction was quenched at r.t. with saturated aqueous NaHCO3 and extracted with Et2O. The layers were separated, the organic phase washed with H2O, brine, and dried over Na2SO4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/CH2Cl2/hexanes (2:8:90)] to yield 3.5h (171 mg, 46%) as an off-white solid. The isomeric ratio of the crude product was determined to be 14:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 3 min., ramp at 2 °C/min. to 260 °C and hold for 10 min.). The isomeric ratio of the purified product was determined
to be >20:1 by $^1$H NMR analysis: M.p. 83–85 °C; $R_f = 0.5$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.92 - 2.70$ (m, 2H), 2.69 - 2.61 (m, 2H), 2.57 (dd, $J = 7.3$, 2.7 Hz, 1H), 2.31 (dd, $J = 14.5$, 2.8 Hz, 1H), 2.26 - 2.10 (m, 3H), 1.70 (s, 6H), 1.57 (s, 6H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.64 (q, $J = 8.0$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 210.1, 176.6, 136.8, 126.2, 125.1, 123.7, 121.1, 49.9, 41.8, 34.6, 33.9, 33.3, 28.8, 19.6, 19.0, 18.9, 18.7, 8.1, 3.2; IR (film): 2869, 1693 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{23}$H$_{36}$SiO+Na]$^+$ 379.2428; found 379.2439.

**Compound 3.5f:** To a solution of 3.1b (242 mg, 1.09 mmol) in CH$_2$Cl$_2$ (6 mL) under N$_2$ atmosphere in a sealed tube was added ethylaluminum dichloride (1.30 mL, 1.30 mmol, 1.0 M in hexanes). The reaction was cooled to 0°C and excess 1,3-butadiene was bubbled through the solution for 5 minutes, then the reaction was warmed to r.t. The reaction was stirred until complete by TLC (10-12 h). The reaction was quenched with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by fractional kugelrohr distillation under 0.15 mmHg at 115 – 125 °C to remove impurities then 135 °C to yield 3.5f (183 mg, 65%) as a colorless oil. The isomeric ratio of the crude product was determined to be >99:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 3 min., ramp at 2 °C/min. to 260 °C and hold for 10 min.). Note: After purification by Kugelrohr distillation a ratio of
28:2:1 of 3.5f/oxidized product S5/unknown isomer was obtained: Rf = 0.6
(EtOAc:hexanes, 1:10); 1H NMR (400 MHz, C6D6): δ = 5.75 – 5.68 (m, 1H), 5.61 – 5.44 (m, 3H), 2.94 – 2.77 (m, 2H), 2.67 (dd, J = 15.0, 6.9, 2.7 Hz, 1H), 2.64 – 2.45 (m, 2H), 2.40 (dd, J = 7.6, 2.6 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.86 – 1.78 (m, 1H), -0.18 (s, 9H); 13C NMR (125 MHz, C6D6): δ = 207.8, 173.2, 136.3, 128.3, 127.1, 125.0, 122.5, 48.7, 40.4, 27.6, 26.2, 25.9, 22.9, -3.1; IR (film): 1705, 1246 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C16H22SiO+Na]⁺ 281.1332; found 281.1332.

**Compound S5:** Purification of 3.5f by column chromatography (silica gel) was also explored, however, we observed a significant increase in the concentration of compound S5. Additionally, S5 can be generated by reacting 3.5f with excess 2,3-dichloro-5,6-dicyano-p-benzoquinone for several days to provide enough material for characterization. The oxidized product S5 was isolated by preparatory thin layer chromatography [EtOAc/hexanes (1:40)] as a pale yellow oil. Note: We only observed oxidation of 3.5f. All other cyclic products appear to be stable to oxidation under ambient conditions and during purification. Rf = 0.25 (EtOAc:hexanes, 1:40); 1H NMR (400 MHz, C6D6): δ = 7.83 – 7.77 (m, 1H), 7.15 – 7.10 (m, 1H), 7.05 – 7.01 (m, 1H), 6.89 – 6.84 (m, 1H), 5.66 (dt, J = 10.0, 2.4 Hz, 1H), 5.58 – 5.52 (m, 1H), 2.67 (dd, J = 7.5, 3.8 Hz, 1H), 2.61 (ddd, J = 15.0, 6.2, 3.9 Hz, 1H), 2.19 – 2.17 (m, 1H), 2.16 (dd, J = 4.2, 2.1 Hz, 1H), 2.14 – 2.03 (m, 1H), -0.22 (s, 9H); 13C NMR (100 MHz, CDCl3): δ = 209.9, 162.5, 137.0, 134.9, 128.5, 127.7, 126.2, 124.6, 123.8, 50.5, 36.6, 29.5, 26.6, -3.7; IR (film): 3048, 2954, 2836, 1708 cm⁻¹; LRMS (EI) m/z calcd for [C16H20SiO]+ 256.1; found 256.1.
**Compound 3.5g:** To a solution of **3.1b** (690 mg, 3.10 mmol) in CH$_2$Cl$_2$ (30 mL) under N$_2$ atmosphere in a sealed tube was added dimethylaluminum chloride (4.50 mL, 4.50 mmol, 1.0 M hexanes) followed by excess isoprene (15 mL). The reaction was stirred until complete by TLC (10-12 h). The reaction was quenched at r.t. with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, EtOAc/hexanes (4:86)] to yield an inseparable mixture of undetermined isomers **3.5g** (476 mg, 54%) as a colorless oil. Four isomers (presumed to be a mixture of regio- and diastereoisomers) were detected by GC analysis of the crude product in a ratio of 7.1:1.4:1:1 (GC-MS method: flow = 1 mL/min; inlet = 250 °C; 200 °C for 4 min., ramp at 2 °C/min. to 260 °C and hold for 10 min.). The isomeric ratio of the purified product was determined to be 7:1:1 by GC analysis. Note: A small amount of a pure fraction of the major isomer could be isolated by column chromatography for NMR characterization (see figures S15 and S16): R$_f$ = 0.5 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, C$_6$D$_6$): δ = 5.45 – 5.39 (m, 1H), 5.30 – 5.24 (m, 1H), 3.02 – 2.82 (m, 2H), 2.75 – 2.49 (m, 3H), 2.45 (dd, $J$ = 7.5, 2.9 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.92 (s, 2H), 1.53 (s, 3H), 1.49 (s, 3H), –0.13 (s, 9H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ = 207.7, 173.0, 136.8, 134.8, 129.1, 120.9, 119.9, 49.0, 40.4, 32.3, 31.2, 26.8, 23.7, 23.5, 23.2, –3.0; IR (film): 2875, 1693.
cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([C_{18}H_{26}SiO+H]^+\) 287.1826; found 287.1821.

**Compound 3.6i**: To a solution of 3.1d (173 mg, 1.63 mmol) in CH\(_2\)Cl\(_2\) (6 mL) under N\(_2\) atmosphere was added ethylaluminum dichloride (1.92 mL, 1.92 mmol, 1 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (670 mg, 8.20 mmol). The reaction was stirred until complete by TLC (13-14 h). The reaction was quenched at r.t. with saturated aqueous NaHCO\(_3\) and extracted with Et\(_2\)O. The layers were separated, the organic phase washed with H\(_2\)O, brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, CH\(_2\)Cl\(_2\)/EtOAc/hexanes (16:1:83)] to yield 3.6i (153 mg, 35%) as an off-white solid. The isomeric ratio of the crude product was determined to be 15:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 3 min., ramp at 2 °C/min. to 260 °C and hold for 10 min.): M.p. 102–105 °C; \(R_f\) = 0.5 (EtOAc:hexanes, 1:10); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 6.63\) (s, 1H), 2.73 (d, \(J = 17.2\) Hz, 1H), 2.44 (dd, \(J = 11.2, 5.7\) Hz, 1H), 2.40 (d, \(J = 17.1\) Hz, 1H), 2.22 (dd, \(J = 17.4, 5.5\) Hz, 1H), 1.98 – 1.88 (m, 1H), 1.80 (s, 3H), 1.79 (s, 3H), 1.78 (d, \(J = 16.4\) Hz, 1H), 1.64 (s, 3H), 1.62 (s, 3H), 1.55 (d, \(J = 16.4\) Hz, 1H), 1.05 (s, 3H), 0.71 (s, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 204.5, 139.8, 135.6, 130.6, 125.5, 123.6, 123.2, 51.7, 41.6, 40.6, 39.3, 39.2, 28.1, 20.7, 19.9, 19.2, 18.5, 18.1, 17.2; IR (film): 2903, 1702, 1579 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for \([C_{19}H_{26}O+H]^+\) 271.2056; found 271.2055.
**Compound 3.6j:** To a solution of 3.1a (197 mg, 0.856 mmol) in CH₂Cl₂ (6 mL) under N₂ atmosphere was added ethylaluminum dichloride (1.0 mL, 1.0 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (351 mg, 4.30 mmol). The reaction was stirred until complete by TLC (24 h). The reaction was quenched at r.t. with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, CH₂Cl₂/EtOAc/hexanes (30:1:69)] to yield 3.6j (92 mg, 27%) as an orange solid. The isomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 3 min., ramp at 1 °C/min. to 280 °C and hold for 10 min.): Rᵋ = 0.6 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 7.39 – 7.08 (m, 9H), 7.03 – 6.96 (m, 1H), 6.98 (s, 1H), 2.73 (dd, J = 10.8, 5.7 Hz, 1H), 2.59 (d, J = 16.4 Hz, 1H), 2.39 – 2.29 (m, 2H), 2.16 – 2.04 (m, 1H), 1.81 (d, J = 16.6 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.58 (s, 3H), 1.48 (s, 2 x CH₃, 6H), 1.34 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 205.9, 142.0, 141.6, 138.4, 138.0, 134.0, 129.3, 128.4, 127.9, 127.7, 127.0, 126.2, 125.7, 124.5, 123.9, 54.2, 52.1, 50.5, 41.6, 41.5, 29.8, 20.5, 20.2, 18.8, 16.6; IR (film): 2900, 1696, 1564, 1439 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C₂₉H₃₀O+Na]⁺ 417.2189; found 417.2182.
**Compound 3.13:** To a solution of 3.1a (109 mg, 0.470 mmol) in C₂H₄Cl₂ (8 mL) under N₂ atmosphere was added ethylaluminum dichloride (0.57 mL, 0.570 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (93 mg, 1.14 mmol). The reaction was heated to reflux and stirred until complete by TLC (8.5 h). The reaction was quenched at r.t. with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, CH₂Cl₂/EtOAc/hexanes (30:1:69)] to yield 3.13 (12 mg, 6%) as an orange solid. Rᵥ = 0.6 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, C₆D₆): δ = 7.15 – 7.10 (m, 4H), 7.06 – 6.95 (m, 6H), 3.06 – 2.95 (m, 4H), 2.75 (dd, J = 7.3 Hz, 2H), 2.29 (d, J = 3.5 Hz, 2H), 1.44 (s, 3H), 1.28 (s, 3H), 1.21 (s, 6H); ¹³C NMR (125 MHz, C₆D₆): δ = 208.4, 168.9, 143.0, 136.3, 130.4, 129.0, 128.4, 127.9, 126.7, 123.0, 122.2, 68.5, 62.4, 47.7, 33.3, 29.9, 18.6, 18.5, 13.3; LRMS (EI) m/z calcd for [C₂₀H₃₀O]+ 394.3; found 394.2.

**Compound 3.7:** To a solution of 3.1a (142 mg, 1.33 mmol) in CH₂Cl₂ (12 mL) at −15 °C under N₂ atmosphere was added boron trichloride (1.33 mL, 1.33 mmol, 1 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (552 mg, 6.70 mmol). The reaction was stirred
until complete by TLC (3 h). The reaction was quenched at $-15^\circ\text{C}$ with saturated aqueous NH$_4$Cl and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, CH$_2$Cl$_2$/EtOAc/hexanes (18:2:80)] to yield **3.7** (115 mg, 32%) as a yellow oil. Four isomers were detected by GC analysis of the crude product in a ratio of 71:12:5:1 (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 3 min., ramp at 2 °C/min. to 260 °C and hold for 10 min.). The isomeric ratio of the purified product was determined to be 22:1 by GC analysis: $R_f = 0.34$ (EtOAc:hexanes, 1:20); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 6.65$ (s, 1H), 6.43 (d, $J = 2.9$ Hz, 1H), 2.73 (d, $J = 17.1$ Hz, 1H), 1.93 – 1.82 (m, 1H), 1.81 (d, $J = 17.5$ Hz, 1H), 1.77 (s, 2 x CH$_3$, 6H), 1.59 – 1.51 (m, 1H), 1.48 (dd, $J = 12.3$, 12.1 Hz, 1H), 1.36 (dd, $J = 12.3$, 3.1 Hz, 1H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.02 (s, 3H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.88 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 193.8$, 146.7, 141.1, 137.2, 135.5, 131.2, 123.2, 43.3, 42.5, 39.0, 38.23, 38.22, 33.1, 27.3, 21.6, 20.7, 20.6, 18.7, 17.4; IR (film): 2956, 1692; 1649, 1583 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{19}$H$_{26}$O+H]$^+$ 271.2056; found 271.2060.

![3.8](image_url)

**Compound 3.8:** To a solution of **3.1a** (215 mg, 0.934 mmol) in CH$_2$Cl$_2$ (10 mL) under N$_2$ atmosphere at $-15^\circ\text{C}$ was added boron trichloride (0.935 mL, 0.935 mmol, 1 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (385 mg, 4.67 mmol). After 3 h the
reaction was warmed to 0 °C and stirred until complete by TLC (an additional 4.5 h). The reaction was quenched at r.t. with saturated aqueous NH₄Cl and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel, Et₂O/hexanes (1:12)] to yield a single isomer of 3.8 (41 mg, 11%) as a yellow solid: Rf = 0.33 (EtOAc:hexanes, 1:20); ¹H NMR (500 MHz, C₆D₆): δ = 7.34 (d, J = 7.8 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H), 7.20 – 7.07 (m, 4H), 7.06 (s, 1H), 7.05 – 6.97 (m, 2H), 6.95 (d, J = 3.2 Hz, 1H), 2.45 (d, J = 16.5 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.43 – 1.35 (m 1H), 1.28 (s, 1H), 1.21 (s, 1H), 1.09 – 1.01 (m, 1H), 0.70 (t, J = 12.6 Hz, 1H), 0.62 (d, J = 7.1 Hz, 3H), 0.56 (d, J = 6.6 Hz, 3H); ¹³C NMR (125 MHz, C₆D₆): δ = 192.9, 147.4, 145.9, 143.7, 140.7, 140.4, 137.9, 134.4, 128.4, 128.2, 128.0, 127.6, 127.1, 126.4, 125.3, 54.5, 52.5, 42.9, 42.3, 39.5, 34.3, 20.3, 20.0, 17.6, 16.2; IR (film): 2944, 1688; 1641, 1567 cm⁻¹; HRMS (ESI-TOF) m/z calcd for [C₂⁹H₃₀O+H]⁺ 395.2369; found 395.2373.

Figure S2. Single crystal X-ray structures of compound 3.5f showing the syn relationship between the methine hydrogen and the TMS group (50% probability).
3.10 References


4 One-pot Synthesis of [6-5-6] Tricyclic Products via a Double Diels-Alder/Nazarov Tandem Reaction of Unsymmetrically-substituted Cross-conjugated Diynones

4.1 Introduction

The use of relatively high-energy starting materials to achieve multiple carbon-carbon bond formation in a single pot reaction is a highly efficient technique to rapidly access advanced intermediates.\textsuperscript{1,2} A number of efficacious examples targeting useful polycyclic substructures have recently been reported in the literature.\textsuperscript{3–5} Five- and six-membered rings are highly prevalent in biologically active compounds; therefore, routes towards these polycyclic structures receive considerable attention.\textsuperscript{6,7} Cycloaddition reactions are one of the most innovative and influential strategies for synthesizing desirable cyclic target molecules. Since its discovery in 1928, the Diels-Alder reaction has been modified to meet current needs in chemistry, particularly by increasing functionality in the products.\textsuperscript{8–10} The Nazarov cyclization is perhaps one of the most effective routes for the stereoselective formation of cyclopentenones.\textsuperscript{11–13} Utilizing the Nazarov and Diels-Alder reactions in a cascade process to generate multiple rings in a one-pot reaction is a very pragmatic approach towards important biological scaffolds.\textsuperscript{14,15} Hirsutellone B and taiwaniaquinol B are characterized by a [6-5-6]-carbotricyclic skeleton which involves numerous steps to construct (Figure 1).\textsuperscript{19–22} Hirsutellone B displays potent activity against tuberculosis;\textsuperscript{19} therefore, the development of efficient methods to obtain the [6-5-6]-tricyclic core shared by these molecules is of value.
4.2 Double Diels-Alder/Nazarov Tandem Reaction of Diynones

Chapter 3 reported the multicomponent double Diels-Alder/Nazarov tandem reaction of symmetric cross-conjugated diynones 3.1b that could be conducted within a single reaction pot (Figure 4-2a). When 1,5-bis(TMS)-1,4-diyn-3-one 3.1b is employed as a substrate, desilylation of one TMS group occurs to ultimately provide product 3.5c with excellent regio- and diastereoselectivity. If the TMS groups in the substrate are exchanged for other groups (\(R^1 = \text{aryl, alkyl}\)) then products 3.6, which contain vicinal quaternary centers, are produced. Unfortunately, the scope of products 3.1b that contain a single quaternary center is limited to trialkylsilyl-substituted adducts. To mend this limitation, we envisioned using unsymmetrically-substituted diynones 4.1 as substrates with diene 4.2, where the TMS will be cleaved during the reaction and the \(R^4\) group retained in the product (Figure 4-2b). Intermediate 4.3 can undergo a second cyclization with a second equivalent of the same diene to give product 4.4 where various substituents (\(R^4\)) can be envisioned at the quaternary center. An added advantage of this method is that one can also utilize a second equivalent of a different diene to afford an even broader scope of products such as 4.5. This chapter describes a one-pot double
Diels-Alder/Nazarov tandem reaction of unsymmetrically-substituted diynones to produce [6-5-6]-tricyclic products with excellent regio- and diastereoselectivity.

**a) Previous work:**

![Diagram of Diels-Alder/Nazarov reaction](image)

**b) This work:**

![Diagram of Diels-Alder/Nazarov reaction](image)

**Figure 4-2:** a) A double Diels-Alder/Nazarov reaction of symmetric diynones to produce [6-5-6] products with a quaternary (3.5) or vicinal quaternary (3.6) centers.\(^\text{17}\) b) Application of method to unsymmetrically-substituted diynones 4.1 and various dienes to broaden the scope of this reaction.

Regiochemical control is a common obstacle that plagues the utility of the Nazarov reaction.\(^\text{24}\) The utilization of the \(\beta\)-silyl effect in the Nazarov reaction to elicit high regiocontrol of the products has proven to be an exceedingly valuable tool.\(^\text{14,20–22}\)

The incorporation of a TMS-substituent in substrate 4.1 not only stabilizes the oxyallyl cation intermediate 4.6 through the \(\beta\)-silyl effect but also results in a very regioselective elimination of the TMS group to provide product 4.4 (Figure 4-3). Using this as the foundation for this work, we set out to survey unsymmetrically-substituted cross-conjugated diynones in a one-pot double Diels-Alder/Nazarov tandem reaction.
We chose to explore the cyclization reaction of bulky diynone 4.1a due to its stability and ease of handling. Use of this diynone also allowed for a direct comparison of the double Diels-Alder cycloaddition with respect to substituents of similar size (TMS vs tert-butyl). We initially attempted to use our previously reported conditions to invoke the tandem cyclization reaction. Unfortunately, compound 4.1a with diene 4.2a only produced monocyclized product 4.3a in the presence of ethylaluminum dichloride with no detection of 4.4a, even at elevated temperatures (Scheme 1). The high regioselectivity of the single Diels-Alder reaction product was interesting as we envisioned that this might prove useful for mixed Diels-Alder reactions (vide infra). Nonetheless, it seemed that ethylaluminum dichloride was not sufficiently strong enough for this one-pot reaction. Thus, we turned to using boron trichloride since we have recently reported the successful use of this catalyst for the cyclization of challenging symmetric diynones.17 Indeed, boron trichloride worked well to provide 4.4a in 43% yield (Scheme 4-1). One should note that this seemingly modest overall yield is the product of two separate Diels-Alder reactions and a Nazarov cyclization that equates to roughly 75% yield per reaction accompanied by the formation of five new carbon-carbon bonds, three new rings, and vicinal quaternary centers. As we had predicted, the elimination of the TMS group provided excellent regioselectivity for the newly formed double bond in compound 4.4a.
(shown in red). The major diastereomer contains a *syn* relationship between the methine hydrogen and the *tert*-butyl group and was assigned based on NOESY NMR experiments. This result is also consistent with what was reported for compound 3.5 (Figure 4-2).\(^{17}\)

![Scheme 4-1: Double Diels-Alder/Nazarov tandem reaction of sterically hindered diynone 4.1a and 2,3-dimethyl-1,3-butadiene 4.2a to generate [6-5-6]-carbotricyclic product 4.4a catalyzed by BCl₃.]

### 4.3 Triethyl Silyl versus Trimethyl Silyl Unsymmetrical Diynones

A suitable choice of substrate was needed first to initiate this project. We were interested in comparing a triethyl silyl diynone with a trimethyl silyl diynone to determine if the use of one over the other provided a synthetic advantage. We initially looked at the relatively inexpensive 4.1b as a dienophile for the tandem reaction. The reaction of 4.1b and 4.2a had predominately formed monocyclized 4.3b and trace Nazarov 4.4b after 3 hours (Scheme 4-2). Formation of 4.4b required additional time, however, these results suggest that for more difficult substrates Al(CH₃)₂Cl may not be sufficient.
Scheme 4-2: The use of Al(CH₃)₂Cl to form a mixture of 4.3b and 4.4b from unsymmetrical diynone 4.1b.

Next, EtAlCl₂ was screened as a reagent to promote the reaction and examination of the ¹H NMR showed a 2:1 ratio of desired 4.4b to monocyclized 4.3b after 19 hours (Scheme 4-3). After further monitoring by TLC, no additional conversion of 4.3b was observed and the reaction did not go to completion. In order to push the reaction to completion it was necessary to reflux the reaction to convert the ketone to the Nazarov product 4.4b using EtAlCl₂. However, after additional studies we determined that EtAlCl₂ gave inconsistent results and therefore decided to try a different Lewis acid. We tried BCl₃ with 4.1b and 4.2a which resulted in the rapid formation of 4.4b in a 27% yield.

Scheme 4-3: The use of EtAlCl₂ to form a mixture of 4.4b and 4.3b from unsymmetrical diynone 4.1b.

We then synthesized a bulkier version, 4.1c to use as the dienophile, which had increased stability. AlBr₃ with 4.1c and 4.2a gave a mixture of 4.3c and 4.4c, although 4.4c appeared to be decomposing (Scheme 4-4). Aluminum is an efficient Lewis acid for more reactive substrates but fails with more difficult ones. Degassing of the liquid
reaction components was done in order to minimize decomposition but it appeared not to solve the problem. Additionally, refluxing in C₄H₄Cl₂ with AlBr₃ is too harsh for the 4.2a to survive. For both AlBr₃ and EtAlCl₂ the reaction conditions were difficult to reproduce. It appears that under higher temperatures too many reaction pathways are accessible and decomposition results. However, BCl₃ was found to strongly activate diynone 4.1c towards the Diels-Alder cycloaddition and successfully formed 4.4c. We planned to optimize conditions and then do an electron deficient and electron rich substrate scope.

\[
\text{TES} \quad 4.1c \quad + \quad \text{Ph} \quad 4.2a \quad \xrightarrow{\text{AlBr}_3} \quad \text{TES} \quad 4.3c \quad + \quad \text{Ph} \quad 4.4c
\]

**Scheme 4-4:** Brief screening with AlBr₃ and BCl₃ for the unsymmetrically-substituted triethyl silyl diynone.

We then went ahead and tried BCl₃ with a few more triethyl silyl diynones. The reaction of diynone 4.1d and 4.2 yielded the expected Nazarov product 4.4d, which was isolated to give a 26% yield (Scheme 4-5). While the product 4.4d oxidizes readily, no oxidation was observed during the reaction.

\[
\text{TES} \quad 4.1d \quad + \quad \text{OMe} \quad 4.2a \quad \xrightarrow{\text{BCl}_3} \quad \text{MeO} \quad 4.4d
\]

**Scheme 4-5:** Reaction of 4.1d and 4.2 in the synthesis of para-methoxy substituted Nazarov product 4.4d.
The reaction of diynone 4.1e and 4.2a yielded the expected Nazarov product 4.4e after nearly three hours at 0 °C (Scheme 4-6). The product 4.4e appears to be fairly stable. Purification was accomplished using column chromatography to give 4.4e in 46% yield.

![Scheme 4-6: Reaction of diynone 4.1e and 4.2a in the synthesis of ortho-bromo substituted Nazarov product 4.4e.](image)

We noted that the triethyl silyl diynones formed the Nazarov product with a lower diastereoselectivity than the analogous trimethylsilyl diynones. Additionally, the triethyl silyl diynones proved to be more difficult substrates in that it requires longer times and higher temperatures than reactions using 4.1b. While we found that diynone 4.1b decomposed within a few weeks even when stored in the freezer, synthetically it was a more efficient substrate and therefore we continued our studies using trimethylsilyl substituted diynones.

### 4.4 Optimization Attempts for the Unsymmetrical Scope

The screening was done to determine a suitable catalyst for the unsymmetrical diynone substrates. The use of aluminum did not work as well, reactions tended to be very slow and often did not go to completion (as observed in Chapter 3). Additionally, we were interested in determining other catalysts that could be applied to the double Diels-Alder/tandem Nazarov reaction sequence. If these reagents were catalytic they
could then be used in an enantioselective version.\textsuperscript{23} The use of aqueous phase catalysts would enable a more environmentally benign system and remove the need for an air/moisture free reaction requiring less expense and expertise. Lewis acids were screened with the relatively reactive TMS/TMS substrate 3.1b (Chapter 3) first to determine whether they would activate diynone 3.1b sufficiently enough to undergo a Diels-Alder cycloaddition with 4.2a at room temperature. Furthermore, the screening process was more practical to conduct with TMS/TMS diynone 3.1b because the unsymmetrical diynones were more expensive and time consuming to synthesize (Table 4-1). Strong Lewis acids, In(OTf)\textsubscript{3}, Bi(OTf)\textsubscript{3}, and TiBr\textsubscript{4} were found to react with the diene 4.2a too quickly for a Diels-Alder cycloaddition to occur.

Stoichiometric and catalytic amounts of BCl\textsubscript{3} were used with diynone 3.1b, the reaction was successful but the Lewis acid was not catalytic with respect to this substrate (entries 1 and 2, Table 4-1). No conversion of starting material 3.1b was observed with Ti(O-i-Pr)\textsubscript{4} or TiF\textsubscript{3} and TiF\textsubscript{3} was found to be partly insoluble in the solvent (entries 3 and 4). No conversion was observed for Yb(OTf)\textsubscript{3} after 1 hour as detected by TLC, the mixture was slightly cloudy as the catalyst is not as soluble in organic solvents as in aqueous mixtures (entry 5). Both reactions using Y(OTf)\textsubscript{3} and Pr(OTf)\textsubscript{3} gave no conversion after 1 hour by TLC, the reactions also displayed a small amount of insolubility (entries 6 and 7). Additionally, when Pr(OTf)\textsubscript{3} was run in an aqueous solvent no conversion by TLC was observed (entry 8). No conversion of starting material 3.1b was seen after 1.5 hours by TLC for Nd(OTf)\textsubscript{3}, and the mixture was slightly cloudy (entry 9). Solubility improved when Nd(OTf)\textsubscript{3} was run in THF/H\textsubscript{2}O; however, no reaction resulted (entry 10). Sm(OTf)\textsubscript{3}, Tb(OTf)\textsubscript{3}, and Dy(OTf)\textsubscript{3} were run in CH\textsubscript{2}Cl\textsubscript{2} and
showed no conversion of $3.1b$ after 1.5 hours. The reactions were also slightly cloudy indicating solubility issues (entries 11-13). No conversion of starting material $3.1b$ occurred, TlCl$_3$ polymerized diene $4.2a$ immediately. This may be a good catalyst for a different reaction, upon addition of the TlCl$_3$ to the substrate a colorless to reddish color change was observed. Since the Lewis acid was added before diene $4.2a$, the color change indicates that the Lewis acid had bound to diynone $3.1b$, forming an activated species (entry 14). Neither Bi(NO$_2$)$_3$ or Zn(OTf)$_2$ reacted with $3.1b$ to initiate the Diels-Alder cycloaddition and both were slightly insoluble (entries 15 and 16).

The Diels-Alder cycloaddition of unsymmetrical diynones with $3.1b$ followed by a Nazarov reaction requires a strong Lewis acid or catalyst to effect the transformations. With past reactions involving similar compounds, we have observed rapid decomposition with several compounds such as diynone $4.1b$. Therefore, it was of interest to us to determine conditions that would not require temperatures much higher than room temperature. This is also of use in pursuing enantioselective catalysts. If heating is required and poor enantioselectivity was observed, decreasing the temperature may not be a feasible solution. The catalyst system would likely need to be altered to become significantly more reactive. Based on our screening thus far, a highly reactive catalyst is necessary to activate the diynone towards a Diels-Alder cycloaddition.
**Table 4-1**: Screening catalysts for unsymmetrical diynone scope

![Diagram of 3.1b and 4.2a reacting with Lewis acid to form 3.5c]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>BCl₃</td>
<td>CH₂Cl₂, 30 minutes</td>
<td>3.5c</td>
</tr>
<tr>
<td>2</td>
<td>BCl₃ 10 mol %</td>
<td>CH₂Cl₂, 40 min</td>
<td>not catalytic</td>
</tr>
<tr>
<td>3</td>
<td>Ti(O-i-Pr)₄</td>
<td>CH₂Cl₂/THF</td>
<td>No Conversion</td>
</tr>
<tr>
<td>4</td>
<td>TiF₃</td>
<td>CH₂Cl₂/THF</td>
<td>No Conversion</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)₃</td>
<td>CH₂Cl₂ and ACN</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>Y(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
<td>7</td>
<td>Pr(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
<td>8</td>
<td>Pr(OTf)₃</td>
<td>4:1 (ethanol:water)</td>
<td>No conversion</td>
</tr>
<tr>
<td>9</td>
<td>Nd(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
<td>10</td>
<td>Nd(OTf)₃</td>
<td>9:1 (THF:water) r.t.</td>
<td>No conversion</td>
</tr>
<tr>
<td>11</td>
<td>Sm(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
<td>12</td>
<td>Tb(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
<td>13</td>
<td>Dy(OTf)₃</td>
<td>CH₂Cl₂</td>
<td>No conversion</td>
</tr>
<tr>
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<td>TiCl₃ hydrate</td>
<td>CH₂Cl₂/THF</td>
<td>No conversion</td>
</tr>
<tr>
<td>15</td>
<td>Bi(NO₂)₃</td>
<td>CH₂Cl₂/THF</td>
<td>No Conversion</td>
</tr>
<tr>
<td>16</td>
<td>Zn(OTf)₂</td>
<td>CH₂Cl₂/THF</td>
<td>No Conversion</td>
</tr>
</tbody>
</table>

In order to monitor the reaction more closely and obtain a yield before the reaction quench occurred, several NMR reactions were run using diynone 4.1a and diene 4.2a (Scheme 4-1). The reactions were attempted in both dry deuterated chloroform and dichloromethane. Amounts of reagents used were carefully measured out in a pre-dried NMR tube and 1.0 mL of solvent was added. Essentially, the NMR reactions were unsuccessful. It was difficult to mimic the controlled round bottom conditions as decomposition occurred rapidly. While actual NMR experiments were run at room temperature, considerable care was taken to ensure the sample was kept at lower temperatures during travel to and from the NMR room to minimize decomposition.
During some reactions, trace Nazarov $4.4\text{a}$ was observed. During the experiments, the spectrum was difficult to read, which is at odds with the $^1\text{H}$ NMR of the crude reaction mixture. Initially we suspected that the mesitylene standard was reacting with the intermediates. The standard was changed to hexamethylbenzene but we still found the reaction difficult to observe. For a general idea of reaction yield, at least before purification, we decided to monitor the reaction by GC-MS with a standard.

![Scheme 4-7](attachment:image.png)

**Scheme 4-7:** NMR reactions conducted with $4.1\text{a}$ and $4.2\text{a}$ using $\text{BCl}_3$ to form product $4.4\text{a}$.

The unsymmetrical diynones gave a lower yield of the Nazarov product than the symmetrical diynones. It was not immediately clear why this should be the case. We wondered if the intermediates were reacting along other pathways, resulting in a lower yield of the desired product. In order to determine if this was the case we performed a dilution study using $4.1\text{a}$ and $4.2\text{a}$ to generate $4.4\text{a}$ (Table 4-2). The reactions were run on a 94-95 mg scale and were conducted at approximately the same time. The crude $^1\text{H}$ NMR for 1.0 M and 0.1 M showed roughly the same amount of oxidized product $4.4\text{a}'$ (5-6%) (entries 1 and 2). The 0.01 M showed approximately 8% oxidized product by $^1\text{H}$ NMR (entry 3). We observed a decrease in yield with respect to a decreased concentration. The yields may be effected by time, both the 1.0 M and 0.1 M reactions reached completion within a half hour of each other, while the 0.01 M solution required seven hours to complete. Since decomposition of the final product is known to occur with
some of the unsymmetrical substrates, a longer reaction time may diminish the yield regardless of the substrate.

**Table 4-2:** Concentration study for diynone 4.1a to obtain information on why the yield is lower for the unsymmetrical scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Molarity</th>
<th>Time (h)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>1.5</td>
<td>37%</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>2</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>0.01</td>
<td>7</td>
<td>13%</td>
</tr>
</tbody>
</table>

### 4.5 Scope of Unsymmetrically-substituted Trimethyl Silyl Diynones

We synthesized a variety of TMS-substituted diynones 4.1 to establish the scope of the unsymmetrically-substituted diynone system and its applicability for targeting a wide range of [6-5-6]-carbotricyclic derivatives (**Table 4-3**). The variety of Nazarov products were compiled for comparison of electron donating and withdrawing substituents and their effects on product formation. Interestingly, we determined that the product with the larger tert-butyl substituent (4.4a, entry 1) was actually obtained in higher yield versus the smaller methyl-substituted derivative (4.4f, entry 2). Diynone 4.1b provided product 4.4b in a moderate 32% yield (entry 3). Not surprisingly, electron-rich aryl groups on substrates 4.1h and 4.1i proved to be more difficult for the Diels-Alder cycloaddition but nevertheless generated the desired tricyclic products 4.4h and 4.4i in modest yields of 24% and 32%, respectively (entries 4 and 5). It should be noted that the skipped cyclohexadiene moiety in product 4.4h (entry 4) had partially oxidized to...
an aromatic ring over the course of the reaction and this side-product was separated and isolated in 6% yield (see supporting information for details). The bromine-substituted aryl derivatives 4.1j and 4.1k (entries 6 and 7) underwent the tandem double Diels-Alder/Nazarov reaction rapidly to generate the corresponding products 4.4j and 4.4k in relatively good yields of 29% and 42%, respectively. The fluorine-substituted aryl derivatives 4.1l and 4.1m (entries 8 and 9) also performed well to give 4.4l and 4.4m in 38% and 43% yield, respectively. All of the tricyclic products 4.4a-4.4i were generated with excellent regio- and diastereoselectivity. As is common with cyclic “skipped dienes”, we observed that products 4.4a-4.4i would begin to oxidize if exposed to air under the reaction conditions or if left under an air atmosphere for an extended period of time.\(^9,\)\(^10\) For many of the reactions, only the two expected diastereomeric products were detected by GC-MS analysis. However, in entries 1 and 2 we observed an additional minor isomer (uncharacterized) that is possibly the result of double bond migration.\(^17\)

**Table 4-3: Substrate scope of diynone 4.1.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R(^4)</th>
<th>Product</th>
<th>Yield [%] (^{[a]})</th>
<th>Isomeric ratio (^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.1a</td>
<td>t-butyl</td>
<td>4.4a</td>
<td>43</td>
<td>15:2:1(^{[c]})</td>
</tr>
<tr>
<td>2</td>
<td>4.1f</td>
<td>Me</td>
<td>4.4f</td>
<td>17</td>
<td>15:1:1(^{[c]})</td>
</tr>
<tr>
<td>3</td>
<td>4.1b</td>
<td>C(_6)H(_5)</td>
<td>4.4b</td>
<td>32</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td>4.1h</td>
<td>o-MeO-C(_6)H(_4)</td>
<td>4.4h</td>
<td>24(^{[d,e]})</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>4.1i</td>
<td>p-MeO-C(_6)H(_4)</td>
<td>4.4i</td>
<td>32</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>6</td>
<td>4.1j</td>
<td>o-Br-C(_6)H(_4)</td>
<td>4.4j</td>
<td>29(^{[e]})</td>
<td>12:1</td>
</tr>
<tr>
<td>7</td>
<td>4.1k</td>
<td>p-Br-C(_6)H(_4)</td>
<td>4.4k</td>
<td>42</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>8</td>
<td>4.1l</td>
<td>o-F-C(_6)H(_4)</td>
<td>4.4l</td>
<td>38(^{[e]})</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>9</td>
<td>4.1m</td>
<td>p-F-C(_6)H(_4)</td>
<td>4.4m</td>
<td>43</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
[a] Isolated yield of major isomer. [b] Crude diastereomeric ratio of products determined by GC-MS analysis. [c] An uncharacterized third minor isomer was detected possibly due to double bond migration in the product. [d] Oxidized/aromatized side-product (S10) was also isolated in 6% yield. [e] The NOESY data was ambiguous; therefore, the stereochemistry was assigned by analogy.

4.6 Multi-diene Reactions

In a previous study described in chapter 3, we noted that at low temperatures we could selectively form the monocyclized product 3.3c in good yield, even in the presence of excess diene (Scheme 4-8).17 With this result we imagined that we could employ a timed double Diels-Alder reaction between compound 4.1a and two different dienes to arrive at highly functionalized [6-5-6]-tricyclic products with excellent regiocontrol.

Scheme 4-8: Exclusive formation of monocyclized 3.3c at -78 °C.

As we had discovered earlier, a multi-diene reaction with TMS ketone 31b generated a mixture of different isomers (Chapter 3). A symmetrical diynone has two chemically equivalent alkynes and therefore has limited utility if reactivity of one alkyne is desired over the other alkyne.

Scheme 4-9: Attempted multi-diene reaction using diynone 3.1b in a reaction with 4.2a, followed by 4.2b.
In order to probe this issue further, we synthesized 4.1n having an alkyne substituted trimethyl silyl as well as a triethyl silyl-substituted alkyne (Scheme 4-10). We were interested to see whether an unsymmetrical silyl substituted diynone would effect a bias in terms of which alkyne reacted first as well as preferential silyl elimination after the Nazarov reaction. We found that using Al(CH₃)₂Cl at room temperature generated monocyclized products 4.3n and 4.3n′ in a 6:1 ratio, respectively (Scheme 4-10a).

However, when EtAlCl₂ was used at -78 °C, the ratio of 4.3n and 4.3n′ was 3:1, respectively (Scheme 4-10b). The experimental results are reasonable since it should be easier for cyclization to occur preferentially on the less hindered alkyne. The decreased ratio observed with EtAlCl₂ was unsurprising since it is a stronger Lewis acid than Al(CH₃)₂Cl. It was necessary for the EtAlCl₂ reaction to be conducted at -78 °C in order to avoid the formation of the Nazarov product. Al(CH₃)₂Cl is weak enough to preferentially form the TMS monocyclized. A 6:1 ratio is nearly favorable, while a 3:1 is not useful if two different dienes were to be used during the reaction since a mixture of products would result. We tried BCl₃ with 4.1n as well and we observed a mixture of 4.3n and 4.3n′ in a very similar ratio to EtAlCl₂, within one hour at -78 °C. These studies provide useful information on which monocyclized product is formed preferentially.
Scheme 4-10: a) Diynone 4.1n reacted to give a 6:1 ratio of monocyclized 4.4n and 4.4n′ under Al(CH$_3$)$_2$Cl conditions. b) The ratio decreased to 3:1 of 4.4n and 4.4n′ when EtAlCl$_2$ was used instead.

Next, we used EtAlCl$_2$ to determine if any preference exists for silyl elimination between TMS and TES after the Nazarov reaction. The first reaction was run at room temperature and we observed a 3.6:1 ratio of 3.5c to 3.5j, indicating that triethyl silyl elimination is favored and formation of X is preferred (Scheme 4-11a). A second scenario was run at 0 °C and interestingly, we found that the ratio of 3.5c to 3.5j increased to 6:1 (Scheme 4-11b). The enhanced electron donating ability of the triethyl silyl must stabilize the intermediate 4.7 more effectively. Since cooling the reaction to 0 °C increased silyl elimination selectivity to 6:1, it’s likely that additional cooling would increase selectivity further. Likewise, increasing the silyl bulk would increase the preference for alkyne reactivity and may also increase the silyl elimination ratio to an even more favorable product mixture. In this case, it would be possible to use an unsymmetrically-substituted silyl diynone with two different dienes, particularly if there was a need for silyl functionality in the product.
Scheme 4-11: a) Room temperature conditions generated a mixture of, 3.5c and 3.5j, in a 3.6:1 ratio. B) lower temperature conditions at 0 °C formed both products 3.5c and 3.5j but in a higher ratio of 6:1.

Monocyclized 3.3c was isolated and used in a multi-diene reaction with isoprene 4.2b to form Nazarov 4.5a successfully (Scheme 4-12a). Additionally, 3.3c was reacted with butadiene 4.2c and was observed to form 4.5b. We were particularly pleased with this result as 4.2c is a notoriously unreactive diene and it reacted with a very hindered tert-butyl alkyne (Scheme 4-12b). These results are very useful as they are evidence of a successful use of two different dienes, our next objective was to accomplish the reactions in one-pot.

Scheme 4-12: Successful preliminary multi-diene reaction starting with monocyclized 3.3c to generate desired product 4.5a and Nazarov product 4.5b.

We were thrilled to find that by carrying out the reaction between unsymmetrically-substituted diynone 4.1a and 1.1 equivalents of 2,3-dimethyl-1,3-butadiene 4.2a at low temperature, the Diels-Alder cycloaddition occurred exclusively with the silyl-substituted alkyne to generate the monocyclic intermediate 4.3a (Scheme 2b). Corey and coworker have also observed that silyl-substituted alkynes react faster as
dienophiles than alkyl-substituted alkynes in an analogous Diels-Alder reaction. After the formation of 4.3a, the addition of an excess amount of a second diene (1,3-butadiene) in the same reaction pot, followed by warming to room temperature, provided asymmetric product 4.5b in a modest 21% yield with excellent regio- and diastereoselectivity. We could also change the order of diene addition to provide 4.5c in 23% yield with excellent regio- and diastereoselectivity. A small amount of oxidized 4.5b′ and 4.5c′ were discovered as side products in the reactions. We should point out that the expected side-product from the double cycloaddition of 1,3-butadiene was not detected upon workup. Presumably, this is because the relative rate of cycloaddition is much higher for 2,3-dimethyl-1,3-butadiene during the second Diels-Alder reaction. This proof-of-concept demonstrates that we can indeed arrive at a host of [6-5-6]-tricyclic products using this timed double Diels-Alder method with a high level of regiocontrol.
Scheme 4-13: Demonstration of a timed double Diels-Alder cycloaddition with two different dienes followed by a Nazarov cyclization to generate 4.5b and 4.5c as the major isomers along with a small amount of oxidized products 4.5b' and 4.5c'.

4.6.1 Synthetic Efforts Towards Biologically Active Compounds

A proposed reaction scheme towards Taiwaniaquinol B utilizing easily accessible and inexpensive dienes to install the alkyl groups and necessary functionality (Scheme 4-14). Both functionalized dienes can be readily synthesized from easily accessible starting materials. The main challenges in the proposed synthesis are the use of highly reactive dienes with a reactive or harsh Lewis acid such as boron or aluminum. Currently work is still underway to address these challenges.
Scheme 4-14: A proposed reaction scheme towards taiwaniaquinol B utilizing easily accessible and inexpensive dienes to install the alkyl groups and necessary functionality.

4.7 Conclusions

In summary, we have demonstrated a double Diels-Alder/Nazarov tandem reaction of unsymmetrically-substituted diynones to yield biologically important [6-5-6] tricyclic scaffolds in a one-pot reaction. Additionally, we have demonstrated that a controlled, multicomponent diene system can undergo a timed double Diels-Alder cycloaddition to generate highly functionalized [6-5-6]-carbotricyclic products in a single reaction pot. The one-pot double Diels-Alder/Nazarov tandem reaction is highly regioselective and diastereoselective, providing very concise and efficient access to important molecules, while also imparting functional handles (isolated and conjugated double bonds and a ketone) for further chemical elaboration.

4.8 Experimental

General Methods:

Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. CH₂Cl₂ and THF were purified using a PureSolv MD 5 solvent purification system. Ethynyltrimethylsilane was distilled before use. Evaporation and concentration in vacuo by rotary evaporation. Where appropriate,
reactions were performed in standard, dry glassware under an inert atmosphere of N2.
Column chromatography: Silica gel irregular 60 Å (40-60 micron) from VWR International. The bulb-to-bulb distillation was performed using a kugelrohr apparatus, Büchi GKR-51. Thin-layer chromatography (TLC): glass sheets covered with silica gel 60 F254 from Millipore a Corporation; visualization by UV light, anisaldehyde stain or KMnO4 stain. Mp: Mel-Temp apparatus; uncorrected. IR spectra (cm⁻¹): Thermo Nicolet 6700 FT-IR (diamond ATR), data are reported as cm⁻¹. ¹H and ¹³C NMR: Varian NMR 400 MHz, 500 MHz at r.t. in CDCl₃; solvent peaks (7.26 ppm and 77.16 ppm for ¹H and ¹³C, respectively) or C₆D₆; solvent peaks (7.16 ppm and 128.06 ppm for ¹H and ¹³C, respectively) as reference. GCMS (EI): Agilent 7890A with a 5970C mass spectrometer with triple axis detector using a 122-5532UI DB-5MS Ui column (30m x 0.25mm). ESI-TOF and APCI-TOF MS: Agilent G6230A instrument with purine and HP-Ø921 as internal calibrants.

**General experimental procedure for 1,4-pentadiyn-3-ols (S1-S9)**

**General procedure A:**²⁹ To a solution of n-butyllithium (1.0 equiv.) in tetrahydrofuran (15 mL) at –78 °C under N₂ atmosphere was added terminal alkyne (1.0 equiv.). After 15 minutes of stirring 3-(trimethylsilyl)-2-propynal (1.1 equiv.) was added slowly and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at –78 °C through the addition of saturated aqueous NH₄Cl and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The mixture was filtered and the solvent was removed in vacuo to provide the crude product.
**General procedure B:** To a solution of \( n \)-butyllithium (1.1 equiv.) in tetrahydrofuran (15 mL) at \(-78 \, ^\circ C\) under \( N_2 \) atmosphere was added ethynyltrimethylsilane (1.1 equiv.). After 15 minutes of stirring the 3-aryl-2-propynal\(^{30,31} \) (1.0 equiv.) was added dropwise and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at \(-78 \, ^\circ C\) through the addition of saturated aqueous \( \text{NH}_4\text{Cl} \) and extracted with \( \text{Et}_2\text{O} \). The layers were separated, the organic phase washed with \( \text{H}_2\text{O}, \text{brine}, \) and dried over \( \text{Na}_2\text{SO}_4 \). The mixture was filtered and the solvent was removed in vacuo to provide the crude product.

![Structure S1](image1)

1-(4-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S1). This reaction was performed according to general procedure A.\(^{29} \) 4-Ethynylanisole (954 mg, 7.20 mmol) in THF (20 mL). Crude alcohol S1 was isolated (1.51 g, 81%) as a light brown oil and was used without purification: \( R_f = 0.3 \) (EtOAc:hexanes, 1:10); \( ^1\text{H} \) NMR (400 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta = 7.25 \, -7.19 \) (m, 2H), 6.48 \, -6.42 (m, 2H), 5.18 (d, \( J = 6.6 \, \text{Hz} \), 1H), 3.07 (s, 3H), 1.72 (d, \( J = 6.8 \, \text{Hz} \), 1H), 0.07 (s, 9H); \( ^{13}\text{C} \) NMR (100 MHz, \( \text{C}_6\text{D}_6 \)): \( \delta = 160.4, 133.7, 114.7, 114.3, 103.5, 89.0, 85.8, 84.8, 54.7, 53.5, -0.3; \) IR (film): 3414, 2961, 2224, 1610, 1511, 1252 cm\(^{-1}\); HRMS (APCI-TOF) \( m/z \) calcd for \([\text{C}_{15}\text{H}_{18}\text{O}_2\text{Si} - \text{OH}]^+ \) 241.1043; found 241.1034.

![Structure S2](image2)
1-(2-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S2). This reaction was performed according to general procedure A. 2-Ethynylanisole (954 mg, 7.20 mmol) in THF (20 mL). Crude alcohol S2 was purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/ CH₂Cl₂/hexanes (1:29:70)] to yield S2 (1.53 g, 82%) as a yellow-orange oil: R_f = 0.2 (CH₂Cl₂:hexanes, 2:3); ^1H NMR (400 MHz, CDCl₃): δ = 7.42 – 7.39 (m, 1H), 7.34 – 7.25 (m, 1H), 6.94 – 6.79 (m, 2H), 5.41 (d, J = 5.2 Hz, 1H), 3.87 (s, 3H), 2.88 (d, J = 6.1 Hz, 1H), 0.19 (s, 9H); ^13C NMR (100 MHz, CDCl₃): δ = 160.3 133.9, 130.4, 120.5, 111.3, 110.8, 102.1, 90.2, 89.5, 80.9, 55.9, 53.3, –0.2; IR (film): 3411, 2952, 2236, 1594, 1492, 1261 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₅H₁₈O₂Si – OH]^+ 241.1043; found 241.1034.

1-(4-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S3). This reaction was performed according to general procedure B. 3-(4-Bromophenyl)-2-propynal (553 mg, 2.65 mmol) in THF (30 mL). Crude alcohol S3 was isolated (770 mg, 95%) as a light brown oil and was used without purification: R_f = 0.4 (EtOAc:hexanes, 1:10); ^1H NMR (500 MHz, CDCl₃): δ = 7.44 – 7.42 (m, 2H), 7.32 – 7.29 (m, 2H), 5.34 (s, 1H), 2.67 (s, 1H), 0.20 (s, 9H); ^13C NMR (100 MHz, CDCl₃): δ = 133.4, 131.7, 123.3, 121.0, 101.6, 90.1, 87.1, 83.5, 53.1, –0.2; IR (film): 3294, 2955, 2236, 2179, 1483, 1245 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₄H₁₅BrOSi – OH]^+ 289.0043; found 289.0033.
1-(2-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S4). This reaction was performed according to general procedure B. 3-(2-Bromophenyl)-2-propynal\textsuperscript{29,30} (986 mg, 4.72 mmol) in THF (20 mL). Crude alcohol S4 was isolated (1.51 g, 81%) as a brown oil and was used without purification: R\textsubscript{f} = 0.4 (EtOAc:hexanes, 1:10); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.59 – 7.54 \text{ (m, 1H)}, 7.51 – 7.44 \text{ (m, 1H)}, 7.27 – 7.21 \text{ (m, 1H)}, 7.19 – 7.13 \text{ (m, 1H)}, 5.39 \text{ (s, 1H)}, 2.68 \text{ (s, 1H)}, 0.20 \text{ (s, 9H)}; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 133.7, 132.5, 130.1, 127.1, 125.9, 124.2, 101.5, 90.4, 90.1, 83.1, 53.2, -0.2; IR (film): 3348, 2961, 2895, 2173, 2097, 1632, 1470 cm\textsuperscript{-1}; HRMS (ESI-TOF) \(m/z\) calcd for \([\text{C}_{14}\text{H}_{15}\text{BrOSi-OH}]^+\) 289.0043; found 289.0036.

1-phenyl-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S5). This compound was synthesized following a known procedure\textsuperscript{32} \textsuperscript{32}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.52 – 7.42 \text{ (m, 2H)}, 7.37 – 7.26 \text{ (m, 3H)}, 5.37 \text{ (d, } J = 5.5 \text{ Hz, 1H)}, 2.73 \text{ (s, 1H)}, 0.22 \text{ (s, 9H)}; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 131.9, 128.9, 128.4, 122.0, 101.9, 89.8, 86.0, 84.5, 53.1, -0.2. \)
1-(4-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S6). This reaction was performed according to general procedure B. 3-(4-Fluorophenyl)-2-propynal\textsuperscript{29,31} (1.08 g, 7.30 mmol) in THF (20 mL). Crude alcohol S6 was isolated (1.49 g, 83\%) as a yellow oil and was used without purification: \( R_f = 0.4 \) (EtOAc:hexanes, 1:10); \( ^1\text{H} \text{NMR (400 MHz, CDCl}_3\)): \( \delta = 7.46 – 7.39 \) (m, 2H), 7.02 – 6.92 (m, 2H), 5.35 (s, 1H), 2.86 (s, 1H), 0.20 (s, 9H); \( ^{13}\text{C NMR (100 MHz, CDCl}_3\)): \( \delta = 162.8 \) (d, \( J = 250.2 \) Hz), 133.9 (d, \( J = 8.7 \) Hz), 118.1 (d, \( J = 3.6 \) Hz), 115.7 (d, \( J = 22.3 \) Hz), 101.8, 89.9, 85.8 (d, \( J = 1.6 \) Hz), 83.5, 53.0, –0.2; \( ^{19}\text{F NMR (376 MHz, CDCl}_3\) \( \delta = -110.0 \); IR (film): 3335, 2961, 2901, 2230, 2179, 1600, 1505 cm\(^{-1}\); HRMS (APCI-TOF) \( m/z \) calcd for [C\(_{14}\)H\(_{15}\)FOSi+H]\(^+\) 247.0949; found 247.0942.

![OH](TMS)\(^{\text{F}}\)S7

1-(2-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S7). This reaction was performed according to general procedure A.\textsuperscript{29} 2-fluorophenylacetylene (239 mg, 1.99 mmol) in THF (10 mL). Crude alcohol S7 was isolated (188 mg, 38\%) as a yellow oil by fractional distillation: \( R_f = 0.4 \) (EtOAc:hexanes, 1:10); \( ^1\text{H} \text{NMR (100 MHz, C}_6\text{D}_6\)): \( \delta = 7.16 – 7.10 \) (m, 1H), 6.77 – 6.68 (m, 1H), 6.67 – 6.61 (m, 1H), 6.60 – 6.53 (m, 1H), 5.22 (s, 1H), 2.29 (s, 1H), 0.10 (s, 9H); \( ^{13}\text{C NMR (125 MHz, C}_6\text{D}_6\)): \( \delta = 163.3 \) (d, \( J = 251.7 \) Hz), 133.9 (d, \( J = 1.2 \) Hz), 130.6 (d, \( J = 7.9 \) Hz), 124.0 (d, \( J = 3.9 \) Hz), 115.6 (d, \( J = 20.9 \) Hz), 111.2 (d, \( J = 15.6 \) Hz), 102.8, 92.3 (d, \( J = 3.0 \) Hz), 89.5, 78.1, 53.3, –0.3; \( ^{19}\text{F NMR (376 MHz, C}_6\text{D}_6\) \( \delta = -109.6 \); IR (film): 3408, 2961, 2278, 1689, 1644, 1492 cm\(^{-1}\); HRMS (APCI-TOF) \( m/z \) calcd for [C\(_{14}\)H\(_{15}\)FOSi+H]\(^+\) 247.0949; found 247.0945.
1-tert-butyl-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (S8). To a solution of n-butyllithium (4.00 mL, 10.0 mmol, 2.50 M in hexanes) in tetrahydrofuran (15 mL) at –78 ºC under N₂ atmosphere was added ethynyltrimethylsilane (1.10 g, 11.2 mmol). After 45 minutes of stirring S8 (1.0 g, 9.0 mmol) was added dropwise and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at –78 ºC through the addition of saturated aqueous NH₄Cl and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo to yield S8 (88%) as a light yellow solid: M.p.: 39–41 ºC; Rₖ = 0.5, (EtOAc:hexanes, 1:5); ¹H NMR (400 MHz, CDCl₃): δ = 5.01 (s, 1H), 3.02 (s, 1H), 1.14 (s, 9H), 0.09 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ = 103.2, 93.0, 88.2, 76.2, 52.4, 30.6, 27.2, −0.3; IR (film): 3326, 2965, 2243, 2173 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₂H₂₀OSi – OH]⁺ 191.1251; found 191.1253.

1-(trimethylsilyl)-1,4-hexadiyn-3-ol (S9). This compound was synthesized following a known procedure.

General experimental procedure for 1,4-pentadiyn-3-one (4.1a-m)
Dichloromethane was added to a mixture of sieves (2 wt. equiv.), celite (2 wt. equiv.), and pyridinium chlorochromate (2 equiv.). A dilute solution of 1,4-pentadiyn-3-ol (4.1a, 4.1b, 4.1i, 4.1l) (1 equiv.) in dichloromethane was added slowly to the reaction mixture and stirred overnight or until complete by TLC. The resulting mixture was filtered through a celite/silica gel plug. The solvent was removed in vacuo and the crude product used without further purification. BaMnO$_4$ (4 equiv.) in dichloromethane was used for 1,4-pentadiyn-3-ol (4.1f, 4.1h, 4.1j, 4.1k, and 4.1m) (1 equiv.) and stirred overnight or until complete by TLC. The resulting mixture was purified by filtering through a celite/silica gel plug.

1-tert-butyl-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1a). Alcohol S8 (5.24 g, 25.2 mmol). The crude product used without further purification, 4.1a (59%) as a pale brown solid: M.p.: 37–40 °C; R$_f$ = 0.6, (EtOAc:hexanes, 1:10); $^1$H NMR (500 MHz, CDCl$_3$): 1.25 (s, 9H), 0.20 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 160.9, 102.9, 102.5, 97.6, 80.8, 29.8, 27.9, −0.9; IR (film): 2975, 2219, 1614 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{12}$H$_{18}$SiO+H]$^+$ 207.1200; found 207.1198.

1-(trimethylsilyl)-1,4-hexadiyn-3-one (4.1f). This compound was synthesized from S9 following a known procedure.$^{33}$
1-phenyl-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1b). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.65 – 7.60 (m, 2H), 7.51 – 7.46 (m, 1H), 7.44 – 7.36 (m, 2H), 0.29 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 160.6, 133.5, 131.4, 128.8, 119.5, 102.8, 99.4, 91.8, 89.4, – 0.7.

1-(2-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1h). Alcohol S2 (1.53 g, 5.90 mmol). Crude ketone 4.1h was isolated (860 mg, 57 %) as a yellow oil and was used without purification: $R_f$ = 0.3 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.53 – 7.47 (m, 1H), 7.41 (ddd, $J$ = 9.1, 7.6, 1.8 Hz, 1H), 6.96 – 6.85 (m, 2H), 3.86 (s, 3H), 0.25 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 162.0, 160.5, 135.2, 133.2, 120.6, 111.0, 108.5, 102.8, 98.8, 93.5, 89.5, 55.9, – 0.8; IR (film): 2968, 2202, 1616, 1489, 1464, 1277, 1245 cm$^{-1}$; HRMS (APCI-TOF) $m/z$ calcd for [C$_{15}$H$_{16}$O$_2$Si+H]$^+$ 257.0992; found 257.0986.

1-(4-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1i). Alcohol S1 (1.51 g, 5.84 mmol). Crude ketone 4.1i was isolated (308 mg, 21%) as a yellow solid and was
used without purification: \( R_f = 0.3 \) (EtOAc:hexanes, 1:10); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): 
\[ \delta = 7.55 - 7.49 (m, 2H), 6.89 - 6.83 (m, 2H), 3.80 (s, 3H), 0.25 (s, 9H); \]
\(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): 
\[ \delta = 162.2, 160.4, 135.5, 114.5, 110.9, 102.8, 98.4, 93.2, 89.6, 55.4, -0.8; \]
IR (film): 2968, 2838, 2195, 1619, 1596, 1515 cm\(^{-1}\); HRMS (ESI-TOF) \( m/z \) calcd for \([\text{C}_{15}\text{H}_{16}\text{O}_2\text{Si} + \text{H}]^+ \) 257.0992; found 257.0989.

![Diagram](image)

1-(2-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1j). Alcohol S4 (1.34 g, 4.36 mmol). Crude alcohol 4.1j was isolated (1.01 g, 76%) as a burnt orange oil and was used without purification: \( R_f = 0.5 \) (EtOAc:hexanes, 1:10); \(^1\text{H} \) NMR (500 MHz, CDCl\(_3\)): 
\[ \delta = 7.63 - 7.53 (m, 2H), 7.35 - 7.22 (m, 2H), 0.26 (s, 9H); \]
\(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): 
\[ \delta = 160.1, 135.0, 132.9, 132.3, 127.4, 127.2, 121.9, 102.6, 100.1, 92.2, 89.6, -0.9; \]
IR (film): 2958, 2202, 2145, 1625, 1461, 1426, 1255 cm\(^{-1}\); HRMS (APCI-TOF) \( m/z \) calcd for \([\text{C}_{14}\text{H}_{13}\text{BrOSi} + \text{H}]^+ \) 304.9992; found 304.9986.

![Diagram](image)

1-(4-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1k). Alcohol S3 (770 mg, 2.51 mmol). Crude ketone 4.1k was isolated (598 mg, 78%) as a yellow oil and was used without purification: \( R_f = 0.4 \) (EtOAc:hexanes, 1:10); \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): 
\[ \delta = 7.53 (dd, J = 8.6, 1.9 \text{ Hz}, 2H), 7.46 (dd, J = 8.5, 2.0 \text{ Hz}, 2H), 0.27 (s, 9H); \]
\(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): 
\[ \delta = 160.3, 134.7, 132.2, 126.3, 118.4, 102.6, 99.8, 90.1, 90.0, -0.8; \]
IR (film): 2965, 2208, 2145, 1616, 1480, 1274 cm\(^{-1}\); HRMS (APCI-TOF) \(m/z\) calcd for \([C_{14}H_{13}BrOSi+H]^+\) 304.9992; found 304.9981.

1-(2-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1l). Alcohol S7 (188 mg, 0.763 mmol). Crude ketone 4.1l was isolated (126 mg, 68%) as a yellow oil and was used without purification: \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta = 6.97 - 6.93\) (m, 1H), 6.76 - 6.70 (m, 1H), 6.57 - 6.41 (m, 2H), 0.00 (s, 9H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta = 164.02\) (d, \(J = 256.3\) Hz), 159.77, 134.9, 133.16 (d, \(J = 8.2\) Hz), 124.3 (d, \(J = 4.0\) Hz), 115.9 (d, \(J = 20.2\) Hz), 108.6 (d, \(J = 15.2\) Hz), 103.4, 99.0, 94.1 (d, \(J = 3.4\) Hz), 84.3, -1.2; \(^{19}\)F NMR (376 MHz, C\(_6\)D\(_6\)) \(\delta = -107.0\); IR (film): 2958, 2211, 1622, 1489, 1258, 1128 cm\(^{-1}\); HRMS (APCI-TOF) \(m/z\) calcd for \([C_{14}H_{13}FOSi+H]^+\) 245.0792; found 245.0807.

1-(4-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (4.1m). Alcohol S6 (1.49 g, 6.05 mmol). Crude ketone 4.1m was isolated (1.16 g, 78%) as a brown oil and was used without purification: \(R_f = 0.6\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.63 - 7.56\) (m, 2H), 7.11 - 7.03 (m, 2H), 0.26 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 164.3\) (d, \(J = 254.9\) Hz), 160.3, 135.8 (d, \(J = 9.0\) Hz), 116.4 (d, \(J = 22.5\) Hz), 115.6 (d, \(J =
3.5 Hz), 102.6, 99.4, 90.5, 89.2 (d, J = 1.5 Hz), –0.8; $^{19}$F NMR (376 MHz, CDCl$_3$): δ = –105.1; IR (film): 2965, 2211, 2148, 1622, 1594, 1502 cm$^{-1}$; HRMS (APCI-TOF) m/z calcd for [C$_{14}$H$_{13}$FOSi+H]$^+$ 245.0792; found 245.0788.

**Experimental procedure for 9H-fluoren-9-ones (6a-i)**

![4.4a](image)

1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(tert-butyl)-9H-fluoren-9-one (4.4a).

To a solution of 4.1a (124 mg, 0.600 mmol) in CH$_2$Cl$_2$ (9 mL) under N$_2$ at 0 °C was added boron trichloride (0.59 mL, 0.59 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (240 mg, 2.96 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield 4.4a (76 mg, 43%) as a white solid. The isomeric ratio of the crude product was determined to be 15:2:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 5 min., ramp at 2 °C/min. to 250 °C and hold for 10 min.). The isomeric ratio of the purified product 6a to all other isomers was determined to be >20:1 by $^1$H NMR analysis: $R_f$ = 0.4 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): δ = 2.93 (dd, J = 15.0, 7.5 Hz, 2H), 2.70 – 2.61 (m, 2H), 2.44 (dd, J = 5.7, 2.5 Hz, 1H), 2.37 (dd, J = 14.4, 2.6 Hz, 1H), 2.24 (dd, J = 13.9, 2.8 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.69 (s,
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3H), 1.67 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 0.95 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 209.6, 173.0, 139.5, 126.8, 125.8, 123.3, 121.7, 56.5, 49.8, 36.4, 35.1, 33.8, 32.9, 28.6, 27.3, 19.5, 19.2, 18.9, 18.6; IR (film): 2965, 2908, 1701, 1644, 1432, 1369 cm$^{-1}$; HRMS (ESI-TOF) m/z calcld for [C$_{21}$H$_{30}$O$+\text{H}^+$] $^+$ 299.2369; found 299.2374.

1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(methyl)-9H-fluoren-9-one (4.4f). To a solution of 4.1f (72 mg, 0.44 mmol) in CH$_2$Cl$_2$ (8 mL) under N$_2$ at 0 °C was added boron trichloride (0.44 mL, 0.44 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (181 mg, 2.20 mmol). The reaction was stirred until complete by TLC (40 min). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield 4.4f (19 mg, 17 %) as an off-white solid. The isomeric ratio of the crude product was determined to be 15:1:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). The isomeric ratio of the purified product 6b to all other isomers was determined to be >20:1 by $^1$H NMR analysis: $R_f = 0.5$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta = 2.81 – 2.72$ (m, 2H), 2.56 – 2.50 (m, 3H), 2.13 (dd, $J = 14.6, 6.4$ Hz, 1H), 2.03 (dd, $J = 6.6, 3.6$ Hz, 1H), 1.80 – 1.70 (m, 2H), 1.63 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 0.88 (s, 3H); $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta = 206.7, 172.3, 137.3, 127.5, 126.1,
124.1, 121.4, 53.9, 45.6, 40.5, 31.9, 30.8, 29.3, 25.0, 19.4, 19.2, 18.8, 18.5; IR (film): 2908, 2851, 1701, 1654, 1442, 1378, 1302 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₁₈H₂₄O+H]⁺ 257.1900; found 257.1904.

1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(phenyl)-9H-fluoren-9-one (4.4b). To a solution of 4.1b (153 mg, 0.676 mmol) in CH₂Cl₂ (10 mL) at 0 °C under N₂ was added boron trichloride (0.68 mL, 0.68 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (276 mg, 3.36 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes at 0 °C to yield 4.4b (68 mg, 32%) as an off-white solid.

The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by GC analysis: Rᵣ = 0.3 (EtOAc:hexanes, 1:20); ¹H NMR (400 MHz, C₆D₆): δ = 7.22 – 7.16 (m, 4H), 7.13 – 7.05 (m, 1H), 2.95 – 2.87 (m, 2H), 2.68 (dd, J = 6.7, 3.1 Hz, 1H), 2.64 – 2.49 (m, 3H), 2.44 – 2.30 (m, 1H), 2.21 (d, J = 14.6 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ¹³C NMR (125 MHz, C₆D₆): δ = 207.5, 172.0, 145.5, 138.6, 129.0, 127.7, 126.8, 126.7, 125.4, 123.6,
121.7, 57.0, 53.7, 36.2, 32.3, 31.6, 29.4, 19.4, 19.1, 18.6, 18.5; IR (film): 2984, 2917, 2854, 1698, 1651 cm\(^{-1}\); HRMS (APCI-TOF) \(m/z\) calcd for [C\(_{23}\)H\(_{26}\)O+H]\(^+\) 319.2056; found 319.2063.

**1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-methoxyphenyl)-9H-fluoren-9-one (4.4h)**. To a solution of 4.1h (138 mg, 0.538 mmol) in CH\(_2\)Cl\(_2\) (10 mL) under N\(_2\) at 0 °C was added boron trichloride (0.54 mL, 0.54 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (222 mg, 2.70 mmol). The reaction was stirred until complete by TLC (2-2.5 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO\(_3\) and extracted with Et\(_2\)O. The layers were separated, the organic phase washed with H\(_2\)O, brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:20)] to yield 4.4h (45 mg, 24%) as a white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by \(^1\)H NMR analysis: \(R_f = 0.4\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.30 – 7.20\) (m, 2H), 6.97 – 6.93 (m, 1H), 6.85 – 6.83 (m, 1H), 3.65 (s, 3H), 2.87 (dd, \(J = 7.1, 3.0\) Hz, 1H), 2.83 – 2.62 (m, 4H), 2.46 (dt, \(J = 22.8, 7.2\) Hz, 1H), 2.35 (dd, \(J = 15.1, 3.1\) Hz, 1H), 2.26 (d, \(J = 14.1\) Hz, 1H), 2.28 – 2.20 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H); \(^{13}\)C
NMR (100 MHz, CDCl$_3$): $\delta$ = 209.8, 172.4, 158.2, 137.2, 132.1, 128.1, 128.0, 127.2, 124.9, 123.5, 121.8, 120.5, 111.8, 55.3, 53.2, 52.2, 37.4, 32.5, 32.1, 29.0, 19.5, 19.0, 18.8, 18.8; IR (film): 2984, 2917, 2854, 1689, 1654, 1486, 1426 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{24}$H$_{28}$O$_2$+H]$^+$ 349.2162; found 349.2159.

1,4,4a,9a-tetrahydro-2,3,6,7-tetramethyl-4a-(2-methoxyphenyl)-9H-fluoren-9-one (S10). $R_f$ = 0.4 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.45 (s, 1H), 7.31 – 7.29 (m, 1H), 7.24 – 7.20 (m, 1H), 7.03 (s, 1H), 6.93 – 6.90 (m, 1H), 6.83 – 6.81 (m, 1H), 3.54 (s, 3H), 3.07 (t, $J$ = 4.9 Hz, 1H), 2.98 (d, $J$ = 14.0 Hz, 1H), 2.45 (d, $J$ = 4.8 Hz, 2H), 2.37 (d, $J$ = 13.9 Hz, 1H), 2.28 (s, 6H), 1.56 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 209.5, 158.9, 157.8, 144.0, 136.5, 135.8, 134.8, 128.0, 127.6, 127.0, 126.5, 125.6, 123.1, 120.3, 112.1, 55.7, 55.1, 50.3, 40.9, 33.5, 21.0, 19.9, 19.6, 19.2; IR (film): 2927, 2851, 1701, 1613, 1486, 1454, 1245 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{24}$H$_{26}$O$_2$+H]$^+$ 347.2006; found 347.2008.
1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-methoxyphenyl)-9H-fluoren-9-one (4.4i). To a solution of 4.1i (89 mg, 0.35 mmol) in CH₂Cl₂ (11 mL) under N₂ at r.t. was added boron trichloride (0.35 mL, 0.35 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (145 mg, 1.77 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at r.t. with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:20)] to yield 4.4i (39 mg, 32%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 35 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ¹H NMR analysis: Rₜ = 0.3 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, C₆D₆): δ = 7.07 – 7.01 (m, 2H), 6.79 – 6.73 (m, 2H), 3.34 (s, 3H), 2.93 – 2.86 (m, 2H), 2.68 (dd, J = 6.6, 3.1 Hz, 1H), 2.61 – 2.50 (m, 3H), 2.46 – 2.33 (m, 1H), 2.23 – 2.11 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); ¹³C NMR (125 MHz, C₆D₆): δ = 207.7, 172.3, 158.8, 138.3, 137.2, 127.8, 127.7, 125.5, 123.7, 121.8, 114.4, 57.0, 54.9, 53.1, 36.5, 32.3, 31.6, 29.4, 19.4, 19.1, 18.6, 18.5; IR (film): 2984, 2923, 2857, 1692, 1651, 1515 cm⁻¹; HRMS (APCI-TOF) m/z calcd for [C₂₄H₂₈O₂+H]⁺ 349.2162; found 349.2169.
1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-bromophenyl)-9H-fluoren-9-one (4.4j). To a solution of 4.1j (162 mg, 0.531 mmol) in CH$_2$Cl$_2$ (10 mL) under N$_2$ at 0 °C was added boron trichloride (0.53 mL, 0.53 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (218 mg, 2.70 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:25)] to yield 4.4j (62 mg, 29 %) as an off-white solid. The diastereomeric ratio of the crude product was determined to be 12:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by $^1$H NMR analysis: R$_f$ = 0.4 (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.60 – 7.54 (m, 1H), 7.37 – 7.27 (m, 2H), 7.12 – 7.08 (m, 1H), 3.12 (dd, $J$ = 7.5, 2.5 Hz, 1H), 2.88 (d, $J$ = 15.2 Hz, 1H), 2.81 – 2.77 (d, 2H), 2.78 – 2.51 (m, 2H), 2.50 (d, $J$ = 16.5 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.22 (d, $J$ = 15.2 Hz, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 208.4, 172.8, 141.4, 138.4, 135.8, 130.1, 128.5, 127.5, 127.2, 123.8, 123.5, 123.4, 121.5, 53.7, 52.5, 39.4, 32.5, 31.1, 29.0, 19.3, 19.0, 18.8, 18.8; IR (film): 2909, 2847, 1701, 1416 cm$^{-1}$; HRMS (APCI-TOF) m/z calcd for [C$_{23}$H$_{28}$BrO$+$H]$^+$ 397.1162; found 397.1139.
1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-bromophenyl)-9H-fluoren-9-one (4.4k). To a solution of 4.1k (154 mg, 0.505 mmol) in CH₂Cl₂ (10 mL) at 0 °C under N₂ was added boron trichloride (0.50 mL, 0.50 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (203 mg, 2.47 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes to yield 4.4k (83 mg, 42%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 230 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ¹H NMR analysis: Rf = 0.5 (EtOAc:hexanes, 1:10); ¹H NMR (400 MHz, CDCl₃): δ = 7.44 – 7.42 (m, 2H), 7.11 – 7.03 (m, 2H), 2.89 – 2.79 (m, 2H), 2.73 – 2.64 (m, 2H), 2.56 (dd, J = 6.7, 3.6 Hz, 1H), 2.46 – 2.17 (m, 4H), 1.71 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 209.2, 173.3, 144.0, 138.4, 131.8, 128.3, 127.4, 125.2, 123.4, 121.6, 120.5, 56.6, 53.5, 36.1, 32.2, 31.5, 28.8, 19.5, 19.0, 18.7, 18.7; IR (film): 2980, 2917, 2854, 2243, 1698, 1685,
1647, 1483, 1429 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for [C\(_{23}\)H\(_{25}\)BrO+H]\(^+\) 397.1162; found 397.1162.

![](image)

**1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-fluorophenyl)-9H-fluoren-9-one (4.4l).** To a solution of 4.11 (95 mg, 0.39 mmol) in CH\(_2\)Cl\(_2\) (7 mL) at 0 °C under N\(_2\) was added boron trichloride (0.39 mL, 0.39 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (160 mg, 1.95 mmol). The reaction was stirred until complete by TLC (< 1 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO\(_3\) and extracted with Et\(_2\)O. The layers were separated, the organic phase washed with H\(_2\)O, brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes at 0 °C to yield 4.4l (50 mg, 38%) as a white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by GC analysis: \(R_f = 0.4\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta = 7.15 – 7.09\) (m, 1H), 6.89 – 6.82 (m, 2H), 6.78 – 6.70 (m, 1H), 2.94 – 2.83 (m, 3H), 2.65 – 2.49 (m, 3H), 2.49 – 2.35 (m, 1H), 2.11 (d, \(J = 14.3\) Hz, 1H), 2.16 – 2.07 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta = 206.6, 169.2, 162.0\) (d, \(J = 248.4\) Hz), 138.6 (d, \(J = 2.3\) Hz), 132.2 (d, \(J = 9.5\) Hz), 128.8, 128.7 (d, \(J = 1.5\) Hz), 128.7, 128.0, 124.3 (d, \(J = 59.3\) Hz), 124.3 (d, \(J =
3.5 Hz), 121.4, 116.8 (d, J = 23.3 Hz), 54.3, 51.6, 37.0, 32.3, 31.9, 29.4, 19.3, 19.1, 18.6, 18.5; \(^{19}\)F NMR (376 MHz, C\(_6\)D\(_6\)): \(\delta = -109.3\); IR (film): 2984, 2920, 2851, 1704, 1654 cm\(^{-1}\); HRMS (ESI-TOF) \(m/z\) calcd for [C\(_{23}\)H\(_{25}\)FO+H\(^+\)] 337.1962; found 337.1960.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{F} & \quad 4.4m
\end{align*}
\]

1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-fluorophenyl)-9H-fluoren-9-one (4.4m). To a solution of 4.1m (135 mg, 0.553 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at 0°C under N\(_2\) was added boron trichloride (0.55 mL, 0.55 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (225 mg, 2.74 mmol). The reaction was stirred until complete by TLC (2.5 h). The reaction was quenched at 0°C with saturated aqueous NaHCO\(_3\) and extracted with Et\(_2\)O. The layers were separated, the organic phase washed with H\(_2\)O, brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes to yield 4.4m (79 mg, 43%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by \(^1\)H NMR analysis: \(R_f = 0.5\) (EtOAc:hexanes, 1:10); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta = 6.91 – 6.83\) (m, 2H), 6.83 – 6.75 (m, 2H), 2.86 (t, \(J = 7.3\) Hz, 2H), 2.56 – 2.43 (m, 3H), 2.40 (d, \(J = 14.3\) Hz, 1H), 2.25 (dt, \(J = 23.2, 7.3\) Hz, 1H), 2.11 – 2.06 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta = 207.2, \)
171.6, 161.9 (d, $J = 245.1$ Hz), 141.1 (d, $J = 3.2$ Hz), 138.7, 128.4 (d, $J = 7.7$ Hz), 127.8, 125.3, 123.7, 121.7, 115.6 (d, $J = 21.1$ Hz), 56.9, 53.2, 36.4, 32.2, 31.5, 29.4, 19.4, 19.1, 18.6, 18.5; $^{19}$F NMR (376 MHz, C$_6$D$_6$): $\delta = -116.5$; IR (film): 2917, 2857, 1689, 1651, 1603, 1505, 1439, 1400 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{23}$H$_{25}$FO+H]$^+$ 337.1962; found 337.1969.

1,4,4a,5,8,9a-hexahydro-6,7-dimethyl-4a-(tert-butyl)-9H-fluoren-9-one (4.5b). To a solution of 4.1a (177 mg, 0.858 mmol) in CH$_2$Cl$_2$ (8 mL) at –40 °C under N$_2$ was added boron trichloride (0.86 mL, 0.86 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (78 mg, 0.95 mmol). The reaction was kept between –40 °C and –10 °C until the ketone was fully converted to monocyclized 4.3a (3 h) after which 1,3-butadiene was bubbled into the solution for 3 minutes. The reaction was warmed to r.t. and stirred until complete by TLC (5-6 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO$_3$ and extracted with Et$_2$O. The layers were separated, the organic phase washed with H$_2$O, brine, and dried over Na$_2$SO$_4$. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield 4.5b (48 mg, 21%) as a pale yellow oil. The diastereomeric and regioisomeric ratio of the crude product were both determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 260 °C and hold for 10 min.).
purified product 4.5b to all other isomers was determined to be >20:1 by $^1$H NMR analysis: $R_f = 0.4$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta = 5.82 – 5.72$ (m, 1H), 5.53 (ddt, $J = 10.0$, 7.3, 2.9 Hz, 1H), 2.93 – 2.59 (m, 5H), 2.42 (dd, $J = 6.5$, 2.1 Hz, 1H), 1.97 (dd, $J = 15.1$, 6.9 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.49 (s, 3H), 1.42 (s, 3H), 0.74 (s, 9H); $^1$$^3$C NMR (125 MHz, C$_6$D$_6$): $\delta = 207.2$, 171.0, 140.0, 128.7, 127.6, 123.7, 121.7, 55.9, 49.3, 36.6, 35.1, 29.2, 27.1, 26.4, 18.8, 18.4; IR (film): 3044, 2965, 2892, 1695, 1644, 1435, 1366, 1302 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{19}$H$_{26}$O+H]$^+$ 271.2056; found 271.2057.

\[ \text{1,4,4a,9a-tetrahydro-6,7-tetramethyl-4a-(tert-butyl)-9H-fluoren-9-one (4.5b'). } \]

$R_f = 0.5$ (EtOAc:hexanes, 1:10); $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta = 7.61$ (s, 1H), 7.15 (s, 1H), 5.70 (ddt, $J = 9.6$, 6.7, 3.3 Hz, 1H), 5.56 (ddt, $J = 9.7$, 6.7, 3.2 Hz, 1H), 2.86 – 2.74 (m, 2H), 2.32 (dd, $J = 14.7$, 6.8 Hz, 1H), 2.19 (dq, $J = 14.6$, 2.8 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.92 (s, 3H), 1.84 (s, 3H), 0.78 (s, 9H); $^1$$^3$C NMR (125 MHz, C$_6$D$_6$): $\delta = 207.1$, 158.3, 143.6, 138.0, 136.4, 129.0, 128.2, 126.8, 123.9, 53.8, 51.4, 37.6, 30.0, 27.5, 26.7, 20.8, 19.3; IR (film): 3037, 2965, 1704, 1613, 1454, 1407, 1363, 1302 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for [C$_{19}$H$_{24}$O+H]$^+$ 269.1900; found 269.1900.
1,4,4a,5,8,9a-hexahydro-2,3-dimethyl-4a-(tert-butyl)-9H-fluoren-9-one (4.5c). To a solution of 4.1a (90 mg, 0.44 mmol) in CH₂Cl₂ (6 mL) at −78 °C under N₂ was added boron trichloride (0.48 mL, 0.48 mmol, 1.0 M in hexanes). 1,3-Butadiene was bubbled into the solution for 3 minutes. The reaction was kept at −78 °C until the ketone was fully converted to the monocyclized 4.3o intermediate (3 h) after which 2,3-dimethyl-1,3-butadiene (excess) was added and the reaction warmed to 0 °C and stirred until complete by TLC (1 h). The reaction was quenched at 0 °C with saturated aqueous NaHCO₃ and extracted with Et₂O. The layers were separated, the organic phase washed with H₂O, brine, and dried over Na₂SO₄. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield 4.5c (27 mg, 23%) as a white solid. The diastereomeric and regioisomeric ratio of the crude product were both determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 °C for 5 min., ramp at 1 °C/min. to 250 °C and hold for 10 min.). The isomeric ratio of the purified major product 4.5c to all other isomers was determined to be >20:1 by ¹H NMR analysis: Rᶠ = 0.3 (EtOAc:hexanes, 1:10); ¹H NMR (500 MHz, C₆D₆): δ = 5.56 – 5.50 (m, 1H), 5.48 – 5.43 (m, 1H), 2.97 – 2.88 (m, 1H), 2.78 – 2.72 (m, 1H), 2.72 – 2.64 (m, 2H), 2.62 (d, J = 2.6 Hz, 1H), 2.37 (dd, J = 5.6, 2.6 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.95 (dddd, J = 15.8, 3.9, 2.6, 1.3 Hz, 1H), 1.77 (d, J = 14.5 Hz, 1H), 1.63 (dt, J = 2.3, 1.2 Hz, 3H), 1.44 (dt, J = 2.3, 1.2 Hz, 3H),
0.71 (s, 9H); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ = 207.4, 170.3, 139.3, 127.4, 125.7, 124.7, 122.9, 56.5, 49.5, 36.2, 33.8, 33.0, 28.2, 27.0, 22.7, 19.4, 19.3; IR (film): 3022, 2957, 2909, 1691, 1672, 1626, 1424, 1401, 1366 cm$^{-1}$; HRMS (APCI-TOF) m/z calcd for [C$_{19}$H$_{26}$O+H]$^+$ 271.2056; found 271.2061.

4.9 References

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5 Conclusions and Future Work

5.1 Conclusions

The work presented in this dissertation entails the investigation of ynones and diynones as high energy starting materials for tandem or cascade method development. An increasing amount of interest has been placed on designing one-pot reactions where multiple carbon-carbon bond formations are achieved to construct useful biological scaffolds economically. The methodologies focus on strategic routes towards advanced biologically relevant polycyclic intermediates having a [6-5-6] core structure.

Chapter 2 introduces recent progress in Nazarov reactions of aryl-vinyl ketones and discusses a tandem Diels-Alder/Nazarov reaction of 3-(trimethylsilyl)-1-aryl and 3-(trimethylsilyl)-1-heteroaryl ynones. Nazarov cyclizations of ary-vinyl ketones are a challenging feat, typically require dication intermediates or polarized substrates. It was found that incorporation of a silyl group onto the alkyne, effectively lowered the energy barrier for the Nazarov cyclization enabling the reaction to proceed under relatively mild conditions. The substrate scope was investigated to demonstrate method utility and found to be applicable to a variety of substituted ynones, allowing for extensive modification of the core structure to yield biologically important polycyclic scaffolds in a one-pot reaction.

Chapter 3 briefly covers recent work conducted on cascade methodology towards polycyclic ring systems. The focus of the chapter is on the utilization of diynones in a multicomponent reaction sequence to form products 3.5 and 3.6. Preliminary studies were conducted on a double Diels-Alder cycloaddition to establish proof of concept. Once the
tandem cycloaddition was successful the method was then expanded to include a Nazarov cyclization in a one-pot reaction. While exploratory efforts have been made into using two different dienes, the results indicate that a symmetrical diynone when reacted with two different dienes will generate nearly a 1:1 ratio of regioisomers. In summary, we have demonstrated the first multicomponent double Diels-Alder/Nazarov tandem reaction of cross-conjugated diynones to yield [6-5-6] tricyclic products in a one-pot reaction. This polycyclization method produces five new carbon-carbon bonds, three new rings, and quaternary or vicinal quaternary centers with high regio- and diastereocontrol. This method provides a tool for rapid access to important [6-5-6] tricyclic terpenoid scaffolds while also imparting useful functional handles for further chemical elaboration.

Chapter 4 expands on the chemistry presented in chapter 3, increasing the applicability of the method to the synthesis of natural products and their respective derivatives. In this chapter, unsymmetrically silyl substituted diynones 4.1 are prepared and used successfully in a double Diels-Alder/Nazarov tandem reaction. A concise substrate scope demonstrates how R can be a variety of aryl or alkyl groups. Additionally, we have demonstrated that a controlled, multicomponent diene system can undergo a timed double Diels-Alder cycloaddition to generate highly functionalized [6-5-6]-carbotricyclic products in a single reaction pot. This development is imperative for method utility. If the retrosynthetic analysis of taiwaniaquinol B is examined, the Diels-Alder cycloadditions require two different dienes. Furthermore, regioselective control is paramount with respect to the two chemically different alkynes. This is accomplished in the multicomponent timed double Diels-Alder reaction. The one-pot double Diels-
Alder/Nazarov tandem reaction of unsymmetrical diynones is also highly regioselective and diastereoselective.

5.2 Future Work

While the foundation for the methods have been established, considerable work is still necessary in order for the methodologies to be truly viable in industry. The most pressing challenge is to make the systems catalytic. Solid progress was made on determining suitable catalyst traits for the system. We have determined that the tandem sequence will require a relatively strong/electron deficient binding center that will not become too deactivated through ligand interactions. Current Lewis acid promoters bind too strongly to the substrates, which removes the potential for turnover. Work in this area is currently ongoing. The Chalifoux laboratory may investigate potential collaborations with a catalysis group to determine suitable catalysts for the Diels-Alder/Nazarov methodologies. Once a catalytic system has been found we can establish an enantioselective assay for the method.

Once an enantioselective catalyst is in hand, we plan to demonstrate the synthetic utility of the enantioselective double Diels-Alder/Nazarov reaction through a total synthesis of a known biologically important molecule. Additionally, we want to explore the biological tunability of the [6-5-6] tricyclic core by developing a range of useful products in collaboration with our Belgium partners at the Rega Institute for Medical Research for screening against high priority viruses. Diynones are valuable substrates towards highly functionalized intermediates and as of yet are a relatively untapped resource in the synthetic organic community.
5.3 References


Chapter 2

Supporting Information for “β-Silyl-Assisted Tandem Diels-Alder/Nazarov Reaction of 1-Aryl-3-(Trimethylsilyl) Ynones”

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Supporting Information for “Multicomponent Double Diels-Alder/Nazarov Tandem Cyclization of Symmetric Cross-conjugated Diynones to Generate [6-5-6] Tricyclic Products”

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