5-Endo-Dig Cyclization of a Carbon-Centered Radical and Utility of Cyclopentene Bromosulfone Product

Jason Nathaniel Abrams

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5-ENO-DIG CYCLIZATION OF A CARBON-CENTERED RADICAL AND UTILITY OF CYCLOPENTENE BROMOSULFONE PRODUCT

By

JASON N. ABRAMS

A Dissertation submitted to the Department of Chemistry & Biochemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Degree Awarded: Fall Semester, 2009
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I would like to acknowledge fellow graduate student Abdul Baroudi who performed the computational calculations on reaction energies for the tandem Claisen/Cope rearrangement followed by endocyclic double bond isomerizations as well as David Jones for help in interpreting the spectra of this product. I would like to thank Dr. Vitaliy Tymokhin for his significant efforts on our 5-endo-dig radical cyclization project. Special thanks to Dr. Ion Ghiviriga of the University of Florida and Dr. Tom Gedris of Florida State University who provided NMR spectroscopic interpretation for our 5-endo-dig radical cyclization products, as well as Professor Ronald Clark of Florida State University who performed X-ray crystallographic analysis on some of our compounds. Finally I would like to acknowledge Professor Igor Alabugin as a mentor, my research group, and the chemistry faculty at Florida State University.
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ABSTRACT

The Baldwin rules provide a robust guideline for predicting the favorability of ring closure of reactive intermediates based upon stereoelectronic considerations. Our group was intrigued by the lack of examples of 5-endo-dig cyclizations with carbon-centered radicals, particularly because these reactions were suggested to be favorable according to the Baldwin rules and to our previous computational investigations using density functional analysis. We therefore set out to fill the gap in the arsenal of radical C-C bond forming processes by using computational data to design a new radical process. The first part of this thesis describes our studies aimed at the discovery of the first efficient 5-endo-dig cyclization of a carbon-centered radical. This is followed by experimental design and synthesis of substrates and finally reaction conditions which yield products through this novel mode of cyclization.

The second part of this thesis explores the synthetic utility of the cyclized cyclopentene bromosulfone products. First, background information for the preparation and utility of vinyl sulfones is provided. This is followed by our results for derivatization of the bromide functional group of our cyclopentene bromosulfone products.

Proper design of substrates and reaction conditions has allowed the 5-endo-dig radical cyclizations to finally become an experimental reality after more than forty years since the original prediction. The cyclized products which are enriched with functionality have been transformed into a variety of other products, emphasizing the importance of this discovery.
CHAPTER 1

INTRODUCTION: 5-ENDO-DIG CYCLIZATION

Over the past few years our research group has become interested in new chemical reactions derived from unique properties of triple bonds in alkynes. Alkynes are versatile functional groups that can undergo an array of reactions such as oxidations, reductions, hydrations, additions, polymerizations, metal-catalyzed carbon-carbon bond forming reactions, etc.\(^1\) Some of these aforementioned reactions can occur in a cascade fashion, another area of our research group’s interests. Our group has had a continued interest in both thermally and photochemically promoted radical reactions, particularly those involve in cascade processes. We therefore set out to discover new methodology in radical cascade chemistry involving triple bonds. Our group became particularly intrigued by the scarcity of literature precedence for a type of radical cyclization classified as a 5-endo-dig closure according to Baldwin’s rules, and one we had suggested was feasible based on computational predictions. Baldwin’s rules are a series of qualitative guidelines predicting the favorability of kinetic ring closure of acyclic compounds. Published in 1976, the rules are contained in one of the most highly-cited journal articles in the past 30 years, and are based upon empirical rules formulated from observations and stereoelectronic reasoning.\(^2\)

Baldwin’s rules for favorability of ring closure depend on a number of factors. By studying previous work from the scientific community, Professor Jack Baldwin concluded that ring closure was guided predominantly by particular combinations of ring size, hybridization character of the bond about to be broken, and relative position of the bond broken during ring closure. All of these factors contribute to the stereoelectronics that govern the trajectory of incipient radicals, cations, or anions for a tethered alkene, alkyne, carbonyl, or carbon-leaving group bond. The guidelines also provide convenient nomenclature for the ring closing process. The size of the ring to be formed has a corresponding prefix number. A bond that is broken within the newly formed ring is called \textit{endo}. On the contrary a bond that is broken outside the newly formed ring is called \textit{exo}. The geometric requirements for bond formation are strongly
dependent on the hybridization of the bond about to be broken. This reaction is classified as tet for sp³, trig for sp², and dig for sp hybrized bonds (see Figure 1 below).

![Exo- and Endo-Trig Cyclization](image)

Figure 1: Endo-Trig vs Exo-Trig Cyclization

The relative favorability of ring formation involving 3-7 membered rings, have been summarized in tabular form by Baldwin, as outlined in Figure 2. The terms favorable or allowed (check mark in green box) and unfavorable or not allowed (x in red box) are used in a relative sense, and do not describe the absolute probability that a reaction will or will not take place. Rather, a disfavored reaction does not have a rate that is able to compete effectively with an alternative favored reaction. However, disfavored product may be observed if there are no alternative allowed reaction pathways.
Since these rules are for rates, they reflect the free energy of activation at the transition state, $\Delta G$, necessary for ring closure. Ring closures that are favorable have a length and nature of linking chain that enables terminal atoms to achieve the optimal trajectory for the formation of the final ring bond, and the angle between the interacting nuclei is maintained through the transition state and into the final product (stable molecules tend to have bond angles that minimize energy). For reactions of alkenes this ideal approach is known as the Bürgi-Dunitz trajectory, the ideal 109° bond angle for nucleophilic attack. Unfavorable ring closures require severe bond angle and distance distortion, to reach the ideal trajectory. In these instances the desired ring closures are predicted to be difficult, and alternative pathways which are available will dominate.

The trajectory for a 5-endo-trig radical cyclization versus a 5-endo-dig radical cyclization is illustrated in Figure 3. As one can observe, the 5-endo-trig cyclization suffers from poor stereoelectronic orbital alignment of the radical approach to the out-of-plane $\pi$-bond. Greater energy is required for this species to approach the ideal Bürgi-Dunitz trajectory.
On the contrary, the 5-endo-dig radical cyclization is predicted to be more favorable according to Baldwin’s rules because the second in-plane $\pi$-bond of an alkyne presents a much better in-plane trajectory for the incoming reactive radical center, thus avoiding the stereoelectronic restrictions inherent to the 5-endo-trig process (Figure 3). What was particularly puzzling for us was the lack of examples for the 5-endo-dig process, in spite of the relative abundance of 5-endo-trig radical cyclizations in the literature, which is considered to be improbable according to the Baldwin rules.

1.1 Examples of 5-Endo-Dig Cyclization

Although there is a dearth of examples of 5-endo-dig radical cyclization, there are several examples of neutral, anionic, and cationic 5-endo-dig cyclizations, and it would be illustrative to highlight some of them. In some reactions, a halogen activates an alkyne towards intramolecular attack by a tethered nucleophile. These substrates have undergone 5-endo-dig cyclizations upon exposure to a source of iodine or bromine. Three representative examples are shown below involving a carbon, nitrogen, and oxygen nucleophile respectively.
The first example in Figure 4 shows how iodocyclopentenes are formed at room temperature within several hours upon exposure of δ-alkynyl-α-ketoesters with iodine. The 5-endo-dig mode of cyclization produces enriched cyclopentenoid species, capable of further elaboration.

![Chemical structure](image)

**Figure 4: Iodine Promoted Formal 5-Endo-Dig Cyclization of δ-Alkynyl-α-Ketoesters**

O-Propargylic hydroxylamine smoothly undergoes a 5-endo-dig cyclization to the corresponding 4-iodo-2, 5-dihydroisoxazole, a useful heterocyclic intermediate (Figure 5).

![Chemical structure](image)

**Figure 5: Iodine Promoted 5-Endo-Dig Cyclisation of Hydroxylamine**

Other heterocycles have been constructed using a halogen-promoted 5-endo-dig cyclization protocol. The electrophilic cyclization of but-3-yn-1-ones with various electrophilic halogen sources (including N-bromosuccinimide or NBS) yields unsymmetrically 2,5-disubstituted 3-halofurans under mild, atom economical, and environmentally friendly conditions as shown in
Figure 6. Many other examples of halogen-promoted 5-endo-dig cyclizations to form heterocycles can be found in the literature. 

\[ \text{R'} = \text{aryl} \]

Figure 6: Bromine Promoted 5-endo-dig Cyclisation of Homopropargylketone

Metal catalyzed carbocyclization has become an important method due to advances in organometallic chemistry, particularly because of the emergence of new catalytic processes. For example, gold (I) and (III) species have developed into excellent catalysts in carbocyclizations due to the exceptional alkynophilicity of gold, and the ability to be employed under exceedingly mild conditions. These properties have enabled the formation of new carbon-carbon and carbon-heteroatom bonds with high turnover efficiency.

The Toste group recently demonstrated the use of cationic gold (I) complexes to catalyze the 5-endo-dig carbocyclization of dicarbonyl compounds onto appended alkynes as shown in Figure 7. The reactions are performed under mild conditions in an open flask and without the need for dry solvents. This reaction, known as a Conia-ene reaction, appears to involve formation of a gold (I) alkyne complex. The authors note that while examples of the transition-metal-catalyzed 5-endo-dig addition of heteroatom nucleophiles to nonterminal alkynes are common, this class of cyclization employing carbon nucleophiles with terminal alkynes is rare.

Figure 7: Gold Catalyzed 5-Endo-Dig Cyclization of δ-Alkynyl-β-Diketone
A similar gold-based chemoselective alkyne activation and subsequent carbocyclization was developed by the Kozmin group. They describe an enyne moiety with tethered alcohol which undergoes a 5-exo-trig followed by 5-endo-dig cyclization to afford the cyclopentene tetrahydrofuran product as seen in Figure 8.8

Figure 8: Sequential Gold Catalyzed 5-Exo-Trig/ 5-Endo-Dig Cyclization

Group 6 metal complexes catalyze the formal 5-endo-dig addition of β-ketoesters and silyl enol ethers to alkynes. These reactions proceed either via intermediate metal vinylidenes or coordination of the metal to the alkyne moiety. In the example below in Figure 9, a tungsten species, W(CO)₅(THF), was used to catalyze a carbocyclization of a 6-siloxy-5-en-1-yne derivative to give the corresponding cyclopentene species in good yield. The authors note that although 5-endo-dig cyclization is a favored process according to the Baldwin’s rules, there are very few reports on this type of cyclization with carbon-centered nucleophiles promoted with transition metals.9
Anionic 5-endo-dig cyclizations have also been accomplished en route to interesting products. For example, a furan-fused heterocycle was constructed by a one-pot sequence of a Sonogashira reaction, triethylamine (Et₃N) induced ether demethylation, and then heteroannulation. This ring closure proceeds through a 5-endo-dig cyclization of the resulting phenoxyde, produced upon demethylation of the pyridinone methyl ether, onto the newly attached alkyne (Figure 10).¹⁰
In another example of an anionic 5-endo-dig cyclization, trifluoroethyl phenyl ether is converted to a benzofuran via a one-pot protocol. Here the starting material is converted into an (aryloxy)acetylene through base-induced elimination. The reactive intermediate that is produced is lithiated at the ortho position of the benzene ring, and cyclizes to provide a lithiated benzofuran. Upon aqueous work-up the desired heterocycle is obtained (Figure 11).
Cationic 5-endo-dig cyclization has also been reported. In the example below (Figure 12), epoxy alkyne is transformed into an alkylidene indanone. This transformation occurs via the intermediacy of a cationic ruthenium ketene alkene species that is produced by an unusual oxygen transfer from epoxide to alkyne. The subsequent 5-endo-dig cyclization provides a zwitterionic species which then becomes the final product under the reaction conditions (Figure 12).12

Figure 12: Formal Cationic 5-Endo-Dig Cyclization: Formation of Alkylidene Indanone

Similarly, another cationic 5-endo-dig cyclization was recently reported involving the transformation of an enyne to a silylated cyclopentene. In this example HfCl₄ catalyzes an intramolecular allylsilation onto the tethered alkyne in a cationic 5-endo-dig fashion (Figure 13).13

Figure 13: Formal Cationic 5-Endo-Dig Cyclization: Formation of Cyclopentene
As one can see, there have been some important examples of neutral, anionic, and cationic 5-endo-dig cyclization reactions. This is in contrast to the scarcity of examples of radical 5-endo-dig cyclizations. One of the few literature examples is provided by Studer who reported a surprisingly efficient 5-endo-dig radical cyclization, as a key step in a reaction sequence which proceeded in overall 55% yield. This cyclization involves a silicon-centered radical generated \textit{in situ} which attacks a tethered alkyne in a 5-endo-dig fashion (Figure 14).^{14}

![Figure 14: Efficient 5-Endo-Dig Cyclization of Silicon-Centered Radical](image)

An earlier report from our research group provided computational rationalization for the efficiency of this process.^{15} This 5-endo-dig cyclization has a very low 6 kcal/mol activation barrier. As noted by our research group, several structural features of the reactant account for the low cyclization barrier. These include a starting material which yields a radical that is connected to the triple bond through a saturated C-O bridge and therefore not deactivated by conjugation. Additionally, the reactant species contains optimal SOMO-LUMO matching: a nucleophilic Si-radical which is a good electron donor, and an electrophilic alkyne that is an excellent acceptor. The alkyne also benefits from electrophilic enhancement via an in-plane π bond which is in hyperconjugation with the vicinal σ*(CO) orbital.
This cyclized vinyl radical intermediate benefits from hyperconjugative stabilization, by way of a relay between the radical center and the donor C-Si bond, and the radical center and the acceptor C-O bond providing an overall captodative stabilization of this species. Importantly, the cyclized product does not exhibit significant strain effects.

An example of a potential 5-endo-dig cyclization involving a carbon-centered radical has been reported, albeit in low yield and as a side product towards polynaphthalene. Diradical polymerization of benzannulated enediynes afforded some products containing terminal fulvene moieties that could have been formed via a 5-endo-dig cyclization with an in situ generated carbon-centered radical, as shown in Figure 15 below.\textsuperscript{16}

![Figure 15: Possible 5-Endo-Dig Cyclization of Carbon-Centered Radical](image)

Under the reaction conditions, high concentration of benzannulated enediyne monomer allowed it to intercept the transient 1,4-didehydronapthalene diradical formed from the Bergman cycloaromatization in low concentration.\textsuperscript{17} If the attack of the diradical onto the diyne monomer occurs at the internal $\alpha$-carbon of the alkyne then it produces a transient vinyl radical which could close onto the vicinal alkyne in a 6-endo-dig fashion to continue chain propagation of the desired polynaphthalene. On the other hand this same vinyl radical could attack the vicinal alkyne in a 5-exo-dig fashion to produce a fulvene species (not shown).\textsuperscript{18} If the attack of the diradical onto the diyne monomer occurs regioselectively at the external $\beta$-carbon, then the
resulting exo vinyl radical can attack the in plane $\pi$-bond of the tethered alkyne in a 5-endo-dig fashion yielding another fulvene species. This cycloaromatization is carried out with neat enediynes, enhancing the likelihood of the 5-endo-dig pathway and minimizing premature hydrogen abstraction. The efficiency of this process seems to be low because the authors reported a considerable amount of unreacted triple bonds in the polymeric products. It is also quite possible that the observed fulvene containing products are formed through a lower barrier 5-exo-dig cyclization of the isomeric vinyl radical.

A recent example by the Matzer group of a 5-endo-dig cyclization with a carbon-centered radical is shown in Figure 16.\textsuperscript{19} Here, a Bergman cycloaromatization produces an intermediate 1,4-didehydrobenzene diradical capable of intercepting the tethered alkyne in a 5-endo-dig mode. The efficiency of this triyne cascade is low, yielding mainly premature hydrogen atom abstraction from 1,4-cyclohexadiene and only 2-3\% of the thiophene product resulting from 5-endo-dig cyclization. Considering that 1,4-cyclohexadiene is a good H-atom donor, this observation suggests that radical 5-endo-cyclization may be rendered efficient with the proper choice of reaction conditions.

![Figure 16: 5-endo-Dig Cyclization of a Carbon-Centered Radical Generated through the Bergman Cyclization](image)

Another explanation for final product formation involves initial cyclization to a didehydrothiophene species followed by a 6-endo-dig cyclization onto the attached triple bond and finally hydrogen atom abstraction (Figure 17).
Figure 17: Alternative 6-Endo-Dig Cyclization Mode
CHAPTER 2

OUR INITIAL STUDIES ON DIGONAL SYSTEMS

Before performing studies of 5-endo-dig cyclization with \textit{in situ} generated carbon-centered radicals, substrates were prepared to investigate how strain effects would influence selectivity for 6-endo-dig over 5-exo-dig cyclization. Specifically we wanted to learn if strain effects alone could override kinetic bias towards 5-exo-dig cascade cyclization and steer reactions in the direction of a 6-endo-dig pathway. Table 1 illustrates the activation energies ($\Delta E^\ddagger$ in kcal/mol) for both 5-exo and 6-endo modes for the prototypical acyclic vinyl radical system (where $N = 0$). Upon annealing a cyclopentene ring to the unsaturated two-carbon bridge between vinyl radical and alkyne (where $N = 3$), the balance between 5-exo and 6-endo selectivity tips towards the latter pathway. These computations suggest that temporary introduction of strain effects can be used for the control of selectivity in such cyclizations.

Table 1: Activation Barriers and Reaction Energies for Acyclic ($n=0$) and Cyclic ($n=3$) Enyne Vinyl Radical Performed at the UB3LYP/631-G** Level with (energy in kcal/mol)

<table>
<thead>
<tr>
<th></th>
<th>5-exo $\Delta E^\ddagger$</th>
<th>6-endo $\Delta E^\ddagger$</th>
<th>5-exo $\Delta E_r$</th>
<th>6-endo $\Delta E_r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N=0$</td>
<td>4.1</td>
<td>4.7</td>
<td>-35.0</td>
<td>-70.8</td>
</tr>
<tr>
<td>$N=3$</td>
<td>6.1</td>
<td>5.4</td>
<td>-28.8</td>
<td>-69.2</td>
</tr>
</tbody>
</table>

In this regard, cyclopentane diynes were readily constructed from $\alpha$-diketones with metal acetylides followed by esterification. We reasoned that size of the cyclic ether ring would control strain in the transition state (TS) and the product. The key element here is the stronger sensitivity of 5-exo-dig cyclization to strain compared with that of 6-endo cyclization.
Thermodynamic bias towards 6-endo-dig processes that is present in completely conjugated systems, such as in enediynes (Figure 18), would be absent in the cases where a saturated bridge is used to link the vicinal alkynes. On the other hand, a thermodynamic influence on 5-exo-dig cyclization is strong if terminal substituents such as phenyl groups can exert a stabilizing conjugative effect on the radical center in the product.

Figure 18: Proposed Diynes for Radical Cyclization

Vinyl radicals are readily generated from a regioselective radical attack of tin radical onto the internal α-carbon of a phenyl alkyne as shown in Figure 19 (P). First, azobisisobutyronitrile (AIBN), a radical initiator, is fragmented in the presence of heat or light (IA) and subsequently abstracts a hydrogen atom from tributyl tin hydride generating a tributyl tin radical (IB). This species intercepts the β-carbon of a triple bond to produce the required vinyl radical (P). A 6-endo-dig or 5-exo-dig cyclization is pathway is subsequently available followed by hydrogen atom abstraction.
Substrates for initial studies were constructed in a straightforward manner, from commercial chemicals that were readily available off the shelf in our lab. Meso and racemic bis(phenylethynyl) diols were synthesized from 2,3-butanedione and acetylides which were prepared in situ from mixing alkynes with \( n \)-butyllithium. Some of the meso diol isomer was subsequently protected as the carbonate with carbonyl diimidazole (Figure 20).
2.1 Attempts to Induce 6-Endo-Dig Cyclization with a Carbon-Centered Radical

Strain-free bis(diphenyl)diyne free diol substrate was subjected to radical cyclization conditions (Figure 21). Accordingly, tributyltin hydride (Bu₃SnH) and azobisisobutyronitrile (AIBN) were combined and slowly added to a refluxing toluene solution of the bis-alkyne substrate under syringe pump conditions. These conditions were employed in order to keep concentrations of tributyltin hydride sufficiently low to prevent premature hydrogen atom abstraction, before the cyclization step (Figure 21).
Regioselectivity of the initial Bu$_3$Sn-radical attack at the α-carbon of one of the alkynes led to generation of a vinyl radical, as expected. Subsequent 5-exo-dig cyclization occurred. The final methylidene cyclopentene products were produced following abstraction of a proton from tributyltin hydride by the cyclized vinyl radical intermediate. As expected, none of the products resulted from 6-endo-dig cyclization.

![Chemical structure](image)

**Figure 22: Initial Cyclization Success: 5-Exo-Trig Cyclization with Free Diol**

We next attempted cyclization with our cyclic carbonate system, hoping that inherent strain in the 5-membered ring would influence the radical cyclization pathway in favor of 6-endo-dig. Using similar syringe-pump conditions as above, cyclized products were formed in high yield. However, again none of the products resulting from 6-endo-dig cyclization were obtained (Figure 23). The stereochemistries of the products were confirmed based on NOESY studies by Dr. Ion Ghiviriga of University of Florida. The configuration of the exocyclic double bond for the *cis*-phenyl products displayed a nOe between the vinyl proton and proximal methyl group. The configuration of the exocyclic double bond for the *trans*-phenyl products displayed a nOe between the vinyl proton and ortho protons on the remote phenyl group.
Figure 23: Initial Cyclization Success: 5-Exo-Trig Cyclization with Protected Diol

The high degree of symmetry from the product resulting from 6-endo-dig cyclization followed by protodestannylation (Figure 24) should have a simplified $^1$H and $^{13}$C NMR spectrum, in which there would be only one peak corresponding to the two vinyl protons, one peak from the methyl protons, as well as fewer peaks in the aromatic region.

Figure 24: Hypothetical Symmetrical Product resulting from 6-Endo-Dig Cyclization followed by Protodestannylation

We were unable to change the course of radical cyclization through strain effects in this short study. However, successful generation of vinyl radicals gave us confidence toward preparation of bis-alkyne substrates which could potentially engage in subsequent 5-endo-dig cyclization. We also reasoned that strain effects of tethered bis-alkyne diols could favor 5-endo-dig cyclization over the competing 4-exo-dig pathway.
2.2 Computational Design of Suitable Substrates for 5-Endo-Dig Cyclizations

We believed the lack of examples of 5-endo-dig processes may have been due in part to thermodynamic contributions because these are sluggish processes that are unable to compete with faster side reactions. With these factors in mind, we set out to look for a substrate pattern which would allow us to discover this elusive cyclization.

The choice of substrate bis(alkynes) was suggested by the computational activation energies and reaction energies obtained at the UB3LYP 6-31G** level of theory (Table 2; relative energies in Kcal/mol). Vinyl radicals b were predicted to be the most favorable relative to other species such as allyl radicals c which suffer from conjugative destabilization, or alkyl radicals a.

Table 2: Computed Activation and Reaction Energies for Several 5-Endo-Dig Cyclizations

<table>
<thead>
<tr>
<th>Pattern</th>
<th>(E_a) (4-exo):</th>
<th>(E_a) (5-endo):</th>
<th>(\Delta E_r) (4-exo):</th>
<th>(\Delta E_r) (5-endo):</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>17.6</td>
<td>17.6</td>
<td>-0.8</td>
<td>-18.2</td>
</tr>
<tr>
<td>b</td>
<td>14.1</td>
<td>14.9</td>
<td>-12.0</td>
<td>-32.1</td>
</tr>
<tr>
<td>c</td>
<td>40.2</td>
<td>40.2</td>
<td>26.4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

We continued to refine the nature of the hypothetical substrate through further theoretical investigations. Utilizing a stereoelectronic preference for two acceptor groups to be gauche to one another\(^{21}\) rather than antiperiplanar allowed us to take advantage of “strain free” conformational control with acyclic bis-alkyne precursors. Outlined below in Figure 25 are computational results for control of the conformational equilibrium in diastereomeric 3,4-dimethylhexa-1,5-diyne-3,4-diols through the gauche effect. Notice in particular the high degree of conformational
preference for the meso-diol in which the unfavorable anti conformer is ca. 4 kcal/mol higher in energy compared with the two identical gauche forms preorganized for the cyclization.

![Figure 25: Control of the Conformational Equilibrium through the Gauche Effects With (Relative Energies in Kcal/mol)](image)

We also preferred to utilize bis-alkynes without terminal substituents in order to take advantage of regioselective preference for radical attack at the terminal β-carbon in lieu of attack at the internal α-carbon, which we have shown in the previous section to lead to the alternative 5-exo-dig cyclization.

Experimentally we initially investigated whether alkyl radicals (pattern A) from Table 2 are suitable substrates for the 5-endo-dig cyclizations. In particular, we were inspired by some interesting tandem cyclization / radical translocation / cyclization processes. For example, dimethylsilyl propargyl ether with an appropriately attached acetal group led to an interesting cascade process (Figure 26), in which the two alkyne carbon atoms were transformed into new stereogenic centers. The one-pot cascade reaction sequence operated in a stereoselective fashion via a sequential radical cyclization, 1,5-hydrogen shift (radical translocation), radical cyclization, and finally reduction. The ultimate product was produced upon cleavage of the silicon-oxygen bond of siloxane.
2.3 Preparation of Substrate for Subsequent 5-Endo-Dig Cyclization with \textit{In Situ} Generated Carbon-Centered Radical

We examined substrates which could undergo 5-endo-dig radical cyclization employing this sequential process. Shown below in Figure 27 is a simple construction of a hexyne substrate which has the necessary functionality. Tetrahydropyran (THP)-protected progargyl ether was alkylated with 1,3-dibromopropane to afford the hexyne species. Lack of conjugation of the radical center generated from bromine atom abstraction, accompanied by stabilization of the 5-endo product through subsequent exothermically favorable $\sigma$-bond formation justified our preparation and investigation of the utility of this substrate toward 5-endo-dig radical cyclization.

Figure 27: Construction of THP-Protected Hexyne as Substrate for 5-Endo-Dig Radical Cyclization
We were interested to determine whether the initial generation of an alkyl radical by tin radical abstraction of a bromine atom would be followed by 5-endo-dig cyclization to form a transient cyclopentene vinyl radical (Figure 28). A subsequent 1,5-radical translocation would be followed by intramolecular attack of the newly formed ketal radical onto the cyclopentene ring. After hydrogen atom abstraction from tributyltin hydride, the final spiroketal product would be formed along with regeneration of the tin radical that could undergo another round of propagation. Part of the thermodynamic driving force for the reaction is the high exothermicity of the anticipated ring formations.

Figure 28: Suggested Preparation of Spiroketal Products through a Radical Cascade Initiated by a 5-Endo-Dig Closure
CHAPTER 3

5-ENO-DIG CYCLIZATION ATTEMPTS WITH TETHERED CARBON-CENTERED RADICALS

3.1 Cyclization Attempts with Alkyl Radicals

Unfortunately, all attempts to induce the 5-endo-dig closure led to the formation of acyclic products due to premature H-atom abstraction from Bu₃SnH, even when syringe pump addition was employed to maintain a low concentration of the hydride source (Figure 29). This experimental result was not unexpected according to our computational predictions, in which less reactive sp³-hybridized alkyl radicals require higher activation energies for 5-endo-dig cyclization in comparison with that of the more reactive sp²-hybridized vinyl radicals. The success of 5-endo-dig cyclization depends on the competition with 4-exo-dig processes and with radical H-atom abstraction.

![Figure 29: Premature Hydrogen Atom Abstraction in the THP-Hexyne System](image)

3.2 Preparation of Substrates which can Generate Vinyl Radicals

We next turned to substrates with a pattern B exo-vinyl radical which we had predicted computationally to be the most favorable according to our computational studies (see Table 2).
These vinyl radicals are readily generated from a regioselective radical attack of tin radical onto the end of a terminal alkyne as shown in Figure 30. The higher reactivity of vinyl radicals resulting from radical addition to an alkyne moiety leads to lower barriers and higher exothermicity of the respective subsequent cyclizations, especially when they are assisted by new conjugation between double bonds in the product. A subsequent 5-endo-dig radical cyclization is one pathway which could be followed to produce a cyclopentene methyldiene moiety.

![Figure 30: Generation of Prototypical Vinyl Radical from Alkyne](image)

We therefore constructed 1,5-diynes on a large scale using efficient literature processes (Figure 31). The 3,4-dimethylhexa-1,5-diyne-3,4-diols were synthesized starting from 2,3-butanedione. Trimethyl silyl (TMS)-acetylide was generated in tetrahydrofuran \textit{in situ} according to standard protocols. Addition of 2,3-butanedione to this solution yielded a diastereomeric mixture of diol products which were separated upon purification. Interestingly, the \textit{racemic} stereoisomer could be selectively crystallized, leaving behind mother liquors which were significantly enriched in the \textit{meso} species. This finding aided subsequent column chromatography purification.
By $^1$H NMR and isolated yields, this reaction produces a roughly 60:40 ratio of racemic: meso stereoisomers. We were interested in preparing the meso isomer stereoselectively, because it is of greater value in our methodology studies. The (five-membered ring) acetonide-protected meso bis(alkyne) has a better chance at undergoing the 5-endo-dig cyclization compared with the acetonide-protected racemic bis(alkyne), according to computational predictions and initial experimental studies. On the other hand, racemic bis(alkyne) has significant strain to disfavor a subsequent 5-endo-dig cyclization. In our initial attempts to create the meso isomer stereoselectively, we decided to prepare the acetylide via a Grignard exchange, and add this slowly to 2,3-butanedione. Our hope was that the first equivalent of Grignard acetylide would produce an $\alpha$-alkoxy ketone which should exhibit a significant chelation effect with the bidentate magnesium metal (Figure 32). The second equivalent of Grignard acetylide should then add in an anti-Felkin sense to the chelated substrate to produce predominantly the meso dialkoxy product, which upon work-up would provide the meso bis(alkyne) diol exclusively. Unfortunately, we were only getting mono-addition products. Subjecting the isolated mono-addition products to reaction with Grignard acetylide proved unfruitful and this study was not pursued further.
Although a method for selectively producing the meso compound remained elusive, we resorted to our improved separation methods of the two diastereomers in which meso isomer mother liquors are enriched by selective recrystallization of the racemic isomers. This was routinely used on several multi-gram scale runs. As mentioned before, this finding abetted subsequent flash column chromatography separations. Removal of the TMS-protecting group of each of the diastereomers under standard conditions afforded the required substrates for attempting the 5-endo-dig radical cyclization as seen in Figure 33.

The simplest bis-alkyne substrates for subsequent 5-endo-dig cyclization are the vicinal diol meso and racemic diastereomers of 3,4-dimethylhexa-1,5-diyne. Other substrates are also produced efficiently from 2,3-butanedione (Figure 35). For example the TMS-bis(alkyne) meso
diol was protected as the dimethyl diether under standard Williamson ether conditions. Subsequent alkyne deprotection afforded the target compound.

![Reaction Scheme](image)

**Figure 34: Preparation of Cyclopentene Bromosulfone with Dimethyl Ether Group**

According to our calculations 4-exo-dig processes are kinetically competitive with the desired 5-endo-dig radical cyclization of our 1,5-diyne system. To minimize this potential side-reaction we decided to anneal a ring to our two-carbon bridge connecting the two alkyne moieties. Our vision was the substrates with annealed ring would rather follow the 5-endo-dig cyclization mode rather than the 4-exo-dig pathway, because the latter is more sensitive to strain effects. Toward this end a 5-membered ring and six-membered ring were formed with the goal of tuning the activation energy, exothermicity of the reaction, and intermolecular distance between C1/ C5 atoms of the reactant.

![Reaction Scheme](image)

**Figure 35: Preparation of Cyclopentene Bromosulfone with Acetonide Group**
In this regard, the vicinal diol of the meso stereoisomer was protected as the acetonide using 2,2-dimethoxypropane, under Dean-Stark conditions. Subsequent alkyne deprotection afforded the acetonide-protected diol. The same reaction sequence was also subjected to the racemic diastereomer starting material.

Figure 36: Preparation of Cyclopentene Bromosulfone with Dioxane Group

The meso diol was also readily protected as the six-membered dioxane ring (above in Figure 36). Here meso starting material reacted with 1,2-dichloroethane under phase-transfer conditions. Interestingly, the protection of the diol and deprotection of the bis-alkynes occur in the same pot. Other protection methods were equally successful. For example, carbonyl diimidazole was used to protect the meso diol starting material as the cyclic carbonate (below in Figure 37). Subsequent deprotection furnished the target compound.

Figure 37: Preparation of Cyclopentene Bromosulfone as Cyclic Carbonate
3.3 Choice of Radical Sources for the Generation of Vinyl Radicals Intermediates in 5-Endo-Dig Cyclization of 1,5-Bis-alkynes

With the substrates in hand, several different radical sources were tried for the cyclization processes by Dr. Vitaliy Tymokhin (Figure 38). The choice of radicals (or radical precursors X-Y) was based upon the computational predictions regarding the effects on the cyclization barriers and reaction energies for a variety of species (Table 3).27

Table 3: Computed Activation and Reaction Energies for 5-Endo-Dig and 4-Exo-Dig Cyclizations (Energy in Kcal/mol)

<table>
<thead>
<tr>
<th></th>
<th>5-endo</th>
<th>4-exo</th>
<th>5-endo</th>
<th>4-exo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_a$</td>
<td>$\Delta E_r$</td>
<td>$E_a$</td>
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<td></td>
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<td>$\Delta E_r$</td>
<td>$E_a$</td>
<td>$\Delta E_r$</td>
</tr>
<tr>
<td>$X = H^a$</td>
<td>16.3</td>
<td>-30.7</td>
<td>14.0</td>
<td>-11.6</td>
</tr>
<tr>
<td>$X = SnMe_3$</td>
<td>17.6</td>
<td>-26.6</td>
<td>14.7</td>
<td>-8.0</td>
</tr>
<tr>
<td>$X = H^b$</td>
<td>14.9</td>
<td>-32.1</td>
<td>14.1</td>
<td>-12.0</td>
</tr>
<tr>
<td>$X = Br^b$</td>
<td>13.5</td>
<td>-33.1</td>
<td>13.3</td>
<td>-13.1</td>
</tr>
<tr>
<td>$X = Ts^b$</td>
<td>11.8</td>
<td>-34.0</td>
<td>12.8</td>
<td>-12.9</td>
</tr>
<tr>
<td>$X = SPh^b$</td>
<td>14.2</td>
<td>-33.1</td>
<td>13.8</td>
<td>-14.0</td>
</tr>
</tbody>
</table>

$^a$ UB3LYP/LANL2DZ $^b$ UB3LYP/6-31G**

Initial attempts using tributyltin hydride (X-Y = Bu$_3$Sn-H) did not give promising results. Bu$_3$SnH-mediated reactions of acyclic diols initiated either with azoisobutyronitrile (AIBN) in refluxing benzene or with Et$_3$B/ air at lower temperatures led to complicated mixtures of products, none of which possessed the characteristic $^1$H NMR signals of the 5-endo-dig product. We next turned to thiol radicals (because thiol-substituted vinyl radicals exhibit lower activation barriers and more favorable reaction energies for 5-endo-dig cyclization compared with the tin-substituted vinyl radicals (Table 3). Unfortunately, thiophenyl (PhS) radicals generated from thiophenol and AIBN as an initiator (X-Y = PhS-H) in refluxing benzene did not provide the desired 5-endo-dig product, but rather lead to benzothiophenes through cyclization of the intermediate vinyl radicals at the phenyl group of the PhS moiety. A few investigations with carbon-centered radicals failed to yield the 5-endo-dig product.
Figure 38: General Depiction of 5-Endo Dig Radical Cyclization of Bis-alkyne Substrate Leading to Cyclopentene Bromosulfone Product

3.4 Initial Success in forming Products from 5-Endo-Dig Cyclization with Carbon-Centered Radical

At this point, we believed that protection of the free diol may be an important feature toward garnering the elusive 5-endo-dig product. In this manner, the 1,5-diyne with annealed six-membered ring dioxane provided about 8-10% of the desired 5-endo-dig cyclized product under Bu₃SnH-mediated conditions with AIBN along with numerous polymer byproducts. Although these reaction conditions provided the desired product in a relatively low yield, this was a promising result and marked a turn for the better in our future endeavors. We continued to look for a radical source that would generate cleaner and more efficient reactions.

After investigating the use of a variety of radical sources, Dr. Vitaliy Tymokhin discovered an interesting example in the literature which would serve as the inspiration for the breakthrough we were searching for.

This example described the use of tosyl (Ts) radicals in reactions involving a dialkyne²⁴ and cyclohexenyl alkyne²⁵ as substrates. Tosyl radicals are versatile electrophilic species that are prepared from tosyl halides, and generated under thermal or photochemical conditions. These radicals were employed in cascade processes to add regioselectively and chemoselectively to the terminal position of alkynes and ultimately produce functionalized cyclic products as shown in Figure 39. It is interesting to note the chemoselectivity of initial tosyl radical addition to substrate in Scheme 39 part A. The electrophilic tosyl radical preferentially attacks the alkyne moiety in lieu of attack on the alkene.

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Our computations (Table 3) showed that Ts-substituted vinyl radicals offer lower activation energies and even more favorable reaction energies for 5-endo-dig cyclization than with those radical sources we had previously employed. Intrigued by these results we prepared tosyl bromide according to the literature procedure, from a room temperature reaction between the sodium salt of p-toluenesulfinic acid and bromine in ethanol (Figure 40).
3.5 Breakthrough Discovery in First Efficient 5-Endo-Dig Cyclization with Carbon-Centered Radical

Finally our breakthrough reaction transpired with the use of tosylbromide (TsBr). Reaction of our meso or racemic vicinal bis-alkyne diol with TsBr under thermal conditions yielded predominantly the desired \((E)\)-cyclopentene bromosulfone along with a minor amount of the \((Z)\)-cyclopentene bromosulfone (Figure 41). Similar results were obtained for reactions performed under photochemical conditions, along with the production of a small amount of cyclopentene dibromide that was not observed before. Still photochemical reactions provided higher yields than their thermal counterparts (vide infra), so these conditions were employed predominantly in subsequent kinetic studies.

![Figure 41: Efficient 5-Endo-Dig Cyclization using TsBr](image)

Figure 42 illustrates the sequence of processes leading to the formation of cyclopentene bromosulfones with the following illustrations. Upon either thermal or photochemical generation of tosyl radical, the latter adds regioselectively to the terminal carbon of our bis-alkyne with the subsequent formation of a reactive vinyl radical precursor for the cyclization step.

![Figure 42: Mechanism of Ts-Br promoted 5-Endo-Dig Cyclization. Part 1](image)
Of the two possible reaction pathways available, 4-exo-dig or 5-endo-dig, the Ts-substituted vinyl radical chooses the latter cyclization route. In this case the 5-endo-dig closure is favored over the 4-exo-dig cyclization kinetically. The cyclized radical abstracts a bromine atom from a nearby tosyl bromide in an atom transfer event to form the final bromosulfone cyclopentene product along with a regeneration of tosyl radical, thus allowing for continued propagation (Figure 43).

![Figure 43: Mechanism of Ts-Br promoted 5-Endo-Dig Cyclization. Part 2](image)

3.6 Mechanistic Rationale for The Efficiency and Stereoselectivity of TsBr-Promoted 5-Endo-Dig Cyclization of Carbon-Centered Radicals

The very high $E$-selectivity of the product results from syn-isomeric vinyl radical addition to tethered alkyne. The vinyl sulfone product stereoselectivity can be rationalized based upon stereoelectronics among other considerations (Figure 44). The relative stabilities of the two possible syn- and anti-configured intermediate radicals are affected by hyperconjugation with the vicinal tosyl (Ts) group. The anti-isomer suffers from a greater hyperconjugative stabilizing affect and consequently is less reactive relative to the syn-isomer. In addition, the syn Ts-substituted vinyl radical intermediate on the right benefits from a hydrogen-bond interaction while the isomeric vinyl radical intermediate on the left suffers from steric repulsion.

In relation to the parent system (where tosyl is replaced by hydrogen) the activation barrier for 5-endo-dig cyclization leading to $E$-configured product is decreased significantly (2-3 kcal/mol) and only moderately (1 kcal/mol) for the respective 4-exo-dig cyclization (Table 3). This is in contrast to a much smaller decrease (less than 1 kcal/mol) in activation barriers for both 5-endo-dig and 4-exo-dig cyclizations leading to $Z$-configured product. As a result of these features, the 5-endo-dig cyclization of the syn-isomer has the lowest activation energy among possible cyclization choices of Ts-substituted radicals.
Intrinsically, reactions which undergo the 5-endo-dig pathway can adopt a favorable 6-membered ring transition state via intramolecular hydrogen-bonding. In contrast reactions which undergo the 4-endo-dig pathway have to proceed through a less favorable 7-membered ring hydrogen-bonding pattern in the transition state (Figure 45).

**Figure 45: Hydrogen Bond Effects on 4-Exo-Dig vs 5-Endo-Dig Cyclizations of Ts-Substituted Vinyl Radicals**

3.7 Optimization of Conditions for 5-Endo-Dig Cyclization

We expected even higher selectivity for the 5-endo pathway with substrates that tied the vicinal diol moiety of our bis-alkyne into a 5-membered ring. As discussed, earlier computational data performed in our group suggested that strain in the transition state (TS) increases the 4-exo activation barrier to a larger extent than the 5-endo activation barrier, and can therefore be used to control the 5-endo/4-exo selectivity.\(^\text{27}\) We were pleased that our experimental results correlated well with our computational predictions as outlined below in Table 4.\(^\text{26}\)
Table 4: Results for TsBr-Mediated Cyclization of 1,5-Diynes

a All photochemical experiments were carried out at room temperature. Yields are determined by $^1$H NMR with Ph$_3$CH internal standard, based on initial 1,5-diyne. b $h$ν/TsBr (3.3 equiv)/C$_6$H$_6$/2 h. c TsBr (2.2 equiv)/AIBN/refluxing C$_6$H$_6$/6 h. d $h$ν/TsBr (4.7 equiv)/C$_6$H$_6$/2 h. e TsBr (3.0 equiv)/AIBN/refluxing C$_6$H$_6$/25 h. f $h$ν/TsBr (4.0 equiv)/C$_6$H$_6$/4 h.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>Yield (E)-5, %</th>
<th>Yield (E)-6, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>![Image]</td>
<td>68$^b$</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15$^c$</td>
<td>-</td>
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<tr>
<td>b</td>
<td>![Image]</td>
<td>51$^b$</td>
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<td></td>
<td>![Image]</td>
<td>23$^c$</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td>![Image]</td>
<td>72$^d$</td>
<td>16</td>
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<tr>
<td></td>
<td>![Image]</td>
<td>16$^e$</td>
<td>3</td>
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<tr>
<td>d</td>
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</tr>
<tr>
<td></td>
<td>![Image]</td>
<td>2$^e$</td>
<td>3</td>
</tr>
</tbody>
</table>

Examining the yields for cyclopentene bromosulfone products produced from reaction of meso 1a and racemic 1b diols under photochemical conditions at room temperature, illustrates the respective cyclization efficiencies (Table 2). One can draw the conclusion that the gauche effect indeed influences conformational control more noticeably in the meso species, and therefore improves its cyclization efficiency relative to the racemic species (e.g., 68% vs 51%, Table 2). The difference in cyclization efficiency of the respective isomers becomes even larger when the reaction is carried out without excess TsBr (1.0 equiv) in CH$_3$CN (35% vs 7%).
The 5-endo cyclizations in our systems are sensitive to ring size. Tethering the diol into a six-membered ring, as in the meso 1c species, does not have an adverse effect on the cyclization. However, the increased ring-strain of the five-membered ring meso 1d species slows down formation of a second five-membered cycle in the cyclization step, (e.g., photochemical yields for 1d vs 1c are 51% vs 72% respectively, Table 1). The racemic diastereomer to 1d (with its alkynes forced into a permanent ca. 180° trans relationship) did not cyclize at all.

![Figure 46: Products Resulting from Radical Cyclization of our 1,5-Diyne Systems](image)

Dr. Vitaliy Tymokhin optimized the general reaction conditions for the 5-endo-dig radical cyclization by using bis-alkyne 1c as the substrate. The products which are formed from photoinitiated cyclization of our substrate 1c with TsBr are depicted above in Figure 46. Different solvent conditions have a substantial effect on the amount of (Z)-isomer (Z)-5 and dibromide (E)-6 by-products. The cyclization proceeds most efficiently in benzene under photochemical conditions where it also provides exclusive (E)-selectivity for cyclopentene bromosulfone product (entries 4, 6, and 7 in Table 5 below), although some dibromide byproduct is produced. On the other hand, dibromide byproduct formation can be minimized without significant loss of efficiency (entries 8-10) by switching to such solvents as CH₂CN, CH₂Cl₂, and acetone. The exclusive formation of E-configured product suggests the importance of intramolecular H-bonding which is absent in the transition state intermediate leading to the Z-configured product.

Longer reaction times in several solvents gave higher conversions at the expense of producing a small amounts of the (Z)-isomer (Z)-5. This suggested that the (Z)-isomer (Z)-5 is formed from the (E)-isomer (E)-5 through a photoequilibration process (Figure 46).
Table 5: Optimization of Reaction Conditions for Photoinitiated Cyclization of 1c

<table>
<thead>
<tr>
<th>entry</th>
<th>TsBr (eq)</th>
<th>solvent</th>
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<th>yield (%)</th>
<th>yield (%)</th>
<th>yield (%)</th>
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<td>CCl₄</td>
<td>15</td>
<td>29</td>
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<td>10</td>
</tr>
</tbody>
</table>

All photochemical experiments were carried out at room temperature. Yields are determined by ¹H NMR with Ph₃CH internal standard, based on initial 1,5-diyne 1c.

For example, in the GHMBC spectrum of bromosulfone (Z)-5d, the proton at 6.29 ppm couples with both carbons at 93.4 and 87.8 ppm, as well as with carbons 144.6 and 159.1 ppm; therefore, its carbon at 129.8 ppm is linked to these latter two carbons, which provides the proof
for the five-membered ring. On the other hand, the proton at 6.21 ppm couples with carbons at 87.8, 129.8, and 159.1 ppm; therefore, its carbon at 123.9 ppm is linked to the carbon at 159.1 ppm. Cross-peaks in the NOESY spectrum between the signals at 7.88 and 6.21 ppm and between those at 7.88 and 1.85 ppm place the Ts group on the exocyclic double bond and syn to the proton at 1.85 ppm, which is confirmed by a strong nuclear Overhauser effect (NOE) between 6.21 and 6.29 ppm. Of the methyl protons at 0.89 and 1.41 ppm, only the former display NOEs with 6.21 and 6.29 ppm; therefore, the 0.89 ppm proton is trans to methyl protons at 1.36 and 1.85 ppm. The presence of the ca.1 Hz long-range coupling constant between the two vinyl hydrogens in the (E)-isomer is useful for rapid assignment of stereochemistry in the isomeric cyclic products.

Figure 47: Complete $^1$H and $^{13}$C NMR Assignments for the Bromosulfone Isomers

Figure 48 shows the $^1$H NMR spectrum of bromosulfone E-5d. Notice the diagnostic vinyl singlets at δ 6.17 and 7.62 ppm as well as the toluene methyl singlet at δ 2.43.
Figure 48: $^1$H NMR Spectrum of Cyclopentene Bromosulfone $E$-$5d$

Figure 49 shows the $^1$H NMR spectrum of bromosulfone $Z$-$5d$. Notice here the diagnostic vinyl singlets are at $\delta$ 6.21 and 6.29 ppm and the toluene methyl singlet is at $\delta$ 2.43 ppm.
Figure 49: $^1$H NMR Spectrum of Cyclopentene Bromosulfone Z-5d

The efficiency of this radical cyclization both thermally and photochemically paves the way toward new organic chemistry methodology.
CHAPTER 4

ALTERNATIVE MECHANISTIC SCENARIO IN LIEU OF 5-ENDO-DIG CYCLIZATION PATHWAY

Although the 5-endo-dig cyclization provides the most direct explanation to the observed experimental results and although the DFT analysis of the 5-endo-dig potential energy surface agrees very well with both the increased efficiency and the (E)-stereoselectivity of Ts-mediated cyclizations, other mechanistic possibilities for the formation of 5-endo-dig products can be suggested a priori. Such possibilities can be broadly divided into two groups: a) ring expansion of the 4-exo-dig products (the top part of Figure 50) and b) a sequence of reactions that involve i) formation of acyclic products due to formal addition of TsX (or Bu3SnH) to one of the triple bonds (vide infra), ii) attack of Ts radical at the second triple bond, iii) 5-endo-trig radical cyclization and iv) termination through β-scission and loss of Ts radical (the bottom part of Figure 50). We will briefly discuss these alternative mechanistic scenarios in the context of available experimental and computational data.

Figure 50: Alternative Mechanistic Scenarios
4.1 Ring-expansion of 4-exo-products

Although the relatively low barriers for the formation of 4-exo-dig cyclizations suggest that their involvement should be considered, three observations argue against this pathway for the formation of the Ts-substituted 5-endo products 5 (in Figure 50).

First, although the Dowd-Beckwith 4-exo/5-endo expansion sequence which involves intramolecular radical addition to the exocyclic double bond of the 4-exo-product with the formation of a bicyclo[4.1.0] intermediate and its subsequent conversion to the 5-endo product through cyclopropyl ring opening is common for trigonal cyclizations, the first step of such a sequence is forbidden for the digonal cyclization product shown below in Figure 51 due to stereoelectronic considerations. Not only is the vinyl radical in the 4-exo-dig product constrained to be orthogonal to the target $\pi$-system but its reaction would also yield a very strained product.

\[ \text{Figure 51: Ring Expansion of 4-Exo Product} \]

Due to the above stereoelectronic restrictions, a direct 1,2-carbon shift remains the only reasonable alternative (Figure 52). However, computational analysis suggests that the activation energy for the 1,2-shift should be prohibitively large for a reaction proceeding at room temperature. The 31.4 kcal/mol UB3LYP/6-31G** barrier calculated for the simple vinyl radical is unlikely to decrease sufficiently with the Ts substitution to allow such a ring expansion under the reaction conditions. The larger barrier for 1,2-migrations in radicals relative to that in cations is
not surprising because the 3e transition state for the radical 1,2-shift is destabilized relative to its 2e counterpart for the cationic 1,2-shift.

![Activation Energy for Radical 1,2-Shift](image)

31.4 kcal/mol (UB3LYP/6-31G**)

**Figure 52: Activation Energy for Radical 1,2-Shift**

The final possible path for the 4-exo/5-endo ring expansion is an intermolecular process which involves the reaction of 4-exo-product with another molecule of TsX (Scheme 53). However, in order to account for the experimentally observed products such a sequence has to include radical attack at the *internal* carbon of the exocyclic double bond, rather than attack at the *external* carbon which produces an allylic radical. Moreover, since the attacking radical species Y can be either Ts or Br, this should lead to the formation of bis-Ts substituted cyclopentenes as well as isomeric bromosulfones with Br at the exocyclic double bond. Neither of these two types of products was observed.

![Scheme 53: Alternative Ring Expansion of 4-Exo Product](image)

**Scheme 53: Alternative Ring Expansion of 4-Exo Product**
The final plausible alternative for the formation of bromosulfones 5 involves transformation of cyclic dibromides 6 through addition of Ts radical to the exocyclic double bond, followed by β-scission of a Br atom (Figure 54). Although analysis of the experimental data at low conversions and computational barriers argues against this pathway as the major route to the cyclic bromosulfones, it is possible that this path occurs to some extent under the photochemical conditions, where both Br and Ts radicals are generated simultaneously through the Ts-Br bond homolysis. Indeed, our independent experiments on the transformation of the cyclic dibromides to the respective bromosulfones found that this reaction does occur on the time scale of our experiments. Although yields of bromosulfones in this reaction are lower than for the reaction of the acyclic bis-diynes 1, and although the transformation of dibromides 6 is slower than direct formation of bromosulfones through the 5-endo-dig path, the secondary chemistry of dibromides should provide an additional pathway to the bromosulfone products.

Figure 54: Possible Mechanism for the Formation of Dibromides and their Transformation into Bromosulfones
CHAPTER 5

CONSTRUCTION OF OTHER DIYNE SYSTEMS FOR UNDERGOING 5-ENDO-DIG CYCLIZATION

Having garnered success with our two carbon bridged 1,5-diyne systems, we next turned toward the design of other alkyne substrates that could also engage in this carbon radical-centered 5-endo-dig cyclization process (Figure 55). Our first ideas centered on constructing 1,4-diyne species. There are examples in the literature which construct 1,4-diyne systems as building blocks towards more complex chemical compounds, and we were able to make use of these procedures.31

**Figure 55: 5-Endo-Dig Cyclization of 1,4-Diyne Vs. 1,5-Diyne**

R = alkyl or aryl
We aimed to design a 1,4-diynie species which had the benefits of a driving force towards cyclization. As one can see in Figure 55 and Figure 56, the 1,4-diynie systems have a one-carbon bridge between the two alkyne moieties as opposed to our previous 1,5-diynie systems which contained a two-carbon bridge. This new 1,4-diynie pattern requires that radicals generated in situ attack the β-internal carbon of one of the alkyynes in order to generate a vinyl radical that could subsequently engage in a 5-endo-dig cyclization. This is an opposite regioselective requirement compared with the 1,5-diynie system. One way of ensuring this proper regioselectivity is through hydrogen-bonding effects that could steer the radical towards the β-internal carbon in an intramolecular fashion. Another approach would be to tether a functional group to the 1,4-diynie system. This species could become a radical under the reaction conditions and subsequently engage in an intramolecular attack of the β-internal carbon to generate the proper vinyl radical for a subsequent 5-endo-dig cyclization.

Shown below in Figure 56 is a diyne system that we propose could engage in chelation controlled addition of an in situ generated radical towards the β-internal carbon of one of the alkyynes. Here, the cyclized intermediate radical CI formed from a 5-endo-dig cyclization is expected to benefit from a captodative stabilizing effect which could lower the activation energy for this pathway. The captodative effect is due to a hyperconjugative interaction between the σ(C-Si) →π(C) interaction as well as a σ(C-O) →π(C) interaction in the cyclized intermediate (CI). Essentially the C-Si sigma bond is a good donor and the C-O sigma bond is a good acceptor moiety. The carbon radical center of the CI serves simultaneously as an acceptor towards the σ(C-Si) donor and as a donor towards the σ(C-O) acceptor, providing an electronic relay between the donor and acceptor orbitals in a captodative fashion. Successful 5-endo-dig radical cyclization for this substrate may minimize the need for additional factors to control selectivity such as H-bonding or chelation, as used in our previous work.
Another way of ensuring proper regioselectivity for the initially generated vinyl radical is to incorporate a tethering unit that can start a cascade radical process through a well-precedented mode of cyclization. This is well exemplified in a review by Malacria, who cites some important examples of the development of the “one-pot reaction” executed in a tandem cascade of ring closing events. Moreover the methodology he discusses contains very elegant new synthetic combinations. We drew inspiration from some of these literature examples, and hoped to apply the general method to 1,4-diynes substrates capable of proceeding through the 5-endo-dig radical cyclization. The following Schemes are representative of the methodology we were hoping to apply to our substrates.

Radical cyclization of bromoacetals was first described by the Stork and the Ueno group. The Yadav group applied this type of methodology to gain access to angular triquinanes (Figure 57). Yadav and coworkers attached a bromoacetal unit to a cyclopentene ring. They found that the initially generated carbon-centered radical readily cyclizes in a 5-exo-trig manner. Moreover, the stereochemistry of the annelation is governed by the lone stereocenter which connects the cyclopentene and acetal units. Further ring closure in a cascade fashion leads to the oxatriquinane product in a 78 % yield. Eventually this material is converted to the final angular triquinane.

Figure 56: 5-Endo-Dig Cyclization of Hyperconjugative Interactions of Cyclized Intermediate
Figure 57: Radical Cascade Reactions using Bromoacetal Ether

In a similar fashion, the Malacria group extended the methodology developed by Stork and Nishiyama\textsuperscript{35} by using (bromomethyl)dimethylsilyl allyl ethers as substrates that can undergo regio- and stereoselective radical 5-exo-trig cyclization (Figure 58).\textsuperscript{36} The initially formed radical is produced through abstraction of a bromine atom by an \textit{in situ} generated tin radical. The Malacria group postulated that the intermediate exocyclic vinyl radical generated from this initial 5-exo-trig cyclization could be trapped intramolecularly by a suitably located unsaturation. In this fashion unsaturated five-membered carbocycles are produced. The second example shown in Figure 58 was a side product from methodology employed towards construction of angular triquinanes.\textsuperscript{37}
Figure 58: Radical Cascade Reaction with (Bromomethyl)dimethylsilyl Propargyl Ether

Another method for generating a transiently formed vinyl radical involves treatment of a vinyl bromide with tributyltin hydride. In Figure 59, tributyl tin hydride reacts with AIBN to generate tin radical which abstracts the bromine atom from the vinyl halide starting material. The newly generated vinyl radical next undergoes a tandem 5-exo-dig cyclization followed by a 5-exo-trig cyclization to produce an intermediate bicyclopentane diene species with a homoallyl radical. This intermediate cyclizes in a 3-exo-trig fashion to generate a bicyclo[3.1.0]hexane attached to a methylenecyclopentane with allyl radical. The best resonance structure of intermediate allyl radical exists with the double bond inside the ring. It is this species which abstracts a hydrogen atom from tributyltin hydride during the last step to produce the functionalized cyclopentene product. Interestingly, thermal rearrangement of this species produces a triquinane motif which could also be envisioned to form from dicyclopentene homoallyl radical intermediate via a 5-exo-trig cyclization.
Figure 59: Vinyl Bromide as Vinyl Radical Precursor

With these literature precedence in mind, we set out to construct the 1,4-diyn systems that could cyclize in a 5-endo-dig cyclization mode. One challenge in designing substrates was to incorporate some functionality which could guide the proper regioselectivity for initial radical generation onto our substrate (attack at the $\beta$-alkyne internal carbon). Optimistically, we hoped this substrate would not only successfully cyclize with tosyl bromide, but with other radical sources as well.

As shown in Figure 60, ethyl phenyl acetate was chosen as a commercially available starting material. This was converted into the diyne alcohol through reaction with two equivalents of TMS-acetylide which was generated in situ. Deprotection of the alkynes occurred under standard conditions to give the free alcohol. This served as one of the 1,4-diyn cyclization precursors.
Figure 60: One-Carbon Bridge Diyne Construction

We intended to test the possibility that the presence of a free hydroxyl group may play a role in directing the tosyl radical to this internal $\beta$-alkyne carbon through hydrogen bonding with one of the sulfonyl oxygens (Figure 61). Additionally, the cyclized radical intermediate exhibits a stabilizing $\beta$-effect of silicon.

Figure 61: Proposed Cyclization of 1,4-Diyne Substrate

We also commenced on construction of a 1,4-diyne substrate which contains a (bromomethyl)dimethylsilyl propargyl ether (Figure 62). Again synthesis began with commercially available ethyl phenyl acetate. Following conversion to the bis-alkyne alcohol, protection with (bromomethyl)dimethylsilyl chloride gave the desired (bromomethyl)dimethylsilyl propargyl ether.
We anticipated the exposure of this (bromomethyl)dimethylsilyl propargyl ether to standard thermal radical conditions using tributyltin hydride and AIBN would ultimately afford the cyclopentadiene motif via a sequential 5-exo dig/5-endo-dig mode of cyclization (Figure 63). The projected intermediates leading to the proposed final cyclized product are displayed below.

One can find many examples of vinyl halides serving as radical progenitors in various cyclizations, particularly those that are used in cascade reactions.
One method of generating these vinyl bromides is by converting a vinyl stannane into a vinyl bromide. Vinyl stannanes can be produced under both radical and metal-catalyzed conditions. In particular, metal catalyzed hydrostannation of an alkene, allene, or alkyne has developed into a widely used method for generation of vinyl stannanes.\textsuperscript{38} It often serves to compliment the hydrostannation of alkynes, alkenes, and allenes under free-radical conditions which, in general, provide a mixture of stereoisomers. Under free-radical conditions the regiochemistry of the vinyl stannane product is often controlled by the relative stability of the two possible intermediate stannyl radicals. The regioselectivity of metal-catalyzed hydrostannation on the other hand is governed by electronic factors, steric factors, and chelation effects. Often with the choice of a proper substrate and reaction conditions the regio- and stereoselective outcome for the metal-catalyzed hydrostannylation can be well controlled.

Active palladium (0) species generated from tetrakis(triphenylphosphine)palladium(0) (Pd(PPh₃)₄) and dichlorobis-(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂) are routinely used. It is postulated that palladium (II) complexes are reduced to catalytically active palladium (0) species by tin hydride under the reaction conditions. To minimize side reactions such as reduction of the alkyne by the \textit{in situ} formed hydrogen gas byproduct, the tin hydride source is maintained at a low concentration, readily achieved by employing syringe pump addition. Purification of stannanes can be problematic due to silica-gel-mediated protonolysis of alkenylstannanes resulting in destannylation, often furnishing low isolated yields.

It is assumed mechanistically that hydrostannation proceeds via a catalytic cycle based upon oxidative addition followed by hydrometallation and finally reductive elimination (Figure 64). Oxidative addition of R₃SnH to the metal center (MLn) (A to B) is followed by coordination of the unsaturated bond to yield complex C, which may then undergo hydrometallation to give metal-alkene D. Finally reductive elimination furnishes the organostannane 1.
Figure 64: Possible Hydrostannylation Mechanism

This mechanism is in agreement with the following general observations from the literature. (i) Hydrostannation occurs with cis stereoselectivity furnishing the (E)-geometric isomer (in the case of alkynes). (ii) The relative steric bulk of R\textsuperscript{1} and R\textsuperscript{2} will affect the regioselectivity of hydrostannation. For example, a bulky R\textsuperscript{1} substituent will prefer to be orientated distal to a bulky R\textsubscript{3} ligand on tin, hence favoring formation of complex C and vinylstannane product 1. (iii) In complex B, the electropositive metal center provides the H-atom with hydridic character. Regioselectivity of addition of R\textsubscript{3}Sn-MLn-H may therefore be affected by polarization of the alkyne by R\textsuperscript{1} and/or R\textsuperscript{2}. Steric and electronic effects will vary in their relative importance depending on the type of substrate and catalyst. Other considerations for regioselectivity of hydrostannation include metal chelation by a suitably positioned heteroatom on R\textsuperscript{1} or R\textsuperscript{2}.

We wished to apply a regioselective metal-catalyzed hydrostannation to one-carbon bridge substrates, in hopes of creating a properly positioned vinyl stannane that could be easily transformed into a vinyl bromide (Figure 65). The vinyl bromide could be envisioned as a
precursor to a vinyl radical, which could engage in a 5-endo-dig cyclization to ultimately produce the cyclopentadiene motif.

Figure 65: Proposed Construction of Vinyl Bromide and Subsequent Cyclization

Construction of the diyne alcohol was straightforward, with ethyl phenyl acetate added to \textit{in situ} prepared hexyne acetylide. However, hydrostannation of the diyne alcohol provided us with a vinyl stannane product with the wrong regiochemistry for subsequent 5-endo-dig radical cyclization (Figure 66).
Figure 66: Hydrostannylation of One-Carbon Bridge Diyne Alcohol

The $^1$H NMR spectrum below (Figure 67) confirms this regiochemistry of hydrostannylation, as the vinyl proton is a triplet. A vinyl stannane with the necessary regiochemistry for undergoing a 5-endo-dig cyclization following its conversion to vinyl iodide would be a singlet (with some splitting by the vicinal tin group).
The above result suggested that coordination of the OH group with Sn atom may control regiochemistry. With this idea in mind, we attempted hydrostannylation of one of our 3,4-dimethylhexa-1,5-diyne-3,4-diol, reasoning that the same regiochemical hydrostannation of this one carbon homologated system would provide the proper substrate for forming the vinyl iodide that could cyclize in a 5-endo-dig mode. Synthesis of the dimethyltetradeca-diyne diol proceeded successfully with 2,3-butanedione addition to in situ prepared hexyne acetylide, followed by separation of the mixture of diastereomeric meso and racemic products. Unfortunately, upon subjecting the meso substrate to hydrostannation conditions we obtained a vinyl stannane product with the wrong regiochemistry for 5-endo-dig cyclization (Figure 68).
Figure 68: Hydrostannylation of Two-Carbon Bridge Diyne Diol

The $^1$H NMR spectrum below (Figure 69) confirms this regiochemistry of hydrostannylation, as the vinyl proton is a singlet (with some vicinal coupling by the neighboring tin group). A vinyl stannane with the necessary regiochemistry for undergoing a 5-endo-dig cyclization following its conversion to vinyl iodide would be a triplet (with additional splitting by the vicinal tin group).
With this regioselectivity issue in mind, we next attempted to eliminate possible hydrogen-bonding effects of the hydroxyl moieties of substrate which would potentially direct tin radical to the β-carbon of one of the alkynes (Figure 70). First, dimethyl ether 1,5-diyne substrates were used for attempted hydrostannylation with appropriate regiocontrol toward installation of a stannyl group at the internal α-position of one of the alkynes. Second, the monomethylated substrate was employed for this same purpose. Protecting one of the hydroxyl moieties of the substrate eliminated the possibility of one of the two possible six-membered transition states that could deliver tin radical to the β-carbon.
Figure 70: Proposed Mechanism for Regioselective Hydrostannylation

Unfortunately reactions using dimethylated and monomethylated substrates suffered from poor conversion and were unsuccessful in producing any type of vinyl stannane (Figure 71).
Attempts to hydrostannylate our original 1,4-diyne system were successful, and finally gave a vinyl stannane product with the correct regiochemistry for 5-endo-dig ring closure (Figure 72).

The $^1$H NMR spectrum below (Figure 73) confirms this regiochemistry of hydrostannylation, as the vinyl protons are two doublets, exhibiting a strong trans coupling (18.9 Hz) with one another.
Figure 73: $^1$H NMR Spectrum of Product from Hydrostannylation of 1,4-Diyne with Correct Regiochemistry

Conversion of the vinyl stannane product to vinyl iodide occurred smoothly (Figure 74).

Figure 74: Conversion of Vinyl Stannane to Vinyl Iodide

Notice in the $^1$H NMR spectrum below (Figure 75), the characteristic vinyl protons have shifted.
Attempts to hydrostannylate our original 1,5-diyne system were also successful, and gave another vinyl stannane product with the correct regiochemistry for 5-endo-dig ring closure (Figure 76).

Figure 76: Successful Hydrostannylation of 1,5-diyne
The $^1$H NMR spectrum below confirms this regiochemistry of hydrostannylation, as the vinyl proton peak at $\delta$ 6.34 ppm is a singlet, exhibiting a strong cis coupling with vicinal tin group. An alkynal proton at $\delta$ 2.47 shows that this hydrostannylation product is not the result of double hydrostannation.

Figure 77: $^1$H NMR Spectrum of Product from Hydrostannylation of 1,5-Diyn with Correct Regiochemistry
CHAPTER 6
SYNTHESIS OF VINYL SULFONES: LITERATURE BACKGROUND

Cyclopentenes are very common motifs in natural products. Understandably, many methods have been developed to make them. Our new 5-endo-dig radical cyclization protocol is a new contribution to the arsenal of available techniques. 5-endo cyclizations are more atom-economical than 5-exo cyclizations which leaves an additional functionality to work with. At this point, we sought to show the utility of this methodology by undertaking an analog development project of the bromosulfone cyclopentene product. The cyclopentene bromosulfone products are enriched with functional handles including an endocyclic vinyl bromide and an exocyclic vinyl sulfone that could be further elaborated.

The carbon skeleton of the cyclopentene products resulting from the 5-endo-dig radical cyclization resembles fulvene, cyclopentenone, and carbosugar structural units, commonly found in natural products and synthetic bioactive compounds (Figure 78). For example, a selective oxidative cleavage of the exocyclic double bond would transform vinyl sulfone cyclopentene into cyclopentenone. These units appear in prostaglandin natural products such as prostaglandin A₁ and are commonly accessed via Pauson-Khand, Nazarov cyclization or through various cycloaddition methods.
A Corey-Winter olefination would transform methylidene cyclopentene with free diols into a fulvene. These motifs have been recently synthesized by strategies involving cyclopentannulation, Schmittel cyclization, intramolecular carbopalladation among others. Fulvenes have also been employed as ligands in organometallic chemistry. In addition to being interesting structural units, fulvenes can be readily transformed into other species via cycloaddition chemistry. A major benefit of our methodology is the incorporation of very useful functional handles in the 5-endo-dig cyclized products that can permit further elaboration. On the other hand functionality for the aforementioned cyclizations often require preinstallation, and therefore limit their scope towards preparation of functionally diverse compounds in a rapid manner.

Interesting examples exist in the literature for construction of methylidene cyclopentenes including regioselective asymmetric dihydroxylation of fulvenes, allylenecyclopropane thermal isomerizations, and olefin-metathesis to form cyclopentenones followed by Tebbe olefination. Important biologically active compounds with our methylidene cyclopentene motif include the chromophore aglycon of the enediyne natural product neocarzinostatin. This
chromophore contains a dihydrofulvene unit as part of the novel bicyclo[7.3.0]dodecadiyne system.50

Oxidation or reduction of the endocyclic double bond along with other synthetic manipulations could transform vinyl sulfone cyclopentene into a carbosugar. The syntheses of carbosugars vary widely, but often make use of optically pure carbohydrate starting materials. Important carbosugars that have been recently synthesized include natural products such as (-) neoplanacin A 51 with antitumor and antiviral activity and non-natural products such as the drug carbovir, a reverse transcriptase inhibitor.52

Before addressing the synthetic utility of these bromosulfone adducts and our results in functionalization, a discussion of background work for making vinyl sulfones is important. An excellent review on the subject of vinyl sulfones and 1,3-dienyl sulfones was recently published by Bäckvall, et.al.53 In this review, an interesting paper was cited which discusses Michael addition reactions to 1,3-dienyl sulfones.54 This sparked our interest in attempting these reactions on our cyclopentene bromosulfone substrates, and will be discussed shortly. Another excellent review on vinyl sulfone construction and application was recently published by Meadows and Gervay-Hague.55 Recently Rayner published a comprehensive book on sulfur chemistry which contains chapters on vinyl sulfones in Advances in Sulfur Chemistry.56

Because these reviews provide a very detailed description of available synthetic approaches to this class of compounds we will limit ourselves to discussion of selected examples provided in the following section.

### 6.1 Literature Methods for the Preparation of Vinyl Sulfones

Vinyl sulfones can be prepared in a variety of ways.55,53 This section summarizes some of the most widely used methods for producing this functionality. Many procedures make use of a sulfonyl-stabilized carbanion as the reactive nucleophile.53 Figure 79 illustrates reactions of such carbanions with carbonyl compounds. In the first example, a sulfonyl-stabilized dicarbanion is coupled with benzaldehyde to ultimately afford vinyl sulfone via a Peterson olefination process.57 Similarly, a sulfone variant of the Horner-Wadsworth-Emmons olefination protocol is
used in the second example to provide the vinyl sulfone. The third example shown is representative of an interrupted Julia Olefination process.

![Chemical structure and reaction scheme](image)

Figure 79: Construction of Vinyl Sulfones through Condensation of α-Sulfonyl Anions with Aldehydes

The Julia olefination (also known as the Julia–Lythgoe olefination) is the chemical reaction of phenyl sulfones with aldehydes (or ketones) to give alkenes. The reaction involves formation of a stabilized α-sulfone anion with a strong base such as n-butyl lithium and using it in an Aldol-type coupling with an aldehyde or ketone to form a β-alkoxy sulfone moiety. This intermediate is subsequently trapped with acetic anhydride to form a β-acetoxy sulfone compound. After isolation and purification this species is subjected to a reductive elimination under reducing metal conditions, by employing sodium amalgam (Na (Hg)) or samarium iodide (SmI₂) to form a double bond, predominantly with a trans-configuration.
In addition, a number of new approaches to vinyl sulfones have become a reality due in large part to the advances in organometallic chemistry. One novel method for preparing vinyl sulfones involves the use of palladium-mediated catalysis and a specialized rigid bidentate phosphine ligand called Xantphos (Figure 81). Under these palladium-mediated conditions, a reaction between an arenesulfinate and a vinyl triflate occurs to yield a vinyl sulfone.

Figure 80: Julia-Olefination Mechanism (Via intermediate Vinyl Sulfone)

Figure 81: Organometallic Method for Vinyl Sulfone Formation
Conjugate addition to acetylenic sulfones provides another route to vinyl sulfones (Figure 82). Here, typically organometallic nucleophiles such as dialkylcuprates and stabilized enolates such as malonates can add in a conjugate fashion to produce the desired vinyl sulfone moiety. Additionally, reduction of the triple bond can occur as shown in the third example. Here the $E$-configuration is adopted upon isomerization from the original $Z$-isomer under the reaction conditions.

![Conjugate Addition to Acetylenic Sulfones](image)

**Figure 82: Conjugate Addition Methods for Vinyl Sulfone Formation**

Acetylenic sulfones are readily synthesized. A good example is provided in Figure 83 below. Freshly prepared $p$-toluenesulfonyl iodide adds regio- and stereoselectively across the triple bond of a variety of alkyne systems. Based-induced dehydrohalogenation provides the product acetylenic sulfones in modest to excellent yields. Side-products included extruded sulfur dioxide to yield the disubstituted acetylenes as well as products resulting from methoxide or hydroxide displacement on the vinyl iodide.
Hydrometallation of alkynyl sulfones followed by trapping of the resulting vinyl metal species with various electrophiles allows for synthesis of unique vinyl sulfones (Figure 84, first reaction scheme). This protocol also works effectively with alkynyl sulfoxides. Following formation of alkenyl zirconium (IV) complexes and subsequent trapping with electrophiles, the alkenyl sulfoxides are oxidized to provide vinyl sulfones.\(^6^5\)

The Schwartz reagent, an organozirconium reagent, reacts in a regio- and stereoselective fashion at the 2-position of alkynyl sulfoxides and alkynyl sulfones to give Z-alkenylzirconium (IV) complexes which can be quenched by addition of water or further functionalized by addition of an external electrophile.\(^6^6\) The position of attachment of the zirconium in the product is governed by sterics. (This regioselectivity reverses with heteroatom substituted alkenes and alkynes due to electronif factors). Formation of the product involves either the regiospecific addition of Zr-H to a double bond (alkene or alkyne) or a positional rearrangement characterized by addition to an internal olefin followed by rapid rearrangement via Zr-H elimination and readdition to place the metal in the less hindered position.\(^6^6\) Terminal alkynes can be regioselectively hydrozirconated with the Schwartz reagent and then quenched with sulfonyl chlorides yielding the \(E\)-vinyl sulfone (Figure 84, second reaction scheme).\(^6^7\)
In the third example of Figure 84, thiophenol is added in a regioselective fashion to enyne under palladium (II) catalyzed conditions. Subsequent oxidation converts the vinyl sulfide to the vinyl sulfone.

\[
\begin{align*}
\text{Ph} &= \text{SO}_2\text{Ph} \\
&\xrightarrow{\text{Cp}_2\text{Zr}(\text{H})\text{Cl}} \text{THF, 25 °C}
\end{align*}
\]

\[
\begin{align*}
\text{E}^+ &= \text{H}_2\text{O}: \quad \text{X} = \text{H} (70 \%) \\
\text{E}^+ &= \text{NCS}, \text{NBS}: \quad \text{X} = \text{Cl}, \text{Br} (60 \%)
\end{align*}
\]

\[
\begin{align*}
\text{Ph} &= \equiv \\
&\xrightarrow{\text{Cp}_2\text{Zr}(\text{H})\text{Cl}} \text{THF}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} &= \equiv \\
&\xrightarrow{\text{Ar}^+\text{SO}_2\text{Cl}} \text{40 °C}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\equiv\equiv\text{R}^2 &\xrightarrow{\text{PhSH}} \text{Pd(OAc)}_2 \text{Pd(OAc)}_2 \\
&\xrightarrow{\text{oxone or } m\text{-CPBA}} \\
&\text{R}^1\equiv\equiv\text{R}^2
\end{align*}
\]

R\(^1\) = H, C\(_{10}\)H\(_{21}\), CH\(_2\)OAc
R\(^2\) = H, Me

**Figure 84: Organometallic Addition across Alkynes to Obtain Vinyl Sulfones**

One interesting method which Fuchs and coworkers exemplified is an addition-elimination protocol (Figure 85). Here, an efficient chlorosulfenylation across a double bond is followed by a dehydrochlorination reaction. This is followed by oxidation of the sulfide to the sulfone, and then dehydrohalogenation to afford the vinyl sulfone product. Another related addition-elimination example involves formation of a mercuronium ion from an alkene and subsequent regioselective opening with sulfinate. Based-induced elimination of the HgX moiety provides the vinyl sulfone.
Figure 85: Selected Examples of Addition/ Elimination Sequences for Preparation of Vinyl Sulfones

Similar addition-elimination sequences have provided vinyl sulfones (Figure 86). In the first example copper-promoted 1,4-addition of phenyl sulfonyl chloride to cyclohexadiene is followed by base-induced dehydrohalogenation to provide the requisite vinylogous vinyl sulfone.\(^{71}\) While 1,2-addition of a selenosulphone produces an adduct that provides the desired cross-conjugated dieneyl sulfone upon oxidation of the phenylseleno group with \(m\)-CPBA to form the selenoxide and promote subsequent elimination.\(^{72}\)

Figure 86: Addition and Elimination for Synthesis of Vinyl Sulfones, Part 2
A trans-vinyl distannane species is transformed into the vinyl sulfide shown, which is subsequently oxidized to vinyl sulfone. 73

![Chemical Reaction](image)

**Figure 87: Organometallic Addition across an Alkene for Synthesis of Vinyl Sulfones**

This species can engage in a radical addition-elimination protocol to yield a modified vinyl sulfone with exclusive $E$-configuration (Figure 88). This process occurs under “non-reducing” conditions without hydrogen atom abstraction to terminate the radical chain. Similarly, simple vinyl sulfones can be converted into more complex vinyl sulfones via Suzuki reaction conditions74 and olefin-cross metathesis.75
Figure 88: Preparation of Modified Vinyl Sulfones from Simple Vinyl Sulfones
Regardless of how they are prepared, the vinyl sulfone products can undergo a number of transformations. This stems from the unique properties of two structural elements of vinyl sulfone moieties—the highly acidic α-proton and the double bond activated to reactions with nucleophiles. The utility of the vinyl sulfone is further enhanced if a good leaving group is vinylogously coupled to the vinyl sulfone moiety. The sulfone functionality is also a potentially good leaving group (Figure 89).

**Figure 89: Reactivity of Vinyl Sulfone**

Due to the electron withdrawing capacity of the sulfone moiety, the α-protons are relatively acidic, and can be abstracted by an appropriate base. The α-proton(s) in sulfones has a pKa around 30, similar to that of the α-proton(s) in esters. The proton α to the vinyl sulfone is even more acidic with a pKa around 25 (Figure 90).
This property allows vinyl sulfones to be treated with a base resulting in removal of the α-proton, followed by addition of an external electrophile (Figure 91).

The acidity of the vinyl sulfone proton has been utilized to form α-sulfonyl stabilized vinyl anions that can intercept an electrophile in a subsequent coupling reaction. For example, the difference in pKa between vinyl sulfone α-proton(s) and ester α-protons has been used elegantly to furnish a cyclized dehydroquinolizidine species. First conjugate addition of a piperidine moiety to an alkynyl sulfone furnished an enamine sulfone. Then this crude material is selectively deprotonated at the α-position of its vinyl sulfone followed by interception of the tethered ester to form the cyclized product. This methodology was used toward the synthesis of the natural product lasubine II, a quinolizidine alkaloid (Figure 92). \textsuperscript{77}
The sulfone moiety imparts a strong polarization to the double bond it is attached to. The resulting partial positive character at the β-carbon allows for efficient conjugate addition to take place with a variety of nucleophiles. The resulting alkyl sulfone products can also engage in subsequent coupling reactions due to the acidity of the protons α to the sulfone moiety (Figure 93).

This strategy has been used toward construction of the polyhydroxylated indolizidine core of iminosugars such as castanospermine. Here, N-substituted γ-oxygenated α,β-unsaturated sulfones have been used as starting materials. First pyrrolidine formation is accomplished by
intramolecular conjugate addition of the nitrogen moiety to the α,β-unsaturated sulfone. This is followed by intramolecular acylation (Figure 94) of the sulfonyle carbanion.

![Chemical structure diagram]

**Figure 94: Intramolecular Acylation of Sulfone-Stabilized Carbanion**

When a good leaving group is attached at the β-carbon, a nucleophilic addition-elimination reaction (AdN-E) yielding a substitution product can take place. Adding to this impressively broad utility is the nature of the sulfone moiety, itself an excellent leaving group. If attached to an alkene, the sulfone can be eliminated to form an alkyne. On the other hand if the sulfone is attached to a saturated alkane, it can be expelled by a nucleophile to form a coupled product. Vinyl sulfones can be employed as substrates in conjugate addition reactions with various nucleophiles. Literature examples of nucleophiles which can be used in these reactions include alkoxides, azides, organocuprates, sulfides, thiolates, nitriles, and soft enolates such as the malonate anion. Shown below (Figure 95) are nucleosides which have been constructed via a conjugate addition of various amines to a vinyl sulfone-modified furanose.⁷⁹
**Figure 95: Simple Nucleophiles for Conjugate Addition to Vinyl Sulfone**

Below (Figure 96) is an example of a dienyl sulfone substrate which has undergone conjugate addition with a variety of nucleophiles.\(^8\)

**Figure 96: Simple Nucleophiles Undergoing Conjugate Addition to Vinylogous Vinyl Sulfones**
There are literature examples of addition-eliminations to β-substituted vinyl sulfones (Figure 97). These examples often constitute substitution reactions, in which a leaving group halide which is vinylogously coupled to sulfone moiety is replaced by an external nucleophile.

![Figure 97: An Addition-Elimination Sequence on β-Substituted Vinyl Sulfones](image)

Interestingly, there are also examples of nucleophiles adding in a conjugate fashion to a moiety that replace the sulfone group (Figure 98). In the example shown below, a vinyl sulfone tethered with a pyridinium moiety is transformed into the vinyl sulfide. In the second example, sodium methoxide and anion of diketone react with the dienyl bissulfone to provide the respective desymmetrized products upon work-up. In the third example, the sulfonyl-substituted vinylogous amide undergoes conjugate addition with a Grignard, a carbon-centered nucleophile, as well as a thiolate, a sulfur-centered nucleophile.
7.1 Other Vinyl Sulfone Transformations/ Removal

The utility of the sulfone moiety is further expanded by its ability to be transformed into something else once its purpose as a coupling partner has been fulfilled. The vinyl sulfone functionality can be transformed under a variety of oxidative conditions to a ketone or aldehyde (Figure 99). The following scheme shows representative examples. In the first example, dihydroxylation of an oxabicyclic vinyl sulfone produces an \( \alpha \)-hydroxy ketone. This transformation occurs via the intermediacy of a diol sulfone that subsequently eliminates a sulfinate anion.

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**Figure 98: Selected Examples of Conjugate Additions on Vinyl Sulfones**

**Figure 99: Use of Oxidative Transformations for Removal of Vinyl Sulfone Moieties**
The starting material cycloheptenyl vinyl sulfone system was constructed in an interesting manner (Figure 100).

Figure 100: Synthesis of Oxabicyclo [3.2.1] Heptane Starting Material

Similar oxidative processes were applied to the cyclic vinylsulfone species in Figure 101. The next example illustrates how epoxy sulfones prepared from the vinyl sulfone have been transformed into \( \alpha \)-bromo ketones. Direct transformation of epoxy sulfones into \( \alpha,\beta \)-unsaturated ketones has been established as illustrated in the last example.
There are a number of methods for reductive removal of the sulfone moiety following its use as a coupling partner. The following example is typical. Here a β-keto sulfone is first coupled to the alkyl halide and then sulfone moiety is eliminated under reductive metal conditions to afford enantiopure α-amino ketone (Figure 102). While these β-keto sulfone moieties were prepared from α-amino acids, note that conjugate addition to vinyl sulfone with potassium hydroxide would also produce a β-keto sulfone.

**Figure 102: Alkylative Transformations/Reductive Removal of Sulfone**

The vinyl sulfone moiety can be transformed into interesting species under a variety of other methods. For example, tin radicals generated from tributyltin hydride and azobisisobutyronitrile (AIBN) react with vinyl sulfones to afford vinyl stannanes (Figure 103).
This formal umpolung transformation is useful because the vinyl stannane can be used in a subsequent carbon-carbon bond forming reaction under Stille reaction conditions. Additionally the vinyl stannane can easily be converted into the vinyl iodide. The vinyl iodide, itself an excellent partner in organometallic transformations, could be subsequently transformed into a vinyl anion and ultimately quenched with a variety of electrophiles.

![Radical Transformations Accompanied by Vinyl Sulfone Removal](image)

**Figure 103: Radical Transformations Accompanied by Vinyl Sulfone Removal**

Nickel-catalyzed coupling of Grignard reagents with vinyl sulfones have been employed to successfully transform the vinyl sulfone moiety directly into substituted alkenes. This is illustrated well in the first example in Figure 104 below. The second, more recent example highlights the ability to couple removal of the sulfone moiety with an umpolung or polarity reversal, upon exposure to zirconacycle and conversion to vinyl zirconacene. This species intercepts various electrophiles to give a variety of products. This sequence of reactions represents the formal electrophilic substitution of sulfone residue in the vinyl moiety.
Figure 104: Organometallic Transformation of Vinyl Sulfones
Electrophilic properties of the vinyl sulfone unit were recently demonstrated to be useful in design of biologically active molecules. For example, vinyl sulfones serve as biological warheads in cysteine protease inhibitors. Cysteine proteases are a class of proteolytic enzymes that are therapeutic targets against such diseases as malaria and central nervous system diseases. To date, three structural classes of cysteine proteases are known. These include the ICE (interleukin-1β-converting enzyme) class, the papain class (e.g., cathepsins), and the picornovirus 3C-protease class.

Falcipain-2 (FP-2) is a papain-family cysteine protease that is crucial for the life cycle of the parasites that cause malaria. Recently a group developed a peptidomimetic inhibitor of Falcipain-2 (Figure 105) which consists of a 1,4-diazepine scaffold that serves as a β-turn mimic and a vinyl sulfone warhead that acts to irreversibly conjugate a cysteine residue of the active site of the cysteine protease. The vinyl sulfone moiety was introduced via an olefin cross metathesis.

![Figure 105: A Peptidomimetic with Vinyl Sulfone Warhead for Malaria Therapy](image)
Vinyl sulfones are known to act as irreversible inhibitors of cysteine proteases by serving as Michael acceptors to the thiol group of cysteine residues. The authors postulated that the active site of the target enzyme contains suitably positioned amino acid residues which can participate in hydrogen bonding with the sulfone oxygen (His-159 and Asp-175) in order to enhance the sulfones electrophilicity. This activation promotes the conjugate addition of the thiol moiety of a cysteine residue (Figure 106). After conjugate addition the resulting stabilized carbanion abstracts a proton from the protonated histidine residue in the active site catalytic pocket. This sequence of steps provides the irreversible covalent bond between inhibitor and Falcipain-2.

Figure 106: Postulated Hydrogen Bonding Interactions of Vinyl Sulfone Warhead

Vinyl sulfones have also been incorporated into chemical compounds used in proteomics research. These compounds, known as affinity based probes, are chemical tools used for study of protein expression and function that have come to compliment other common technologies such as gel electrophoresis and protein microarray analysis. Affinity based probes allow for the activity-based profiling of enzymes, and consist of a warhead which becomes covalently attached to the protein, a linker, and a reporter consisting of a fluorescent tag or affinity tag (such as biotin). Affinity based probes that incorporate vinyl sulfones as the warhead have been recently designed to selectively modify cysteine proteases. An example of such a chemical probe is shown in Figure 107.
Figure 107: Affinity Based Probe with Vinyl Sulfone Warhead
CHAPTER 9

METHODOLOGIES INCORPORATING THE VINYL SULFONE MOIETY

Vinyl sulfones have been widely incorporated into emerging methodologies, with seminal contributions in this area provided by the research groups of Fuchs and Padwa. These moieties are useful because they are thermally stable yet also have diverse reactivity. Importantly, once the sulfone has served its purpose, it can be removed either through base-induced elimination or under reductive metal conditions.

Fuchs has incorporated vinylsulfones in methodologies for elaboration of carbocycles. Here, double Lawton $S_N2'$ addition onto epoxy vinylsulfones was performed to provide a stereodefined polypropionate moiety of Aplyronine A (Figure 108).  

![Figure 108: Vinyl Sulfone Methodology: Double Lawton $S_N2'$ Addition](image)

1. O$_3$
2. MeOH
3. (CH$_3$)$_2$S

Figure 108: Vinyl Sulfone Methodology: Double Lawton $S_N2'$ Addition
In addition to Michael addition reactions and coupling reactions of sulfonyl-stabilized carbanions, vinyl sulfones are well regarded as excellent dienophiles in Diels-Alder reactions. This is due in part to the higher reactivity of sulfones compared to other electron withdrawing groups. Sulfonyl-substituted dienophiles offer many other benefits. For example, sulfonyl substituents of the products are easily removed under mild conditions.\(^\text{96}\) Because of this, these dienophiles can formally achieve regiochemical reversal in Diels-Alder reactions, rebelling against customary stereoelectronic considerations. Furthermore, the crystallinity imparted to molecules containing the phenylsulfonyl unit facilitates subsequent isolation and characterization.\(^\text{99}\)

Shown below in Figure 109 is a simple intramolecular Diels-Alder reaction between diene and tethered vinyl sulfone to furnish a functionalized bicyclic product.

![Intramolecular Diels-Alder Reaction](image)

**Figure 109: Typical Sulfonyl-Substituted Dienophile in Diels-Alder Reaction**

While vinyl sulfones are excellent dienophiles in normal-electron-demand Diels-Alder reactions, 1,3-dienyl sulfones serve as good dienes in inverse-electron-demand Diels-Alder reactions. The first\(^\text{100}\) and second example\(^\text{101}\) is representative (Figure 110).
2,3-Dienyl sulfones are also useful dienes for inverse-demand Diels-Alder reactions. Figure 111 shows an interesting method for the preparation of 2,3-dienyl sulfones. Here, 2-butyne-1,4-diol reacts with phenyl sulfenyl chloride to form intermediate disulfenate ester. This species rapidly undergoes two consecutive propargylic [2,3]-sigmatropic rearrangements to produce the disulfoxide (Figure 111). In the subsequent step, hydrogen peroxide oxidation of the disulfoxide produces the requisite [2,3]-bis(phenylsulfonyl)-1,3-butadiene. 102
As shown (Figure 112), 2,3-dienyl sulfone reacts with an electron rich enamine to produce an octahydropentaphene.\textsuperscript{103,104} The $\alpha$-keto sulfone interacts with isobutyl vinyl ether to yield a dihydro pyran through an inverse-electron-demand Hetero Diels-Alder reaction (Figure 113).\textsuperscript{105}

![Figure 112: Inverse-Demand Diels-Alder Reaction with 2,3-Bis(Phenylsulfonyl)-1,3-Butadiene](image1)

Vinyl sulfones can also undergo [3 +2] dipolar cycloadditions as shown in Scheme 114. In this example the reaction between azomethine and vinyl sulfone forms the pyrrole compound.\textsuperscript{106}
Scheme 114: [2 +3] Cycloaddition with Vinyl Sulfone as the Dienophile

Construction of trans-4,7,7-tricarbomethoxy-2-phenylsulfonylbicyclo[3.3.0]oct-1-ene occurs in an interesting double conjugate addition/elimination sequence employing 2,3-bis(phenylsulfonyl)-1,3-butadiene and the anion derived from dimethyl (E)-5-methoxycarbonyl-2-hexene-dioate (Figure 115).\textsuperscript{107}

Figure 115: Construction of Bicyclo[3.3.0]oct-1-ene via Double Conjugate Addition/Elimination
A very interesting methodology incorporating vinyl sulfones was recently reported by the Prunet group. Here (Figure 116) vinyl sulfone is produced through a dehydrohalogenation following tosyl iodide addition across the terminal alkene of homo allylic alcohol. Subsequent base-catalyzed acetal formation followed by intramolecular conjugated addition affords a syn-1,3-diol motif. The benzylidene protecting group is reduced regioselectively to furnish β-hydroxysulfone. Subsequent alkylation employing Julia coupling, followed by reductive removal of the sulfone moiety affords a stereotriad with modest diastereoselectivity.\(^{108}\)

Figure 116: Intramolecular Conjugate Addition to Vinyl Sulfone/ Aldol Coupling Reaction
CHAPTER 10

VINYL SULFONE METHODOLOGY USED TOWARDS NATURAL PRODUCT SYNTHESES

High and diverse reactivity of vinyl sulfones along with their synthetic accessibility has led to numerous applications of this functional group in a multitude of natural product syntheses. Outlined below (Figure 117) are a few interesting examples. Recently the iminosugar swainsonine was synthesized by incorporating vinyl sulfone methodology. Following cross-metathesis, the resulting functionalized vinyl sulfone is transformed under asymmetric dihydroxylation conditions to afford a chiral $\alpha$-hydroxy aldehyde. This species subsequently undergoes a boron-Mannich reaction to produce an anti-1,2-amino alcohol in high enantioselectivity. This important chiral building block was then transformed into an advanced intermediate, representing a short formal total synthesis of (-) swainsonine.$^{109}$

Figure 117: Vinyl Sulfone Methodology Employed towards the Natural Product Swainsonine
The Fuchs group used cyclopentene sulfone in an important three component coupling protocol (Figure 118). Conjugate addition of the lithiated piperonal derivative to the cyclopentene sulfone forms a stabilized carbanion which is subsequently trapped with azido iodide. It was envisioned that the resulting species could be transformed into the desired 11-hydroxycephalotaxine by a spirocyclization method. Although attempts with this route to form the target compound did not reach fruition, the advanced intermediate shown below displays the power of incorporating vinyl sulfones into a multi-component coupling strategy. A similar one-pot multi-component coupling strategy en route towards total synthesis of the *Cephalotaxus* Alkaloid cephalotaxinone was successful.\textsuperscript{110}

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**Figure 118: Vinyl Sulfone Methodology Employed towards 11–Hydroxycephalotaxine**

Another interesting protocol that incorporates vinyl sulfone methodology for the synthesis of a natural product is outlined below. Here an L-alanine derived compound is coupled with $\beta$-keto-sulfone A to form the dihydropiperidine species (Figure 119). This is transformed into the tri-substituted piperidine aldehyde which is then homologated to the vinyl sulfone under Horner-Wadsworth-Emmons conditions. A stereoselective conjugate addition of free amine onto the vinyl sulfone provides the quinolizidine core of the natural product. A subsequent Julia-type olefination followed by protecting group removal provides the final product clavepictine A which has interesting anti-cancer activity.\textsuperscript{111} This synthetic sequence illustrates how vinyl sulfones can
be used as a linchpin which connects to two reactive species of opposite polarity (an electrophile and nucleophile).

Figure 119: Vinyl Sulfone Methodology Employed towards Clavepictines A and B and Pictamine

Evidence for vinyl sulfone utility has been provided by examples in which these moieties have been used towards construction of a variety of chemical building blocks (e.g. Diels-Alder reactions) and examples where the vinyl sulfone entity is used to couple building blocks (e.g. Fuchs three-component coupling protocol). The versatility of vinyl sulfones is enhanced by the ability to transform them into other entities or to remove them altogether in a chemoselective fashion. Giving credibility to the value of vinyl sulfones as chemical building blocks is the number of literature examples toward construction of natural products and drug-like compounds, a few of which having just been described.
Our initial investigations lead us to consider modifications to the vinylogous bromide portion of our vinyl sulfone cyclopentene species. One can argue that vinyl bromides represent one of the most important building blocks in organic chemistry as they can be transformed into a variety of moieties. For example, one can rely upon organometallic transformations to convert a vinyl halide into a carbon-carbon bond under Sonogashira, Negeishi, Suzuki, and Stille reaction conditions. Because the vinyl bromide of our substrate is conjugated to a strong acceptor sulfone moiety, we postulated it could become engaged in a conjugate addition with an appropriate nucleophile followed by sequential expulsion of bromide anion.
We have a multifunctional moiety with several electrophilic centers (Figure 120). In order to fully uncover the synthetic potential of this group, it is important to probe selectivity of its reactions with simple model N, O, S, and C-centered nucleophiles.

Figure 120: Multifunctional Reactivity of Cyclopentene Bromosulfone

We initially investigated reactions involving an addition-elimination sequence between cyclopentene bromo sulfones and various simple nucleophiles in order to gain access to enol and thiol ethers, enamines, among other functionality. The literature is replete with reactions of “soft” nucleophiles such as thiols, amines, and nitriles participating in conjugate addition reactions, but often in a protic environment where the incipient carbanion can be quickly quenched. This of course eliminates the possibility of further elaboration in a cascade fashion with other electrophiles.

Nucleophilic substitution of vinylic halogen in conjugated π-electron systems have been the subject of numerous investigations. Activated vinyl halides such as vinylogous acyl and
sulfonyl vinyl halides are much more reactive toward nucleophilic substitution. These species engage in nucleophilic substitution by a $\pi$-route where the nucleophile approaches perpendicular to the plane of the C-C double bond, and the mechanism portrays some features similar to nucleophilic aromatic substitution. Significant evidence indicates this addition-elimination mechanism, termed (Ad$_n$-E), occurs through a multi-step addition-elimination process, particularly with activated vinyl halides.$^{113}$ As seen in (Figure 121), first (in the addition part of the mechanism) the nucleophile attacks the terminal carbon of the $\pi$ system, perpendicular to the molecular plane. This step gives rise to a zwitterionic intermediate with a terminal carbon that has gone from sp$^2$ to sp$^3$ hybridization. After a proton transfer, a subsequent elimination occurs, involving carbanion migration back to reform a $\pi$ bond while concomitantly excising the leaving group.

![Figure 121: Generic Addition-Elimination Mechanism (Ad$_n$-E)](image)

The regioselectivity of nucleophilic addition to our cyclopentene bromosulfone substrate can be understood by inspection of its frontier molecular orbitals. Frontier Molecular Orbital Theory explains reaction control through orbital interactions, in which HOMO-LUMO interactions between the highest occupied molecular orbital (HOMO) of nucleophile (reagent in our case) and lowest unoccupied molecular orbital (LUMO) of electrophile (substrate in our case) dictate regioselectivity. Many of the nucleophiles in our studies include amines and thiols as well as thiolates which behave as soft nucleophiles and seek out soft-soft interactions with an appropriate vacant orbital of the electrophile (coulombic or electrostatic forces have a negligible
effect and can be largely ignored). Using a Simple Huckel Molecular Orbital theory calculator\textsuperscript{114} we see that the conjugated part of the cyclopentene bromosulfone substrate has a larger coefficient at the $\beta$ and $\delta$ carbons for the LUMO, with the $\delta$ carbon having the largest coefficient (Figure 122). This is in agreement with other group’s theoretical work.\textsuperscript{115}

![Figure 122: LUMO of Cyclopentene Bromosulfone using SHMO](image)

Figure 122: LUMO of Cyclopentene Bromosulfone using SHMO

Figure 123 shows a ball and stick representation of our acetonide protected cyclopentene bromosulfone product in its lowest energy conformation depicted on the left along with its lowest unoccupied molecular orbital (LUMO) depicted on the right. The LUMO energy level was calculated at the B3LYP/6-31G** (d, p) level. As one can see, the LUMO is delocalized in the diene system.

![Figure 123: Ball and Stick Representation of Bromosulfone Product (left drawing) and its LUMO (right drawing)](image)
CHAPTER 12

DISCUSSION OF PROPERTIES OF OUR CYCLOPENTENE BROMOSULFONE PRODUCTS

Figure 124 outlines a depiction of the variety of products which have been successfully produced from our protected bromosulfone cyclopentene substrate.

Figure 124: Summary of Successful Reactions of Bromosulfone Cyclopentenes
We were pleased at the variety of substrates which could engage in functionalization of our starting material. This list includes not only such reactive nucleophiles as primary and secondary amines, alkoxides, and sulfides but also delocalized anions as sulfinates. Boronic acids, alkynes, and heterocycles were good substrates for metal-catalyzed Suzuki, Sonogashira, and Ullmann coupling reactions.

The success for these aforementioned addition-elimination (AdN-E) reactions depended in part on the leaving group ability of our substrate. The leaving group is the functional group that is eliminated with electrons of the σ bond. The nature of the leaving group is important in substitution reactions: the better the leaving group the faster the reaction. The relative leaving group ability is influenced by strength of the R-Y bond, polarizability of the R-Y bond, stability of Y-, and the degree of stabilization through solvation of Y-. In general good leaving groups are large, of moderate electronegativity, and low nucleophilicity. A good leaving group should have a very weak and polarizable R-Y bond, in which its strength can often be related to pKa values of the conjugate acid of Y-. A low pKa often makes for a weak R-Y bond.

We reasoned that amines would be well matched nucleophiles to our substrate. The pKa of the conjugate acid of the bromide anion, HBr, is around -7, while the pKa of the conjugate acid of an amine, R₂NH⁺, is around 11. In addition, C-Br bond is more polarizable than that of C-NR₂ bond. Therefore, because it has both a weaker and more polarizable bond, bromide should be readily expelled from the substrate during the elimination part of the addition-elimination reaction.

Reactions can be carried out in neat amines which served the dual role as both nucleophile and as a polar protic solvent. Since the substrate and nucleophile are both neutral but the initial product is charged, the polar protic solvent should enhance the reaction rate by solvating and separating the developing charge in the transition state through hydrogen bonding interactions. Additionally, the amine species should act as a base to deprotonate the initially charged amine product.

We were happy that these predictions culminated in experimental success. Refluxing the acetonide protected cyclopentene vinyl sulfone in neat N-butylamine provided the N-butylamine substitution product. Secondary amines such as piperidine and diethyl amine were also
effective as nucleophiles (Figure 125). Interestingly, the use of piperidine as a nucleophile provides a product which is a Stork enamine. 116 In this regard, the enamine product could be quite useful in subsequent transformations with electrophiles. For example, the Stork-Enamine reaction involves the addition of an enamine to an $\alpha$, $\beta$-unsaturated carbonyl compound in a process similar to the Michael reaction. The initial iminium product is subsequently hydrolyzed by aqueous acid during the work-up to afford a 1,5-dicarbonyl compound.

Figure 125: Ad$_n$-E Reaction with Amine Nucleophiles

Using neat amines at 0.1 M concentration of the starting material gave an overall ratio of amine:substrate of 1000:1. We were interested in reducing this ratio to 5 or 10 equivalents. Initial reaction attempts with acetonitrile and tetrahydrofuran were unsuccessful, possibly due in part to the inability of these solvents to form adequate hydrogen bonds with the developing charge in the transition state of the reaction. Additionally tetrahydrofuran has a relatively low dielectric constant and its reflux temperature of 65 °C is below the threshold for successful reaction conversions. Success was finally achieved upon switching to $t$-butanol as solvent and reacting with 4 equivalents of amine. The physical properties of $t$-butanol are amenable to the reaction, because it is nonnucleophilic and has polar protic character and a reflux temperature of 82.4 °C.

As the result of an Ad$_n$-E reaction, the diagnostic vinyl protons of the starting material $E$-5d cyclopentene bromosulfone shift upon conversion to product. Below is shown a portion of the $^1$H NMR of starting material $E$-5d with vinyl proton chemical shifts of $\delta$ 6.17 ppm and $\delta$ 7.62 ppm (Figure 126 below).
In the \( n \)-butyl amine product these vinyl peaks have shifted to \( \delta \) 5.64 ppm and \( \delta \) 5.89 ppm (Figure 127). All of the substitution products resulting from addition-elimination exhibit this type of diagnostic chemical shift of vinyl peaks. For substituents that are good \( \pi \)-donors, the vinyl peaks shift in an upfield fashion due to a characteristic shielding phenomenon.
Thiolates and sulfinates reacted with the vinyl bromide moiety to produce vinyl sulfides and sulfoxones, respectively (Figure 128). Notwithstanding the steric hindrance, thiolates derived from 2-mercaptobenzoxazole (SBox) and isobutyl mercaptan provided the desired product.

Despite low reactivity of the delocalized anion, addition of the sodium salt of toluene sulfinic acid gave an interesting product with differentiated endo and exo vinyl sulfoxones.\(^{117}\)

![Figure 128: Ad\(_N\)-E Reactions with Sulfur-Centered Nucleophiles](image)

Sulfonyl-substituted 1,3-dienes have found broad utility in organic synthesis, and have garnered attention as useful dienes in inverse-electron-demand Diels-Alder reactions and 1,3-dipolar cycloadditions.\(^{53}\) For example, Padwa and coworkers demonstrated the use of 1,3- and 2,3-bis(phenylsulfonyl)-1,3-butadienes as versatile building blocks in Diels-Alder and dipolar cycloaddition reactions as described before.

On the other hand, the utility of 1,4-bis(sulfonyl)-1,3-butadienes is less understood because of a scarcity of synthetic preparations. Deprotection of the acetonide of our substrate followed by oxidative cleavage of the vicinal diol could afford 1,4-bis(sulfonyl)-1,3-butadienes.

As shown in Figure 129 oxygen species were also effective nucleophiles.
Sodium hydroxide addition to vinyl bromide produced keto species, while alkoxides added to produce enol ethers. In addition to delivering the desired isopropoxide product, sodium isopropoxide addition to cyclopentene bromosulfone also produced the keto species, as confirmed by $^1$H NMR. This product may have resulted from excess sodium isopropoxide in the reaction leading to a double conjugate addition-elimination sequence to yield diacetal. This species could have been subsequently attacked by sodium isopropoxide to deliver the keto product and diisopropyl ether (Figure 130). It is also possible that the keto product resulted from hydrolysis of a diisopropoxide compound during aqueous work-up.
The enol ether derived from allyl alcohol engaged in a subsequent tandem Claisen/ Cope rearrangement sequence, which will be discussed shortly.\textsuperscript{118}

Carbon-centered nucleophiles were less efficient but entry into carbon-carbon bonds materialized through a variety of organometallic reactions including some success with Suzuki, Sonogashira, Heck, and Ullmann reactions. Finally, the vinyl bromide moiety could be modified to a stannane, effectively reversing its reactivity in an umpolung fashion. The utility of this species will be discussed shortly in one of the following sections.

![Figure 131: Organometallic Reactions with Cyclopentene Bromosulfone Starting Material](image)

Below in Figure 132 is the key part of a \textsuperscript{1}H NMR Spectrum of product resulting from Sonogashira reaction between starting material cyclopentene bromosulfone and ethynyl anisole. Here the vinyl protons appear at $\delta$ 6.18 ppm and $\delta$ 7.55 ppm.
The efficient formation of the carbon-nitrogen bond by the palladium-catalyzed coupling of aryl halides with amines was independently discovered by Buchwald and Hartwig. This amination procedure has become a very useful synthetic tool for organic chemists, and superseded the copper-mediated Ullmann condensation which operates under harsher conditions. Recently, however, advances in the Ullmann condensation have resulted in efficient reactions under milder conditions that have opened up new opportunities toward routine use of this methodology.

Among the important modifications to the classical Ullmann condensation is the use of ligands to provide an accelerating effect on the reaction rate. Amino acids serve as the best activators. Reactions that routinely required heating to 150 °C require heating only to 95 °C to undergo completion in the presence of amino acid ligands. Typically only 2-20 mol % copper catalyst loading is required (see Figure 133 below). The structural features of the amino acids contribute to the accelerating effect by acting as a bidentate chelating ligand to copper (I) species through the carboxyl and amino groups. It is postulated that these chelates might play a key role in the catalytic cycle. The best coordinating amino acid ligands are L-proline or N,N-
dimethylglycine. These conveniently available and inexpensive catalysts also tolerate many functional groups, and do not couple readily to substrates.

![Chemical Reaction](image)

**Figure 133: Rate Acceleration of Ullmann Coupling by Chelation Effects of Amino Acid Ligand**

The amino acid ligand accelerates the Ullmann reaction most likely during the oxidative addition step. In this regard, the ligand chelates with Cu (I) to make a more reactive Cu (I) species. Other possibilities include ligand-induced stabilization of the oxidative addition intermediates, which in turn promotes the coupling reaction.

On the basis of this new success with Ullmann reactions between various heterocycles and amino acids, a plausible catalytic cycle for the present reaction is shown in Figure 134.
First, cuprous ion reacts with an amino acid salt to form the chelate A, which coordinates with a suitable aryl halide to provide complex B. Next, intramolecular nucleophilic substitution occurs at the aromatic ring to give the transition state complex C. This step might be the rate-determining step, and the intramolecular attack would lower the activation energy of this step. This hypothesis could be used to explain the accelerating effect induced by the structure of the amino acid. Finally, HX is removed from C with the assistance of potassium carbonate to deliver complex D, which could decompose to produce the coupling product and regenerate the cuprous ion.

Imidazoles are important functional groups found in a variety of medicinal compounds. Before the advent of the modified Ullmann conditions, the Lam-Chan reaction was the method of choice for producing medicinal compounds with imidazole moieties. The Lam-Chan reaction is a Cu-catalyzed cross-coupling between imidazoles and aryl boronic acids that requires much lower temperatures than traditional Ullmann conditions.120
The new Ullmann reaction conditions complement the Lam-Chan conditions, using vinyl halides in lieu of boronic acids. Subjecting our cyclopentene bromosulfone substrate to the modified Ullmann conditions afforded the imiazole-substituted product efficiently as seen in Figure 135.

![Ullmann Coupling Applied to Cyclopentene Bromosulfone](image)

**Figure 135: Ullmann Coupling Applied to Cyclopentene Bromosulfone**

Interestingly, in the Ullmann coupling product (Figure 136) the imidazole protons are all singlets. This is consistent with the literature data.\(^{121}\)

![Portion of \(^1\)H NMR Spectrum of Ullmann Coupling Product](image)

**Figure 136: Portion of \(^1\)H NMR Spectrum of Ullmann Coupling Product**
The Claisen and Cope rearrangements are concerted [3, 3] sigmatropic pericyclic reactions (Figure 137).\textsuperscript{122} They have developed into powerful synthetic methodologies in synthetic organic chemistry. The Claisen rearrangement makes use of an allyl vinyl ether that rearranges to a $\gamma,\delta$-unsaturated carbonyl compound while the Cope rearrangement employs a 1,5-hexadiene that rearranges to another 1,5-hexadiene.

The two reactions have been employed successfully in a tandem fashion, with seminal work from the Thomas and Cookson groups. The tandem Claisen-Cope rearrangement can be successfully executed, because the often lower activation energy, irreversible Claisen rearrangement generates a species which permits a subsequent Cope rearrangement to proceed.\textsuperscript{123} The thermodynamic balance of the reversible Cope rearrangement is tipped towards the formation of more highly substituted olefins in the equilibrium mixture. Interestingly, because the lower activation energy Claisen rearrangement precedes the higher activation energy Cope rearrangement, an opportunity is created for the isolation of intermediates.

An example of a tandem Claisen-Cope rearrangement is shown below in Figure 138. When the ortho-position of a benzene ring is substituted, rearomatization cannot take place after the initial
Claisen rearrangement. The allyl group must undergo a subsequent Cope Rearrangement to the para-position before rearomatization can occur.

Figure 138: Example of Tandem Claisen-Cope Rearrangement

Our initial allyl vinyl ether was prepared from starting material and allyl alkoxide prepared in situ and the reaction was run in allyl alcohol under refluxing conditions (Figure 139). The allyl vinyl ether product could be isolated after a few hours or the reaction mixture could be refluxed for an additional 24-48 hours. An isolatable Claisen rearrangement product (2-1 and 2-2) is produced which eventually is converted into a Cope product (3-1 and 3-2) followed by endocyclic double bond isomerization. Isolation of the purified allyl vinyl ether product provided more efficient entry to the tandem Claisen/ Cope rearranged product.

Figure 139: Proposed Tandem Claisen-Cope Rearrangement for Our System
Below (Figure 140) is the original allyl vinyl ether product (taken in deuterated benzene: C₆D₆). Notice the vinyl peaks at δ 6.70 ppm and 6.20 ppm. Notice the aromatic doublet at δ 7.94 (A). Also, notice the multiplet at δ 5.52 ppm (B), the doublet at δ 5.10 ppm, and the doublet at δ 4.94 ppm (both collectively called C).

Figure 140: ¹H NMR Spectrum of Allyl Vinyl Ether Product (in C₆D₆)
After refluxing in deutrated benzene for seven hours the reaction progress is shown below (Figure 141). Notice emerging peaks at δ 7.64 ppm (A'), 6.70 ppm, 5.83 ppm (B'), 5.20 ppm, (C'). Also notice that A, B, and C are disappearing.

Figure 141: Reaction Progress (as Determined by ¹H NMR) of Allyl Vinyl Ether Rearrangement after Seven Hours

In the spectrum below (Figure 142) we see continued reaction progress after an additional fourteen hours. Notice that peaks at A', B' and C' are much higher in intensity (new product) while peaks at A, B, and C are now significantly lower in intensity. The starting material allyl vinyl alcohol is almost gone.
Figure 142: Reaction Progress (as Determined by $^1$H NMR) of Allyl Vinyl Ether Rearrangement after Twenty One Hours

Below in Figure 143 is the $^1$H NMR of allyl vinyl ether starting material taken in CDCl$_3$. Notice the diagnostic vinyl peaks at δ 6.38 ppm and δ 5.95 ppm which partially overlays the terminal alkene proton peaks which reside at δ 5.95 ppm to about δ 5.30 ppm.
In contrast, the purified product resulting from tandem Claisen/ Cope rearrangement followed by endocyclic double bond isomerization only displays vinyl protons from the terminal alkene (Figure 144).
The $^1$H NMR spectrum (Figure 144) shows protons correlating to one terminal vinyl group. The diagnostic vinyl proton(s) of the cyclopentene moiety have disappeared, indicating that the initial Cope/Claisen rearrangement is followed by a double bond isomerization of the endocyclic alkene to provide. This conclusion is further enhanced by appearance of the two doublets peaks at $\delta$ 4.3 ppm and $\delta$ 4.2 ppm which correspond to the geminal allylic protons $\alpha$ to the carbonyl functional group.

The COSY spectrum (Figure 145) shows that the other allylic protons (ca. $\delta$ 3.2 ppm) are coupled to the internal proton of the terminal alkene (ca. $\delta$ 5.75 ppm).
Additionally our acetonide-protected cyclopentene products display a chemical shift of ca. δ 150-160 ppm for the β-carbon of the exocyclic vinyl sulfone moiety. In the carbon spectrum (Figure 146) there is a peak at δ 155.97 ppm which is in the chemical shift range for this β-carbon. The peak at δ 155.97 ppm does not show up in the DEPT spectrum (Figure 147). This indicates that it is not connected to any protons. In the same regard, the α-carbon of vinylsulfone moiety with a chemical shift of δ 137.49 ppm along with ipso carbons of the tosyl group at δ 145.48 ppm and 142.53 ppm and the carbonyl carbon at δ 202.58 ppm also do not appear in the DEPT spectra.
Figure 146: $^{13}$C Spectrum of Product Resulting from a Tandem Claisen/Cope Rearrangement Followed by Endocyclic Double Bond Isomerization
The $^1$H NMR of the tandem Claisen/ Cope rearranged product has some similarities to the ketone product resulting from sodium hydroxide addition to cyclopentene bromosulfone (Figure 148). In particular, both spectra have two doublets at around $\delta$ 4.3 ppm and $\delta$ 4.2 ppm corresponding to the allylic protons $\alpha$ to carbonyl.
13.1 Computations for Predicting the Product of Allyl Vinyl Ether Rearrangement Under Thermal Conditions

Below are computations computed at the B3LYP/6-31G* level for the possible products starting with allyl vinyl ether starting material (Table 6). Note that the Cope products (sigmatropic 3-1 and sigmatropic 3-2) have the most favorable reaction energies. These diastereomeric product structures are indicated in Figure 139. These calculations fit well with our experimental results.
Table 6: Reaction Energies for Claisen (Sigmatropic 2-1 and 2-2) and Subsequent Cope (Sigmatropic 3-1 and 3-2) Computed at the 6-31 G* Level

<table>
<thead>
<tr>
<th>Compound</th>
<th>HF (hartrees)</th>
<th>ΔE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl Ether 1</td>
<td>-1590.084638</td>
<td>0</td>
</tr>
<tr>
<td>Sigmatropic 2-1 (Claisen)</td>
<td>-1590.093651</td>
<td>-5.65566</td>
</tr>
<tr>
<td>Sigmatropic 2-2 (Claisen)</td>
<td>-1590.094984</td>
<td>-6.49168</td>
</tr>
<tr>
<td>Sigmatropic 3-1 (Cope)</td>
<td>-1590.101776</td>
<td>-10.754</td>
</tr>
<tr>
<td>Sigmatropic 3-2 (Cope)</td>
<td>-1590.107107</td>
<td>-14.0994</td>
</tr>
</tbody>
</table>

13.2 Attempts at Thermal Rearrangement of Allyl Amine Product

Below are \(^1\)H NMR spectra of the allyl amine product starting material taken in CDCl\(_3\) (Figure 149) and C\(_6\)D\(_6\) (Figure 150).

Figure 149: \(^1\)H NMR Spectrum of of Allyl Enamine in CDCl\(_3\)
Figure 150: $^1$H NMR Spectrum of of Allyl Enamine in C$_6$D$_6$

The rearrangement of this allylamine product was monitored by $^1$H NMR, however after refluxing in deuterated benzene for several days, no significant reaction had taken place, as depicted in the partial spectrum below (Figure 151).
13.3 Other Successful Reactions with Carbon-Centered Nucleophiles

Simple carbon nucleophiles such as sodium cyanide and methyl magnesium bromide were effective in providing modest yields of products (Figure 152).
An unusual reaction occurred when our cyclopentene bromosulfone interacted with allyltributyltin under Stille conditions (Figure 153). Here, instead of the desired allyl moiety two other products were formed, an \(n\)-butyl adduct and another product which we tentatively assign as a homoallyl product as shown in Figure 153 below. The reaction was repeated under similar conditions and gave the same results of a roughly 1:1 ratio of \(n\)-butyl and homoallyl adduct.

**Figure 153: Interesting Stille Reaction Leading to Unexpected Products**
The $n$-butyl product is an unusual one, because the rate of ligand transfer (transmetallation) from tin is as follows: alkynyl > alkenyl > aryl > allyl = benzyl > α-alkoxyalkyl > alkyl. For the $n$-butyl product (Figure 154), the $^1$H NMR spectrum reveals vinylic protons with a chemical shift of δ 7.05 ppm and δ 6.08 ppm while the toluene methyl singlet is at δ 2.42 ppm. Additionally, note the allylic resonance at δ 2.30 as part of the $n$-butyl group.

![Figure 154: $^1$H NMR Spectrum of $n$-Butyl Product](image)

The $^1$H NMR below indicates the possibility of a homoallyl product (Figure 155). This is even more unusual than formation of the $n$-butyl product. Note the diagnostic terminal vinyl peaks at δ 9.70, 7.24, and 6.83 along with cyclopentene bromosulfone vinyl protons at δ 7.68 and 6.33.
Formation of vinyl stannane was achieved with our cyclopentene bromosulfone (Figure 156) under standard stannylation conditions. A methyl-substituted byproduct was also formed during the stannylation, via methyl transfer from tin. The $^1$H NMR of this product is the same as the product resulting from methyl magnesium bromide addition-elimination to cyclopentene bromosulfone.

Figure 156: Stannylation of Cyclopentene Bromosulfone
The $^1$H NMR of the stannylated product reveals the diagnostic vinyl protons at $\delta$ 7.42 ppm and $\delta$ 6.05 ppm as shown below (Figure 157). The stannane methyl resonance appears at $\delta$ 0.31 ppm.

Figure 157: $^1$H NMR Spectrum of Stannane Product
As noted in the literature review, there are several methods for removing the toluenesulfonyl (Ts) group after it has served its common role as a directing and activating moiety. Removal of the Ts group of our substrate under standard conditions\textsuperscript{125} was marginally successful (Figure 158). Work-up of the reaction with dilute HCl was difficult because the magnesium turnings had formed a stiff emulsion. This reaction was repeated giving similar results. A future repeat of this reaction should be performed on a larger scale (both reactions were performed on a 15 mg scale of starting material).

As seen in the \textsuperscript{1}H NMR spectrum below (Figure 159), the toluenesulfonyl group has been completely removed, and the vinyl protons appear at $\delta$ 6.40 and 5.13 ppm.

\textbf{Figure 158: Desulfonylation of Cyclopentene Bromosulfone (E)-5d}
Figure 159: $^1$H NMR Spectrum of Possible Desulfonylation Product
CHAPTER 16

COMPOUNDS WITH THE BEST UTILITY

The most interesting transformations of the cyclopentene bromosulfone are shown in Figure 160. These products have incorporated versatile functional handles which can be transformed into a variety of analogs in a rapid manner.

Figure 160: Cyclopentene Bromosulfone Analogs with Potential High Utility

For example, the nitrile species could serve as a dipolarophile and undergo a [2 + 3] dipolar cycloaddition with a variety of azides serving as 1,3-dipoles to provide tetrazoles (Figure 161). The tetrazole moiety is considered a biological isostere of carboxylic acids. This type of

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126 The tetrazole moiety is considered a biological isostere of carboxylic acids. 127 This type of
dipolar cycloaddition toward tetrazoles has been widely incorporated in a combinatorial setting in drug discovery. In fact an increasing number of drugs contain tetrazole rings because they are more metabolically stable than the carboxylic acid group. This [2 + 3] dipolar cycloaddition has found prominence in cutting-edge biology where it is considered a “green” aqueous reaction. Here, this reaction serves as a “click” ligation route toward biological probes such as in profiling of proteases. It has also been applied for the preparation of nanomaterials such as dendrimers. Recent applications of “click” ligation include construction of peptidomimetics and in bioconjugations.128

The nitrile can also be converted into an amide or primary amine species, both of which could then become incorporated into various analogs. Both the amide and primary amine, for example, could be coupled to a side chain through a peptide bond.

Figure 161: Cyclopentene Bromosulfone Analogs with High Utility: Nitrile Group
Likewise, the acetylene unit could be converted into a triazole via a [2 + 3] dipolar cycloaddition between an azide and alkyne (Figure 162). This reaction is even more expeditious than the complementary dipolar cycloaddition between azide and nitrile which forms tetrazole, due to the larger reaction energy of stabilization for formation of the triazole. This property makes this particular cycoaddition reaction the most suitable for performing “click” reactions. 129

Interestingly, we were able to convert the bromine functionality into a stannane, and essentially provide an umpolung effect for this functional group’s reactivity. The stannane is an extremely versatile handle that can couple with a variety of vinyl halides and triflates under Stille conditions to provide the much desired carbon-carbon bond in a robust manner (Figure 163, first reaction scheme).130 This type of reaction is also widely incorporated as part of the medicinal chemist’s toolset in drug discovery.

Finally, the transformation of the vinyl bromide into the ketone functionality opens the pipeline for formation of a versatile group of analogs via Aldol type coupling (Figure 163, second reaction scheme). This reaction is one of the most important carbon-carbon bond forming reactions that has been discovered in organic chemistry, and chemists have developed many methods for controlling the stereoselectivity for this bond forming event.131

Figure 162: Cyclopentene Bromosulfone Analogs with High Utility: Alkyne Group
Figure 163: Cyclopentene Bromosulfone Analogs with High Utility: Umpolung Reactivity
A summary of the successful substitution results are outlined in Table 7 below. Notice some of the trends in chemical shift of the vinyl peaks in comparison with starting material cyclopentene bromosulfone. In particular the amine-substituted products have more shielded vinyl protons. This data suggests that the nature of the substituents should have a pronounced effect on subsequent reactions.

Table 7: Summary of Substitution Reactions with Vinyl Chemical Shifts

<table>
<thead>
<tr>
<th>Substituent X</th>
<th>Product number</th>
<th>Vinyl Chemical Shifts $\delta$ (ppm)</th>
<th>Yield</th>
<th>Notes</th>
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<td>7.63 &amp; 6.17</td>
<td>51</td>
<td>a, b</td>
<td></td>
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<tr>
<td>hydrogen</td>
<td>7.37, 6.47 &amp; 6.20</td>
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<td>d</td>
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<tr>
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<td>d</td>
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* More Downfield Vinyl Proton is Vicinal to Substituent X; * isolated yield; * side-product from attempted Suzuki reaction; * yield $^1$H NMR (using internal standard)
In this section I would like to quickly outline preliminary experiments which have not led to expected products. These experiments are important as well because they define the scope of possible synthetic transformations of these densely functionalized reactants.

“Hard nucleophiles” are nucleophilic species such as organolithiums and Grignards with a localized negative charge and not very polarizable. They often prefer to react at a hard reaction site in the electrophile such as the carbonyl carbon in an enone.

We understood that when “hard” nucleophiles add to vinyl sulfones in a conjugate fashion, difficulties could potentially occur from competing side reactions involving metallation (or deprotonation). This deprotonation occurs in the same plane as the sulfone group, orthogonal
to the pathway of conjugate addition (Figure 164). This side reaction is likely to be a problem with more complex organolithium and Grignard species which are sterically more demanding. However, simple organolithium and Grignards should behave more strictly as classical nucleophiles and therefore yield a diminished amount of metallation product.

The strong electronegativity of the oxygens on the sulfone causes the sulfur atom to be a highly electrophilic center. Hard Soft Acid Base (HSAB) theory would predict that “hard” nucleophiles may prefer reacting at this site, and this is another possible side reaction. Direct attack of the sulfone moiety of a vinyl sulfone by a “hard” nucleophile is analogous to attack of the carbonyl carbon in an enone.

Direct attack on sulfur of a sulfone is a rare event. Most of the few examples that exist utilize sulfones which are sterically accessible as well as strained, and prone to direct displacement. Such is the case as shown in the example given below in Figure 165 with norbornadienyl sulfone. Other cases reporting this pathway involve leaving groups which were only moderately stabilized or in systems where no other electrophilic centers existed.

The steric bulk of the sulfone group should be responsible for impeding the pathway of its direct displacement. However this pathway can occur more easily in systems with enhanced steric accessibility. In the example below, norbornadienyl sulfone has its sulfone in a strained four-membered ring and more exposed for nucleophilic attack. Our system didn’t exhibit these characteristics, suggesting that this side reaction would not become a problem with “hard” nucleophiles.

![Figure 165: Direct Displacement of Sulfone on Norbornadienyl Species](image)
Moreover, we were interested in recent results from the Fuchs group on the regio- and stereoselective intramolecular-assisted delivery of a simple alkyllithium to a cyclic vinyl sulfone, to provide a cis-configured product (Figure 166). The Fuchs group has shown how a free hydroxyl at the γ-position of vinyl sulfones can serve as a directing group for conjugate addition of simple organolithium reagents to provide products with cis stereochemistry. On the other hand, silyl protected γ-alcohols, which cannot benefit equally from chelation control, provided products with trans stereochemistry for sp³ functionalized nucleophiles and cis stereochemistry for sp hybridized nucleophiles such as acetylides. It is interesting to note that the use of anions with potassium counterions were much more active, often yielding products where the corresponding anions with lithium counterions had failed. We were interested in applying this methodology to our cyclopentene bromosulfone substrates.

Figure 166: Fuchs Chelation Controlled vs Non-Chelation Controlled Conjugate Addition

We hoped for similar success with addition of n-butyllithium to a THF solution of trans-free diol cyclopentene bromide vinyl sulfone. Unfortunately, no reaction occurred after the addition of 5 equivalents of n-butyllithium, warming the reaction from –40 °C to room temperature, and stirring the reaction at this temperature for several hours (Figure 167).

Figure 167: Unsuccessful Reaction of Cyclopentene Bromosulfone with n-Butyllithium
Other reactions with both cis- and trans-free diol were attempted (Figure 168) and also failed to give the desired products included hard anionic nucleophiles such as sodium methoxide and softer nucleophiles such as butyl amine simply giving back unreacted starting material or provided difficulty during purification of crude. No reaction also occurred under Sonogashira conditions with simple alkyne TMS-acetylene. In fact, a few different attempts to avert this unreactivity by first alkylating the trans-free diol product failed.

![Failed Reactions with Cyclopentene Bromosulfone Free Diol](image1)

**Figure 168: Failed Reactions with Cyclopentene Bromosulfone Free Diol**

Reaction of trans-free diol cyclopentene bromosulfone with n-butylamine appeared promising at first (Figure 169). $^1$H NMR of crude reaction mixtures showed characteristic chemical shifts of vinyl peaks (δ 7.02 and 6.85 ppm) (Figure 170). However isolation of pure product proved unattainable. It seems this product may suffer from stability issues upon application to a preparatory TLC plate. A crude product which corresponded to two spots before purification became a complicated mixture afterwards.

![Reaction of n-Butyl Amine with Trans-Free Diol](image2)

**Figure 169: Reaction of n-Butyl Amine with Trans-Free Diol**
One reaction which showed promise with cis-free diol cyclopentene bromosulfone was a benzylolation reaction under neutral conditions (Figure 171 and Figure 172).\textsuperscript{135}

![Figure 170: Partial $^1$H NMR Spectrum of Crude n-Butyl Amine Product](image)

One reaction which showed promise with cis-free diol cyclopentene bromosulfone was a benzylolation reaction under neutral conditions (Figure 171 and Figure 172).\textsuperscript{135}

![Figure 171: Benzylation of Cyclopentene Bromosulfone Diol Using Dudley’s Benzylation Reagent](image)

Below the first two $^1$H NMR spectra most likely correspond with isomeric monobenzylated products and the third $^1$H NMR spectrum is probably that of the dibenzylated product (Figure
173 and Figure 174). These reactions were performed on a small scale and a scale-up would be beneficial to fully elucidate these structures.

Figure 172: Expected Products from Benzylation

Figure 173: $^1$H NMR Spectrum of Monobenzylated Product
Figure 174: $^1$H NMR Spectrum of Isomeric Monobenzylated Product

Below in Figure 175 is the $^1$H NMR spectrum of the possible dibenzylated product.

Figure 175: $^1$H NMR Spectrum of Dibenzyalted Product
Several reactions which were not successful with the acetonide protected cyclopentene bromosulfone are worth noting and are shown below in Figure 176.

Figure 176: Unsuccessful Reactions with Protected Cyclopentene Bromosulfone
Despite the huge success in coupling various primary and secondary amines with cyclopentene bromosulfones, coupling with amines of amino acids, amino acid derivatives and dipeptides met with little success. These would have been interesting functional handles that could have served as a unit to attach to other peptides. Solubility of glycine and glycine methyl ester in a variety of organic solvents including methylene chloride, tetrahydrofuran, and dimethyl formamide, was poor even at refluxing temperatures of the respective solvents and this could have been reflected in its poor reactivity. Typically these reactions were refluxed overnight in the lower boiling solvents or heated toward 80 °C in DMF and monitored by TLC. The reaction often darkened, but little conversion was observed so additional equivalents of amino acid or amino acid derivative were added (up to 30 equivalents) and refluxed for additional time (24-48 hours total time). However these condition changes were not successful.

Grignard reactions and organolithium reactions to cyclopentene bromosulfones were also usually unsuccessful. Reaction with the Grignard reagent formed from para bromoanisole and 2-propenyl Grignard was unsuccessful, often leaving the starting material unchanged. The reaction was carried out initially at 0 °C in tetrahydrofuran and eventually reaction temperature was increased to refluxing conditions. Even the lithium salt of trimethylacetylide anion failed to give the desired enyne product, which was readily accessible via the Sonogashira coupling route.

Sometimes the reaction conditions were tweaked by the addition of copper iodide and additional equivalents of Grignard reagent, but to no avail. The lone Grignard reaction which met with marginal success was commercially available methyl Grignard. Only after the addition of multiple equivalents of Grignard reagent (24 equivalents was ultimately added), and reaction under refluxing tetrahydrofuran for 48 hours, was some starting material converted into the desired product. Some conversion started after 8 equivalents of Grignard and 6 hours of reaction time. However, the additional reaction time and increased equivalents of Grignard were not enough to allow the reaction to proceed past partial completion.

Another interesting reaction type which failed the transformation of the vinyl bromide employed phosphonates as nucleophiles. Phosphonates are found in some important biologically active compounds such as cyclophostin, which is an acetylcholinesterase inhibitor. Phosphono
esters have been used extensively as haptens for the production of catalytic antibodies. The phosphonate moiety, furthermore, can serve as a chelating species which can coordinate to a
variety of metals. Phosphonodiesters and especially fluorophosphonoesters have shown antioxidant effects, where the latter have also shown cytoprotective properties. We first attempted to install the phosphonate moiety via an Arbuzov reaction with triethylphosphite. The reaction was run in benzene as well as toluene under refluxing conditions for up to 48 hours and with as much as 8 equivalents of triethylphosphite, but none of the desired product as seen by a shift in the vinyl peaks or toluene methyl peak was observed and mainly starting material remained. Additionally it was very difficult to remove the triethyl phosphite in the work-up conditions. Attempts to install the phosphonate using diethyl phosphite also failed. Under these conditions potassium t-butoxide was added to a solution of diethyl phosphite and starting material in tetrahydrofuran at 0 °C. The reaction was heated to reflux. Again under these conditions mainly starting material remained.

The Heck reaction is a very useful robust carbon-carbon bond forming reaction that has also gained great utility in organic chemistry. The chemical reaction occurs between an unsaturated halide (or triflate) and an alkene with at least one proton to form a substituted alkene. A strong base such sodium acetate or potassium carbonate and palladium (0) catalyst (usually formed in situ from a palladium (II) species) are also required. The best alkene substrates are those that are electron deficient, because they are most suitable for promoting the oxidative addition step of the catalytic cycle. Interestingly we foresaw our Heck products used in subsequent Diels-Alder reactions or electrocyclizations. The one type of Heck reaction that was attempted with methyl methacrylate appeared to give some desired product. However it was very poor yielding and gave product in insufficient quantities. Jeffery’s ligandless conditions were used. Under these conditions, palladium diacetate is transformed into palladium (0) by sacrificing a small amount of starting material which undergoes oxidative coupling. Additional reagents include tetrabutylammonium bromide, potassium carbonate and dimethyl formamide as the reaction solvent.

A Heck coupling reaction was attempted between acetonide-protected cyclopentene bromosulfone and methyl methacrylate (Figure 177).
Below are $^1$H NMR spectra of purified products (Figure 178 and Scheme 179). These reactions were performed on small-scales employing 15 mg starting material cyclopentene bromosulfone. Because only a small amount of products were isolated, it might be beneficial to scale-up this reaction to 50-100 mg of starting material cyclopentene bromosulfone.
Scheme 179: $^1$H NMR spectrum (in C$_6$D$_6$) of Possible Heck Product Resulting from Reaction between Cyclopentene Bromosulfone and Methyl Methacrylate

Some crude reaction mixtures were apparently unstable to purification conditions. Such was the case of reaction between sodium azide and cyclopentene bromosulfone (Figure 180). The crude $^1$H NMR appeared very promising (Figure 181), showing diagnostic chemical shifts of vinyl protons ($\delta$ 6.11 ppm and 5.76 ppm) as well as chemical shifts of the toluene methyl group ($\delta$ 2.39 ppm).

Figure 180: Azide Product Resulting from Reaction of Cyclopentene Bromosulfone with Sodium Azide
Unfortunately, isolation of pure compound was unsuccessful, even after a repeated attempt under similar reaction and work-up conditions. A possible solution to this problem is to add a trapping agent to the reaction mixture before work-up. For example, an alkyne moiety could be added to the reaction mixture with the goal of isolating a triazole product resulting from [3 + 2] dipolar cycloaddition.

![Figure 181: 1H NMR Spectrum of Crude Azide Reaction](image)

A Suzuki reaction between phenyl boronic acid and cyclopentene bromosulfone (E)-5d was attempted. However, only a reduction product was isolated as indicated by the 1H NMR given below in Figure 182. Notice the cyclopentene vinyl peaks at δ 7.37 ppm, δ 6.48 ppm, and, and δ 6.20 ppm indicate that the bromine of starting material has indeed been substituted for a hydrogen.
Figure 182: $^1$H NMR of Reduction Product from Suzuki Reaction between (E)-5d and Phenyl Boronic Acid
CHAPTER 20

FUTURE WORK AND CONCLUSIONS

A large-scale synthesis of acetonide-protected cyclopentene bromosulfone is underway. In this
regard, 11 grams of pure meso TMS-protected bis(alkyne) diol has been prepared and about
half of this material has been taken forward through the next step of acetonide protection with
2,2-dimethoxypropane. Multi-gram quantities of the acetonide-protected cyclopentene
bromosulfone will allow for further analog development, including the employment of more
elaborate nucleophiles as coupling partners and perhaps species that could enable
cycloaddition reactions.

This dissertation has discussed the discovery of a new efficient radical process, the 5-endo-dig
cyclization of a carbon-centered radical, fostered by rational experimental design. In addition to
proving the experimental feasibility of this overlooked process, we have demonstrated the utility
of the 5-endo-dig cyclized products through a variety of synthetically useful transformations.

Over the past few decades an active interest in the preparation and use of sulfone-containing
compounds in medicinal chemistry and natural product synthesis has arisen due not only to the
reactivity imparted by the sulfone moiety, but also the ease of its removal or transformation into
another functional group.

The presence of the sulfone group on the diene modifies its character, making it remarkably
reactive toward addition. Overall it was shown that simple nucleophiles can add to vinylogous
vinyl sulfones in a conjugate addition-elimination fashion. Another unique property imparted by
the sulfone moiety is the acidity of the $\alpha$-proton. Future work of our cyclopentene
bromosulfones may be directed towards exploiting this feature. Additionally, some of the
products formed from addition-elimination can undergo further interesting transformations and
these should be investigated as well.
We are proud to illustrate that with proper design the previously predicted but experimentally unachievable intriguing 5-endo-dig cyclization of a carbon-centered radical can be executed in an efficient manner. Our success in elaboration of the cyclized products should validate this process to become a part of the synthetic arsenal of useful transformations, and allow other chemists to carry out our design principles towards their endeavours.\textsuperscript{138} Importantly, the achievement of excellent agreement between computational predictions and experimental results for 5-endo-dig radical cyclization should continue to bolster their expansive melding in future work, and continue to guide the creative process of organic synthesis through rational approaches.
SUPPORTING INFORMATION

**Chemicals.** Tosyl bromide (TsBr) was prepared according to the known procedure. Unless otherwise noted, all other reagents were commercially available and were used without purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl.

**General.** All manipulations of oxygen- and moisture-sensitive materials were conducted under an argon atmosphere. Silica gel chromatography employed silica gel F254 (230-499 mesh particle size). Preparative silica gel plate chromatography used Analtech Uniplate (20x20 cm, 1000 microns). Analytical thin layer chromatography (TLC) was performed on aluminum backed Whatman (250 μm silica) plates. Visualization was accomplished with UV light (254 nm) and alkaline KMnO₄ or anisaldehyde solution followed by heating.

**Apparatus.** Proton and carbon nuclear magnetic resonance spectra (¹H and ¹³C NMR) were recorded on a Varian Gemini 300 (¹H, 300 MHz; ¹³C, 75 MHz) spectrometer with solvent resonance (¹H NMR, CHCl₃, at δ 7.26 ppm; ¹H NMR data are reported as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. The chemical shifts (δ) are reported in parts per million (ppm) for all compounds. High-Resolution mass spectra were recorded on a Jeol JMS-600H instrument using chemical ionization (CI), electron ionization (EI), or fast atom bombardment (FAB) methods as indicated in text. The isolated yields refer to material judged to be > 95% pure by ¹H NMR spectroscopy. The yields and product ratios for Bu₃SnH- and TsBr-mediated cyclization reactions were determined by ¹H NMR relative to a known concentration of triphenyl methane or bibenzyl as a ¹H NMR internal standard added to the reaction mixture after the reaction was complete. Photochemical experiments were carried out in standard pyrex NMR tubes and preparative scale irradiation experiments were carried out in pyrex tubes (25x1 cm). Ace Glass medium pressure Hg lamp (450W) was used for irradiation.
SYNTHESIS OF STARTING MATERIALS

2-(6-bromohex-2-ynyloxy)tetrahydro-2H-pyran:
To THP propargyl ether (1.50 g, 10.7 mmol, 1.0 equivalent) in 9 ml tetrahydrofuran stirring at – 78 °C was added a 1.6M solution of n-butyllithium (n-BuLi) in hexanes (7.36 ml, 1.1 equivalents). The reaction was warmed to 0 °C and then 1,3-dibromopropane (2.59g, 1.3 ml, 12.8 mmol, 1.2 equivalents) was added. The reaction was heated to 45 °C for 12 hours and then quenched with water. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to a crude oil. The reaction was purified by silica gel column chromatography (hexanes/EtOAc, 98:2 to 96:5) to provide 2.90 g of the final hexyne product. Final yield of the product is 86 %. ¹H NMR (300 Hz, CDCl₃): δ 4.80 (t, J = 3.3 Hz, 1H), 4.24 (tq, J = 2.1 Hz, 14.7 Hz, 2H), 3.88-3.80 (m, 1H), 3.56-3.54 (m, 1H), 3.52 (t, J = 8.1 Hz, 2H), 2.43 (tt, J = 6.9, 2.1 Hz, 2H), 2.04 (p, J = 6.6 Hz, 2H), 1.75-1.50 (m, 6H).
3-benzyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol:

3.6 mL of \( \text{n-BuLi} \) (1.6 M in hexanes, 5.17 mmol, 2.0 equivalents) was slowly added to a 10 ml THF solution of trimethylsilylacetylene (0.589 g, 0.847 mL, 5.99 mol, 2.1 equivalents) at -78 °C. The reaction mixture was kept at this temperature for 60 minutes and then warmed to 0°C. After 45 minutes the reaction mixture was recooled to -78°C and a solution of ethyl phenyl acetate (0.469 g, 0.455 ml, 2.856 mmol, 1 equivalent) in 6 mL THF was added over 20 minutes. The reaction mixture was warmed to room temperature and then quenched with 20 mL of saturated aqueous ammonium chloride after 5 hours of stirring. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated \textit{in vacuo} to an oil and purified by silica gel column chromatography (hexanes/EtOAc, 100:2 to 100:4) to a
pure light orange oil weighing 810 mg. Yield is 90 %. \( ^{1}H \text{NMR (300 Hz, CDCl}_3): \delta 7.25-7.35 \text{ (m, 5H), 3.61 (s, 1H), 3.18 (s, 2H), 0.167 (s, 18H).} \)

\[
\begin{align*}
\text{(3-benzyl-3-((bromomethyl)dimethylsilyloxy)penta-1,4-diyn-1,5-diyl)bis(trimethylsilane)} &: \text{Bromomethyl dimethylsilylchloride (0.095g, 0.508, 1.6 equivalents) was added to a 4 ml DMF (dimethyl formamide) solution of starting material 3-benzyl-1,5-bis(trimethylsilyl)penta-1,4-diyn-3-ol (100 mg, 0.317 mol, 1 equivalent) and imidazole (65 mg, 0.956 mmol, 3 equivalents) at room temperature. After 6 hours the reaction mixture was quenched with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated \textit{in vacuo} to yield a clear oil and purified by silica gel column chromatography (hexanes/EtOAc, 100:2 to 100:96) to give 27 mg of compound. Yield is 19 %.
\end{align*}
\]

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$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.25-7.29 (m, 5H), 3.108 (s, 2H), 2.494 (s, 2H), 0.30 (s, 6H), 0.161 (s, 18H).

3-benzylpenta-1,4-diyn-3-ol: Potassium carbonate (K$_2$CO$_3$: 0.237 g, 17 mmol, 1.5 equivalents) was added to a 10 mL MeOH/CH$_2$Cl$_2$ solution (1:1 v/v) of starting material (360 mg, 11.4 mmol, 1.0 equivalents). The resulting slurry was stirred for 2 h before being filtered through celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5 to 88:12) to afford product as an oil weighing 180 mg. Yield is 92%. $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.26-7.39 (m, 5H), 3.24 (s, 2H), 2.046 (s, 1H).
(3-benzylpenta-1,4-diyn-3-yloxy)(bromomethyl)dimethylsilane
Bromomethyl dimethylsilyl chloride (0.275g, 1.47 mmol, 2.5 equivalents) was added to a 3 ml DMF (dimethyl formamide) solution of starting material 3-benzylpenta-1,4-diyn-3-ol (100 mg, 0.588 mmol, 1 equivalent) and imidazole (184 mg, 2.72 mmol, 4.6 equivalents) at room temperature. The reaction mixture was quenched with 10 mL of saturated aqueous ammonium chloride after 5 hours of stirring at room temperature. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to a clear oil and purified by silica gel column chromatography (hexanes/EtOAc, 100:2 to 100:96) to a product weighing 70 mg (37 % yield).

$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.27-7.36 (m, 5H), 3.18 (s, 2H), 2.61 (s, 2H), 2.52 (s, 2H), 0.334 (s, 6H).
(+/-) (E)-3-benzyl-1-(tributylstannyl)pent-1-en-4-yn-3-ol:

Bu₃SnH (34.0 mg, 12.93 mmol, 1.1 equivalents) and PdCl₂(PPh₃)₂ (1.6 mg, 0.0023 mmol, 0.02 equivalents) was added to a 2 ml THF (tetrahydrofuran) solution of starting material 3-benzylpenta-1,4-diyn-3-ol (20.0 mg, 11.75 mol, 1 equivalent) at room temperature. After 1.5 hours additional Bu₃SnH (34.0 mg, 12.93 mmol, 1.1 equivalents) was added. After 15 hours of stirring at room temperature the reaction was concentrated in vacuo to a black tar. The crude product was purified by silica gel plate chromatography (hexanes/EtOAc, 90:10) to 10 mg. Yield is 18 %.

¹H NMR (300 Hz, CDCl₃): δ 7.35-7.28 (m, 5H), 6.44 (d, J = 18.9 Hz, 1H) 6.04 (d, J = 18.9 Hz, 1H), 3.01 (s, 2H), 2.605 (s, 1H), 1.30-1.22 (m, 12 H), 1.0-0.80 (m, 15H).
To a solution of starting material (E)-3-benzyl-1-(tributylstannyl)pent-1-en-4-yn-3-ol (25.0 mg, 0.181 mmol, 1 equivalents) in THF (1 ml) was added iodine (45.0 mg, 0.177 mmol, 1 equivalent) at room temperature. After five hours the reaction was worked up by concentration and then purified by plate chromatography (hexanes: ethyl acetate 95:5) to 4 mg. Yield is 53 %. \(^1\)H NMR (300 Hz, CDCl\(_3\)): δ 7.35-7.28 (m, 5H), 6.71 (d, \(J = 14.4\) Hz, 1H), 6.62 (d, \(J = 14.4\) Hz, 1H), 3.00 (s, 2H), 2.657 (s, 1H), 2.208 (s, 1H), 1.57 (s, 6H).
7-benzyltrideca-5,8-diyn-7-ol: 31 mL (1.6 M in hexanes, 48.7 mmol, 4.0 equivalents) of n-BuLi was slowly added to a 30 mL THF solution of hexyne (5.59 mL, 4.0 g, 48.7 mmol, 4 equivalents) at -78 °C. The reaction mixture was kept at this temperature for 60 minutes and then warmed to 0°C. After 45 minutes the reaction mixture was recooled to -78°C and a solution of ethyl phenyl acetate (2.00 g, 2.03 mL, 12.18 mmol, 1.0 equivalent) in 10 mL THF was added over 10 minutes. The reaction mixture was warmed to room temperature and then quenched with 100 mL of saturated aqueous ammonium chloride after 15 hours of stirring. The aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to an oil and
purified by silica gel column chromatography (hexanes/EtOAc, 100:0 to 98:2) to a pure product weighing 645 mg (18 %) yield.

(7-benzyltrideca-5,8-diyn-7-yloxy)(bromomethyl)dimethylsilane:
(Bromomethyl)dimethylsilyl chloride (125 mg, 0.665 mmol, 2.5 equivalents) was added to a 2 ml DMF (dimethyl formamide) solution of starting material 7-benzyltrideca-5,8-diyn-7-ol (75 mg, 0.266 mmol, 1 equivalent) and imidazole (72 mg, 1.06 mmol, 4 equivalents) at room temperature. After 6 hours of room temperature stirring, the reaction mixture was quenched with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to a clear oil and purified by silica gel column
chromatography (hexanes/EtOAc, 100:0 to 98:2) to a pure product weighing 40 mg (33 % yield. 

$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.24-7.31 (m, 5H), 3.09 (s, 2H), 2.81 (s, 2H), 2.19 (t, $J = 6.9$ Hz, 4H), 1.26-1.47 (m, 4H), 0.862-0.979 (m, 4H), 0.885 (t, $J = 6.9$ Hz, 6H) 0.272 (s, 6H). $^{13}$C$^1$H NMR (CDCl$_3$, 75.5 MHz) $\delta$ 135.9, 131.3, 127.4, 126.7, 85.4, 81.2, 65.1, 51.8, 34.7, 34.5, 31.6, 30.6, 30.3, 25.3, 22.6, 22.0, 20.7, 18.4, 14.1, 13.5.
(2-(hex-1-ynyl)-2-methoxyoct-3-ynyl)benzene:
0.44 mL of n-Butyllithium (n-BuLi) (1.6 M in hexanes, 0.708 mmol, 2.0 equivalents) was slowly added to a 2 ml THF (tetrahydrofuran) solution of starting material 7-benzyltrideca-5,8-diyn-7-ol (100 mg, 0.354 mol, 1.0 equivalent) stirring at -78 °C. After a few minutes methyl iodide was added (0.804 g, 5.66 mmol, 16.0 equivalents). The reaction mixture was warmed to -25°C and gradually warmed to room temperature. After 5 hours the reaction mixture was quenched at room temperature with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to a clear oil and then purified by silica gel column chromatography (hexanes/EtOAc, 100:2 to 100:4) to a pure product weighing 40 mg. Final yield is 38 %. ^1H NMR (300 Hz, CDCl₃): δ 7.27-7.36 (m, 5H), 3.45 (s, 3H), 3.13 (s, 2H), 2.21 (t, J = 6.9, 4H), 1.32-1.50 (m, 8H), 0.89 (t, J = 6.9, 6H).
(E)-7-benzyl-6-(tributylstannyl)tridec-5-en-8-yn-7-ol:
Bu$_3$SnH (0.113 g, 0.389 mmol, 1.1 equivalents) and PdCl$_2$(PPh$_3$)$_2$ (49 mg, 0.071 mmol, 0.2 equivalents) was added to a 3 ml THF (tetrahydrofuran) solution of starting material 7-benzyltrideca-5,8-diyn-7-ol (100 mg, 0.354 mol, 1 equivalent) at room temperature. After 15 hours the reaction was concentrated in vacuo to a black tar. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 100:0 to 99:1) to a pure product weighing 70 mg. Yield is 34 %. $^1$H NMR (300 Hz, CDCl$_3$): δ 7.73-7.26 (m, 5H), 5.53 (t, $J = 6$Hz, 1H), 3.03 (d, $J = 12$ Hz, 1H), 2.81 (d, $J = 12$ Hz, 1H), 1.50-1.25 (m, 10H), 1.21 (t, $J = 6.9$ Hz, 2H), 0.89 (m, $J = 7.2$ Hz, 15 H).
(7S,8S)-7,8-dimethyltetradeca-5,9-diyne-7,8-diol: 29 ml of \( n \)-Butyllithium (\( n \)-BuLi) (1.6 M in hexanes, 46.4 mmol, 4 equivalents) was slowly added to a THF (60 ml) solution of 1-hexyne (3.91 g, 47.63 mmol, 4.1 equivalents) stirring at -78 °C. The reaction mixture was kept at this temperature for 60 minutes and then warmed to 0°C. After 45 minutes the reaction mixture was recooled to -78°C and a solution of 2,3-butanedione (1.0 g, 11.6 mmol, 1.0 equivalent) was added drop-wise via syringe over 10 minutes. The reaction mixture was allowed to warm to room temperature overnight (15 hours) and then quenched with 100 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 70 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated \textit{in vacuo} to a clear oil and purified by silica gel column chromatography (hexanes/ EtOAc, 96:4 to 88:12). Two products were obtained (0.430 g meso and 0.465 g racemic) for which yields were 15 % and 16 % respectively. \(^1\)H NMR (300 Hz, CDCl\(_3\)): \( \delta \) 2.54 (s, 2H), 2.20 (t, \( J = 8.1 \) Hz, 4H), 1.57 (s, 6H), 1.55-1.40 (m, 8H), 0.908 (t, \( J = 7.2 \) Hz, 6H).
(7R,8S)-7,8-dimethyltetradeca-5,9-diyn-7,8-diol: $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 2.573 (s, 2H), 2.22 (t, $J$ = 6.3 Hz, 4H), 1.541-1.378 (m, 8H), 0.912 (t, $J$ = 7.2 Hz, 6H).
(7R,8S)-7,8-dimethoxy-7,8-dimethyltetradeca-5,9-diyne:

0.26 mL of n-Butyllithium (n-BuLi) (1.6 M in hexanes, 0.416 mmol, 1 equivalent) was slowly added to a 2 ml THF (tetrahydrofuran) solution of starting material (105 mg, 0.419 mol, 1 equivalent) at -78 °C. After a few minutes methyl iodide was added (0.178 g, 1.258 mmol, 3 equivalents). The reaction mixture was warmed to -25°C and gradually warmed to room temperature. After 5 hours the reaction mixture showed some remaining starting material so more n-BuLi (1.6 M in hexanes, 0.520 ml, 0.832 mmol, 2 equivalents) and methyl iodide (0.178 g, 1.26 mmol, 3 equivalents) were added. After stirring for another 24 hrs at room temperature the reaction was quenched with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium
sulfate, filtered and the filtrate was concentrated *in vacuo* to a clear oil and purified by silica gel column chromatography (hexanes/ EtOAc, 97:3) to two clear oils weighing 5 mg (dimethyl ether) and 50 mg (monomethyl ether). Yield of two products are 4 % and 43 % respectively.

**Dimethyl ether** $^1$H NMR (300 Hz, CDCl$_3$): δ 3.40 (s, 6H), 2.24 (t, $J$ = 6 Hz, 4H) 1.51 (s, 6H), 1.42-1.52 (m, 4H), 1.15 (s, 6H), 0.94 (t, $J$ = 6 Hz, 6H), 4H).
(7S,8R)-8-methoxy-7,8-dimethyltetradeca-5,9-diyn-7-ol:
$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 3.41 (s, 3H), 2.22-2.26 (m, 4H), 2.01 (s, 1H), 1.50 (s, 6H), 1.42-1.55 (m, 8H), 0.88-0.94 (m, 6H).

(7S,8S,E)-7,8-dimethyl-6-(tributylstannyl)tetradec-5-en-9-yne-7,8-diol: Bu$_3$SnH (0.099 g, 0.344 mmol, 1.0 equivalent) was added to a 3 ml THF (tetrahydrofuran) solution of PdCl$_2$(PPh$_3$)$_2$ (5 mg, 0.0071 mmol, 0.02 equivalents) and starting material (7R,8S)-7,8-dimethyltetradeca-5,9-diyn-7,8-diol (86 mg, 0.344 mmol, 1 equivalent) at room temperature. After 15 hours the reaction shown little progress by TLC so an additional amount of Bu$_3$SnH (0.074 g, 0.254 mmol, 0.73 equivalents) and PdCl$_2$(PPh$_3$)$_2$ (3 mg, 0.004 mmol, 0.02 equivalents) was added and stirring continued at room temperature. After 10 hours the reaction was concentrated in vacuo to a black tar. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 100:0 to 99:1) to 40 mg. Yield is 20 %. $^1$H NMR (300 Hz,
CDCl₃: δ 5.85 (s, J_{SnH} = 78.0 Hz), 1.55-1.25 (m, 8H), 1.448 (s, 3H), 1.372 (s, 3H), 0.95-0.84 (m, 10 H).

(3S,4S)-3,4-dimethyl-2-(tributylstannyl)hex-1-en-5-yne-3,4-diol: Bu₃SnH (0.116 g, 0.399 mmol, 1.1 equivalents) was added to a 3 ml THF (tetrahydrofuran) solution of PdCl₂(PPh₃)₂ (5 mg, 0.0072 mmol, 0.02 equivalents) and starting material (7R,8S)-7,8-dimethyltetradeca-5,9-diyne-7,8-diol (50 mg, 0.363 mmol, 1 equivalent) at room temperature. After 15 hours the reaction was concentrated in vacuo to a black tar. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 100:0 to 88:12) to 40 mg. Yield is 26 %. ¹H NMR (300 Hz, CDCl₃): δ 6.34 (s, J_{SnH} = 67.0 Hz), 2.47 (s, 1H), 2.27 (s, 1H), 1.6-1.2 (m, 18 H), 1.48 (s, 3H), 1.35 (s, 3H), 0.88 (t, J = 7.2 Hz, 9H).
TMS-Acetylide addition to 2,3-butanedione gave a diastereomeric mixture of meso and racemic diol products which were separated upon purification. Interestingly, the racemic stereoisomer could be selectively crystallized, leaving behind mother liquors which were significantly enriched in the meso stereoisomeric species. As a result, subsequent column chromatography became easier.

3,4-Dimethyl-1,6-Bis(trimethylsilyl)hexa-1,5–diyne-3,4-diols: 60 mL of n-BuLi (1.6 M in hexanes, 0.096 mol, 2.8 equivalents) was slowly added to a 150 ml THF solution of trimethylsilylacetylene (15.8 mL, 11.0 g, 0.112 mol, 3.2 equivalents) at -78 °C. The reaction
mixture was kept at this temperature for 60 minutes and then warmed to 0°C. After 45 minutes the reaction mixture was recooled to -78°C and a solution of 2,3-butanedione (3.00 g, 3.0 mL, 0.035 mol, 1.0 equivalent) in 6 mL THF was added over 20 minutes. The reaction mixture was warmed to room and then quenched with 100 mL of saturated aqueous ammonium chloride after 5 hours of stirring. The aqueous layer was extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was partially concentrated in vacuo to induce crystallization of a white solid which was almost exclusively that of racemic isomer rac-12. The mother liquors, enriched in meso isomer meso-11, where concentrated to a yellow solid and purified by silica gel column chromatography (hexanes/EtOAc, 100:4 to 10:1). Final yields of products were 3.22 g (33%) of meso-11, Rf = 0.25 (hexanes/EtOAc, 10:1), 4.28 g (44%) rac-12, Rf = 0.20

meso-3,4-Dimethyl-1,6-bis-trimethylsilyl-hexa-1,5-diyne-3,4-diol (meso-11). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.65 (s, 2H), 1.50 (s, 6H), 0.18 (s, 18H). $^{13}$C{1H} NMR (CDCl$_3$, 75.5 MHz) $\delta$ 106.77, 89.64, 73.90, 22.60, - 0.20. MS (FAB+) calcd for [C14H26O2Si2Na]$^+$: 305.1369; found 305.1372. The spectral data for this compound are consistent with literature data.
**rac-3,4-Dimethyl-1,6-bis-trimethylsilyl-hexa-1,5-diyne-3,4-diol (rac-12).** \( ^1\)H NMR (CDCl\(_3\), 300 MHz) \( \delta \) 2.56 (s, 2H), 1.57 (s, 6H), 0.18 (s, 18H). \( ^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\), 75.5 MHz) \( \delta \) 105.97, 90.12, 73.85, 24.36, - 0.19. MS (FAB+) calcd for [C\(_{14}\)H\(_{26}\)O\(_2\)Si\(_2\)Na]+: 305.1369, found 305.1372. The spectral data for this compound are consistent with the literature data. The X-ray crystal structure for this compound determined by Dr. Ronald Clark (Department of Chemistry and Biochemistry, Florida State University) confirmed its relative configuration.
meso-3,4-Dimethyl-hexa-1,5-diyne-3,4-diol (1a): 9 mL of aqueous 1N NaOH (9 mmol, 3.6 equiv) was added to a 9 mL methanol solution of meso-12 (0.71 g, 2.51 mmol, 1.0 equiv) over 5 minutes. The resulting mixture was stirred for 8 h and then worked up with 10 mL of saturated aqueous ammonium chloride. The aqueous layer was extracted with Et2O (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo*, and taken up in benzene (3x4 mL) to azeotropically remove excess water. The product 1a was purified by column chromatography on silica gel (hexanes/EtOAc, 70:30 to 50:50) to afford a white solid (0.35 g, 100%). Rf = 0.12 (hexanes/EtOAc, 8:1). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 3.02 (s, 2H), 2.54 (s, 2H), 1.52 (s, 6H). $^{13}$C{1H} NMR (CDCl$_3$, 75.5 MHz) $\delta$ 85.05, 73.49, 73.38, 22.93.
rac-3,4-Dimethyl-hexa-1,5-diyne-3,4-diol (1b): Potassium carbonate (K₂CO₃: 1.91 g, 13.80 mmol, 1.5 equiv) was added to a 32 mL MeOH/CH₂Cl₂ solution (1:1 v/v) of rac-12 (2.6 g, 9.20 mmol, 1.0 equiv). The resulting slurry was stirred for 2 h before being filtered through celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 70:30 to 50:50) to afford product 1b as a white solid (1.51g, 100%). Rf = 0.10 (hexanes/EtOAc, 8:1). ¹H NMR (CDCl₃, 300 MHz) δ 3.46 (bs, 2H), 2.54 (s, 2H), 1.63 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 75.5 MHz) δ 84.28, 73.74, 73.44, 24.81.
meso-2,3-Diethynyl-2,3-dimethyl-[1,4]dioxane (1c): 35 mL NaOH (35 w/w % aqueous solution), 35 mL 1,2-dichloroethane, meso-12 (1.14 g, 8.22 mmol, 1 equiv) and tetrabutylammonium bromide (0.52 g, 1.64 mmol, 0.2 equiv) were combined in a flask and stirred thoroughly between 50 to 55 °C for 64 h. Water was added to the reaction (100 mL) and the reaction mixture was extracted with Et₂O (4x50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo. The crude product was purified using silica gel column chromatography (hexanes/EtOAc, 85:15 to 55:45) to afford 1c as a white solid (0.64 g, 3.90 mmol, 47%). Rf = 0.18 (hexanes/EtOAc, 8:1). ¹H NMR (CDCl₃, 300 MHz) δ 4.01-3.94 (m, 2H), 3.79-3.71 (m, 2H), 2.59 (s, 2H), 1.58 (s, 6H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 83.41, 74.30, 74.27, 60.87, 21.89. MS (Cl+) calcd for [C₁₀H₁₂O₂ + H]⁺: 165.0916; found 165.0926.
**meso-3,4 bis (trimethylsiloxy) 3,4-Dimethyl-1,6-bis-trimethylsilyl-hexa-1,5-Diyne** To starting material **meso-3,4-Dimethyl-1,6-bis-trimethylsilyl-hexa-1,5-diyne-3,4-diol** (150 mg, 0.532 mmol, 1 equivalent) in CH$_2$Cl$_2$ (5 ml) was added triethylamine (Et$_3$N) (0.215 g, 2.13 mmol, 4 equivalents) and trimethylsilylchloride (0.23 g, 2.13 mmol, 4 equivalents). The reaction mixture was stirred at room temperature for 24 hours and then water was added. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo* to a clear oil and purified by silica gel column chromatography (hexanes/EtOAc, 99:1). Yield is 210 mg, 93%. $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 1.48 (s, 6H), 0.18 (s, 18H), 0.15 (s, 18H).
meso-3,4 bis (trimethylsiloxy) 3,4-Dimethyl-hexa-1,5 Diyne  To starting material meso-3,4-Dimethyl-hexa-1,5-diyne-3,4-diol (100 mg, 0.725 mmol, 1 equivalent) in CH₂Cl₂ (5 ml) was added triethylamine (Et₃N) (0.293 g, 2.898 mmol, 4 equivalents) and trimethylsilylchloride (0.31 g, 2.90 mmol, 4 equivalents). The reaction mixture was stirred at room temperature for 24 hours. TLC showed about 25 % remaining starting material so additional Et₃N (0.145 mg, 1.45 mmol, 2 equivalents) and trimethylsilyltriflate (TMSOTf)(100 ul, 0.553 mmol, 0.76 equivalents) was added. After another 5 hours reaction appeared complete and then water was added. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to a clear oil and purified by silica gel column chromatography (hexanes/EtOAc, 95:5). Yield was 180 mg, 88 %. ¹H NMR (300 Hz, CDCl₃): δ 2.41 (s, 2H), 1.55 (s, 6H), 0.167 (s, 18H).
((3R,4S)-3,4-dimethoxy-3,4-dimethylhexa-1,5-diyne-1,6-diyl)bis(trimethylsilane): S. M. D

(3R,4S)-3,4-dimethoxy-3,4-dimethylhexa-1,5-diyne: To starting material D (90 mg, 0.290 mmol, 1 equivalent) was added MeOH (2 ml) and 1N NaOH (2 ml) at room temperature. The reaction was stirred for 3 hours and then saturated ammonium chloride was added (10 ml). This solution was extracted with dichloromethane (3 X 20 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated in vacuo to a white solid.
No purification was necessary. Yield was 50 mg, 100%. $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 3.46 (s, 6H), 2.56 (s, 2H), 1.57 (s, 6H).

**meso-2,3-Diethynyl-2,3-dimethyl-[1,4]dioxane (1c):** 35 mL NaOH (35 w/w % aqueous solution), 35 mL 1,2-dichloroethane, *meso-11* (1.14 g, 8.22 mmol, 1 equivalent) and tetrabutylammonium bromide (0.52 g, 1.64 mmol, 0.2 equivalent) were combined in a flask and stirred thoroughly between 50 to 55 °C for 64 h. Water was added to the reaction (100 mL) and the reaction mixture was extracted with Et$_2$O (4 x 50 mL). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated *in vacuo*. The crude product was purified using silica gel column chromatography (hexanes/ EtOAc, 85:15 to 55:45) to afford 1c as a white solid (0.64 g.
3.90 mmol, 47%). Rf = 0.18 (hexanes/EtOAc, 8:1). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 4.01-3.94 (m, 2H), 3.79-3.71 (m, 2H), 2.59 (s, 2H), 1.58 (s, 6H). $^{13}$C($^1$H) NMR (CDCl$_3$, 75 MHz) $\delta$ 83.41, 74.30, 74.27, 60.87, 21.89. MS (Cl+) calcd for [C$_{10}$H$_{12}$O$_2$ + H]+: 165.0916; found 165.0926.
meso-4,5-Di(trimethylsilylethynyl)-2,2,4,5-tetramethyl-1,3-dioxolane (meso-13):
A mixture of meso-11 (100 mg, 0.354 mmol, 1 equivalent), ρ-TsOH.H2O (3 mg, 0.014 mmol, 0.04 equiv), and 2,2'-dimethoxypropane (55 mg, 0.53 mmol, 1.5 equivalent) in 6 mL cyclohexane was refluxed with a Dean-Stark trap. After 3h, the reaction was concentrated in vacuo to afford a pale yellow oil which was chromatographed on a silica gel column (hexanes/EtOAc, 99:1 to 96:4) to afford meso-13 as a colorless liquid (95 mg, 83%). Rf = 0.32 (hexanes/EtOAc, 8:1). $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.67 (s, 3H), 1.50 (s, 6H), 1.40 (s, 3H), 0.17 (s, 18H). $^{13}$C($^1$H) NMR(CDCl$_3$, 75.5 MHz) δ 110.04, 105.61, 90.75, 80.10, 29.40, 27.34, 24.27, -0.20. Spectral data are consistent with the literature.$^{140}$
**rac-4,5-Di(trimethylsilylthynyl)-2,2,4,5-tetramethyl-1,3-dioxolane (rac-13).** A mixture of rac-12 (0.50 g, 1.8 mmol, 1 equiv), p-TsOH·H2O (0.02 g, 0.1 mmol, 0.06 equiv), and 2,2'-dimethoxypropane (0.45 mL, 0.38 g, 3.67 mmol, 2.1 equiv) in 15 mL of benzene was heated at 50°C for 24 h and then worked up with 10 mL of a saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (3x75 mL). Organic layers were combined, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated in vacuo to a pale yellow oil. The crude product was purified using silica gel column chromatography (hexanes/EtOAc, 100:2) to afford rac-13 as a colorless oil (0.25 g, 44%). Rf = 0.3 (hexanes/EtOAc, 8:1). \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ 1.63 (s, 6H), 1.55 (s, 6H), 0.16 (s, 18H).

\(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\), 75.5 MHz) δ 110.10, 105.59, 91.84, 79.68, 27.53, 24.36, -0.362. The spectral data for this compound are consistent with literature data.\(^{140}\)
rac-4,5-Diethynyl-2,2,4,5-tetramethyl-1,3-dioxolane (rac-1d): 2.5 ml (3.2 equiv) of 1 N NaOH was added to a 5 mL methanol solution of rac-13 (0.25 g, 0.78 mmol, 1 equiv). After 8 h of stirring at room temperature the reaction was worked up with a concentrated solution of ammonium chloride. The aqueous layer was extracted with CH$_2$Cl$_2$ (3x50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to a residue which was purified by flash column chromatography on silica (hexanes/EtOAc, 95:5) to give product rac-1d (0.12 g, 83%) as a white solid. Rf = 0.20 (hexanes/EtOAc, 8:1). $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.58 (s, 2H), 1.70 (s, 6H), 1.57 (s, 6H). $^{13}$C ($^1$H) NMR (CDCl$_3$, 75.5 MHz) δ 110.49, 83.69, 79.43, 75.50, 27.57, 24.54. The spectral data for this compound are consistent with literature data.\textsuperscript{141}
meso-4,5-Diethynyl-2,2,4,5-tetramethyl-1,3-dioxolane (meso-1d): 93 mg of meso-13 (0.29 mmol, 1 equiv) was dissolved in a 10 mL solution of CH₂Cl₂/MeOH (1:1 v/v). Powdered K₂CO₃ (60 mg, 0.432 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 3h. The solid was removed by suction filtration through celite. After removal of solvent in vacuo the crude product was purified by flash column chromatography on silica (hexanes/EtOAc, 95:5) to yield meso-1d as a colorless oil (46 mg, 90%). Rf = 0.22 (hexanes/EtOAc, 8:1). ¹H NMR (CDCl₃, 300 MHz) δ 2.64 (s, 2H), 1.68 (s, 3H), 1.56 (s, 6H), 1.43 (s, 3H). ¹³C(¹H) NMR (CDCl₃, 75.5 MHz) δ 110.49, 84.06, 79.77, 74.79, 29.34, 27.42, 24.09. The spectral data for this compound are consistent with literature data.¹⁴¹
TsBr-mediated cyclization of 1b. Method A. 1b 1a (8.1 mg, 0.0586 mmol, 1.0 equiv), tosyl bromide (46 mg, 0.19 mmol, 3.3 equiv), and 6 mL of benzene were added to a 25 ml pyrex tube. The mixture was outgassed with a stream of argon for 30 minutes, placed inside of an AceGlass photoreactor, and irradiated for 2 h using a 450W medium pressure Hg lamp. The reaction mixture was concentrated in vacuo to a yellow oil. Ph₃CH (11.5 mg, 0.0470 mmol) was added as an NMR internal standard and the yield of 5a determined by $^1$H NMR (68%). The product 5a was purified by silica gel plate chromatography. Crude was purified by silica gel chromatography (Hexanes: Ethyl Acetate 85: 15 to 60: 40).

(1R*,2R*,5E)-dimethyl-3-Bromo-5-(toluenesulfonyl-1-ylidenemethyl)-cyclopent-3-ene-1,2-diol (5a): $^1$H NMR (CDCl₃, 300 MHz) δ 7.76 (d, J = 8.1 Hz, 2H), 7.67 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.21 (s, 1H), 3.03 (s, 1H), 2.61 (s, 1H), 2.44 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H).
$^{13}$C\(^{1}H\) NMR (CDCl\(_{3}, 75\) MHz) \(\delta\) 159.6, 145.5, 144.7, 138.6, 130.3, 127.5, 120.7, 82.0, 80.2, 24.3, 21.9, 20.8.
TsBr-mediated cyclization of 1a. Method A. 1a (11.2 mg, 0.0811 mmol, 1.0 equiv), tosyl bromide (87.6 mg, 0.0877 mmol, 4.6 equiv), and 6 mL of benzene were added to a 25 mL pyrex tube. The mixture was outgassed with a stream of argon for 30 minutes, placed inside an AceGlass photoreactor, and irradiated for 2 h using a 450W medium pressure Hg lamp. The reaction mixture was concentrated in vacuo to a yellow oil.
Ph₃CH (10.6 mg, 0.0434 mmol) was added as an internal standard and yield of 5b (56%) was determined by ¹H NMR. Crude was purified by silica gel chromatography (Hexanes: Ethyl Acetate 85: 15 to 60: 40).

**(1R*,2S*,5E)-dimethyl-3-Bromo-5-(toluenesulfonyl-1-ylidenemethyl)-cyclopent-3-ene-1,2-diol: (5b).** ¹H NMR (CD₃CN, 300 MHz) δ 7.75 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 7.40 (s, 1H), 6.13 (s, 1H), 3.66 (s, 1H), 3.56 (s, 1H), 2.42 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H). ¹³C{¹H} NMR (CD₃CN, 75 MHz) δ 162.22, 150.10, 145.20, 140.80, 131.61, 128.50, 128.42, 120.17, 118.90, 85.31, 84.77, 26.67, 24.28, 22.24. MS (ESI+) calcd for [C₁₅H₁₇BrO₄Na]⁺: 394.9929; found 394.9930.
**TsBr-mediated cyclization of 1d. Method A.** 1d (14.0 mg, 0.079 mmol, 1.0 equiv), tosyl bromide (26.0 mg, 0.11 mmol, 1.3 equiv), and 6 mL of CH$_3$CN were combined in a 25 ml pyrex tube. The mixture was outgassed with a stream of argon for 30 minutes, placed inside an AceGlass photoreactor, and irradiated for 13 h using a 450 W medium
pressure Hg lamp. The reaction mixture was concentrated in vacuo to a brown oil. Ph₃CH (11.7 mg, 0.0479 mmol) was added as an internal standard and the yield (E-5d (37%), Z-5d (8%) and 6d (9%)) determined by ¹H NMR. Products E-5d, Z-5d and 6d were isolated and purified by silica gel plate chromatography (hexanes/EtOAc, 95:5).

(3aS*,6aS*,6E)-4-bromo-2,2,3a,6-tetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole (E-5d). ¹H NMR (CDCl₃, 300 MHz) δ 7.76 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.17 (s, 1H), 2.43 (s, 3H), 1.37 (s, 3H), 1.36 (s, 6H), 1.14 (s, 3H). ¹³C(¹H) NMR (CDCl₃, 75 MHz) δ 156.99, 146.84, 144.42, 138.37, 129.96, 129.29, 127.22, 121.07, 111.38, 91.33, 87.68, 29.77, 26.87, 21.60, 21.42, 20.11.
(3aS*,6aS*,6E)-4Bromo-2,2,3a,6a-tetramethyl-6-(bromo-1-ylidenemethyl)-cyclopenta[1,3]dioxole (6d): $^1$H NMR (CDCl$_3$, 300 MHz) $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 6.67 (d, $J$ = 1.2Hz, 1H), 6.24 (d, $J$ = 0.9Hz, 1H), 1.42 (s, 6H), 1.35 (s, 3H), 1.32 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$, 75 MHz) $\delta$ 149.2, 139.6, 131.4, 110.9, 101.7, 93.9, 87.6, 30.1, 27.5, 21.4, 20.3.
(3aS*,6aS*,6Z)-4-bromo-2,2,3a,6a-tetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole (Z-5d): $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.88 (d, $J$ = 8.4 Hz, 2H), 7.32 (d, $J$ = 7.8 Hz, 2H), 6.29 (s, 1H), 6.21 (s, 1H), 2.43 (s, 3H), 1.85 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 0.89 (s, 3H). $^{13}$C($^1$H) NMR (CDCl$_3$, 75 MHz) $\delta$ 159.1, 144.6, 143.9, 139.2, 134.4, 129.8, 128.5, 123.9, 112.2, 93.4, 87.8, 30.1, 26.4, 22.7, 21.9, 21.1.
(3aS*,6aR*,6E)-4-p-ethynl anisole-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-

ylidemethyl)-cyclopenta[1,3]dioxole: Starting material A (20 mg, 0.050 mmol, 1. equivalent), Cul (1 mg, 0.005 mmol, 0.1 equivalents), PdCl₂(PPh₃) and diisopropylamine (1 ml) were combined in a reaction vessel and subjected to oxygen removal using a freeze-pump-thaw method. P-methoxy phenyl acetylene (7.3 mg, 0.055 mmol, 1.1 equivalents) was then added and reaction took place in a sealed tube at 90 °C for 4.5 hours. The reaction was worked up by concentration and crude submitted to plate chromatography using hexanes: EtOAc (95:5) to afford compound weighing 7 mg. Yield is 30 %. ¹H NMR (300 Hz, CDCl₃): δ 7.78 (d, J = 8.1 Hz, 2H), 7.55 (1H, s), 7.49 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 9 Hz, 2H), 6.18 (1H, s), 3.85 (3H, s), 2.43 (3H, s), 1.55 (3H, s), 1.47 (3H, s), 1.37 (6H, s), 1.11 (3H, s). ¹³C NMR (75 Hz, CDCl₃): δ 160.9, 160.0, 144.4, 144.0, 138.9, 134.3, 130.5, 130.2, 127.4, 121.4, 114.5, 111.2, 102.8, 91.2, 88.5, 83.7, 55.6, 30.0, 27.2, 21.9, 21.8, 20.6. MS (Cl⁺) calcd for [C₂₇H₂₈O₅S+ Na⁺]: 487.16; found 487.1545.
(3aS*,6aR*,6E)-4-aminobutyl-2,2,3a,6atetramethyl-6-
toluenesulfonyl-1-yldenemethyl)-cyclopenta[1,3]dioxole: Starting
material A (15 mg, 0.038 mmol, 1 equivalent) and 1 ml n-butylamine
(0.740 g, 10.1 mmol, 270 equivalents) were added to a 10 ml single
neck round bottom flask. The mixture was heated to a reflux of 78 °C for one hour until no
starting material was observed (via TLC). The reaction was then cooled, concentrated, and
finally purified by plate chromatography using 10 % EtOAc in hexanes. Yield by 1H NMR is 53%
(bibenzyl as internal standard). 1H NMR (300 Hz, CDCl3) δ 7.78 (d, J = 8.2 Hz, 2H), 7.25 (d,
J = 8.1 Hz, 2H), 5.91 (s, 1H), 5.65 (s, 1H), 4.54 (t, J = 5.5 Hz, 1H), 3.22 (dq, J = 13.0 Hz, 6.5 Hz,
1H), 3.19 (dq, J = 13.3 Hz, 6.7 Hz, 1H), 2.39 (s, 3H), 1.60 (cv, J = 7.3 Hz, 2H), 1.41 (sx, J = 7.4
Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.05 (s, 3H), 0.96 (t, J = 7.4 Hz, 3H). 13C NMR
(75 Hz, CDCl3): δ 163.9, 162.8, 142.8, 141.4, 129.6, 126.6, 110.8, 106.9, 92.8, 89.2, 87.9, 44.5,
31.0, 29.9, 27.0, 21.7, 21.6, 20.3, 20.2, 14.0. MS (ESI+) calcd for [C22H31NO4S+ H]+: 406.20;
found 406.2038.

Modified procedure: To a 10 ml single neck flask was added starting material A (15 mg, 0.038
mmol, 1 equivalent), n-butylamine (prepared from stock solution, 6 mg, 0.075 mmol, 2
equivalents), potassium carbonate (10 mg, 0.072 mmol, 2.0 equivalents) and 1 ml t-butanol.
The reaction was heated to reflux (82 ° C). After an additional 6 hours, more n-butylamine (6
mg, 0.075 mmol, 2 equivalents) was added and the reaction was heated at reflux for an
additional 30 hours at which time crude NMR showed complete conversion of starting material.
Starting material A (15 mg, 0.038 mmol, 1 equivalent) and 1 ml diethylamine (0.707 g, 9.68 mmol, 254 equivalents) were combined and reacted in a sealed tube at 90 °C for 13 hours. At this time the reaction was cooled, concentrated, and purified by plate chromatography using 15 % EtOAc in hexanes. Yield by $^1$H NMR is 38 % (benzyl phenyl ether as internal standard) $^1$H NMR (300 Hz, CDCl$_3$): δ 7.77 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 7.8$ Hz, 2H), 5.81 (s, 1H), 5.53 (s, 1H), 3.34 (cv, $J = 6$ Hz, 2H), 2.38 (s, 3H), 1.422 (s, 3H), 1.357 (s, 6H), 1.200 (t, $J = 7.2$ Hz, 6H), 1.10 (s, 3H).
Starting material A (15 mg, 0.038 mmol, 1 equivalent), and sodium methoxide (4 mg, 0.074 mmol, 2 equivalents) and 1 ml methanol were combined in a 10 ml single neck round bottom flask and heated to a reflux of 65 °C for eight hours. Because TLC at this time indicated presence of some starting material, additional sodium methoxide (8 mg, 0.148 mmol, 4 equivalents) was added and the reaction was heating again to a reflux for 10 more hours. Still some starting material remained, with product to starting material ratio of about 3:1 (via TLC). Again more sodium methoxide (8 mg, 0.148 mmol, 4 equivalents) was added and the reaction was heated at reflux for another 12 hours, at which time little starting material remained (via TLC). The reaction was then cooled, concentrated and purified by plate chromatography using 15 % EtOAc in hexanes to a solid weighing 7 mg. Yield is 53 %. $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.76 (d, $J = 8.1$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 6.39 (s, 1H), 5.95 (s, 1H), 3.91 (s, 3H), 2.41 (s, 3H), 1.33 (s, 9H), 1.07 (s, 3H). $^{13}$C NMR (75 Hz, CDCl$_3$): $\delta$ 174.17, 160.73, 143.58, 139.78, 129.74, 129.64, 114.81, 111.07, 97.47, 88.02, 87.09, 58.50, 29.64, 27.00, 21.61, 21.53, 18.53. MS (ESI+) calcd for [C19H24O5S+ Na]+: 387.12; found 387.1241.
(3aS,6aS,E)-2,2,3a,6a-tetramethyl-6-(tosylmethylene)dihydro-3aH-cyclopenta[d][1,3]dioxol-4(5H)-one: Starting material A (17 mg, 0.043 mmol, 1 equivalent), potassium hydroxide (10 mg, 0.18 mmol, 5 equivalents) 18-crown-6 (12 mg, 0.045 mmol, 1 equivalent) and 1 ml benzene were combined in a 10 ml single neck round bottom flask and heated to a reflux of 80 °C for eighteen hours. At this time no starting material remained (TLC control). The reaction was subsequently cooled, concentrated, and purified by plate chromatography using 10 % EtOAc in hexanes to 25 % EtOAc in hexanes. Yield by $^1$H NMR is 25 % (benzyl phenyl ether as an internal standard). $^1$H NMR (300 Hz, CDCl$_3$): δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 6.401 (s, 1H), 4.23 (dd, $J = 15.6$ Hz, 1.2 Hz, 1H), 4.14 (dd, $J = 15.9$ Hz, 0.9 Hz, 1H), 2.46 (s, 3H), 1.36 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.04 (s, 3H). $^{13}$C NMR (75 Hz, CDCl$_3$): δ 145.66, 130.14, 128.41, 112.54, 89.03, 84.43, 54.41, 30.01, 27.60, 21.65, 19.30, 16.68. MS (ESI +) calcd for [C$_{18}$H$_{22}$O$_5$S+Na]$^+$: 373.11; found 373.1075.
trimethyl((3aS,6aS,E)-2,2,3a,6a-tetramethyl-6-(tosylmethylene)-6,6a-
dihydro-3H-cyclopenta[d][1,3]dioxol-4-yl)stannane: Starting material A
(5 mg, 0.0125 mmol, 1. equivalent), Pd(PPh₃)₄ (1 mg, 8.0 x 10⁻⁴ mmol, 0.05
equivalents), hexamethylditin (8 mg, 5 µl, 0.0241 mmol, 2 equivalents) and
benzene were combined and then subjected to a stream of argon for 20 minutes. After this
outgassing the contents were heated to 120 °C for 15 hours in a sealed tube. The reaction was
subsequently cooled, worked up by concentration, and purified by plate chromatography using
10 % EtOAc in hexanes to a solid weighing 2 mg. Yield is 33 %. ¹H NMR (300 Hz, CDCl₃): δ
7.77 (d, J = 8.4 Hz, 2H), 7.42 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 6.06 (s, 1H), 2.42 (s, 3H), 1.34 (s,
6H), 1.31 (s, 3H), 1.26 (s, 3H), 0.31 (s, 9H). ¹³C NMR (75 Hz, CDCl₃): δ 164.37, 157.36,
148.30, 140.10, 137.13, 134.07, 134.02, 131.46, 124.08, 124.05, 114.62, 100.52, 92.29, 73.19,
64.64, 63.47, 34.40, 31.79, 25.84, 25.44, 25.29, 18.48.
(3aS,6aS,E)-6-(isobutylthio)-2,2,3a,6a-tetramethyl-4-(tosylmethylene)-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxole: To a 10 ml single neck flask added sodium hydride (60 mol % as mineral oil dispersion, 75 mg, 1.88 mmol, 50 equivalents) and isobutylmercaptan (300 µl, 2.79 mmol, 75 equivalents) in 1 ml tetrahydrofuran. The contents were heated to 40 °C for 15 minutes to ensure formation of thiolate. At this time starting material A (15 mg, 0.038 mmol, 1 equivalent) was added and the reaction mixture was heated to reflux (66 °C) for 12 hours. The reaction was subsequently cooled, worked up by extractions with methylene chloride (3 x 10 ml), dried over sodium sulfate, and concentrated. Crude product was purified by plate chromatography using 5 % EtOAc in hexanes. Yield is 47 % by ¹H NMR (internal standard dibenzyl ether). ¹H NMR (300 Hz, CDCl₃): δ 7.76 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.92 (s, 1H), 5.93 (s, 1H), 2.85 (dd, J = 2.4 Hz, 6.6 Hz, 2H), 2.42 (s, 3H), 2.05-1.96 (m, 1H), 1.38 (s, 6H), 1.349 (s, 3H), 1.33 (s, 3H), 1.104 (s, 3H), 1.077 (s, 3H). ¹³C NMR (75 Hz, CDCl₃): δ 170.48, 164.98, 159.15, 155.68, 146.99, 143.75, 139.52, 138.11, 129.71, 126.85,
(3aS*,6aR*,6E)-4-phenyl-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidinemethyl)-cyclopenta[1,3]dioxole: To a single neck 10 ml flask added starting material A (12 mg, 0.0301 mmol, 1 equivalent) followed by Pd(Ph3)4 (3.4 mg, 0.003 mmol, 0.1 equivalents), sodium carbonate (4 mg, 0.038 mmol, 1.25 equivalents), phenyl boronic acid (4 mg, 0.033 mmol, 1 equivalent) and 2 ml of tetrahydrofuran. The contents were outgassed with a stream of argon for 20 minutes and then heated to 50°C for 15 hours. Significant starting material remained (TLC control) so contents were heated at reflux (66 °C) for 48 hours at which time no starting material remained by TLC. The reaction was subsequently cooled, concentrated, and purified by plate chromatography using 15 % EtOAc in hexanes to a pure compound weighing 1 mg (10 % yield).

$^1$H NMR (300 Hz, CDCl3): δ 7.76 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 5.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.47 (dd, J = 6 Hz, 1.5 Hz, 1H), 6.202 (s, 1H), 2.42 (s, 3H), 1.348 (s, 12 H).
To a 10 ml single neck flask was added starting material A (15 mg, 0.038 mmol, 1 equivalent) and 0.5 ml cyclohexylamine (8.76 mmol, 233 equivalents). The contents were heated to 80 °C and the reaction was monitored by TLC until no starting material remained after 12 hours. At this time the reaction was cooled, concentrated, and purified by plate chromatography using 10 % EtOAc in hexanes. Yield by $^1$H NMR is 30 % (internal standard is dibenzyl malonate). $^1$H NMR (300 Hz, CDCl$_3$) δ 7.77 (d, J = 9 Hz, 2H), 7.235 (d, J = 9 Hz, 2H), 5.85 (s, 1H), 5.63 (s, 1H), 4.50 (d, J = 6 Hz, 1H), 3.35-3.23 (m, 1H), 2.38 (s, 3H), 2.02-1.93 (m, 3H), 1.80-1.60 (m, 6H), 1.47-1.10 (m, 4H), 1.32 (s, 6H), 1.31 (s, 3H). $^{13}$C NMR (75 Hz, CDCl$_3$): δ 162.75, 162.62, 142.59, 141.13, 131.10, 130.12, 129.27, 128.94, 128.37, 126.36, 125.92, 110.47, 106.19, 92.41, 88.63, 87.62, 52.76, 32.65, 31.97, 29.59, 26.63, 25.48, 25.54, 24.47, 21.66, 21.25, 20.09. MS (ESI+) calcd for [C$_{24}$H$_{33}$NO$_4$S+ H]$^+$: 432.22; found 432.2192.
(3aS*,6aR*,6E)-4-isoproxy-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask added starting material A (15 mg, 0.038 mmol, 1 equivalent) and potassium isopropoxide (prepared from stock solution; 15 mg, 0.113 mmol, 3 equivalents) in isopropanol (2 ml). The contents were heated to a reflux of 82 °C for several hours until no starting material remained (TLC control). At this time the reaction was cooled, concentrated and purified by plate chromatography using 10 % EtOAc in hexanes. [Note: A stock solution of potassium isopropoxide (0.25 M) was prepared from isopropanol and sodium metal and then used for this reaction.] Yield by $^1$H NMR is 23 % (internal standard is dibenzyl malonate). $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.76 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 10.5$ Hz, 2H), 6.30 (s, 1H), 5.92 (s, 1H), 4.55 (6 Hz), 2.41 (s, 3H), 1.06 (s, 6H), 0.092 (d, $J = 13.5$ Hz, 2H). $^{13}$C NMR (75 Hz, CDCl$_3$): $\delta$ 172.40, 161.33, 143.45, 140.01, 129.59, 126.68, 113.82, 110.79, 100.14, 97.61, 87.47, 87.45, 74.23, 29.62, 26.90, 21.53, 21.07, 18.62, 1.03. MS (ESI +) calcd for
[C_{19}H_{24}NO_4S + Na]^+: 371.13; found 371.13. MS (ESI +) calcd for [C_{21}H_{28}NaO_5S + Na]^+: 415.16; found 415.1.
(3aS*,6aR*,6E)-4-methyl-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-yldienemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask was added starting material A (15 mg, 0.0376 mmol, 1 equivalent) and 1 ml THF. A 1.4 M toluene-THF solution of methyl magnesium bromide (200 µl, 0.280 mmol, 7.5 equivalents) was added slowly via microsyringe. After 3 hours TLC indicated mainly unreacted starting material, so the reaction was subsequently heated at a reflux of 66°C for four more hours. At this time TLC indicated mainly unreacted starting material along with appearance of a new spot indicating possible product formation. Again, more 1.4 M methylmagnesium bromide (200 µl, 0.280 mmol, 7.5 equivalents) was added and the reaction mixture was allowed to reflux for 16 more hours. TLC indicated some reaction progress along with significant amounts of starting material. Copper iodide (1 mg, 0.005 mmol, 0.1 equivalents) was then added to the reaction mixture and the reaction was refluxed for another 9 hours. At
this time more 1.4 M methylmagnesium bromide (200 µl, 0.280 mmol, 7.5 equivalents) was added and reaction was refluxed for an additional 15 hours. Finally, with some starting material remaining (TLC control) reaction was cooled, concentrated, and purified by plate chromatography using 5% EtOAc in hexanes to a solid weighing 2 mg. Yield is 15%. $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.76 (d, $J$ = 8.1 Hz, 2H), 7.30 (d, $J$ = 8.1 Hz, 2H), 7.06 (s, 1H), 6.08 (s, 1H), 2.42 (s, 3H), 2.01 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H), 0.881 (s, 3H). MS (ESI +) calcd for [C$_{19}$H$_{24}$NO$_4$S+ Na]+: 371.13; found 371.13.

(3aS*,6aR*,6E)-4-toluenesulfonyl-2,2,3a,6-tetramethyl-6-(toluenesulfonyl-1-yldenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask added starting material A (10 mg, 0.025 mmol, 1 equivalent), 1 ml DMF, and $p$-toluenesulfinic acid sodium salt (13 mg,
0.073 mmol, 3 equivalents). The contents were heated to a reflux of 80 °C for 30 minutes. At this time the reaction was cooled, concentrated and purified by plate chromatography using 15 % EtOAc in hexanes. Yield by \(^1\)H NMR is 66 % (benzyl ether as internal standard). \(^1\)H NMR (300 Hz, CDCl\(_3\)): \(\delta\) 8.07 (s, 1H), 7.88 (d, \(J = 8.4\) Hz, 2H), 7.74 (d, \(J = 8.4\) Hz, 2H), 7.36 (t, \(J = 8.1\) Hz, 4H), 6.44 (s, 1H), 2.47 (s, 3H), 2.46 (s, 3H), 1.53 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 0.68 (s, 3H). \(^13\)C NMR (75 Hz, CDCl\(_3\)): \(\delta\) 157.71, 155.04, 145.28, 145.10, 137.48, 136.95, 135.02, 130.15, 129.82, 128.99, 128.59, 127.55, 111.92, 90.43, 90.35, 77.81, 77.80, 77.42, 77.20, 77.00, 76.58, 29.71, 29.41, 21.71, 21.65, 21.53, 20.93. MS (ESI +) calcd for \([C_{25}H_{28}O_6S_2 + Na]^+\): 511.12; found 511.1.
(3S*,6aR*,6E)-4-imdazole-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask added starting material A (20 mg, 0.050 mmol, 1 equivalent), 1 ml dimethoxyethane, imidazole (4mg, 0.059 mmol, 1.2 equivalents), copper iodide (1 mg, 0.005 mmol, 0.1 equivalents), potassium carbonate (12 mg, 0.087 mmol, 1.5 equivalents), and L-proline (6mg, 0.052 mmol, 1.05 equivalents). The reaction mixture was refluxed for 48 hours at which time water was added. The reaction was then worked up by extraction with methylene chloride (3 x 10 ml). The organic layers were combined, dried over sodium sulfate, concentrated, and purified by plate chromatography using 15 % EtOAc in hexanes to a solid weighing 6 mg. Yield is 31 %. 1H NMR (300 Hz, CDCl3) δ 8.13 (s, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.43 (s, 1H), 7.33 (d, J = 9.9 Hz, 2H), 7.31 (s, 1H), 7.20 (s, 1H), 6.24 (s, 1H), 2.43 (s, 3H), 1.49 (s, 3H), 1.41 (s, 6H), 1.13 (s, 3H). 13C NMR (75 Hz, CDCl3): 155.99, 144.41, 138.57, 129.96, 128.32, 127.14, 121.41, 112.15, 111.90, 88.99, 88.78, 63.01, 62.55,
60.36, 29.70, 27.18, 21.59, 20.838, 20.38, 14.20, 13.20. MS (ESI +) calcd for [C$_{21}$H$_{25}$N$_2$O$_4$S + H]$^+$: 401.15; found 401.15.
(3aS*, 6αR*, 6E)-4-aminoallyl-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidinemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask was added starting material A (10 mg, 0.025 mmol, 1 equivalent) and 1 ml allylamine (0.763 g, 13.36 mmol, 534 equivalents). The reaction mixture was refluxed (98 °C) and progress of reaction was monitored (by ^1H NMR). Complete consumption of starting material and appearance of a new product was apparent after 12 hours. The reaction was reheated in attempts to transform this initial product, via a subsequent aza-cope reaction. After an additional 5 hours of heating at reflux no new products had emerged. At this time the reaction was cooled, concentrated, and then purified by plate chromatography (EtOAc/ hexanes 8:92 to 12:88) to afford a white compound weighing 3 mg. Yield is 30%. ^1H NMR (300 Hz, CDCl3): δ 7.76 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.94 (1H, s), 5.91-5.82 (m, 1H), 5.67 (s, 1H), 5.29 (dd, J = 15.6 Hz, 1.2 Hz, 1H), 5.24 (dd, J = 10.2 Hz, 1.2 Hz, 1H), 4.67 (m, 1H), 3.83 (t, J = 5.7 Hz, 5.7 Hz, 2H), 2.39 (s, 3H), 1.33 (s, 9H), 1.028 (s, 3H). ^13C NMR (75 Hz, CDCl3): δ 171.11, 163.25, 162.57, 147.18, 142.69, 140.99,
132.58, 129.32, 129.25, 128.95, 126.49, 126.38, 126.31, 126.28, 126.13, 117.65, 110.66, 107.67, 93.41, 88.94, 87.56, 60.37, 55.27, 46.88, 29.68, 26.72, 21.47, 21.42, 21.02, 19.93, 14.186. MS (ESI +) calcd for [C21H26NO4S+ Na + H]+: 412.16; found 412.2.
\[ {^1}H\text{ NMR (300 Hz, C}_6\text{D}_6):\ \delta 8.013\ (d, J = 8.4\ \text{Hz}, 2\text{H}),\ 6.8015\ (d, J = 8.4\ \text{Hz}, 2\text{H}),\ 6.343\ (s, 1\text{H}),\ 6.013\ (s, 1\text{H}),\ 5.419-5.291\ (m, 1\text{H}),\ 4.9385\ (ddd, J = 7.8\ \text{Hz}, 3.0\ \text{Hz}, 1.5\ \text{Hz}, 1\text{H}),\ 4.893\ (t, J = 1.2\ \text{Hz}, 1\text{H}),\ 3.924\ (s, 1\text{H}),\ 3.585-3.541\ (m, 1\text{H}),\ 3.172-3.108\ (m, 1\text{H}),\ 1.867\ (s, 3\text{H}),\ 1.272\ (s, 3\text{H}),\ 1.078\ (s, 6\text{H}),\ 0.918\ (s, 3\text{H}).\]
(3aS*,6aR*,6E)-4-piperidine-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask was added starting material A (15 mg, 0.038 mmol, 1 equivalent) and 1 ml piperidine (10.12 mmol, 270 equivalents). The reaction mixture was refluxed (106 °C) for 12 hours and then cooled and concentrated. Crude product was purified by plate chromatography using 15 % EtOAc in hexanes. Yield by ¹H NMR is 48 % (benzyl phenyl ether internal standard). ¹H NMR (300 Hz, CDCl₃): δ 7.76 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 5.95 (s, 1H), 5.54 (s, 1 H), 2.95 (bs, 4H), 2.38 (s, 3H), 1.67 (bs, 6H), 1.40 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.12 (s, 3H). ¹³C NMR (75 Hz, CDCl₃): δ 168.08, 166.97, 146.90, 146.50, 133.59, 130.64, 114.88, 111.10, 96.90, 93.22, 91.80, 81.71, 81.29, 80.86, 48.63, 35.08, 33.93, 30.99, 25.74, 25.65, 24.32, 18.00. MS (ESI+) calcd for [C23H31NO4S+ Na]+: 440.19; found 440.1853.
(3aS*,6aR*,6E)-4-allyloxy-2,2,3a,6-tetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask was added starting material A (30 mg, 0.075 mmol, 1 equivalent) and sodium allyl alkoxide (100 μl, 87 mg, 1.5 mmol, 20 equivalents) in (1 ml allyl alcohol (0.854 g, mmol, 14.7 mmol, 196 equivalents). The reaction mixture was refluxed (97 °C) and progress of reaction was monitored (by ¹H NMR). Complete consumption of starting material and appearance of a new product was apparent after 12 hours. The reaction was reheated in attempts to transform this initial product, via a subsequent Cope reaction. After an additional 24 hours of heating at reflux, initial product remained. At this time the reaction was cooled, concentrated, and then purified by plate chromatography using 8 % EtOAc in hexanes to 15 % EtOAc in hexanes to yield 7 mg of product. Yield is 25 %. ¹H NMR (300 Hz, CDCl₃): δ 7.73 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.38 (s, 1H), 5.95-5.90 (m, 1H), 5.95 (s, 1H), 5.44 (d, J = 17.4 Hz, 1H), 5.39 (d, J = 11.7 Hz, 1H) 4.61 (m, 2H), 2.41 (s, 3H), 1.34 (s, 9H), 1.05 (s, 3H). ¹³C NMR (75 Hz, CDCl₃): δ 172.72, 160.96, 143.54, 139.18, 131.14, 129.62, 126.73,
In deuterated CDCl3
In deuterated C6D6

(3aS,6aS,E)-2,2,3a,6a-tetramethyl-6-(1-tosylbut-3-enylidene)dihydro-3aH-cyclopenta[d][1,3]dioxol-4(5H)-one: To purified allyl vinyl ether product (10 mg, 0.026 mmol) was added 1ml of deuterated benzene. The reaction was refluxed for 36 hours, carefully monitoring the reaction for progression to final product, at which time the reaction was cooled and concentrated. The resulting crude product was purified by plate chromatography using 15 % EtOAc in hexanes to provide ca. 6 mg of product. Yield is 60 %.

δ 7.85 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 5.74-5.69 (m, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 6 Hz, 1H), 4.30 (d, J = 13.5 Hz, 2H), 4.20 (d, J = 13.5 Hz, 2H), 3.23-3.15 (m, 2H), 2.48 (s, 3H), 1.48 (s, 3H), 1.38 (3H), 1.35 (s,3H), 1.12 (s, 3H). δ 202.58, 155.97, 145.48, 142.53, 137.49, 131.87, 130.18, 127.98, 117.57, 111.93, 88.16, 84.52, 54.89, 30.06, 29.69, 28.14, 27.82, 21.68, 20.08, 16.91, 14.09.
3-phenyl-2-((3aS,6aR,E)-2,2,3a,6a-tetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[d][1,3]dioxol-4-ylamino)propanoic acid: To a 10 ml single neck flask added starting material A (20 mg, 0.050 mmol, 1 equivalent), 1.5 ml dimethoxyethane, L-phenyl alanine (9 mg, 0.073 mmol, 1.45 equivalent), copper iodide (1 mg, 0.005 mmol, 0.1 equivalents), and potassium carbonate (12 mg, 0.087 mmol, 1.5 equivalents). The reaction mixture was refluxed (97 °C) for 72 hours at which time TLC showed significant starting material remaining. More copper iodide (1 mg, 0.005 mmol, 0.1 equivalents) was added and the reaction was refluxed for another 5 more days with intermittent TLC evaluation of reaction. At this time the reaction was worked up by extraction with methylene chloride (3 x 10 ml), organic layers were combined, dried over sodium sulfate, concentrated to a crude solid and purified by plate chromatography using (Hexanes: EtOAc 90:10) to a white solid weighing 3 mg (18 % yield).
$^1$H NMR (300 Hz, CDCl$_3$) $\delta$ 8.066 (s, 1H), 7.8755 (d, $J = 8.1$ Hz, 2H), 7.7405 (d, $J = 8.1$ Hz, 2H), 7.40-7.28 (m, 5H), 6.441 (s, 1H), 2.465 (s, 3H), 2.448 (s, 3H), 1.580 (s, 3H), 1.527 (s, 3H), 1.299 (s, 3H), 1.236 (s, 3H).
(3aS*,6aR*,6E)-4-butyl-2,2,3a,6-tetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To a 10 ml single neck flask was added starting material A (15 mg, 0.038 mmol, 1. equivalent)
Pd(PPh₃)₄ (2.2 mg, 0.0019 mmol, 0.05 equivalents) copper iodide (1 mg, 0.0052507 mmol, 0.14 equivalents) CsF (11.4 mg, 0.0750 mmol, 2.0 equivalents) in DMF (1 ml). The reaction mixture was heated (80 °C) for 15 hours and then cooled and concentrated. Crude product was purified by plate chromatography (Hexanes: Ethyl Acetate 95:5) to solid weighing 3 mg (21% yield) (Reaction was also repeated without the additive cesium fluoride and gave the same results). ¹H NMR (300 Hz, CDCl₃): δ 7.63 (d, J = 6 Hz, 2H), 7.30 (d, J = 6 Hz, 2H), 7.05 (s, 1H), 6.08 (s, 1H), 2.42 (s, 3H), 1.56 (s, 6H), 1.70-1.58 (m, ), 1.46-1.24 (m, ), 1.05-0.87 (m, ) 1.02 (s, 3H), 0.97 (m, 3H). ¹³C NMR (75 Hz, CDCl₃): δ 193.44, 156.30, 154.93, 144.65, 142.89, 138.13, 134.39, 131.35, 130.04, 127.35, 124.76, 111.47, 90.47, 89.27, 53.39, 29.86, 27.14, 20.67, 20.40, 17.53, 13.57, 1.01. MS (ESI +) calcd for [C₂₂H₃₀O₄S+ Na]+: 413.14; found 413.2.
(3aS,6aR,E)-6-(but-3-enyl)-2,2,3a,6a-tetramethyl-4-(tosylmethyleno)-
4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxole

$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 9.70 (d, $J = 8.1$ Hz, 1H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.68 (s, 1H), 7.34 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 16.2$ Hz, 1H), 6.83 (dd, $J = 16.2$ Hz, 7.8 Hz, 1H), 6.33 (s, 1H), 2.44 (s, 3H), 1.56 (s, 3H), 1.43 (s, 3H), 1.37 (s, 6H), 0.92 (s, 4H).  $^{13}$C NMR (75 Hz, CDCl$_3$): $\delta$ 197.729, 160.583, 159.220, 148.932, 147.421, 138.682, 135.632, 134.327, 131.639, 129.050, 115.758, 94.760, 93.560, 81.287, 80.864, 57.675, 34.147, 31.428, 25.910, 24.956, 24.690.  MS (ESI +) calcd for [C$_{22}$H$_{28}$O$_4$S + Na]+: 411.16; found 411.2.
(3aS*,6aR*,6E)-4-benzthiazole-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole:

To a 10 ml single neck flask was added 2-mercaptobenzoxazole (15 mg, 0.099 mmol, 2 equivalents) in 1 ml dimethyl formamide (DMF). The solution was cooled to 0 °C and sodium hydride (60 mol % dispersion in mineral oil, 2.5 mg, 0.063 mmol, 1.25 equivalents) was added in portions. After stirring for 30 minutes, starting material A (20 mg, 0.050 mmol, 1 equivalent) was slowly added and subsequently the reaction was warmed to room temperature. The reaction mixture was heated (70 °C) for 24 hours and then cooled and concentrated. Crude product was purified by plate chromatography using 15 % EtOAc in hexanes. Isolated yield is 2 mg, 10 %. ¹H NMR (300 Hz, CDCl₃): δ 7.99 (s, 1H), 7.80 (m, 1H), 7.79 (d, J = 9 Hz, 2H), 7.56 (m, 1H), 7.38 (m, 2H), 7.26 (d, J = 9 Hz, 2H), 6.20 (s, 1H), 2.43 (s, 3H), 1.39 (s, 3H), 1.36 (s, 6H), 1.13 (s, 3H). ¹³C NMR (75 Hz, CDCl₃): δ 157.59, 152.42,
151.71, 144.14, 141.57, 144.14, 138.81, 129.82, 127.26, 125.64, 125.52, 124.00, 120.68, 119.89, 111.58, 110.42, 91.59, 88.78, 29.75, 26.88, 21.57, 21.28, 20.67.
(3aS*,6aR*,6E)-4-cyano-2,2,3a,6atetramethyl-6-(toluenesulfonyl-1-ylidenemethyl)-cyclopenta[1,3]dioxole: To starting material A (40 mg, 0.100 mmol, 1 equivalent) in dimethyl formamide (1 ml) was added sodium cyanide (6 mg, 0.122 mmol, 1.22 equivalents). The reaction was stirred overnight at 100 °C for 12 hours and cooled. Water (20 ml) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to a crude solid. Yield by 1H NMR was 25 % (internal standard benzyl phenyl ether). The reaction was purified by silica gel plate chromatography (hexanes/ EtOAc, 95:5). 1H NMR (300 Hz, CDCl₃): δ 8.05 (s, 1H), 7.75 (d, J = 9 Hz, 2H), 7.37 (d, J = 9 Hz, 2H), 6.42 (s, 1H), 2.45 (s, 3H), 1.47 (s, 3H), 1.36 (s, 6H), 1.12 (s, 3H). 13C NMR (75 Hz, CDCl₃): δ 159.973, 149.489, 143.160, 141.559, 135.451,
(3aS,6aS)-6-bromo-2,2,3a,6a-tetramethyl-4-methylene-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxole: To magnesium turnings (40 mg, activated by dry-stirring overnight) was added 2 ml of anhydrous methanol (prepared from distillation of methanol over calcium hydride). A few small bubbles were noticed while this mixture was heated to 50 °C. The reaction was mildly exothermic, but an oil bath was still needed as an external heat source to maintain this temperature. After two hours starting material A (25 mg, 0.063 mmol, 1 equivalent) was added. After two hours of stirring the reaction mixture between 40-45 °C more magnesium turnings (20 mg) were added. After a total of four hours the reaction was quenched with dilute HCL. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and then concentrated in vacuo to a crude oil weighing 12 mg. The reaction was purified by silica gel plate chromatography (hexanes/ EtOAc, 92:8) to
provide a product weighing 3 mg. $^{1}\text{H NMR (300 Hz, CDCl}_3\text{): } \delta 6.40 \text{ (s, 1H), 5.13 (s, 1H), 5.12 (s, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H).}$

To starting material $\text{A (11 mg, 0.0308 mmol, 1 equivalent)}$ was added MgO (2.5 mg, 0.0616 mmol, 2 equivalents), Dudley’s reagent (2-Benzylxy-1-methylpyridinium triflate) (11 mg, 0.0616 mmol, 2 equivalents), and finally $\alpha,\alpha,\alpha$-trifluorotoluene (2 ml). The reaction was heated to 85 °C. After 3 hours, TLC of reaction appeared promising. The reaction was maintained at ca. 85 °C for 15 hours. At this time because starting material was still present according to TLC, more Dudley’s reagent (11 mg, 0.0616 mmol, 2 equivalents) and MgO (2.5 mg, 0.0616 mmol, 2 equivalents) was added. After five hours of stirring reaction mixture at 85 °C, TLC showed no starting material left and the reaction was worked up. Accordingly, the reaction was diluted with methylene chloride and subsequently poured through a bed of celite and concentrated. The reaction was purified by silica gel plate chromatography (hexanes/EtOAc, 95:5) to provide three products weighing 2 mg each.
Dibenzylated product A': $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.90 (s, 1H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.32-7.22 (m, 4H), 7.19-7.11 (m, 3H) 4.75 (d, $J = 10.5$ Hz, 2H), 4.67 (d, $J = 10.8$ Hz, 2H), 4.33 (d, $J = 10.5$ Hz, 2H), 4.14 (d, $J = 10.5$ Hz, 2H), 2.37 (s, 3H), 1.48 (s, 3H), 1.43 (s, 3H).

Monobenzylated Product B or C: $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.78 (d, $J = 8.1$ Hz, 2H), 7.51 (s, 1H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.29-7.26 (m, 3H), 7.07-7.04 (m, 2H), 6.11 (s, 1H), 4.33 (d, $J = 10.8$ Hz, 2H), 4.13 (d, $J = 10.5$ Hz, 2H), 2.43 2.27 (s, 1H), 1.43 (s, 3H), 1.40 (s, 3H).
Other Monobenzylated Product: Additional vinyl peak in $^1$H NMR spectrum shown below.
To starting material C (42 mg, 1 equivalents) in toluene (3 ml) under refluxing conditions was added AIBN (2.4 mg, 0.0146 mmol, 0.10 equivalents) and Bu₃SnH (48 mg, 44 uL, 0.1633 mmol, 1.2 equivalents) in toluene (3 ml) via syringe pump. The addition took over an hour. After 15 hours the reaction mixture was worked up by concentration. The products were purified by flash column chromatography (hexanes: ethyl acetate 97:3) to yield two white solids (22mg: 27 % yield (88-2) and 29 mg: 35 % (88-4). ¹H NMR (300 Hz, CDCl₃): δ 7.46 (d, J = 6.7 Hz, 2H), 7.44-7.42 (m, 3H), 7.33 (t, J = 7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 2H), 7.26-7.20 (m, 2H), 6.34 (s, 1H), 1.58 (s, 3H), 1.48 (s, 3H), 1.40-1.30 (m, 4H), 1.25 (sX, J = 7.1 Hz, 4H), 0.87 (t, J = 6.9 Hz, 6H), 0.80-0.70 (m, 4H).¹³C NMR (75 Hz, CDCl₃): δ 158.8, 152.3, 145.5, 136.8, 135.8, 129.7, 129.0, 128.6, 128.5, 128.1, 98.9, 89.1, 29.2, 27.5, 21.9, 18.5, 13.8, 10.7.
\(^1\)H NMR (300 Hz, CDCl\(_3\)): \(\delta\) 7.04 (t, \(J = 7.4\) Hz, 1H), 6.96 (t, \(J = 7.1\) Hz, 1H), 6.91 (t, \(J = 7.7\) Hz, 1H), 6.88 (d, \(J = 9.8\) Hz, 3H), 6.84 (t, \(J = 7.6\) Hz, 3H), 6.74 (s, 1H), 6.72 (d, \(J = 7.4\) Hz, 2H), 1.72 (s, 3H), 1.61 (s, 3H), 1.40-1.30 (m, 4H), 1.22 (sx, \(J = 7.1\) Hz, 3H), 0.84 (t, \(J = 7.3\) Hz, 6H), 0.79 (ddd, \(J = 12.7\) Hz, 10.5 Hz, 6.0 Hz, 2H), 0.71 (ddd, \(J = 12.8\) Hz, 10.8 Hz, 5.8 Hz, 2H). \(^{13}\)C NMR (499 Hz, CDCl\(_3\)): \(\delta\) 157.8, 155.4, 142.2, 137.6, 135.0, 128.9, 128.7, 127.7, 127.2, 127.0, 126.7, 97.2, 92.2, 29.2, 27.4, 20.7, 19.4, 13.8, 11.2.
To starting material D (40 mg, 0.1378 mmol, 1 equivalents) in toluene (3.5 ml) under refluxing conditions was added AIBN (3 mg, 0.0183 mmol, 0.13 equivalents) and Bu₃SnH (52 uL, 56.3 mg, 0.1933 mmol, 1.4 equivalents) in toluene (3.5 ml) via syringe pump. The addition took over an hour. After 15 hours the reaction mixture was worked up by concentration. The products were purified by flash column chromatography (hexanes: ethyl acetate 95:5) to afford two compounds as white solids: 58-2b (25 mg, 31 %) and 58-2c (40 mg, 50 %)

58b ¹H NMR (300 Hz, CDCl₃): δ 7.59 (d, J = 8Hz, 2H), 7.42-7.34 (m, 3H), 7.29 (t, J = 7.7 Hz, 3H), 7.20 (t, J = 9.0 Hz, 3H), 7.19 (d, J = 9.2 Hz, H), 6.09 (s, 1H), 3.23 (s, 1H), 2.25 (s, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.40-1.30 (m, 4H), 1.23 (sx, J = 7.2 Hz, 4H), 0.86 (t, J = 7.2 Hz, 6H), 0.72-0.68 (m, 4H). ¹³C NMR (75 Hz, CDCl₃): δ 158.4, 156.1, 151.1, 138.3, 136.4, 130.5, 129.5, 128.6, 128.4, 128.1, 127.1, 126.3, 87.4, 80.9, 29.3, 27.5, 22.9, 21.9, 13.8, 10.9.
$^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.00 (t, $J = 7.0$ Hz, 1H), 6.96 (t, $J = 7.4$ Hz, 2H), 6.90 (d, $J = 7.2$ Hz, 2H), 6.85 (t, $J = 6.0$ Hz, 2H), 6.83 (t, $J = 7.5$ Hz, 2H), 6.72 (d, $J = 7.2$ Hz, 2H), 6.58 (s, 1H), 2.99 (s, 1H), 2.44 (s, 1H), 1.50 (s, 3H), 1.34 (s, 3H), 1.40-1.30 (m, 4H), 1.22 (sx, $J = 7.1$ Hz, 4H), 0.84 (t, $J = 7.1$ Hz, 6H),
0.80-0.40 (m, 4H). $^{13}$C NMR (75 Hz, CDCl$_3$): $\delta$ 164.5, 152.6, 148.4, 138.7, 136.1, 129.0, 128.9, 128.8, 127.6, 127.0, 126.1, 123.0, 87.0, 84.1, 29.3, 27.6, 23.9, 20.8, 13.9, 11.6.
X-Ray crystal structure: \((3aS^*,6aR^*,6E)-4\text{-}\text{aminobutyl}-2,2,3a,6\text{-}\text{tetramethyl-6-}(\text{toluenesulfonyl-1-ylidenemethyl})\text{-}\text{cyclopenta[1,3]}\text{dioxole}\)
Bu₃SnH (0.116 g, 0.3985 mmol, 1.1 equivalents) was added to a 3 ml THF (tetrahydrofuran) solution of Pd(Cl₂)(PPh₃)₂ (5 mg, 0.0072 mmol, 0.02 equivalents) and starting material meso-3,4-Dimethyl-hexa-1,5-diyne-3,4-diol (1a) (50 mg, 0.362 mmol, 1 equivalent) at room temperature. After 224 hours the reaction was concentrated in vacuo to a black tar. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 98:2 to 88:11) to yield 40 mg of compound. Yield is 26 %. ¹H NMR (300 Hz, CDCl₃): δ 6.343 (s, 2H), 2.475 (s, 1H), 2.268 (s, 1H), 1.53-1.45 (m, 12 H) 1.484 (s, 3H), 1.35 (s, 3H), 1.291 (t, J = 7.2 Hz, 6H), 0.887 (t, J = 7.2 Hz, 9H).
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Also, from a more general perspective, it is hard to reconcile the increased efficiency which is observed only for the Ts radical-mediated reactions with a scenario where the above paths provide major road to the 5-endo products.


Modena; Todesco *Gazzetta Chimica Italiana* **1959**, *89*, 866.


114 SHMO The Simple Hückel Molecular Orbital Theory Calculator http://www.chem.ucalgary.ca/SHMO/index.html


Jason Abrams obtained a Bachelor of Science in chemistry from the University of Florida in the summer of 1996. After working for three years in the pharmaceutical industry in both medicinal chemistry and process development chemistry, notably at Roche, he went to graduate school at the University of Minnesota where he obtained his master of science degree under the joint tutelage of Professor George O'Doherty and Professor Craig Forsyth. There he worked on sugar chemistry routes towards swainsonine and okadaic acid. After completing his master of science in the spring of 2002 he went to work at Abbott Laboratories as a medicinal chemist in the cancer therapeutic area. After a two and a half year stint at Abbott Labs he returned to graduate school at Florida State University in order to complete his Ph.D., where he has been since the Fall of 2005 in the research group of Professor Igor Alabugin.

Publications:


