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Ring-Closing Metathesis Reactions of Acyloxysulfones: Synthesis of γ-Alkylidene Butenolides

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Ring-Closing Metathesis Reactions of Acyloxysulfones: Synthesis of γ-Alkylidene Butenolides

By
Iris T. Phan

Accepted in Partial Completion
Of the Requirements of the Degree
Master of Science

Kathleen L. Kitto, Dean of the Graduate School

ADVISORY COMMITTEE

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Dr. Mark Bussell
MASTER’S THESIS

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Iris Phan
March 29th, 2016
Ring-Closing Metathesis Reactions of Acyloxysulfones: Synthesis of $\gamma$-Alkylidene Butenolides

A Thesis
Presented to
The Faculty of
Western Washington University

In Partial Fulfillment
Of the Requirements for the Degree
Master of Science

By
Iris T. Phan
March 2016
Abstract

As we set out to investigate ring-closing methatesis reactions of acyloxsulfones, we discovered that treatment with triethylamine resulted in its quantitative conversion into the $\gamma$-alkylidene butenolides. $\gamma$-Alkylidene Butenolides are common to a number of biologically important natural products, and have been of great interest. To date, there has been no metathesis-based synthesis of $\gamma$-alkylidene butenolides making our approach the first. Development of the metathesis-based approach has allowed us to synthesize a variety of $\gamma$-alkylidene butenolides from the RCM products in high yields (69-100%). The elimination is proposed to proceed via an E1cb mechanism leading to ($Z$)-$\gamma$-alkylidene butenolides as the major products. In an attempt to showcase this method in the context of complex $\gamma$-alkylidene butenolide natural products, we successfully synthesized two model spirocyclic butenolides (5,5- and 6,5-). The synthesis of the model compounds will lead us one step closer in achieving the total synthesis of a natural spiro-butenolide product.
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Research Advisor: Dr. Gregory W. O’Neil

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## List of Abbreviations

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<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>Diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric ratio</td>
</tr>
<tr>
<td>EAA</td>
<td>Ethyl acetoaceteate</td>
</tr>
<tr>
<td>Et₂N</td>
<td>Triethlyamine</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron withdrawing group</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>Potassium tert-butoxide</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
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</table>
Me  Methyl
MTBE  Methyl tert-butyl ether

\(n\)-BuNH\(_2\)  \(n\)-Butylamine

\(n\)-BuLi  \(n\)-Butyllithium

NBS  \(N\)-Bromosuccinimide

NMR  Nuclear magnetic resonance

OAc  Acetate

o/n  Overnight

Ph  Phenyl

PhMe  Toluene

P(OEt)\(_3\)  Triethyl phosphite

PPh\(_3\)  Triphenylphosphine

ppm  Parts-per-million

Pyr  Pyridine

RCM  Ring-closing metathesis

rt  Room temperature

TBDMS  \textit{tert}-Butyldimethylsilyl

TBDPS  \textit{tert}-Butyldiphenylsilyl

TBS  \textit{tert}-Butyldimethylsilyl

TEA  Triethylamine

TEMPO  \(2,2,6,6\text{-Tetramethylpiperidin-1-yl}\)oxyl, or \(2,2,6,6\text{-tetramethylpiperidin-1-yl}\)oxidanyl

THF  Tetrahydrofuran
Chapter 1. Introduction

1.1 The Utilization of Acyloxysulfone Cross Metathesis in Polyene Synthesis

Olefin metathesis has developed as one of the most widely used carbon-carbon bond-forming reactions in organic and polymer chemistry, particularly with the development of well-defined and functional group tolerant catalysts like those shown in Figure 1. Although catalysts of this type have been successful in synthesizing a wide range of structurally diverse compounds, there are fundamental limitations of olefin metathesis in polyene systems due to the problems associated with chemoselectivity. Chemoselectivity is defined as the preferential outcome of one reaction over a set of plausible reactions. In the absence of chemoselectivity, indiscriminate metathesis occurs in the presence of multiple alkenes. Scheme 1-1 is an example of a non-chemoselective olefin metathesis reaction with no selectivity for cross metathesis, homodimerization, or a competing ring closing metathesis.

![Ru-1](image1.png)  ![Ru-2](image2.png)  ![Ru-3](image3.png)  ![Ru-4](image4.png)

Figure 1-1 Structures of well-defined catalysts
To overcome the shortcomings accompanying poor chemoselectivity, several strategies have been implemented including steric and/or electronic deactivation of one or more alkenes toward metathesis. In 2004, Bouzbouz and coworkers had used steric hindrance to induce regioselective cross metathesis by placing a bulky hydroxy protecting group in olefins of type 1 with olefins of type 2 to produce compounds of type 3 in generally 70% yield or greater (Scheme 1-2).¹

In 2004, Grubbs and coworkers had also studied the use of steric hindrance as well as electronic deactivation for influencing chemoselectivity.² In their study they had tried to deactivate one of the olefins in compound 4 by attaching an electron withdrawing ester group (Scheme 1-3).² It was thought that by attaching an electron withdrawing group, the olefin would no longer coordinate to the metal catalyst which is the first step in the olefin metathesis mechanism. They found that both of the olefins in 4 were too deactivated to react with Ru-3, whereas the more active catalyst Ru-2 reacted with both olefins to yield 6 and 7 as an 80:20
mixture.\textsuperscript{2} Because the ester functionality was not sufficiently deactivating when Ru-2 was used as the catalyst, the electron density in the α,β-double bond was further reduced by introducing a vinylic bromide at the α-carbon (Scheme 1-4). Cross-metathesis between allylbenzene 8 and 9 with Ru-2 showed that the α,β-double bond was sufficiently deactivated relative to the γ,δ-double bond to form the desired product 10 in 68% yield.\textsuperscript{2}

Scheme 1-3 Electronic Deactivation of an Alkene With an Ester

\[
\begin{align*}
\text{4} & \quad \text{Ru-2} \quad \text{5} \\
\text{OEt} & \quad \text{OAc} \\
\end{align*}
\]

\[
\text{6 (E/Z = 10:1)} \quad \text{6:7 = 80/20}
\]

Scheme 1-4 Electronic Deactivation of an Alkene by a Vinylic Bromide Introduction

\[
\begin{align*}
\text{8} & \quad \text{Ru-2} \quad \text{9} \\
\text{Br} & \quad \text{OEt} \\
\text{OEt} & \quad \text{OEt} \\
\end{align*}
\]

\[
\text{10}
\]

Our group has been working on an alternative approach to addressing the problem of chemoselectivity, which involves the idea of ‘masking’ one or more of the alkenes as an inert functional group toward metathesis.\textsuperscript{3} Post-metathesis elimination of the masking elements (X and Y) would then allow for a metathesis approach to different polyenes that have previously been difficult to synthesize by standard metathesis technology (Scheme 1-5).\textsuperscript{4}

Scheme 1-5 Proposed Masking of an Alkene

\[
\begin{align*}
\text{X} & \quad \text{R}_1 \quad \text{Y} \\
\text{R}_2 & \quad \text{metathesis} \\
\text{X} & \quad \text{R}_1 \quad \text{Y} \\
\text{R}_2 & \quad \text{elimination} - \text{XY} \\
\end{align*}
\]

\[
\text{R}_1 \quad \text{R}_2
\]
For this purpose, our group has been investigating the use of β-acyloxsulfones in which X is an acyl group and Y is a sulfone (Scheme 1-6). β-acyloxsulfones are well-known intermediates in the classical Julia olefination reaction. The Julia olefination was first described in 1973 by Julia and Paris as an approach toward olefin synthesis in which β-acyloxsulfones were reductively eliminated to corresponding di-, tri-, and tetra- substituted alkenes. The classical Julia olefination typically occurs in three steps: (1) The first step involves the addition of an α-metallated sulfone to an aldehyde or ketone to produce the β-hydroxysulfone. (2) The β-hydroxysulfone is then acylated with acetic anhydride to generate the corresponding β-acetyloxsulfone. (3) Finally, reductive elimination of both the acyl and sulfone groups with Na/Hg amalgam produces the corresponding trans-alkene predominantly. More recently samarium diiodide has also been shown to promote the β-acyloxsulfone reduction elimination. Originally it was assumed that both the Na/Hg and SmI₂ elimination protocols proceeded via the same mechanism. However further mechanistic studies have proven this to be not entirely correct (vide infra).

Scheme 1-6 Classical Julia Olefination

It was originally proposed that Na/Hg and SmI₂ act both as a single electron donor to produce an alkyl radical that is then further reduced to the alkyl anion. The anion then collapses to produce acetate and the corresponding alkene. Volz and co-workers confirmed that SmI₂ does indeed eliminate in an analogous fashion to the original proposed route; however, they also confirmed that it can eliminate via the route proposed by Marko in 1996. Unlike the
acctyloxsulfone elimination, the mechanism involves first transfer of an electron to the benzoyl group, followed by loss of benzoate and elimination of the sulfone. Volz and co-workers found that the route of elimination was dependent on the substrate structure, more specifically initial loss of either the sulfonyl or benzoyl group. Transfer of the electron is likely reversible, and can occur into both acceptor groups. The rate determining step occurs during formation of the carbon radical, thus depending on the stability of the carbon radical itself; the reductive-elimination can occur through either route.

**Scheme 1-7 Accepted Mechanism for SmI₂ Mediated Reductive Elimination of b-acyloxysulfones**

The current accepted mechanism for acyloxysulfone elimination with Na/Hg amalgam was proposed by Keck in 1995. The first step involves the deprotonation of the acetoxy sulfone leading to the vinyl sulfone. The vinyl sulfone is then reduced to the vinyl radical which is even further reduced to a vinyl anion with sodium as a counterion. The anion is then quenched to produce the desired alkene.
Scheme 1-8 Accepted Mechanism for Na/Hg Amalgam Mediated Reductive Elimination of β-acyloxysulfones

For our purposes, we did not immediately reductively eliminate the β-acyloxysulfones. Rather, our intention was to investigate their use as masked alkenes in metathesis reactions to provide access to polyenes that would otherwise be difficult to synthesize by olefin metathesis (Scheme 1-9). Prior to my own work, the focus had been on cross-metathesis reactions of acyloxysulfones, exemplified by the total synthesis of haminol A (Scheme 1-10). Since both the cross-metathesis reaction and subsequent acyloxysulfone elimination with either Na/Hg or SmI₂ lead to the formation of trans-alkenes, this approach is limited to synthesis of all-trans polyenes.

Scheme 1-9 Synthesis of Polyene Subunits Using β-acyloxysulfone Cross Metathesis

For our purposes, we did not immediately reductively eliminate the β-acyloxysulfones. Rather, our intention was to investigate their use as masked alkenes in metathesis reactions to provide access to polyenes that would otherwise be difficult to synthesize by olefin metathesis (Scheme 1-9). Prior to my own work, the focus had been on cross-metathesis reactions of acyloxysulfones, exemplified by the total synthesis of haminol A (Scheme 1-10). Since both the cross-metathesis reaction and subsequent acyloxysulfone elimination with either Na/Hg or SmI₂ lead to the formation of trans-alkenes, this approach is limited to synthesis of all-trans polyenes.

Scheme 1-9 Synthesis of Polyene Subunits Using β-acyloxysulfone Cross Metathesis
Many natural products, however, include both cis- and trans- olefins such as macrolactin A (Figure 1-2). To further extend the scope of these β-acyloxysulfones as masked alkene intermediates, we set out to investigate incorporation of cis-alkenes by using RCM. RCM stereoselectivity is dependent on the catalyst, ring strain, and starting diene. Z-isomers predominate in smaller rings as the more stable product because it allows for the minimization of ring strain; whereas macrocycles tend to favor E-isomers as it is more thermodynamically stable.\(^\text{11}\) To achieve the cis-alkene we would therefore target smaller rings such as cyclopentenes and cyclohexenes for our RCM.

**Figure 1-2 Natural Product macrolactin A**

### 1.2 Proposed Route Towards the Synthesis of E/Z-Dienoic Acid

Similar to the use of acyloxysulfones in cross metathesis, β-acyloxysulfone RCM substrates would be synthesized via two complementary methods as outlined in Scheme 1-11, β-acyloxysulfones would then undergo RCM to give cis-alkene containing products. With the cis-
alkene formed, it was envisioned that reductive elimination of the acyloxysulfone with either SmI₂ or Na/Hg amalgam would produce the corresponding E,Z-dienoic acid 23 (Scheme 1-12).

Scheme 1-11 Complementary Methods for Synthesizing Acyloxysulfones

\[
\text{BuLi, RCHO} \quad \text{then} \quad \text{Cl} \quad \text{then} \quad \text{Cl} \\
\text{SO₂Ph} \quad \text{CO} \quad \text{SO₂Ph} \\
\text{17} \quad \text{18} \\
\text{R} \quad \text{SO₂Ph} \quad \text{BuLi, OHC} \quad \text{then} \quad \text{Cl} \quad \text{then} \quad \text{Cl} \\
\text{19} \quad \text{20} \\
\]

Scheme 1-12 E,Z-Dienoic Acid Synthesis by Ring-Closing Metathesis/Elimination

\[
\text{RCM} \quad \text{RCM} \\
\text{SO₂Ph} \quad \text{SO₂Ph} \quad \text{SO₂Ph} \quad \text{SO₂Ph} \\
\text{22} \quad \text{20} \quad \text{18} \quad \text{21} \\
\text{R} \quad \text{R} \quad \text{R} \quad \text{R} \\
\text{Sml₂ or} \quad \text{Sml₂ or} \\
\text{Na/Hg} \quad \text{Na/Hg} \\
\text{R} \quad \text{E} \quad \text{Z} \quad \text{cis} \\
\text{23} \\
\]

1.3 Unexpected Synthesis of γ-Alkylidenebutenolides

Our initial investigations began with the synthesis of compounds of type 18 and 20 (Scheme 1-11). One approach involved the addition of lithiated (allylsulfonyl)benzene 17 to benzaldehyde, followed by an in situ acylation with acryloyl chloride affording the dienylacyloxysulfone 18 in 55% yield. The complementary approach involved the addition of lithiated benzyl phenyl sulfone 19 to acrolein followed by acylation with acryloyl chloride to obtain the
acyloxsulfone in 64% yield. An RCM was then performed on the resulting β-acyloxsulfones using Ru-2 as the catalyst (Table 1-1). After several failed attempts to get the six-membered ring to close from compound 18a, we decided to focus solely on the five-membered ring. The first attempt at an RCM on the β-acyloxsulfone 20a gave only a 10% yield, after several attempts to optimize the conditions, we found that the RCM gave the highest yield when toluene was the solvent, the temperature was at 80 °C, and 3 batches of 2.5 mole % of the catalyst was added in 6 hour intervals.

**Table 1-1 Optimization of β-acyloxsulfone RCM**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>10</td>
<td>Toluene</td>
<td>60</td>
<td>0%</td>
</tr>
<tr>
<td>18a</td>
<td>10</td>
<td>Toluene</td>
<td>80</td>
<td>0%</td>
</tr>
<tr>
<td>20a</td>
<td>5</td>
<td>DCM</td>
<td>45</td>
<td>10%</td>
</tr>
<tr>
<td>20a</td>
<td>5</td>
<td>Toluene</td>
<td>60</td>
<td>15%</td>
</tr>
<tr>
<td>20a</td>
<td>3 x 2.5</td>
<td>Toluene</td>
<td>80</td>
<td>64%</td>
</tr>
</tbody>
</table>

As originally proposed, several reductive elimination conditions including the use of Na/Hg amalgam and SmI₂ were then examined to try and achieve the desired E,Z-dienoic acid which is common to a number of important natural products including the previously mentioned macrolactin A (Figure 1-1). After numerous attempts, all that was obtained under various conditions with both reagents was a complex mixture of products and no indication of the desired E,Z-dienoic acid (Scheme 1-12). Unsuccessful with the reductive eliminations, we then set out to investigate a sequential elimination.
The acyl-group would be eliminated first, followed by a reductive cleavage of the resulting vinyl sulfone. This was based on previous work from Keck et al. who had performed similar reactions in which a number vinyl sulfones were prepared by the elimination of acetoxy sulfones with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by the use of SmI$_2$ to reductively cleave the vinyl sulfone (Scheme 1-13). To that end, our RCM product 22a was treated with DBU at room temperature and left to stir overnight in an attempt to produce vinyl sulfone 27 (Scheme 1-14). After obtaining a $^1$H NMR spectrum of the crude product mixture, it was concluded that this reaction did not produce the desired vinyl sulfone but it also had completely destroyed the starting material. In a second attempt to produce the vinyl sulfone, TEA, a milder base was used in place of DBU. From the crude $^1$H NMR there was potential that we had made the desired vinyl sulfone 27, uncertain, the sample was sent off for a mass spectral analysis. Receiving the mass spectrum there was a clear molecular ion peak at m/z =172, unfortunately the vinyl sulfone we were expecting has a molecular weight of 314. From the mass spectrum combined with the $^1$H NMR, it was concluded that elimination with TEA had not produced vinyl sulfone 27. TEA had instead eliminated the phenyl sulfone making the unexpected $\gamma$-alkyldenebutenolide 28.
Scheme 1-13 Sequential Elimination with DBU and SmI$_2$

$$\begin{align*}
\text{R} \text{SO}_2\text{Ph} & \xrightarrow{\text{DBU}} \text{R} \text{SO}_2\text{Ph} & \xrightarrow{\text{SmI}_2} \text{R} \text{R}' \\
24 & \rightarrow 25 & \rightarrow 26
\end{align*}$$

Scheme 1-14 Unexpected Synthesis of $\gamma$-alkylidenebutenolide

$$\begin{align*}
\text{PhSO}_2\text{Ph} & \xrightarrow{\text{1. n-BuLi, R, OHC}} \text{PhSO}_2\text{Ph} & \xrightarrow{\text{2. Cl=CH}_2} \text{PhSO}_2\text{Ph} & \xrightarrow{\text{DBU}} \text{PhSO}_2\text{Ph} \\
19a & \rightarrow 20a & \rightarrow 22a & \rightarrow 27 \\
\text{PhMe, 80°C} & & \text{TEA} & \text{R} \text{R}' \text{COOH} \\
22a & & & 28 \\
\text{28} & & \rightarrow & \text{R} \text{R}' \text{COOH}
\end{align*}$$

$\alpha,\beta$-Unsaturated $\gamma$-lactones with the alkylidene substituent in the $\gamma$-position (i.e. $\gamma$-alkylidenebutenolides) are in fact of great interest. Many biologically active molecules contain this structural motif, most often with the exocyclic $\text{C}_\gamma=\text{C}$ bond possessing the $\text{Z}$-configuration.$^{12}$ Our acyloxysulfone RCM/elimination sequence therefore provided a novel method for the preparation of this important class of compounds.
Chapter 2. Biological Importance and Previous Syntheses of γ-Alkylidenebutenolide

2.1 Biological Importance of γ-Alkylidene Butenolides

Butenolides and their analogues represent a wide range of natural compounds that have both medicinal and biological importance. Biologically active γ-alkylidene butenolide-containing natural products include the rubrolides, nostoclides, uncinine and pulvinones (Figure 2-1). These natural products display various biological activities including antibacterial, anticancer, antibiotic and phospholipase A2 inhibition activity. The simplest representation of a compound of this type is γ-methylenebutenolide, a natural product known as protoanemonin which is known to be an antibiotic (Figure 2-1). Some highly unsaturated representations of γ-alkylidenebutenolide are dihydroxerulin and xerulin (Figure 2-1). These compounds were isolated as 90:10-65:35 mixtures from Xerula melanotricha and were found to inhibit the biosynthesis of cholesterol without being cytotoxic.

![Figure 2-1. Representative examples of γ-alkylidenebutenolides](image)

γ-methylenebutenolide  xerulin  dihydroxerulin

Figure 2-2. Varying structures of γ-alkylidenebutenolides
Recently there has been a strong interest in glucosidase inhibitors, which has led to many types of natural and synthetic inhibitors. This interest ultimately aided in discovering the mechanism by which glucosidase acts and the development of potential pharmaceuticals such as anti-tumor agents, anti-viral agents, and immunoregulatory agents.\textsuperscript{15} Searching for glucosidase inhibitors led Xu and co-workers to the discovery of some andrographolide derivatives which were proven to be potent and specific $\alpha$-glucosidase inhibitors.\textsuperscript{15} Due to some glucosidase inhibitors showing anti-tumor metastasis and anti-HIV activities as well as clinically proven to help treat diabetes, Xu and co-workers studied andrographolide in depth in hopes of synthesizing a new and stronger glucosidase inhibitor. Andrographolides contain three important structures: (1) an $\alpha$-alkylidene-$\gamma$-butyrolactone moiety, (2) two double bonds $\Delta^{8(17)}$ and $\Delta^{12(13)}$, (3) three hydroxyls at C-3, C-19, and C-14; andrographolide derivatives were synthesized by modification of the above structural features.\textsuperscript{15} The results indicated that the $\gamma$-alkylidene butenolide moiety and the aromatic group at 3,19-hydroxyls favored $\alpha$-glucosidase inhibitory activity. Of the 15 derivatives, compounds 29 and 30 were the best $\alpha$-glucosidase inhibitors with an IC\textsubscript{50} value of 16 $\mu$M and 6 $\mu$M, both containing the $\gamma$-alkylidene butenolide moiety (Figure 2-3). Due to the significance of the $\gamma$-alkylidene butenolide moiety in these biologically active compounds, it is important to explore different routes toward synthesizing this moiety. The following sections will discuss different approaches towards synthesizing $\gamma$-alkylidene butenolides.
Figure 2-3. Most active andrographolide derivatives for α-glucosidase inhibition

2.2 Alkylidenation of Five-Membered Oxygen-Containing Heterocycles

The most widely used strategy for synthesizing γ-alkylidenebutenolides is the alkylidenation of five-membered oxygen-containing heterocycles. In 2000, Bruckner and co-workers had stereoselectively synthesized freelingyne 35 and related γ-alkylidenebutenolides by Mukaiyama aldol additions between siloxyfurans and suitable aldehydes.16 Stephens-Castro couplings of the resulting butenolides followed by anti-elimination of water provided freelynge 35 and associated γ-alkylidenebutenolides in good yield and selectivity.16 Although the Mukaiyama aldol addition reaction coupled with the Stephens-Castro coupling results in good yield and selectivity for the γ-alkylidenebutenolides, the starting aldehydes 31 and siloxyfurans 32 themselves require additional steps usually resulting in mediocre to poor yields (Scheme 2-2).16
An alternative strategy to synthesizing γ-alkylidenebutenolides involves a Horner-Emmons reaction with butenolides as shown in **Scheme 2-3**. In 2001, David and co-workers had developed a short and practical route to the tricyclic core of an unnatural pseudopterosin diastereomer. Key features of their approach involved an arene alkylation with γ-alkylidene butenolide followed by an elaborate reduction sequence. Synthesis of the intermediate γ-alkylidene butenolide was achieved through a Horner-Emmons reaction with butenolide 41 and aldehyde 38 affording intermediate 42 in high yields.
Scheme 2-3 Synthesizing $\gamma$-alkylidenebutenolides via a Horner Emmons Reaction

Starting from a maleic anhydride derivative, $\gamma$-alkylidenebutenolides can also be achieved by nucleophilic addition of an organometallic reagent followed by a Wittig condensation and base-catalyzed rearrangement. Babu and co-workers had discovered the antifungal lead coruscanone A (Figure 2-4) from the ethanol extract of the piperaceous plant *Piper coruscans* in the midst of searching for a prototype antifungal agent from natural sources.\(^\text{18}\) Coruscanone A showed strong antifungal activity against two major pathogens *C. albicans* and *C. neoformans* associated with immunocompromised patients (AIDS, cancer, or organ transplant). In addition, coruscanone A had displayed acceptable in vitro cytotoxicity against mammalian Vero cells.\(^\text{18}\) In order to develop a robust pharmacophoric model and to better understand the mechanism for which coruscanone A acts as an antifungal agent, its structural moieties were modified independently in order to facilitate the systematic refinement of the search for increasingly effective analogues. One of the structural features of coruscanone A includes the $\gamma$-alkylidenebutenolide moiety. Preparation of the analogues began with a Wittig condensation with a maleic anhydride derivative 43 and phosphorene 44 achieving the $\gamma$-alkylidenebutenolide intermediate 45 (Scheme 2-4). The phosphoranes were prepared from the corresponding $\alpha$-methyl ketone in a three-step sequence via brominated $\alpha$-methyl ketone and
phosphonium salt. Although preparation of the phosphoranes were generally high, the preparation of the bromoethyl ketones and phosphonium salt themselves ranged anywhere from 56-90%, generally on the lower side of that scale. Following the Wittig condensation was a base-catalyzed rearrangement of the resulting 4-ylidenebutenolide, making the corresponding cyclopentenedione. The enolic hydroxyl-substituted product was then achieved followed by an alkylation or acylation.

![Figure 2-4 Coruscanone A](image)

**Scheme 2-4 Synthesizing γ-alkylidenebutenolides via a Wittig Condensation**

**2.3 Cyclization of γ-oxoacids**

Pd-catalyzed C,C-couplings between alkenes or organo-metallic compounds and alkenyl or aryl halides or triflates have become crucial in organic synthesis. Investigating these couplings led Sorg and co-workers towards developing a novel method for synthesizing γ-alkylidenebutenolides stereoselectively in 2003. gem-Dibromoolefin and 1,3-dibromo’diene’ were prepared from readily available dibromolevulinic acid by treatment with 2:1 concentrated
H₂SO₄/oleum and concentrated H₂SO₄. A single isomer was obtained under the following conditions: the combination 50-60 °C/ 6 minutes provided 53 in 28% yield whereas 20-85 °C/ 30 min generated 49 in 41%. Both 49 and 53 underwent Pd-catalyzed couplings with phenyl- or styrltributylstannane giving mono-bromobutenolides with good stereo- and regeiocontrol. The mono-bromobutenolides were then either reduced with Zn or was subjected to a second Stille coupling to produce bromine-free γ-alkylidenebutenolides as single stereoisomers 51, 52, 55, 56. In 2005, Sorg and co-worker had further explored the above methods and successfully synthesized the anti-biotic lissoclinolide 59 in 66% yield.²¹ This synthesis of lissoclinolide is the shortest reported to date, comprising of just five steps from levulinic acid and is the only one accomplished without using protecting groups. By comparison, Negishi’s synthesis of lissoclinolide required nine steps²², Rossi’s eight steps²³, and Görth’s earlier synthesis from their laboratory six steps²⁴. As selective and accessible as it was, the method developed by Sorg and co-workers often achieved poor yields early in the process. Preparation of the starting gem - dibromoolefin and 1,3-dibromo’diene’ resulted in yields only ranging from 28-41%, thus using this method would achieve highly selective γ-alkylidenebutenolide but in poor yield.²¹
Scheme 2-5 Pd-catalyzed cross-coupling to achieve γ-alkyldenebutenolides

Scheme 2-6 Total Synthesis of lissoclinolide

2.4 Lactonization Reactions of Alk-4-ynoic and Alk-4-enoic Acids

In 2002, Anastasia and co-workers reported that the preparation of (Z)-5-organoyl-2-en-4-ynoic acids by the Pd-catalyzed alkynylzinc-β-haloacrylic acid coupling followed by Ag₂CO₃ catalyzed lactonization provided a far superior two-step method for selective synthesis of (Z)-5-alkyldenefuran-2(5H)-ones 62, compared to the one-pot alkyne-alkene coupling-lactonization
tandem process run under Sonogashira coupling conditions (Table 2-1).\textsuperscript{25} Two of the problems faced with the one-pot Pd-catalyzed cross-coupling-lactonization tandem process, alkyne dimerization and Michael-type addition reactions were not observed in the two-step process (Scheme 2-7,8).\textsuperscript{26,27}

Table 2-1 Comparison of Ag-catalyzed lactonization of (Z)-2-en-4-ynoic acids with Pd-catalyzed alkyne-alkene cross-coupling lactonization tandem process

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne</th>
<th>procedure\textsuperscript{a}</th>
<th>61 : 62</th>
<th>yield of 61 + 62 (%)</th>
<th>based on 1</th>
<th>based on alkyne</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>n-Hex</td>
<td>A</td>
<td>4 : 96</td>
<td>96</td>
<td>90</td>
<td>77</td>
</tr>
<tr>
<td>1B</td>
<td></td>
<td>B</td>
<td>34 : 66</td>
<td></td>
<td>b</td>
<td>77</td>
</tr>
<tr>
<td>2A</td>
<td></td>
<td>A</td>
<td>5 : 95</td>
<td>99</td>
<td>93</td>
<td>75</td>
</tr>
<tr>
<td>2B</td>
<td></td>
<td>B</td>
<td>20 : 80</td>
<td></td>
<td>b</td>
<td>75</td>
</tr>
<tr>
<td>3A</td>
<td></td>
<td>A</td>
<td>3 : 97</td>
<td>95</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td>3B</td>
<td></td>
<td>B</td>
<td>20 : 80</td>
<td></td>
<td>b</td>
<td>65</td>
</tr>
<tr>
<td>4A</td>
<td></td>
<td>A</td>
<td>2 : 98</td>
<td>95</td>
<td>86</td>
<td>76</td>
</tr>
<tr>
<td>4B</td>
<td></td>
<td>B</td>
<td>3 : 97</td>
<td></td>
<td>b</td>
<td>76</td>
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<tr>
<td>5A</td>
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<td>A</td>
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</tr>
<tr>
<td>5B</td>
<td></td>
<td>B</td>
<td></td>
<td></td>
<td>b</td>
<td>46</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Procedure A: AgX, procedure B: AgX.
Another lactonization reaction towards the synthesis of \( \gamma \)-alkylidene butenolides was demonstrated by Rousset and co-workers back in 2000.\(^{28}\) Their method involved the halolactonization of conjugated dienoic acids followed by DBU-promoted elimination to selectively yield alkylidene butenolides (Scheme 2-9). The dienoic acids 63 were prepared via Stille cross-coupling between vinyl tin reagents and (Z)-3-iodoalk-2-enoic acids. They then focused on formation of the exocyclic double bond via base-mediated \textit{anti} elimination. After testing a variety of different bases (TEA and DBN), they found that the most efficient base for the elimination reaction to occur was DBU in dichloromethane. Their method of elimination was selective for the \((E)\)-isomer 65, contrasting the selectivity for the \((Z)\)-stereoisomer 66 from other approaches (Scheme 2-9).\(^{28}\) This methodology was then applied to the synthesis of analogues of retinoic acid containing the alkylidene butenolide moiety, achieving the desired product such as butenolide 69 in 65\% yield (Scheme 2-10).\(^{28}\)
2.5 Vinylogous Aldol Reactions

A more recent synthesis of γ-alkylidene butenolides was reported starting from commercially available 6-aminopenicillanic acid.\textsuperscript{29} Yu and co-workers had previously identified that γ-alkylidene butenolides based derivatives showed moderate to excellent biological activities and could also regulate the intercellular Na\textsuperscript{+} concentration.\textsuperscript{30} As part of their ongoing efforts to identify new biological agents, they discovered that the vinylogous aldol reaction between different aldehydes or ketones with 70 afforded a series of novel γ-alkylidene butenolides \textbf{71} (Scheme 2-11). 70 was prepared through the base catalyzed intramolecular cascade sequence in one-pot under mild conditions. The cascade sequence involved three reactions: (a) substitution reaction of the chloride with hydroxide anion; (b) the intramolecular transesterification; (c) base promoted isomerization of double bond.\textsuperscript{29} The vinylogous aldol reaction of different aldehydes or ketones with 70 produced the γ-alkylidene butenolides \textbf{71} in 53-86\% yields with differing ratios of Z- or E-isomer depending on the R\textsubscript{1} and R\textsubscript{2} groups.\textsuperscript{29}
Scheme 2-11 Synthesis of $\gamma$-alkylidenebutenolides via vinylogous aldol reaction

It is noteworthy that of the syntheses mentioned, none have been a metathesis-based approach towards synthesizing $\gamma$-alkylidene butenolides.
Chapter 3. Synthesis of γ-Alkylidene Butenolides

Our unique metathesis-based approach has led us towards investigating the scope of our method. As mentioned previously in Chapter 1, in an effort to access cis-alkene containing polyenes we set out to investigate ring-closing metathesis reactions of acyloxysulfones of type 20. During the course of investigating elimination reactions of acyloxysulfone RCM product of type 22, we discovered that treatment with triethylamine resulted in its quantitative conversion into the γ-alkylidene butenolide of type 28. Initially we were concerned, however, that this reaction might be limited only to substrates of type 22a with elimination favored due to formation of fully conjugated butenolides of type 28a.

3.1 Synthesis of Acyloxysulfones Derivatives

In an effort to explore the scope of γ-alkylidene butenolide synthesis via elimination of acyloxysulfone RCM products, we first synthesized a variety of acyloxysulfones following the general scheme shown in Table 3-1. Initially we had performed a two-step addition/acylation reaction with (ethylsulfonyl)benzene using crotonaldehyde and acryloyl chloride, achieving acyloxysulfone 20b in 91% yield (Table 3-1). To simplify the two-step process the addition/acylation reactions could be combined into a one-step process, no longer having to isolate the intermediate hydroxysulfone (Table 3-1). After synthesizing a range of acyloxysulfones, we found that in general, the one-step synthesis was preferred and so the two-step was not performed if high yields were achieved.
Table 3-1 Synthesis of Acyloxysulfone RCM Substrates

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>X</th>
<th>Two-step yield (%)</th>
<th>One-step yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20a</td>
<td>Ph</td>
<td>H</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>20b</td>
<td>Me</td>
<td>Me</td>
<td>91</td>
<td>79</td>
</tr>
<tr>
<td>20c</td>
<td>i-Pr</td>
<td>Me</td>
<td>74</td>
<td>83</td>
</tr>
<tr>
<td>20d</td>
<td>(CH₂)₂Ph</td>
<td>Me</td>
<td>64</td>
<td>92</td>
</tr>
<tr>
<td>20e</td>
<td>n-BuLi</td>
<td>Me</td>
<td>ND</td>
<td>98</td>
</tr>
<tr>
<td>20f</td>
<td>CH=CHPh</td>
<td>Me</td>
<td>ND</td>
<td>91</td>
</tr>
<tr>
<td>20g</td>
<td>CH=CH₂</td>
<td>H</td>
<td>ND</td>
<td>78</td>
</tr>
</tbody>
</table>

### 3.2 Ring-closing Metathesis of Acyloxysulfones

Our initial effort towards accessing the cis-alkene involved a ring-closing metathesis (RCM) reaction. RCM is a widely used olefin metathesis reaction in organic chemistry for the synthesis of various unsaturated rings; it involves an intramolecular metathesis of two alkenes. Like many of the other olefin metathesis, both E- or Z- isomers may form. Many factors influence the stereoselectivity of RCM including: (1) catalyst, (2) ring strain, and (3) starting diene as previously discussed in chapter one. Although E- isomers tend to be favored thermodynamically, in smaller rings, the Z- isomers predominate as the more stable product due to ring-strain minimization. To incorporate the cis- alkene in our polyene systems, we thus decided to do an RCM on the acyloxysulfones to form either a 5- or 6- membered rings. As stated previously, we were unsuccessful in forming the 6- membered ring and decided to focus...
solely on the 5-membered RCM. The RCM reaction of compounds 20a-g proved somewhat challenging with similar reactivity observed for both the acrolein-derived compound 20a and the crotonaldehyde-derived compounds 20b-g. After going through a variety of conditions to optimize the reaction, we found that the yields were best when the catalyst was loaded in three separate batches in 6 h increments. With these conditions, we were able to subject acyloxysulfones 20a-g to the RCM and achieve yields ranging from 51-76% (Scheme 3-1).

Scheme 3-1 Ring-closing metathesis reactions of acyloxysulfones

3.3 Elimination of Ring-closing Metathesis

Our initial proposal was to do a subsequent reductive elimination to the RCM product to attain the second alkene that had been masked by formation of the acyloxysulfone. Referring back to chapter one, because elimination of acyloxysulfones favors trans- alkenes, we expected reductive elimination of the RCM product would give us the anticipated cis-, trans- polyene. With multiple failed attempts to reductively eliminate the RCM product using typical Julia
olefination reagents (SmI₂, Na/Hg) we set out to try a sequential elimination. The sequential elimination would proceed first with an elimination of the acyl-group, followed by a reductive cleavage of the resulting vinyl sulfone. Initially we had tried DBU as outlined by a previous group⁷; unsuccessful we moved on to TEA and came across the unexpected synthesis of γ-alkylidene butenolide 28a.

The unexpected synthesis of compound 28a led us to the focus of our research; exploring the scope of γ-alkylidene butenolide synthesis by elimination of RCM acyloxysulfones. Our initial thought was that proton H₆ would be more acidic than H₅, resulting in the vinyl sulfone which could then be followed by a reductive cleavage to achieve the originally desired cis-, trans-polyene. Unanticipated, H₅ was more acidic in the case of benzyl phenyl sulfone leading to the synthesis of compound 28a in high yield.

![Chemical structure](image)

**Figure 3-1 Expected product when elimination with TEA**

We were concerned that this acyloxysulfone RCM/elimination approach would be limited to benzyl sulfones due to the resulting butenolide being fully conjugated. To explore the scope of this reaction, (ethylsulfonyl)benzene was then subjected through the entire sequence, and to our delight the corresponding non-conjugated γ-alkylidene butenolide 28b was formed in excellent yield (Scheme 3-2). Excited that the elimination worked so clean and well, we synthesized four more γ-alkylidene butenolides with yields 95% or greater (Scheme 3-2). In addition to the ease
of the reaction itself (TEA, DCM, and room temperature), often TEA could simply be pumped off needing no further purification to obtain pure product.

**Scheme 3-2 Scope of γ-alkylidene butenolide synthesis**

![Scheme 3-2](image)

With seven γ-alkylidene butenolides in hand, we wanted to better understand the mechanism of the elimination itself. At first glance, it seems like a simple E2 elimination takes place (**Scheme 3-3**), however; this would suggest that the ratio of diastereomers of the product should be identical to that of the starting material, which is not the case (**Scheme 3-1,2**).
Throughout the entire sequence up to the RCM product, the ratio of diastereomers consistently remains about 1:1 (Scheme 3-1), where as you can see in Scheme 3-2, it is clear that the ratio is no longer 1:1, instead favoring the Z- diastereomer.

3.4 Mechanistic Study

The change in ratio of diastereomers towards favoring the Z- diastereomer was suggestive of an E1cb mechanism. As seen in Scheme 3-4 the steric hindrance of the β- substituent would aid in the epimerization of the anti- configuration towards the γ-alkylidene butenolide with Z- configuration thus making it the major diastereomer.
We attempted to better understand the elimination process by investigating an acyclic equivalent compound as detailed in **Scheme 3-5**. Even after prolonged reaction times (72 h), no apparent elimination was detected upon treatment with TEA. The failure of the acyclic compound 72 to react with TEA suggests that it is less acidic than its alternative cyclic compounds 23a-g. This reactivity trend has been recognized in other cases. A prime example is the comparison of acidity between Meldrum’s acid (pKa = 7.32) and dimethyl malonate (pKa = 15.78)\textsuperscript{31} with the difference in acidity explained by dipole minimization.\textsuperscript{32} In our case, the propensity of compounds 23a-g toward elimination and failure of 72 might best be explained by considering the aromatic nature, and thus increased stability and ease of formation, of the conjugate base for each cyclic compound. Further efforts will be made to validate this rationalization; for now, the elimination mechanism is best explained by occurring via E1cb and is apparently dependent on the increased acidity afforded to the cyclic RCM products.

**Scheme 3-5  Comparison of cyclic vs. acyclic acyloxysulfone eliminations with TEA**

3.5 Investigating Limitations

We found that elimination of RCM acyloxysulfone products could be applied to a variety of di- substituted RCM products to achieve the desired γ-alkylidene butenolides; however, we
found that many $\gamma$-alkylidene butenolides are tri- or even tetra-substituted. To access these compounds, we first began by synthesizing tri-substituted $\gamma$-alkylidene butenolides containing a methyl group at either the C$_2$ or C$_3$ position (Scheme 3-6). Using the same method as the di-substituted, both tri-substituted $\gamma$-alkylidene butenolides were synthesized in good yields (79-100%).

**Scheme 3-6 Synthesis of tri-substituted $\gamma$-alkylidene butenolide**

Synthesizing a tetra-substituted $\gamma$-alkylidene butenolide proved to be challenging. The starting acyloxysulfone 74 was prepared by addition with methacrolein (84% yield) followed by acylation with methacryloyl chloride (76% yield). Our first attempt at forming the tetra-substituted RCM product using our previous conditions with Ru-1 catalyst failed and resulted in recovery of starting material. Based on a previous study by Stewart and co-workers, they showed that a higher conversion for the tetra-substituted RCM of diethyl dimethallylmalonate was achieved with Ru-4 catalyst. In a second attempt to reach the tetra-substituted RCM product we tried the Ru-4 catalyst at 60, 80, and 110 °C but once again only starting material was detected.
Thus far our metathesis based approach towards γ-alkylidene butenolides seemed limited to only di- and tri-substituted γ-alkylidene butenolides. Understanding the limitation to tri-substituted substrates, we wanted to investigate what groups could be tolerated at those positions. We first set out on probing whether a halogen could be at the C₂ position. Compound 19a was acylated with 2-bromoacryloyl chloride 76 to attain β-acyloxysulfone 77. Unfortunately, the RCM reaction with Ru-1 did not achieve the desired product 78 and only starting material was detected, thus adding another limitation to our approach. Although this is perhaps not surprising given the electron-deficient nature of the bromosubstituted alkene in 77.

Scheme 3-8 Attempted bromo-butenolide RCM

Failing to tolerate a halogen group, we then set out to investigate whether we could include a phenyl group at the C₃ position. We first had to synthesize the aldehyde itself in order for us to access the phenyl group in the correct position. Alcohol 80 was synthesized via a Grignard reaction with 79. After several attempts at different oxidation reactions, DMP proved to
be the most successful in synthesizing aldehyde 81. A two-step addition/acylation was then executed with 2-phenylacrylaldehyde 81 and acryloyl chloride and benzyl phenylsulfone to achieve the desired β-acyloxsulfone 83. We then attempted to do an RCM to get the phenyl tri-substituted ring; however even after several attempts with Ru-1 at 80°C and 110°C, no product was identified. In one last attempt to close the ring with Ru-1, titanium isopropoxide was used as an additive to prevent any potential catalyst poisoning that could take place. The reaction was placed in DCM and refluxed for 12 h, even then, no product was detected. Recalling the study done by Stewart, we tried using the Ru-4 catalyst to close the ring. Once again, the phenyl tri-substituted ring failed to close. From all of the RCM reactions (Table 3-2), only starting material was detected. This is surprising given the report from Chaven describing successful RCMs of this type.39 This is also unfortunate because it would have given us access to the rubrolide natural products (Figure 3-2).

**Scheme 3-9 Synthesis of 2-phenylacrylaldehyde**

\[
\text{Scheme 3-9 Synthesis of 2-phenylacrylaldehyde}^{1-11}
\]
Scheme 3-10 Attempted phenyl-substituted butenolide RCM

Table 3-2 Conditions for RCM of acyloxysulfone 83

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru-1</td>
<td>Toluene</td>
<td>24 h</td>
<td>80</td>
</tr>
<tr>
<td>Ru-1</td>
<td>Toluene</td>
<td>24 h</td>
<td>110</td>
</tr>
<tr>
<td>Ru-1*</td>
<td>DCM</td>
<td>12 h</td>
<td>reflux</td>
</tr>
<tr>
<td>Ru-4</td>
<td>Toluene</td>
<td>24 h</td>
<td>80</td>
</tr>
</tbody>
</table>

*titanium isopropoxide was added

Rubrolides

Rubrolide A: R = Z = H; K = L = X = Y = Br
Rubrolide B: R = H; K = L = X = Y = Br; Z = Cl
Rubrolide C: R = K = Y = Z = H; L = X = Br
Rubrolide D: R = L = Z = X = H; K = Y = Br
Rubrolide E: R = L = K = X = Y = Z = H
Rubrolide F: R = Me; L = K = X = Y = Z = H
Rubrolide I: R = K = H; L = X = Y = Br; Z = Cl
Rubrolide J: R = K = Z = H; L = X = Y = Br
Rubrolide K: R = K = Y = H; X = Y = Br; Z = Cl
Rubrolide L: R = K = Y = H; L = X = Br; Z = Cl
Rubrolide M: R = K = L = Y = H; X = Br; Z = Cl
Rubrolide N: R = K = L = H; Y = Cl, Z = X = Br

Figure 3-2 Natural product rubrolide derivatives
Chapter 4. Application Towards Naturally Occurring γ-Alkyldene Butenolides

4.1 Attempt at synthesizing Rubrolide via Heck-coupling

Failure to access the Rubrolide core through a tri-phenyl substituted RCM was disappointing; however, we had already synthesized a majority of the structure (compound 19a). A second attempt at synthesizing Rubrolide was done via Heck-coupling to 19a. Aware of the many potential products that could be formed, 19a was still subjected to the Heck reaction simply due to the abundance of the material at that time. After several different conditions and reagents, not only did the Heck-coupling reaction fail to form the C-C bond between C3 of 19a and the bromide compound to make 85, all the starting material was recovered.

Table 4-1 Synthesis of Rubrolide via Heck-coupling

<table>
<thead>
<tr>
<th>R</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Pd(Oac)₂</td>
<td>PPh₃</td>
<td>TEA</td>
</tr>
<tr>
<td>H</td>
<td>Pd(dba)₂</td>
<td>none</td>
<td>K₃PO₄</td>
</tr>
<tr>
<td>Me</td>
<td>Pd(Oac)₂</td>
<td>PPh₃</td>
<td>TEA</td>
</tr>
<tr>
<td>Me</td>
<td>Pd(dba)₂</td>
<td>none</td>
<td>K₃PO₄</td>
</tr>
</tbody>
</table>
4.2 Spirobutenolide Synthesis

While researching natural products that contained the γ-alkylidene butenolide moiety, we came across a paper by Engstrom and co-workers who had synthesized pyrenolide D 87 in a two-step, one-pot transformation using γ-alkylidene butenolide 86. The reaction involved an initial hydrolysis of the γ-alkylidene butenolide with LiOH, followed by acid-mediated TBS-deprotection with HF and spiroketalization to form 87. Excited that we could potentially synthesize a variety of γ-alkylidene butenolides and spirocyclize them meant that we could access several spirobutenolide natural products (Figure 4-1).

Scheme 4-1 Synthesis of pyrenolide D in a two-step, one-pot transformation using γ-alkylidene butenolide

![Scheme 4-1](image)

Figure 4-1 Natural product spirobutenolides
Often times model compounds of natural products are first synthesized first to show proof-of-principle before attempting the actual product (Figure 4-2). For pyrenolide D 87, we imagined synthesizing a 5,5-spirobutenolide starting from a TBS-protected γ-alkylidene butenolide 96. To get to the TBS-protected sulfone, we had to first synthesize the TBS-protected alcohol 89 (Scheme 4-2). A mono TBS-protection on propanediol 88 was followed by an iodination and sulfone displacement to achieve the desired sulfone 91. Once the TBS-protected sulfone was purified, we could then apply our metathesis approach to get the γ-alkylidene butenolide. We began with an addition of the TBS-protected sulfone to crotonaldehyde followed by acylation with acryloyl chloride to get 92 in 46% yield. A ring-closing metathesis on β-acyloxy sulfone 92 was then achieved with Ru-1 in 74% yield. The final step in attaining γ-alkylidene butenolide 96 was completed by reductive elimination of 95 with TEA. Once the TBS-protected γ-alkylidene butenolide 96 was synthesized, spirocyclization of the compound was attempted according to the procedure outlined in the paper by Engstrom and co-workers. 34 On the very first attempt, formation of the γ- 5,5-spirobutenolide 97 was successful (the low yield of 97 was due to loss of material while transferring).

Figure 4-2 Retrosynthesis of 5,5-spirobutenolide
Wanting to better understand the mechanism in which the γ-alkylidene butenolide spirocyclization, we found a paper in which they described the cyclization as a “5-endo-trig ring closure process” (Scheme 4-5). This paper suggests that spirocyclization can occur in the absence of LiOH and that HF-pyr will deprotect the TBS-protected alcohol to allow for a 5-endo-trig cyclization to occur (Scheme 4-6). According to Baldwins’ Rules, deprotection

---

Scheme 4-2 Synthesis of TBS-protected sulfone

Scheme 4-3 Synthesis of TBS-protected γ-alkylidene butenolide

Scheme 4-4 Synthesis of 5,5-spirobutenolide
followed by a 5-endo-trig process is unlikely and highly unfavorable.\textsuperscript{36} Instead, the more likely route in which the \(\gamma\)-alkylidene butenolide spirocyclizes is via the 5-exo-trig process (Scheme 4-7). Nonetheless, from their results HF-pyridine should be sufficient alone to promote spirocyclization according to this report.

Scheme 4-5 Example of spirocyclization process by Popsavin\textsuperscript{35}

Scheme 4-6 5-endo-trig ring closure

Scheme 4-7 5-exo-trig ring closure
Yang and co-workers recently reported the isolation of a spirocyclic butenolide natural product abiespiroside A (Figure 4-3), which they described as possessing “diverse forms of bioactivity such as anti-inflammatory, antitumor, antibacterial, and insecticide activity”. Wanting to first investigate the 6/6/5 ring system, we set out to synthesize a model 6,5-spirobutenolide (Scheme 4-8,9). Similar to the 5,5-spirobutenolide, we began with a mono TBS protection on cis-butenediol 101. This was followed by a hydrogenation, although the hydrogenation gave a mixture of the alcohol 103 and aldehyde 104. The aldehyde was easily converted to the desired alcohol 103 by reduction with NaBH₄. Compound 103 was then subjected to an iodination followed by a sulfone displacement producing the desired starting sulfone 105. We were then able to take sulfone 105 through our RCM/elimination sequence to ultimately get γ-alkyldene butenolide 109. Wanting to confirm if Popsavin was in fact correct, an attempt to spirocyclize 109 with just HF-pyr was executed (Scheme 4-10). Unfortunately, in the presence of just HF-pyr 109 did not spirocyclize but had instead completely decomposed. In a second attempt to spirocyclize 109, we followed the conditions previously outlined by Engstrom involving first LiOH followed by HF and was successful in synthesizing 6,5-spirobutenolide 110 in 77% yield. This result now sets the stage for a completion of the total synthesis of abiespiroside A.

Figure 4-3 Structure of abiespiroside A
Scheme 4-8 Synthesis of alcohol 103

\[
\text{HO-} - \text{OH} \xrightarrow{\text{TBSCI, imidazole, THF, rt, o/n}} \text{HSO-} - \text{OH} \xrightarrow{H_2, \text{EtOAc, Pd}} \text{HSO-} - \text{OH} + \text{HSO-} - \text{OH} \xrightarrow{\text{NaBH}_4, \text{MeOH, 0°C}} \text{HSO-} - \text{OH}
\]

Scheme 4-9 Synthesis of TBS-protected \(\gamma\)-alkyldene butenolide 109

\[
\text{TBSO-} - \text{SO_2Ph} \xrightarrow{\text{H, allenate, 79%}} \text{TBSO-} - \text{SO_2Ph} \xrightarrow{\text{H, allenate, 57%}} \text{TBSO-} - \text{SO_2Ph} \xrightarrow{\text{GHII, Toluene, 80°C, 62%}} \text{TBSO-} - \text{SO_2Ph}
\]

Scheme 4-10 Synthesis of 6,6-spirobutenolide
Chapter 5. Conclusion

5.1 Discovery and Development of a Metathesis-Based Approach Synthesis of γ-Alkylidene Butenolides

In the midst of investigating an olefin metathesis based approach towards accessing cis-trans- polyene subunits, we unexpectedly synthesized a γ-alkylidene butenolide 28a. γ-Alkylidene butenolides are an interesting class of compounds due to their range of biological properties which includes antitumor, anti-inflammatory, antibacterial, and cholesterol biosynthesis inhibition.12-15 Utilizing the Julia reaction, a variety of acyloxy sulfones were successfully synthesized using either a two-step or a one-pot addition-acylation method. Ring-closing metathesis reactions of the acyloxy sulfones allowed for ring closure of di- and tri-substituted rings with limitations thus far to methyl groups. A mild triethylamine-mediated sulfone elimination produced the corresponding γ-alkylidene butenolides. After optimization, yields for the sequence were overall high (69-100%), giving γ-alkylidene butenolide products with up to 15:1 selectivity for the Z-isomer. The mechanism for elimination appears to be E1cb and is apparently dependent on the increased acidity afforded to the cyclic RCM products.

In an attempt to showcase this method in the context of complex γ-alkylidene butenolide natural product synthesis, we came across a paper by Engstrom34 that had described using a γ-alkylidene butenolide as a precursor for synthesizing Pyrenolide D, a natural product spirobutenolide. Using our metathesis-based approach, we were able to synthesize a γ-alkylidene butenolide that was able to spirocyclize to a 5,5-spirobutenolide as a model compound for Pyrenolide D. The same approach was successfully applied to the successful synthesis of the abiespiroside A 6,5-spirobutenolide.
5.2 Future Work

In conclusion, the metathesis-based synthesis of \( \gamma \)-alkylidene butenolides has allowed for the synthesis of a 6,5-spirobutenolide which was a model compound for the natural spirobutenolide Abiespiroside A.\(^{37}\) Due to the complex stereochemistry of Abiespiroside A, our next goal is to synthesize a more intricate representation as shown in Figure 5-1. Access to this model would then allow us to further develop a method for the total synthesis of Abiespiroside A.

![Figure 5-1 Model compound for Abiespiroside A](image)

As we work towards a total synthesis of a natural spirobutenolide, we would also like to overcome the challenges with our metathesis-based approach for synthesizing \( \gamma \)-alkylidene butenolide. Thus far our limitations include not having a halogen at the C\(_2\) position, a phenyl group at the C\(_3\) position, and tetra- substituted \( \gamma \)-alkylidene butenolides (Figure 5-2). Overcoming these challenges would allow access to many more complex \( \gamma \)-alkylidene butenolide natural product synthesis.

![Figure 5-2 Limitations to the metathesis-based synthesis of \( \gamma \)-alkylidene butenolides](image)
Chapter 6. Experimentals

All reactions were carried out under N₂ in flame-dried glassware. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All other reagents were purchased and used as received. All TLC analysis used 0.25 mm silica layer fluorescence UV254 plates. Flash chromatography: SilaCycle silica gel P60 (230-400 mesh). IR: Nicolet iS10 spectrometer, wavenumbers (ν) in cm⁻¹. NMR: Spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The solvent signals were used as references (CDCl₃: δC = 77.0 ppm; residual CHCl₃ in CDCl₃: δH = 7.26 ppm). MS(ESI): Waters LCT Premier mass spectrometer.

(isobutylsulfonyl)benzene. Benzenesulfinic acid sodium salt (4.00 g, 24.37 mmol, 2.0 equiv.) was added to a flask containing DMSO (8.53 mL). 1-Bromo-2-methylpropane (1.31 mL, 12.18 mmol, 1.0 equiv.) was then added and the mixture was heated to 100°C and stirred for 15 h. The reaction was cooled to room temperature, quenched with water (25 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave (isobutylsulfonyl)benzene (4.23 g, 89%) as an oil.
IR (ATR): 1302, 1143, 1085, 595 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.92 (d, $J = 7.5$ Hz, 2H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.57 (t, $J = 7.7$ Hz, 2H), 2.99 (d, $J = 6.5$ Hz, 2H), 2.22 (m, 1H), 1.06 (d, $J = 6.8$, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 140.2, 133.5, 129.3, 127.8, 64.0, 24.1, 22.7. TOFMS (ES+): m/z calcd for C$_{15}$H$_{16}$O$_2$SNa [M + Na]$^+$: 221.0612; found: 221.0618.

((3-phenylpropyl)sulfonyl)benzene. Benzenesulfinic acid sodium salt (2.80 g, 17.08 mmol, 2.0 equiv.) was added to a flask containing DMSO (8.53 mL). 1-Bromo-3-phenylpropane (1.30 mL, 8.53 mmol, 1.0 equiv.) was then added and the mixture was heated to 100°C and stirred for 15 h. The reaction was cooled to room temperature, quenched with water (25 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by recrystallization with ethanol afforded ((3-phenylpropyl)sulfonyl)benzene (3.55 g, 80%) as a white solid.

IR (ATR): 1452, 1295, 1187, 1145, 1126, 580, 529 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, $J = 8.0$ Hz, 2H), 7.66 (m, 1H), 7.56 (t, $J = 7.9$, 2H), 7.27 (t, $J = 7.3$ Hz, 2H), 7.2 (t, $J = 7.4$ Hz, 1H), 7.10 (d, $J = 6.9$ Hz, 2H), 3.08 (m, 2H), 2.70 (t, $J = 7.5$ Hz, 2H), 2.05 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 139.8, 139.2, 133.6, 129.3, 128.6, 128.4, 128.0, 126.4, 55.4, 34.1, 24.2. TOFMS (ES+): m/z calcd for C$_{15}$H$_{16}$O$_2$SNa [M + Na]$^+$: 283.0769; found: 283.0764.
(E)-(3-phenylallylsulfonyl)benzene. To a solution of 3-bromoprop-1-ene (1.40 g, 11.6 mmol) in DMSO (11.57 ml) at 100 °C was added benzenesulfinic acid sodium salt (3.80 g, 23.1 mmol) and the mixture was stirred for 15 h. The reaction was quenched with H₂O (35 ml) and extracted with DCM (2 x 30 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by recrystallization in ethanol afforded (E)-(3-phenylallylsulfonyl)benzene (2.39 g, 91%).

IR (ATR) 3012, 2974, 2905, 2871, 1292, 1054 cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ 7.89 (dd, J = 8.2, 1.1 Hz, 2H) 7.64 (m, 1H), 7.54 (m, 2H), 7.33 – 7.21 (m, 5H), 6.37 (d, J = 15.8 Hz, 1H), 6.11 (td, J = 15.3, 7.8 Hz, 1H), 3.96 (dd, J = 7.6, 1.1Hz, 2H,). ¹³C NMR (75 MHz, CDCl₃): δ 139.2, 138.4, 135.7, 133.8, 129.1 (2C), 128.9 (2C), 128.8 (2C), 126.6 (2C), 115.1, 60.5. TOFMS (ES+): m/z calcd for C₁₅H₁₄O₂SNa [M + Na]⁺: 281.0612; found: 281.0611.

(allylsulfonyl)benzene⁴⁰. To a solution of cinnamyl bromide (2.00 g, 10.15 mmol) in DMSO (10.2 ml) at 100 °C was added benzenesulfinic acid sodium salt (3.33 g, 20.3 mmol) and the mixture was stirred for 15 h. The reaction was quenched with H₂O (35 ml) and extracted with DCM (2 x 30 ml). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo.
Purification by flash column chromatography on silica (1:1 hexanes:ethyl acetate) gave (allylsulfonyl)benzene (1.6 g, 76%) as an oil.

1-phényl-1-(phénylsulfonyl)but-3-en-2-yl acrylate (20a). Two-step method: To a solution of benzyl phenyl sulfone (300 mg, 1.29 mmol, 1.0 equiv.) in THF (6.5 mL) at -78 °C was added n-BuLi (1.6 M, 2.42 mL, 3.87 mmol, 3.0 equiv.) and the mixture was stirred for 1 h before adding acrolein (0.43 mL, 6.45 mmol, 5.0 equiv.) and stirring for 2 h. The reaction was quenched with water (20 mL) and extracted with MTBE (2 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave the corresponding hydroxysulfone (0.24 g, 64%) as an inseparable mixture of diastereomers.

Spectral data for the mixture of diastereomers: IR (ATR): 3538, 3475, 1494, 1346, 1142, 688 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.59 (d, J = 7.7 Hz, 2H), 7.56-7.49 (m, 4H), 7.39-7.32 (m, 6H), 7.30-7.17 (m, 6H), 7.00 (d, J = 7.4 Hz, 2H), 5.69 (m, 1H), 5.54 (m, 1H), 5.35 (d, J = 15.6 Hz, 1H), 5.31 (d, J = 15.0 Hz, 1H), 5.26 (d, J = 6.4 Hz, 1H), 5.24 (d, J = 6.2 Hz, 1H), 5.12 (d, J = 10.5, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.18 (s, 1H), 4.16 (d, J = 9.4 Hz, 1H), 4.09 (d, J = 2.7 Hz, 1H), 3.19 (s, 1H). ¹³C NMR (125 MHz, CDCl₃) δ 137.7, 137.3, 136.2, 135.7, 133.9, 133.7, 131.3, 130.7,
TOFMS (ES+): $m/z$ calcd for C_{16}H_{16}O_{3}SNa $[M + Na]^+$: 311.0718; found: 311.0707.

To a solution of 1-phenyl-1-(phenylsulfonyl)but-3-en-2-ol (0.24 g, 0.82 mmol) in DCM (4.0 mL) at 0°C was added triethylamine (0.29 mL, 2.05 mmol, 2.5 equiv.) followed by acryloyl chloride (0.13 mL, 1.64 mmol, 2.0 equiv.) and the mixture was allowed to slowly warm to room temperature over 15 h. The reaction was quenched with aq. sodium bicarbonate (20 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound **20a** (82 mg, 100%) as an inseparable mixture of diastereomers.

**One-step method:** To a solution of benzyl phenyl sulfone (300 mg, 1.29 mmol, 1.0 equiv.) in THF (6.40 mL) at -78°C was added $n$-BuLi (1.6M, 2.42 mL, 3.87 mmol, 3.0 equiv.) and the mixture was stirred for 1 h before adding acrolein (0.43 mL, 6.45 mmol, 5.0 equiv.) and stirring for 2 h. The mixture was warmed to 0°C followed by the dropwise addition of acryloyl chloride (0.52 mL, 6.45 mmol, 5.0 equiv.) and the resulting mixture was allowed to slowly warm to room temperature over 12 h. The reaction was quenched with aq. NH$_4$Cl (20 mL) and extracted with MTBE (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound **20a** (0.29 g, 65%) as an inseparable mixture of diastereomers.
Spectral data for the mixture of diastereomers: IR (ATR): 1727, 1405, 1308, 1293, 1260, 1175, 1145 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 7.5$ Hz, 2H), 7.55-7.50 (m, 4H), 7.40-7.35 (m, 4H), 7.33-7.22 (m, 10H), 6.38 (dd, $J = 17.0$, 10.0 Hz, 2H), 6.34 (m, 1H), 6.27 (m, 1H), 6.07 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.94 (dd, $J = 17.4$, 10.5 Hz, 1H), 5.85 (dd, $J = 10.5$, 1.3 Hz, 1H), 5.81 (dd, $J = 10.5$, 1.3 Hz, 1H), 5.75-5.60 (m, 2H), 5.33 (dd, $J = 17.1$, 1.1 Hz, 1H), 5.24 (dd, $J = 17.1$, 1.1 Hz, 1H), 5.21 (dd, $J = 10.4$, 1.0 Hz, 1H), 5.12 (dd, $J = 10.5$, 1.0 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.4, 164.3, 139.2, 138.0, 133.7, 133.4, 132.9, 132.6, 131.8, 131.7, 131.2, 130.7, 130.0, 129.6, 129.2, 129.1, 128.8, 128.7, 128.6, 128.3, 127.9, 127.8, 119.7, 119.6, 74.0, 73.4, 72.5, 71.5.

TOFMS (ES+): m/z calcd for C$_{19}$H$_{18}$O$_4$SNa [M + Na]$^+$: 365.0823; found: 365.0808.

(E)-2-(phenylsulfonyl)hex-4-en-3-yl acrylate (20b). To a solution of ethyl phenyl sulfone (1.00 g, 5.87 mmol, 1.0 equiv.) in THF (29.0 mL), at -78°C was added n-BuLi (1.6M, 4.40 mL, 7.05 mmol, 1.2 equiv.) and the mixture was stirred for 1 h before adding crotonaldehyde (0.96 mL, 11.74 mmol, 2.0 equiv.) and stirring for 2 h. The reaction was then quenched with water (50 mL) and extracted with MTBE (2 x 25 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave the corresponding hydroxysulfone (1.21 g, 91%) as a separable mixture of diastereomers ($\alpha$ and $\beta$).
Spectral data for isomer α: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J$ = 7.5 Hz, 2H), 7.68 (t, $J$ = 7.5 Hz, 1H), 7.58 (t, $J$ = 7.7 Hz, 2H), 5.75 (m, 1H), 5.38 (dd, $J$ = 15.3, 4.4 Hz, 1H), 4.76 (d, $J$ = 5.3 Hz, 1H), 3.08 (qd, $J$ = 7.1, 1.1 Hz, 1H), 2.97 (s, 1H), 1.68 (d, $J$ = 6.5 Hz, 3H), 1.30 (d, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.6, 134.0, 129.3, 128.9, 128.8, 128.7, 68.8, 64.0, 17.7, 6.8

Spectral data for isomer β: IR (ATR): 1447, 1286, 1140, 1084, 730 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J$ = 7.65 Hz, 2H), 7.68 (t, $J$ = 7.4 Hz, 1H), 7.58 (t, $J$ = 7.6 Hz, 2H), 5.74 (m, 1H), 5.38 (qd, $J$ = 7.7, 1.2 Hz, 1H), 4.38 (t, $J$ = 8.0 Hz, 1H), 3.85 (s, 1H), 3.18 (m, 1H), 1.69 (d, $J$ = 6.6 Hz, 3H), 1.10 (d, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.2, 134.0, 130.7, 129.2, 129.0, 129.9, 72.1, 64.8, 17.7, 12.2. TOFMS (ES+): m/z calcd for C$_{11}$H$_{14}$O$_3$SNa [M + Na]$^+$: 263.0718; found: 263.0718.

To a mixture of (E)-2-(phenylsulfonyl)hex-4-en-3-ol isomers α and β (300 mg, 1.25 mmol, 1.0 equiv.) in DCM (4.1 mL) at 0°C was added triethylamine (0.44 mL, 3.12 mmol, 2.5 equiv.) and acryloyl chloride (0.15 mL, 1.87 mmol, 1.5 equiv.) and the mixture was allowed to slowly warm to room temperature over 15 h. The reaction was quenched with aq. sodium bicarbonate (20 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 20b (0.21 g, 59%) as an inseparable mixture of diastereomers.
One-step method: To a solution of ethyl phenyl sulfone (500 mg, 2.94 mmol, 1.0 equiv.) in THF (14.7 mL) at -78°C was added n-BuLi (1.6M, 2.20 mL, 3.52 mmol, 1.2 equiv.) and the mixture was stirred for 1 h before adding crotonaldehyde (0.48 mL, 5.88 mmol, 2.0 equiv.) and stirring for 10 min. The mixture was warmed to 0°C and then acryloyl chloride (0.49 mL, 5.88 mmol, 2.0 equiv.) was added and the resulting mixture was allowed to slowly warm to room temperature over 15 h. The reaction was then quenched with aq. NH₄Cl (30 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 20b (0.64 g, 78%) as an inseparable mixture of diastereomers.

Spectral data for the mixture of diastereomers: IR (ATR): 1792, 1745, 1149, 797, 765, 740, 719 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.88-7.84 (m, 4H), 7.65-7.61 (m, 2H), 7.56-7.52 (m, 4H), 6.26-6.21 (m, 3H), 5.88-5.71 (m, 6H), 5.63 (t, J = 7.5 Hz, 1H), 5.47-5.36 (m, 2H), 3.51 (dq, J = 8.0, 8.0 Hz, 1H), 3.25 (m, 1H), 1.71 (d, J = 6.5 Hz, 3H), 1.68 (d, J = 6.5 Hz, 3H), 1.47-1.45 (m, 3H), 1.37-1.35 (m, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 164.3, 164.3, 138.9, 133.8, 133.7, 132.9, 131.3, 131.0, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 128.2, 127.9, 125.6, 124.7, 72.8, 70.8, 63.6, 62.2, 17.8, 17.7, 10.1, 8.4. TOFMS (ES+): m/z calcd for C₁₄H₁₆O₄SNa [M + Na]^+: 317.0823; found: 317.0816.
(E)-6-methyl-5-(phenylsulfonyl)hept-2-en-4-yl acrylate (20c). **One-step method:** To a solution of (isobutylsulfonyl)benzene (500 mg, 2.52 mmol, 1.0 equiv.) in THF (12.6 mL) at -78 °C was added n-BuLi (1.6M, 1.89 mL, 3.03 mmol, 1.2 equiv.) and the mixture was stirred for 1 h. Crotonaldehyde (0.41 mL, 5.04 mmol, 2.0 equiv.) was then added and the reaction was stirred for 10 min then warmed to 0°C for 10 min followed by the addition of acryloyl chloride (0.41 mL, 5.04 mmol, 2.0 equiv.). The mixture was allowed to slowly warm to room temperature over 15 h before quenching with aq. NH₄Cl (20 mL) and extracting with DCM (2 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 20c (0.67 g, 83%) as an inseparable mixture of diastereomers.

**Spectral data for the mixture of diastereomers:** IR (ATR): 1724, 1447, 1303, 1177, 1143, 619, 608, 591 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, J = 7.5 Hz, 4H), 7.63 (dd, J = 9.0, 8.0 Hz, 2 H), 7.53 (dd, J = 8.5, 8.0 Hz, 4H), 7.31-7.18 (m, 6H), 7.16 (d, J = 7.5 Hz, 2H), 7.10 (d, J = 7.0 Hz, 2H), 6.23 (d, J = 17.5 Hz, 2H), 5.88-5.68 (m, 7H), 5.61 (m, 1H), 5.51 (dd, J = 15.0, 7.0 Hz, 1H), 5.27 (dd, J = 15.0, 6.5 Hz, 1H), 3.39 (q, J = 5.5 Hz, 1H), 3.17 (m, 1H), 2.96-2.73 (m, 4H), 2.40-2.29 (m, 2H), 2.18-2.08 (m, 2H), 1.73 (d, J = 6.5 Hz, 3H), 1.63 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 164.4, 164.3, 140.3, 139.5, 133.8, 133.7, 132.5, 131.5, 131.4, 130.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 127.9, 127.8, 126.4, 126.3, 126.3, 125.7, 124.6,
72.2, 71.3, 66.6, 65.6, 34.0, 33.2, 26.6, 25.8, 17.9, 17.7. TOFMS (ES+): m/z calcd for C_{16}H_{20}O_{4}SNa \[ M + Na \]^+: 345.1136; found: 345.1125.

(E)-7-phenyl-5-(phenylsulfonyl)hept-2-en-4-yl acrylate (20d). To a solution of ((3-phenylpropyl)sulfonyl)benzene (300 mg, 1.15 mmol, 1.0 equiv.) in THF (5.75 mL) at -78 °C was added n-BuLi (1.6M, 0.86 mL, 1.38 mmol, 1.2 equiv.) and the mixture was stirred for 1 h before adding crotonaldehyde (0.19 mL, 2.3 mmol, 2.0 equiv.) and stirring for 10 min. The mixture was warmed to 0°C and then acryloyl chloride (0.19 mL, 2.30 mmol, 2.0 equiv.) and the resulting mixture was allowed to slowly warm to room temperature over 15 h. The reaction was quenched with aq. NH₄Cl (15 mL) and extracted with DCM (2 x 15 mL). Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 20d (407 mg, 92%) as an inseparable mixture of diastereomers.

Spectral data for the mixture of diastereomers: IR (ATR): 1743, 1497, 1304, 1176, 1144, 728, 690 cm⁻¹. \(^1\)H NMR (500 MHz, CDCl₃) δ) 7.50 (d, \( J = 7.5 \) Hz, 4H), 7.63 (dd, \( J = 9.0, 8.0 \) Hz, 2H), 7.53 (dd, \( J = 8.5, 8.0 \) Hz, 4H), 7.31-7.18 (m, 6H), 7.16 (d, \( J = 7.5 \) Hz, 2H), 7.10 (d, \( J = 7.0 \) Hz, 2H), 6.23 (d, \( J = 17.5 \) Hz, 2H), 5.88-5.68 (m, 7H), 5.61 (m, 1H), 5.51 (dd, \( J = 15.0, 7.0 \) Hz, 1H), 5.27 (dd, \( J = 15.0, 6.5 \) Hz, 1H), 3.39 (q, \( J = 5.5 \) Hz, 1H), 3.17 (m, 1H), 2.96-2.73 (m, 4H), 2.40-2.29 (m, 2H), 2.18-2.08 (m, 2H), 1.73 (d, \( J = 6.5 \) Hz, 3H), 1.63 (d, \( J = 6.5 \) Hz, 3H). \(^{13}\)C NMR (125
MHZ, CDCl$\textsubscript{3}$) $\delta$ 164.4, 164.3, 140.3, 139.5, 133.8, 133.7, 132.5, 131.5, 131.4, 130.8, 129.3, 129.2, 129.0, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 127.9, 127.8, 126.4, 126.3, 125.7, 124.6, 72.2, 71.3, 66.6, 65.6, 34.0, 33.2, 26.6, 25.8, 17.9, 17.7. TOFMS (ES+): $m/z$ calcd for C$\textsubscript{21}$H$\textsubscript{22}$O$\textsubscript{4}$SNa $[M + Na]^+$: 407.1293; found: 407.1292.

(E)-5-((phenylperoxy)thio)non-2-en-4-yl acrylate (20e). To a solution of pentyl phenyl sulfone (500mg, 2.35 mmol) in THF (11.7 mL) at $-78 \, ^\circ\text{C}$ was added $n$-BuLi (1.6M, 1.8 mL) and the mixture was stirred for one hour before adding crotonaldehyde (0.387ml, 4.71 mmol) and stirring for 10 min. The mixture was then warmed to 0 °C and acryloyl chloride (0.38 ml, 4.71 mmol) was then added and the reaction was allowed to warm to room temperature overnight (~15 h). The reaction was quenched with H$\textsubscript{2}$O (30 ml) and extracted with EtOAc (2 x 20 ml). The combined organic extracts were dried over MgSO$\textsubscript{4}$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 to 1:1 hexanes:ethyl acetate) afforded compound 20e (792 mg, 96%) as a 1:1 inseparable mixture of diastereomers.

*Spectral data for the mixture of diastereomers:* IR (ATR) 3021, 2957, 2871, 1725, 1144 cm$^{-1}$. $^1$H NMR (500MHz, CDCl$\textsubscript{3}$): δ 7.86 - 7.81 (m, 4H), 7.62 -7.56 (m, 2H), 7.53 - 7.48 (m, 4H), 6.22 - 6.16 (m, 2H), 5.83 - 5.64 (m, 8H), 5.53 - 5.44 (m, 2H), 3.33 (dt, $J = 6.6, 5.1$ Hz, 1H), 3.16 (ddd, $J = 6.1, 2.4, 2.4$ Hz, 1H), 2.04-1.90 (m, 2H), 1.83-1.74 (m, 2H), 1.69-1.65 (m, 6H), 1.83-1.20 (m,
8H), 0.88 (t, J = 7.6 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H).  

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 164.7, 164.5, 139.9, 139.1, 133.8, 133.7, 132.5, 131.5 (2C), 131.4, 129.3 (4C), 129.1 (2C), 128.8 (2C), 128.1, 128.0, 125.9, 124.9, 72.6, 71.9, 67.1, 68.2, 30.4, 26.6, 24.7, 24.1, 22.7, 22.6, 18.0, 17.9, 13.9, 13.8.


(1E,5E)-1-phenyl-3-((phenylperoxy)thio)hepta-1,5-dien-4-yl acrylate (20f). To a solution of (E)-((3-phenylallyl)sulfonyl)benzene (500 mg, 1.95 mmol) in THF (9.7 mL) at -78 °C, was added n-BuLi (1.6 M, 1.2 ml) and the mixture was stirred for one hour, before adding crotonaldehyde (0.3 ml, 3.87 mmol) and stirring for 10 min. The mixture was then warmed to 0 °C and acryloyl chloride (0.3 ml, 3.87 mmol) was then added and the reaction was allowed to warm to room temperature overnight (~15 h). The reaction was quenched with H$_2$O (30 ml) and extracted with EtOAc (2 x 20 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 to 1:1 hexanes:ethyl acetate) afforded compound 20f (680 mg, 91%) as a 1.5:1 mixture of diastereomers.

Spectral data for the major diastereomer FT-IR (ATR) 3027, 2945, 1724, 1305, 1259, 1175, 1145 cm$^{-1}$. $^1$H NMR (500MHz, CDCl$_3$): δ 7.82 (d, J = 8.2 Hz, 2H) 7.58 (t, J = 7.9 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.32 - 7.23 (m, 5H), 6.32 (dd, J = 17.3, 1.4 Hz, 1H), 6.30 (d, J = 15.8 Hz, 1H), 6.00-5.86 (m, 4H), 5.76 (dd, J = 1.6, 10.5 Hz, 1H), 5.55 (ddd, J = 1.4, 7.5, 9.3, 1H), 4.11 (dd, J = 9.9, 1.4 Hz, 1H).
6.3 Hz, 1H), 1.70 (dd, J = 6.6, 1.6 Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 164.8, 139.9, 138.8, 135.9, 133.9, 133.0, 131.6, 129.3 (2C), 129.1 (2C), 128.9 (2C), 128.8 (2C), 128.2, 126.9, 125.1, 117.1, 72.1, 71.8, 18.1.

4-((phenylperoxy)thio)hexa-1,5-dien-3-yl acrylate (20g). To a solution of (allylsulfonyl)benzene (300 mg, 1.65 mmol, 1.0 equiv.) in THF (3.67 mL) at -0°C was added n-BuLi (1.6M, 1.03 mL, 1.65 mmol, 1.0 equiv.) and the mixture was stirred for 30 min before adding acrolein (0.22 mL, 3.30 mmol, 2.0 equiv.) and stirring for 4 h at -50°C. Dropwise addition of acryloyl chloride (0.52 mL, 6.45 mmol, 5.0 equiv.) was done at -50°C and the resulting mixture was allowed to slowly warm to room temperature over 12 h. The reaction was quenched with aq. NH$_4$Cl (20 mL) and extracted with MTBE (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 hexanes:ethyl acetate) gave compound 20g (0.38 g, 78%) as an inseparable mixture of diastereomers.

$^1$H NMR (300 MHz, CDCl$_3$) δ (signals for mixture of diastereomers) 7.83 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.61-7.58 (m, 2H), 7.49 (dd, J = 16.3, 8.2 Hz, 4H), 6.44 (d, J = 17.4 Hz, 1H), 6.30 (t, J = 15.4 Hz, 2H), 6.06 (d, J = 7.7 Hz, 1H), 5.96-5.83 (m, 5H), 5.77 (d, J = 10.6 Hz, 2H),
5.74 (m, 1H), 5.46 (d, $J = 11.6$ Hz, 1H), 5.37-5.20 (m, 6H), 5.07 (d, $J = 18.3$ Hz, 1H), 3.97 (dd, $J = 9.4, 6.7$ Hz, 1H), 3.68 (d, $J = 10.1$ Hz, 1H).

5-(phenyl(phenylsulfonyl)methyl)furan-2(5H)-one (22a). To a solution of compound 20a (92 mg, 0.27 mmol, 1.0 equiv.) in toluene (17.9 mL) at 80 °C was added batchwise catalyst Ru-2 (3 x 6 mg, 0.075 equiv.) over 18 h. The reaction was then cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 22a (54 mg, 64%) as an oil.

IR (ATR): 1749, 1314, 1147, 753, 727, 715 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (signals for one diastereomer) 7.93 (d, $J = 9.5$ Hz, 1H), 7.63-7.45 (m, 3H), 7.36 (t, $J = 12.9$ Hz, 2H), 7.32-7.16 (m, 3H), 7.08 (d, $J = 12.3$ Hz, 2H), 6.17 (dd, $J = 9.5, 2.7$ Hz, 1H), 6.00 (d, $J = 12.0$ Hz, 1H), (d, $J = 12.2$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 171.6, 171.1, 154.4, 153.5, 137.8, 136.5, 134.2, 130.4, 130.0, 129.7, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 127.7, 123.3, 122.6, 79.7, 79.6, 73.5, 72.8. TOFMS (ES+): $m/z$ calcd for C$_{17}$H$_{14}$O$_4$Na [M + Na]$^+$: 337.0511; found: 337.0519.
5-(1-(phenylsulfonyl)ethyl)furan-2(5H)-one (22b). To a solution of compound 20b (203 mg, 0.69 mmol, 1.0 equiv.) in toluene (45.9 mL) at 80°C was added batchwise catalyst Ru-2 (3 x 15 mg, 0.075 equiv) over 18 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 22b (125 mg, 72%) as an oil.

*Spectral data for the major isomer:* IR (ATR): 1752, 1306, 1070, 1147, 1035, 739, 689, 589 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.93 (d, \(J = 7.9\) Hz, 2H), 7.77 (dd, \(J = 5.8, 1.4\) Hz, 1H), 7.74 (t, \(J = 7.6\) Hz, 1H), 7.63 (t, \(J = 7.9\) Hz, 2H), 6.26 (dd, \(J = 5.8, 1.9\) Hz, 1H), 5.60 (m, 1H), 3.71 (m, 1H), 1.10 (d, \(J = 7.0\) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.42, 153.16, 137.18, 134.55, 129.73, 128.73, 123.59, 79.08, 60.93, 7.74. TOFMS (ES+): \(m/z\) calcd for C\(_{12}\)H\(_{12}\)O\(_4\)SNa [M + Na]\(^+\): 275.0354; found: 275.0346.

5-(2-methyl-1-(phenylsulfonyl)propyl)furan-2(5H)-one (22c). To a solution of compound 20c (400 mg, 1.24 mmol, 1.0 equiv.) in toluene (82.7 mL) at 80 °C. was added batchwise catalyst Ru-2 (3 x 31 mg, 0.075 equiv.) over 18 h. The reaction was then cooled to room temperature and
concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 22c (185 mg, 51%) as an oil.

IR (ATR): 1755, 1447, 1304, 1146, 892, 593, 556 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (signals for diastereomer \(\alpha\)) 7.99 (dd, \(J = 5.8, 1.6 \) Hz, 1H), 7.88 (d, \(J = 7.9 \) Hz, 2H), 7.66-7.60 (m, 3H), 6.19 (dd, \(J = 5.8, 2.1 \) Hz, 1H), 5.47 (ddd, \(J = 6.8, 1.8, 1.8 \) Hz, 1H), 3.33 (dd, \(J = 6.8, 1.7 \) Hz, 1H), 2.44 (sepd, \(J = 7.0, 1.6 \) Hz, 1H), 1.22 (d, \(J = 7.2 \) Hz, 3H), 1.22 (d, \(J = 7.0 \) Hz, 3H). (signals for diastereomer \(\beta\)) 7.96 (d, \(J = 8.6 \) Hz, 2H) 7.91 (dd, \(J = 5.8, 1.6 \) Hz, 1H), 7.75-7.70 (m, 3H), 6.24 (dd, \(J = 5.7, 2.0 \) Hz, 1H), 5.36 (ddd, \(J = 4.0, 4.0, 2.0 \) Hz, 1H), 3.57 (dd, \(J = 4.0, 2.3 \) Hz, 1H), 2.27(sepd, \(J = 7.1, 2.0 \) Hz, 1H), 1.24 (d, \(J = 7.1 \) Hz, 3H), 1.14 (d, \(J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) (signals for one diastereomer) 171.5, 171.3, 155.4, 154.4, 139.2, 138.4, 134.3, 129.5, 128.4, 122.5, 121.8, 79.4, 78.6, 71.0, 70.4, 27.4, 26.1, 22.4, 21.1, 20.4, 17.3. TOFMS (ES+): \(m/z\) calcd for C\(_{14}\)H\(_{16}\)O\(_4\)SNa [M + Na]\(^{+}\): 303.0667; found: 303.0656.

5-(1-(phenylsulfonyl)pentyl)furan-2(5H)-one (22d). To a solution of compound 20d (100 mg, 0.297 mmol, 1.0 equiv.) in toluene (59.5 mL) at 80 °C was added batchwise catalyst Ru-2 (3 x 19 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 to 1:1 hexanes: ethyl acetate) gave compound 22d (50 mg, 62%) as an inseperable ~1:1 mixture of diastereomers.
IR (ATR) 3021, 2959, 2872, 1757, 1146 cm$^{-1}$. *Spectral data for one diastereomer:* $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 7.90 (m, 2H), 7.73 (dd, $J = 5.8$, 1.5 Hz, 1H), 7.70 (td, $J = 7.6$, 1.3 Hz, 1H), 7.60 (m, 2H), 6.22 (dd, $J = 5.8$, 1.9 Hz, 1H), 5.47-5.46 (m, 1H), 3.54 (ddd, $J = 5.9$, 5.9, 3.7 Hz, 1H), 1.78 – 1.71 (m, 2H), 1.40 – 1.33 (m, 2H), 1.23 – 1.13 (m, 2H) 0.74 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.7, 153.7, 138.0, 134.7, 129.8 (2C), 128.8(2C), 123.7, 79.7, 65.5, 30.1, 23.5, 22.4, 13.7. TOFMS (ES+): $m/z$ calcd for C$_{15}$H$_{18}$O$_4$SNa [M + Na]$^+$: 317.0823; found: 317.0829.

5-(3-phenyl-1-(phenylsulfonyl)propyl)furan-2(5H)-one (22e). To a solution of compound 20e (330 mg, 0.86 mmol, 1.0 equiv.) in toluene (57 mL) at 80 °C was added batchwise catalyst Ru-2 (3 x 18.2 mg, 0.075 equiv.) over 18 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 22e (117 mg, 61%) as an oil.

IR (ATR): 1758, 1447, 1306, 1145, 728, 688 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (signals for one diastereomer) 7.86 (d, $J = 7.9$ Hz, 2H), 7.78 (dd, $J = 5.8$, 1.5 Hz, 1H), 7.73 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 8.1$ Hz, 2H), 7.24-7.15 (m, 3H), 7.97 (d, $J = 7.6$ Hz, 2H), 6.27 (dd, $J = 5.8$, 2.1 Hz, 1H), 5.51 (m, 1H), 3.6 (m, 1H), 2.60 (m, 2H), 2.08 (m, 1H), 1.71 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (signals for one diastereomer) 171.4, 153.5, 139.2, 137.6, 134.5, 129.7, 128.6, 128.4,

(E)-5-(3-phenyl-1-(phenylsulfonyl)allyl)furan-2(5H)-one (22f). To a solution of compound 20f (279 mg, 0.729 mmol, 1.0 equiv.) in toluene (48.6 mL) at 80 °C was added batchwise catalyst Ru-2 (3 x 16 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 to 1:1 hexanes:ethyl acetate) gave compound 22f (190 mg, 76 %) as an inseparable ~1:1 mixture of diastereomers.

IR (ATR) 3061, 2955, 1758, 1306, 1145, 1083 cm$^{-1}$. Signals for one diastereomer: $^1$H NMR (500MHz, CDCl$_3$): δ 7.88 - 7.84 (m, 2H), 7.66-7.61 (m, 2H), 7.52 (t, $J = 7.7$ Hz, 2H), 7.28 – 7.25 (m, 3H), 7.20 – 7.16 (m, 2H), 6.26 – 6.23 (m, 2H), 5.82 (m, 1H), 5.77 (dd, $J = 15.7$, 10.1 Hz, 1H), 4.26 (dd, $J = 10.2$, 4.1 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 171.3, 153.0, 141.8, 137.1, 135.0, 134.6, 129.3 (2C), 129.0, 128.9 (2C), 128.7 (2C), 126.8 (2C), 123.8, 113.7, 78.8, 70.8. TOFMS (ES+): $m/z$ calcd for C$_{22}$H$_{22}$O$_4$Na [M + Na]$^+$: 405.1136; found: 405.1142.
5-(1-(phenylsulfonyl)allyl)furan-2(5H)-one (22g). To a solution of compound 20g (100 mg, 0.342 mmol, 1.0 equiv.) in toluene (17.1 mL) at 80 °C was added batchwise catalyst Ru-2 (3 x 5.4 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography on silica (10:1 to 4:1 to 1:1 hexanes:ethyl acetate) gave compound 22g (78 mg, 86 %) as an inseparable ~1:1 mixture of diastereomers.

\[\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) \delta (\text{signals for one diastereomer}) 7.87 (d, J = 7.6 Hz, 2H), 7.71-7.55 (m, 4H), 6.2 (d, J = 1.6 Hz, 1H), 5.73 (s), 5.58-5.46 (m, 1H), 5.38 (d, J = 10 Hz, 1H), 5.18 (d, J = 16 Hz, 1H), 3.79 (dd, J = 9.2 Hz, 1H).\]

(Z)-5-benzylidenefuran-2(5H)-one (28a). To a solution of compound 22a (34 mg, 0.11 mmol) in DCM (1.5 mL) at room temperature was added triethylamine (0.090 mL, 0.65 mmol, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO\(_4\), filtered, and concentrated in vacuo. Purification by flash column chromatography on florisil (10:1 to 4:1 hexanes:ethyl acetate) gave 28a (19 mg, 98%) as a 6:1 mixture of Z:E isomers. Spectral data for the major isomer matched
that previously reported for (Z)-28a\textsuperscript{41}: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.80 (d, \(J = 7.5\) Hz, 2H), 7.50 (d, \(J = 5.3\) Hz, 1H), 7.42-7.33 (m, 3H), 3.22 (d, \(J = 5.293\) Hz, 1H), 6.04 (s, 1H).

(Z)-5-ethyldienefuran-2(5H)-one (28b). To a solution of compound 22b (106 mg, 0.42 mmol, 1.0 equiv.) in DCM (5.8 mL) at room temperature was added triethylamine (0.35 mL, 2.52 mmol) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO\(_4\), filtered, and carefully concentrated in vacuo (volatile compound) giving 28b as a 7:1 mixture of Z:E isomers. Spectral data for the major isomer matched that previously reported for (Z)-28b\textsuperscript{42}: \(^1\)H NMR (300MHz, CDCl\(_3\)) \(\delta\): 7.32 (d, \(J = 5.6\) Hz, 1H), 6.15 (d, \(J = 5.4\) Hz, 1H), 5.33 (q, \(J = 7.6\) Hz, 1H), 1.98 (d, \(J = 8.3\) Hz, 3H).

(Z)-5-(2-methylpropylidene)furan-2(5H)-one (28c). To a solution of compound 22c (166.2 mg, 0.59 mmol, 1.0 equiv.) in DCM (5.8 mL) at room temperature was added triethylamine (0.50 mL, 3.56 mmol, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO\(_4\),
filtered, and carefully concentrated *in vacuo*. Purification by flash column chromatography on florisil (4:1 hexanes:MTBE) gave 28c (76 mg, 95%) as a 4:1 mixture of Z:E isomers. Spectral data for the major isomer matched that previously for the (Z)-28c.43

IR (ATR): 2963, 1770, 1749, 1556, 1135, 879 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (signals for major stereoisomer) 7.33 (d, $J = 5.4$ Hz, 1H), 6.17 (d, $J = 5.5$ Hz, 1H), 5.18 (d, $J = 9.7$ Hz, 1H), 3.05 (m, 1H), 1.13 (d, $J = 6.8$ Hz, 6H). (signals for minor stereoisomer) 7.66 (d, $J = 5.6$ Hz, 1H), 6.22 (dd, $J = 5.6$, 1.85 Hz, 1H), 5.67 (dd, $J = 10.8$, 1.8 Hz, 1H), 2.73 (m, 1H), 1.16 (d, $J = 6.7$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 170.13, 148.0, 143.9, 139.6 124.3, 123.5, 120.1, 119.0, 29.8, 26.5, 23.4, 22.5. TOFMS (Cl$^+$): $m/z$ calcd for C$_8$H$_{14}$O$_2$N [M + NH$_4$]$^+$: 156.1024; found: 156.1024.

**(Z)-5-pentylidenefuran-2(5H)-one (28e).** To a solution of compound 22e (32 mg, 0.107 mmol) in DCM (2.0 mL) at room temperature was added triethylamine (0.1 ml, 0.64 mmol) and the mixture was stirred for 15 h. The reaction was quenched with H$_2$O (15 ml) and extracted with MTBE (2 x 15 ml). The combined organic extracts were dried over MgSO$_4$, filtered, and carefully concentrated *in vacuo*. Purification by flash column chromatography on florisil (6:1 hexanes:methyl tert-butyl ether) gave compound 28e (17 mg, 100%) as an 8:1 mixture of Z:E isomers. Spectral data for the major isomer matched that previously reported for the (Z)-28e.4
Spectral data for the major isomer: IR (ATR) 3027, 2929, 2868, 1779, 1128 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.29 (d, \(J = 5.5\) Hz, 1H), 6.12 (d, \(J = 5.4\) Hz, 1H), 5.28 (t, \(J = 5.3\) Hz, 1H), 2.39 (q, \(J = 7.6, 1.6, 1.6\) Hz, 2H), 1.45 (quin, \(J = 7.1\) Hz, 2H) 1.35 (sext, \(J = 7.2\) Hz, 2H), 0.90 (t, \(J = 7.2\) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 170.4, 149.9, 143.8, 119.2, 118.0, 31.2, 26.4, 22.6, 14.0.

\(\text{(Z)}\)-5-(3-phenylpropylidene)furan-2(5H)-one (28d). To a solution of compound 22d (127 mg, 0.37 mmol, 1.0 equiv.) in DCM (7.4 mL) at room temperature was added triethylamine (0.31 mL, 2.22 mmol, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO\(_4\), filtered, and concentrated \textit{in vacuo}. Purification by flash column chromatography on florisil (4:1 hexanes:ethyl acetate) gave 22d (72 mg, 98%) as a 5:1 mixture of Z:E isomers.

Spectral data for the major isomer: IR (ATR): 1772, 1732, 1496, 1151, 1074, 700 cm\(^{-1}\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.30 (m, 3H), 7.26-7.23 (m, 3H), 6.18 (d, \(J = 5.5\) Hz, 1H), 5.31 (t, \(J = 7.7\) Hz, 1H), 2.86-2.75 (m, 4H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.0, 150.0, 143.5, 140.7, 128.5, 128.4, 126.3, 119.3, 116.2, 34.9, 27.9.
(Z)-5-((E)-3-phenylallylidene)furan-2(5H)-one (28f). To a solution of compound 22f (32 mg, 0.107 mmol) in DCM (2.0 mL) at room temperature was added triethylamine (0.1 ml, 0.642 mmol) and the mixture was stirred for 15 h. The reaction was quenched with H2O (15 ml) and extracted with MTBE (2 x 15 ml). The combined organic extracts were dried over MgSO4, filtered, and carefully concentrated in vacuo. Purification by flash column chromatography on florisil (6:1 hexanes:methyl tert-butyl ether) afforded compound 28f (17 mg, 98%) as a 3:1 mixture of Z:E isomers.

Spectral data for the major isomer: IR (ATR) 3009, 2966, 1772, 1743, 1537, 1107 cm⁻¹. ¹H NMR (500MHz, CDCl₃): δ 7.25 (dd, J = 15.8, 11.4 Hz, 1H), 7.18 – 7.11 (m, 5H), 7.08-7.02 (m, 5H), 6.64 (d, J = 5.5 Hz, 1H), 6.48 (dd, J = 15.3, 11.7 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 6.32 (d, J = 5.3 Hz, 1H), 6.24 (d, J = 15.5 Hz, 1H), 6.01 (m, 1H), 5.56 (dd, J = 5.4, 1.9 Hz, 1H), 5.53 (d, J = 5.3, 1H), 5.22 (d, J = 11.5, 1H). ¹³C NMR (75 MHz, CDCl₃): 168.4, 150.8, 149.0, 141.9, 137.4, 137.0, 136.5, 136.4, 128.7 (2C), 128.6 (2C), 128.4, 128.0 (2C), 127.8, 125.6, 127.1 (2C), 126.7, 121.6, 120.9, 119.0, 118.4, 114.6, 113.7. TOFMS (ES+): m/z calcd for C₁₃H₁₀O₂Na [M + Na]⁺: 221.0578; found: 221.0584.
(Z)-5-allylidenefuran-2(5H)-one (28g). To a solution of compound 22g (38.8 mg, 0.140 mmol) in DCM (2.0 mL) at room temperature was added triethylamine (0.12 ml, 0.88 mmol) and the mixture was stirred for 15 h. The reaction was quenched with H₂O (15 ml) and extracted with MTBE (2 x 15 ml). The combined organic extracts were dried over MgSO₄, filtered, and carefully concentrated in vacuo. Purification by flash column chromatography on florisil (6:1 hexanes:methyl tert-butyl ether) afforded compound 28g (16 mg, 94%) as a 2:1 mixture of Z:E isomers.

1H NMR (300 MHz, CDCl₃) δ (signals for one diastereomer) 7.38 (d, J = 5.6 Hz, 1H), 6.87 (dt, J = 17.0, 10.7 Hz, 1H), 6.21 (d, J = 6.3 Hz, 1H), 5.83 (d, J = 11.3 Hz, 1H), 5.45 (d, J = 10.8 Hz, 2H).

Compound 73a. To a solution of ((3-phenylpropyl)sulfonyl)benzene (500 mg, 1.92 mmol, 1.0 equiv.) in THF (9.6 mL) at -78 °C was added n-BuLi (1.6 M, 1.44 mL, 2.30 mmol, 1.2 equiv.) and the mixture was stirred for 1 h before adding methacrolein (0.32 mL, 3.84 mmol, 2.0 equiv.) and stirring for 10 min. The mixture was warmed to 0 °C followed by the addition of acryloyl chloride.
(0.31 mL, 3.84 mmol, 2.0 equiv.) and the mixture was allowed to slowly warm to room temperature over 15 h. The reaction was quenched with aq. NH₄Cl (20 mL) and extracted with DCM (2 x 15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave 73a (0.7 g, 92%) as an inseparable mixture of diastereomers.

*Spectral data for the mixture of diastereomers:* IR (ATR): 1728, 1305, 1174, 1142, 727, 690 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.87 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 7.6 Hz, 2H), 7.63-7.57 (m, 3H), 7.53-7.48 (m, 3H), 7.27 (t, J = 7.4 Hz, 3H), 7.21-7.18 (m, 4H), 7.14 (d, J = 7.6 Hz, 3H), 6.25 (d, J = 19.5 Hz, 1H), 6.08 (d, J = 16.7 Hz, 1H), 5.89 (m, 1H), 5.76-5.56 (m, 5H), 5.14 (s, 1H), 5.08 (s, 1H), 4.87 (s, 1H), 4.79 (s, 1H), 3.53 (m, 1H), 3.17 (m, 1H), 2.97-2.83 (m, 4H), 2.32-2.02 (m, 4H), 1.54 (s, 3H), 1.32 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 164.0, 163.9, 140.8, 140.4, 140.3, 139.8, 139.2, 137.8, 134.0, 133.4, 131.6, 131.5, 129.3, 129.2, 129.0, 128.8, 128.6 (3C), 128.2, 127.6, 127.5, 126.4, 117.7, 112.6, 77.3, 75.6, 72.7, 64.1, 63.7, 33.7, 33.0, 27.6, 25.0, 19.0, 17.6. TOFMS (ES+): m/z calcd for C₂₂H₂₄O₄SNa [M + Na]⁺: 407.1293; found: 407.1287.

![Chemical structure](image)

**4-methyl-5-(3-phenyl-1-(phenylsulfonyl)propyl)furan-2(5H)-one.** To a solution of compound 73a (100.0 mg, 0.26 mmol, 1.0 equiv.) in toluene (17.3 mL) at 80 °C was added batchwise catalyst Ru-1 (3 x 4 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and
concentrated in vacuo. Purification by flash chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave the RCM product (45 mg, 49%) as an inseparable mixture of diastereomers.

To a solution of the RCM adduct above (56.0 mg, 0.16 mmol, 1.0 equiv.) in DCM (3.27 mL) at room temperature was added triethylamine (0.14 mL, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on florisil (4:1 hexanes:ethyl acetate) gave the eliminated product (34 mg 100%) as a mixture of isomers.

*Spectral data for the major isomer:* IR (ATR): 1762, 920, 749, 699 cm⁻¹. ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.20 (m, 5H), 5.90 (s, 1H), 5.30 (m, 1H), 2.80 (m, 2H), 2.72 (m, 2H), 2.11 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 169.4, 154.5, 151.0, 140.8, 128.5, 128.4, 126.2, 116.2, 111.8, 35.0, 27.7, 11.7. TOFMS (ES+): m/z calcd for C₁₄H₁₄O₂Na [M + Na]⁺: 237.0891; found: 237.0887.

**Compound 73b.** To a solution of ((3-phenylpropyl)sulfonyl)benzene (300 mg, 1.15 mmol, 1.0 equiv.) in THF (5.8 mL) at -78 °C was added n-BuLi (1.6 M, 0.86 mL, 1.38 mmol, 1.2 equiv.) and the mixture was stirred for 1 h before adding crotonaldehyde (0.19 mL, 2.30 mmol, 2.0 equiv.)
and stirring for 10 min. The mixture was warmed to 0 °C followed by the addition of methacryloyl chloride (0.23 mL, 2.30 mmol, 2.0 equiv.) and the mixture was allowed to slowly warm to room temperature over 15 h. The reaction was quenched with aq. NH₄Cl (20 mL) and extracted with DCM (2 x 15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 73b (0.3 g, 65%) as an inseparable mixture of diastereomers.

¹H NMR (500 MHz, CDCl₃) δ (signals for mixture of diastereomers) 7.87-7.84 (m, 4 H), 7.64-7.60 (m, 2H), 7.55-7.50 (m, 4H), 7.31-7.15 (m, 8H), 7.06 (d, J = 7.24 Hz, 2H), 5.89 (s, 2H), 5.87-5.80 (m, 2H), 5.71 (dd, J = 5.9, 5.6 Hz, 1H), 5.62-5.53 (m, 2H), 5.48 (s, 1H), 5.45 (s, 1H), 5.22 (dd, J = 15.3, 6.1 Hz, 1H), 3.42 (dt, J = 5.6, 5.6 Hz, 1H), 3.16 (t, J = 5.4 Hz, 1H), 2.97-2.81 (m, 3H), 2.73 (m, 1H), 2.39-2.28 (m, 2H), 2.22-2.10 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H), 1.73 (d, J = 6.5 Hz, 3H), 1.62 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (signals for mixture of diastereomers) 165.6, 165.5, 140.4, 140.3, 139.3, 138.3, 133.8, 133.7, 131.9, 130.3, 129.2, 129.0, 128.7, 128.6, 128.4, 126.4, 126.3, 126.2, 126.1, 126.0, 124.7, 72.1, 71.1, 66.7, 65.6, 34.0, 33.3, 26.6, 25.7, 18.1, 18.0, 17.9, 17.7.

IR (ATR): 1717, 1447, 1305, 1143, 728, 689 cm⁻¹
(Z)-3-methyl-5-(3-phenylpropylidene)furan-2(5H)-one. To a solution of compound 73b (100.0 mg, 0.25 mmol, 1.0 equiv.) in toluene (16.7 mL) at 80 °C was added batchwise catalyst Ru-1 (3 x 5 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave the RCM product (65 mg, 72%) as an inseparable mixture of diastereomers.

To a solution of the RCM adduct above (64.5 mg, 0.18 mmol, 1.0 equiv.) in DCM (2.51 mL) at room temperature was added triethylamine (0.15 mL, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. Purification by flash column chromatography on florisil (4:1 hexanes:ethyl acetate) gave the eliminated product (31 mg 79%) as a mixture of isomers.

$^1$H NMR (500 MHz, CDCl₃) δ (signals for mixture of diastereomers) 7.31-7.26 (m, 4H), 7.22-7.19 (m, 4H), 7.14 (d, $J$ = 7.4 Hz, 2H), 7.10 (s, 1H), 6.95 (s, 1H), 5.64 (t, $J$ = 8.5 Hz, 1H), 5.13 (t, $J$ = 7.7 Hz, 1H), 2.80-2.69 (m, 6H), 2.54 (dt, $J$ = 7.8 Hz, 2H), 1.99 (s, 1H), 1.97 (s, 1H). $^{13}$C NMR (125 MHz, CDCl₃) δ (signals for mixture of diastereomers) 171.1, 170.9, 149.1, 148.6, 140.8, 140.4, 137.6, 133.5, 130.4, 129.3, 128.5, 128.4, 126.3, 126.1, 113.2, 112.3, 36.0, 35.1, 28.4, 27.6, 10.7, 10.5.
(E)-7-((tert-butyltrimethylsilyloxy)-5-(phenylsulfonyl)hept-2-en-4-ol (93). tert-
butyldimethyl(3-(phenylsulfonyl)propoxy)silane (92) (210.4 mg, 0.67 mmol, 1.0 equiv.) was
added to a 10-mL shlenk tube and dissolved in THF (3.34 mL, 0.20 M) at -78°C. n-BuLi (0.32
mL, 0.80 mmol, 1.2 equiv.) was added drop wise and stirred for 1 h. Crotonaldehyde (0.11 mL,
1.34 mmol, 2.0 equiv.) was then added drop wise and continued to stir for 10 min. The reaction
was then quenched with water and extracted with MTBE. Purification by column chromatography
on silica (10:1 hexanes:ethyl acetate) gave product 93 (182.6 mg, 71%) as a mixture.

\[\text{IR (ATR): 2954, 2929, 2884, 2856, 1472, 1447, 1287, 1254, 1144, 1082, 966, 833, 776, 723, 688 cm}^{-1}\]
(E)-7-((tert-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)hept-2-en-4-yl acrylate (94). DCM (2.38 mL, 0.20 M) was used to transfer (E)-7-((tert-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)hept-2-en-4-ol (93) (182.6 mg, 0.48 mmol, 1.0 equiv.) to a 10-mL shlenk tube. The mixture was cooled to 0°C and Triethylamine (0.10 mL, 0.71 mmol, 1.5 equiv.) was added. The reaction mixture continued to stir for 15 min. Acryloyl Chloride (0.05 mL, 0.57 mmol, 1.2 equiv.) was then added dropwise to the mixture to stir for 1 h. The reaction was quenched at 0°C with Sodium Bicarbonate and extracted with DCM. Purification by column chromatography on silica (10:1 hexanes:ethyl acetate) gave product 94 (98.5 mg, 46%) as a mixture.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (signals for mixture of diastereomers) 7.88 (d, \(J = 7.9\) Hz, 2 H), 7.85 (d, \(J = 8.0\) Hz, 2H), 7.64-7.59 (m, 2H), 7.56-7.51 (m, 4H), 6.28-6.20 (m, 2H), 5.87-5.79 (m, 3H), 5.75-5.66 (m, 3H), 5.58 (dd, \(J = 15.2, 7.1\) Hz, 1H), 5.42 (dd, \(J = 15.1, 6.2\) Hz, 1H), 3.83-3.67 (m, 5H), 3.46 (m, 1H), 2.26-2.15 (m, 3H), 2.09 (m, 1H), 2.00-1.93 (m, 2H), 1.71 (d, \(J = 6.4\) Hz, 3H), 1.65 (d, \(J = 6.4\) Hz, 1H), 0.87 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), -0.01 (s, 6H), -0.03 (s, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 164.4, 164.4, 139.7, 138.5, 133.7, 133.6, 132.1, 131.3, 131.1, 130.8, 129.2, 129.1, 128.9, 128.5, 128.0, 127.9, 126.0, 124.9, 72.1, 71.2, 63.8, 62.8, 60.2, 59.9, 28.0, 27.3, 25.8, 18.2, 18.1, 17.8, 17.7, -5.4, -5.5.
(Z)-5-(3-((tert-butyldimethylsilyl)oxy)propyldene)furan-2(5H)-one (96). To a solution of compound 94 (98.5 mg, 0.22 mmol, 1.0 equiv.) in toluene (14.5 mL) at 80 °C was added batchwise catalyst Ru-1 (3 x 4 mg, 0.075 equiv.) over 18 h. The reaction was cooled to room temperature and concentrated in vacuo. Purification by column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave product 95 (63.7 mg, 74%) as an inseparable mixture of diastereomers.

To a solution of the RCM adduct above (95) (63.7 mg, 0.16 mmol, 1.0 equiv.) in DCM (2.22 mL) at room temperature was added triethylamine (0.13 mL, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The crude product 96 was taken into the next step without purification.

1H NMR (500 MHz, CDCl3) δ (signals for major diastereomer) 7.34 (d, J = 5.8 Hz, 1H), 6.16 (d, J = 5.4 Hz, 1H), 5.41 (t, J = 3.74 Hz, 2H), 2.63-2.59 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). (signals for minor diastereomer) 7.63 (d, J = 6.3 Hz, 1H), 6.20 (d, J = 5.4 Hz, 1H), 5.79 (t, J = 8.3 Hz, 1H), 3.71 (t, J = 6.4 Hz, 2H), 2.47 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H). 13C NMR (125 MHz, CDCl3) δ (signals for mixture of diastereomers) 170.0, 151.1, 150.3, 143.5, 140.0, 120.2, 119.3, 114.3, 113.2, 61.7, 45.8, 30.1, 29.8, 25.9, 25.8, 18.3, 18.2, 8.6, -5.3, -5.4.
1,6-dioxaspiro[4.4]non-3-en-2-one (97). Compound 96 (31.4 mg, 0.12 mmol, 1.0 equiv.) was transferred to a 25-mL round bottom with THF (4.97 mL, 0.024 M). LiOH (4.97 mL) was added slowly and left to stir for 2 h at room temperature. The reaction mixture was then cooled to 0°C. HF-Pyridine (1.25 mL, 70% HF, 0.011M) was then slowly added and left to stir overnight. The reaction mixture was then slowly quenched with Sodium Bicarbonate at 0°C and extracted with Ethyl Acetate affording the product (17.24 mg, 100% (via nmr)). Spectral data matched that previously reported for 97.\(^{44}\) \(1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.13 (d, \(J = 5.5\) Hz, 1H), 6.14 (d, \(J = 5.6\) Hz, 1H), 4.26 (m, 1H), 4.12 (m, 1H), 2.36-2.12 (m, 4H). \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) 169.9, 151.8, 124.3, 114.5, 70.6, 35.4, 24.2.

(E)-8-((tert-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)oct-2-en-4-ol (106). tert-butyldimethyl(4-(phenylsulfonyl)butoxy)silane (105) (263.0 mg, 0.80 mmol, 1.0 equiv.) was added to a 10-mL shlenk tube and dissolved in THF (4.01 mL, 0.20 M) at -78°C. n-BuLi (0.38 mL, 0.96 mmol, 1.2 equiv.) was added drop wise and stirred for 1 h. Crotonaldehyde (0.13 mL, 1.60 mmol, 2.0 equiv.) was then added drop wise and continued to stir for 10 min. The reaction was then quenched with water and extracted with MTBE. Purification by column chromatography
on silica (10:1 hexanes:ethyl acetate) gave product 106 (245.0 mg, 79%) as an inseparable mixture of diastereomers.

\[ \text{H NMR (500 MHz, CDCl}_3\text{)} \delta \text{ (signals for mixture of diastereomers) } 7.91-7.88 \text{ (m, 4H), 7.65 (m, 2H), 7.58-7.54 \text{ (m, 4H), 5.78-5.70 \text{ (m, 2H), 5.48-5.43 \text{ (m, 2H), 4.65 \text{ (d, } J = 4.8 \text{ Hz, 1H), 4.47 \text{ (dd, } J = 8.1 \text{ Hz, 1H), 3.52-3.46 \text{ (m, 4H), 3.17 \text{ (dd, } J = 12.3, 5.8 \text{ Hz, 1H), 3.09 \text{ (t, } J = 5.0 \text{ Hz, 1H), 1.97-1.83 \text{ (m, 2H), 1.75 \text{ (m, 1H), 1.67 \text{ (d, } J = 6.2 \text{ Hz, 6H), 1.64-1.47 \text{ (m, 5H), 0.84 \text{ (s, 18H), 0.02 \text{ (s, 12H).}}}}\]

\[ \text{C NMR (125 MHz, CDCl}_3\text{)} \delta \text{ (signals for mixture of diastereomers) } 138.5, 138.2, 133.9, 133.8, 129.9, 129.4, 129.3, 129.1, 128.9, 128.7, 128.6, 71.5, 69.6, 69.0, 68.7, 62.4, 31.3, 30.4, 25.9, 23.0, 19.8, 18.2, 17.7, -5.4. \]

\[ \text{(E)-8-((tert-butylidimethylsilyloxy)-5-(phenylsulfonyl)oct-2-en-4-yl methacrylate (107).} \]

DCM (3.15 mL, 0.20 M) was used to transfer (E)-8-((tert-butylidimethylsilyloxy)-5-(phenylsulfonyl)oct-2-en-4-ol (106) (251.3 mg, 0.63 mmol, 1.0 equiv.) to a 10-mL shlenk tube. The mixture was cooled to 0°C and Triethylamine (0.13 mL, 0.95 mmol, 1.5 equiv.) was added. The reaction mixture continued to stir for 15 min. Methacryloyl Chloride (0.12 mL, 1.26 mmol, 2 equiv.) was then added dropwise to the mixture to stir for 3 h. The reaction was quenched at 0°C with Sodium Bicarbonate and extracted with DCM. The crude product was then purified using
column chromatography on silica affording the product 107 (160.8 mg, 57%) as an inseparable mixture of diastereomers.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 7.88 (d, $J = 7.6$ Hz, 2H), 7.85 (d, $J = 7.7$ Hz, 2H), 7.67-7.58 (m, 2H), 7.56-7.50 (m, 4H), 5.91 (s, 1H), 5.97 (s, 1H), 5.85-5.77 (m, 2H), 5.77-5.73 (m, 2H), 5.56 (dd, $J = 15.4$, 7.0 Hz, 1H), 5.47 (s, 1H), 5.43 (dd, $J = 14.8$, 7.3 Hz, 1H), 5.42 (s, 1H), 3.58 (m, 2H), 3.56 (m, 2H), 3.43 (m, 1H), 3.21 (m, 1H), 2.07-1.79 (m, 8H), 1.81 (s, 3H), 1.74 (s, 3H), 1.71 (d, $J = 6.3$ Hz, 3H), 1.67 (d, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.04 (s, 6H), 0.01 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 165.6, 165.5, 139.4, 138.3, 133.6, 133.5, 132.0, 130.8, 129.1, 129.0, 128.6, 126.1, 126.0, 124.7, 72.2, 71.5, 68.2, 66.9, 62.5, 62.4, 31.3, 30.5, 25.8, 21.9, 21.2, 18.2, 18.1, 18.0, 17.8, 17.7, -5.4.

(Z)-5-((tert-butyldimethylsilyl)oxy)butylidene)-3-methylfuran-2(5H)-one. (109). (E)-8-((tert-butyldimethylsilyl)oxy)-5-(phenylsulfonyl)oct-2-en-4-yl methacrylate (107) (143.8 mg, 0.31 mmol, 1.0 equiv.) was added to a 25-mL shlenk tube with toluene (20.53 mL, 0.015 M) and heated to 80°C. Ru-1 (4.83 mg, 0.0077 mmol, 0.025 equiv.) was then added to the mixture in four hour increments two times and left to stir overnight. The crude product was then purified using column chromatography on silica affording the product 108 (53.3 mg, 62 %) as a mixture.
To a solution of the RCM adduct above (108) (53.3 mg, 0.13 mmol, 1.0 equiv.) in DCM (1.75 mL) at room temperature was added triethylamine (0.11 mL, 6.0 equiv.) and the mixture was stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with DCM (2 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was then purified using column chromatography on silica affording the product 109 (26.1 mg, 71%) as a mixture.

1H NMR (500 MHz, CDCl₃) δ (signals for mixture of diastereomers) 7.30 (s, 1H), 6.97 (s, 1H), 5.62 (t, J = 8.8 Hz, 1H), 5.17 (t, J = 7.5 Hz, 1H), 3.66-3.61 (m, 4H), 2.44 (dt, J = 7.7 Hz, 2H), 2.34 (dt, J = 7.3 Hz, 2H), 2.00 (d, J = 10.5 Hz, 6H), 1.67 (m, 4H), 0.88 (s, 18H), 0.05 (s, 12H).

3-methyl-1,6-dioxaspiro[4.5]dec-3-en-2-one (110). Compound 109 (53.0 mg, 0.19 mmol, 1.0 equiv.) was transferred to a 25-mL round bottom with THF (7.82 mL, 0.024 M). LiOH (7.82 mL) was added slowly and left to stir for 2 h at room temperature. The reaction mixture was then cooled to 0°C. HF-Pyridine (1.95 mL, 70% HF, 0.011M) was then slowly added and left to stir overnight. The reaction mixture was then slowly quenched with Sodium Bicarbonate at 0°C and extracted with Ethyl Acetate affording the product 110 (24.6 mg, 77%).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.74 (s, 1H), 4.01 (t, $J = 10.5$ Hz, 1H), 3.89 (d, $J = 12.8$ Hz, 1H), 1.90 (s, 3H), 1.85-1.79 (m, 2H), 1.72-1.63 (m, 4H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.0, 147.2, 131.9, 104.8, 65.0, 32.3, 24.1, 19.1, 10.5.

1-phenyl-1-((phenylperoxy)thio)but-3-en-2-yl 2-bromoacrylate (77). To a solution of 1-phenyl-1-(phenylsulfonyl)but-3-en-2-ol (0.40 g, 1.40 mmol) in DCM (7.0 mL) at 0°C was added triethylamine (0.29 mL, 2.10 mmol, 1.5 equiv.) followed by compound $^{76}$ (0.28 mg, 1.68 mmol, 1.2 equiv.) for 1 h. The reaction was quenched with aq. sodium bicarbonate (20 mL) and extracted with DCM (2 x 20 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica (4:1 to 1:1 hexanes:ethyl acetate) gave compound 77 (0.29 g, 49%) as an inseparable mixture of diastereomers.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 7.60 (d, $J = 7.6$ Hz, 2H), 7.55-7.48 (m, 4H), 7.39-7.22 (m, 12H), 7.18 (d, $J = 7.5$ Hz, 2H) 6.96 (s, 1H), 6.94 (s, 1H), 6.35 (m, 1H), 6.28-6.25 (m, 3H), 5.64 (m, 2H), 5.39-5.13 (m, 4H), 4.54 (d, $J = 9.2$ Hz, 1H), 4.28 (d, $J = 4.3$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ (signals for mixture of diastereomers) 160.4, 160.3, 138.7, 137.8, 133.8, 133.6, 132.2, 132.0, 131.7, 131.6, 131.2, 130.6, 129.8, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 120.7, 120.6, 120.5, 74.7, 73.7, 73.2.
1-phenyl-1-((phenylsulfonyl)but-3-en-2-ol
Sample name: 22a
Data Collected on:
Inorganic Chemistry, University of California
Archive directory:
Sample directory:
Plot name: PA-PA-14799-10እእ addItem
Plot name: PA-PA-14799-10�እ addItem

22a

Sample name: 22a
Data Collected on:
Inorganic Chemistry, University of California
Archive directory:
Sample directory:
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22a

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22a

Sample name: 22a
Data Collected on:
Inorganic Chemistry, University of California
Archive directory:
Sample directory:
Plot name: PA-PA-14799-10�エルaddItem
Plot name: PA-PA-14799-10�エルaddItem

22a

Sample name: 22a
Data Collected on:
Inorganic Chemistry, University of California
Archive directory:
Sample Name: PhO-Pa-094PURE
Data Collected on: 11 July 2015
Archive directory:

Sample directory:

PuSh-Ph-Pa-094PURE

Pulse Sequence: PROTON 1D
Solute: cct3
Date collected on: 11 July 2015

Temp: 298.1 K
Operator name:

Relax delay: 1000 sec
Pulse: 45°
Acq. time: 2.730 sec
Width: 0.664 Hz
16 repetitions

DSS as int. 400.13 MHz
DATA PROCESSING
FT size: 32768
Total time: 3 min 0 sec

Sample Name: PhO-Pa-146CARB
Data Collected on: 11 July 2015
Archive directory:

Sample directory:

PuSh-Ph-Pa-146CARB

Pulse Sequence: CARBON 1D
Solute: cct3
Date collected on: 11 July 2015

Temp: 298.1 K
Operator name:

Relax delay: 1000 sec
Pulse: 45°
Acq. time: 1.043 sec
Width: 3446.5 Hz
1200 repetitions

DSS as int. 135, 125, 66000007 MHz
DECSOFT 2HR, 490.147065 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening: 15.1 Hz
FT size: 65536
Total time: 14 min
Sample Name: PH-PA-141
Data Collected on:
Archive directory:

Sample details:
File No: PH-PA-141
Pulse Sequence: PROTON (sptx)
Solvent: cdb3
Data collected on: Dec 15 2014

Temp: 25.0 °C / 298.1 K
Operator: phui
Relax delay: 1000 sec
Pulse 90.0 degrees
Acq. time 2.750 sec
640000 Hz
16 repetitions
OBSERVE: 6L, 499.742969 MHz
DATA PROCESSING
FT size 12738
Total time 1 min 0 sec

((3-phenylpropyl)sulfonyl)benzene

Sample Name: PH-PA-141
Data Collected on: Archive directory:

Sample details:
File No: PH-PA-141
Pulse Sequence: CARBON (sptx)
Solvent: cdb3
Data collected on: Dec 15 2014

Temp: 25.0 °C / 298.1 K
Operator: phui
Relax delay: 1000 sec
Pulse 90.0 degrees
Acq. time 1.042 sec
Width 3.3486.1 Hz
20000 repetitions
OBSERVE: 13C, 156.4690007 MHz
DECUPLE: 1H, 499.742969 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 11 hr, 23 min

((3-phenylpropyl)sulfonyl)benzene
Sample name:
Pb-Pb_140
Data Collected on:
isoscan.chem.ens.fr/nuo/500
Archive directory:

Sample directory:

Plotname: Pb-Pb_140_14SF21_pl0001

Sample name:
Pb-Pb_140
Data Collected on:
isoscan.chem.ens.fr/nuo/500
Archive directory:

Sample directory:

Plotname: Pb-Pb_140CARB_pl0001

(isobutylsulfonyl)benzene

(isobutylsulfonyl)benzene
Sample Name:  
ggg-gg145pure

Data Collected on:

Archive directory:

Sample directory:

Pulse Sequence: PROTON (a2pu)

Solvent: cd53

Data collected on Feb 13 2015

Temp. 29.0 C / 298.1 K

Operator gilberg

Relax delay 1000 sec

Pulse 45.0 degrees

Acq. time 2.346 sec.

Width 6900.0 Hz

16 repetitions

OBSERVE H, 499.742054 MHz

DATA PROCESSING

FT size 32768

Total time 1 min 54 sec

---

Gradient Shimming

Sample Name:  
ggg-gg145pure

Data Collected on:

Archive directory:

Sample directory:

Pulse Sequence: CARBON (a2cu)

Solvent: cd53

Data collected on Feb 13 2015

Temp. 29.0 C / 298.1 K

Operator gilberg

Relax delay 2000 sec

Pulse 45.0 degrees

Acq. time 3.0 sec.

Width 18115.9 Hz

1000 repetitions

OBSERVE C, 75.4718049 MHz

DECOUPLE H, 300.147634 MHz

Power 27 dB

Continuously on

WALTZ: 16-modulated

DATA PROCESSING

Line-broadening 0.5 Hz

FT size 32768

Total time 49 min
Sample Name:  
grtg-143pure  
Data Collected on:  
Mar 01 2015  
Archive directory:  

**Proton (1H)**  
Temp: 25.0°C / 298.1 K  
Operator: glbindung  
Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 2.346 sec  
Width 0.865 Hz  
16 repetitions  
OBSERVE H1, 493.7423689 MHz  
DATA PROCESSING  
FT spec 32704  
Total time 5 min 54 sec

Sample Name:  
grtg-143pure  
Data Collected on:  
Mar 01 2015  
Archive directory:  

**Carbon (13C)**  
Temp: 25.0°C / 298.1 K  
Operator: glbindung  
Relax. delay 1.000 sec  
Pulse 45.0 degrees  
Acq. time 1.086 sec  
Width 3076.5 Hz  
1200 repetitions  
OBSERVE C13, 125.6602793 MHz  
DECoupled H1, 493.7447905 MHz  
Power 43 dB  
continuously on  
WALTZ-16 modulated  
DATA PROCESSING  
Line broadening 0.5 Hz  
FT spec 65280  
Total time 24 min
pure

Sample Name: PM-P1-P154
Date Collected: 15/04/2015
Sample Directory: S00064-chemend.edu.hk

Pulse Sequence: PROTON (1H, 13C, 19F)
Solute: sb/05
Data collected on: 24/05/2015

Temp: 293 K
Operator: phani

Relax delay: 1000 sec
Pulse 45.0 degrees
Acq. time 2.330 sec
Width 1.000 sec
16 repetitions

Radiation: 515,7412970 MHz
DATA PROCESSING
FT size 2048
Total time 1 min 0 sec

Phenyl (allylsulfonyl)benzene

ppm
Sample Name: PNI-PB-116
Data Collected on: swanlin@chemistry.wisc.edu innova5000
Archive directory:
Sample directory:
File: PNI-PB-116 CLEAN
Pulse Sequence: PROTON (2 pulse)
Solvent: d6-dcc
Data collected on: Jun 30 2015
Temp. 25.0 C / 298.1 K
Operator: ghant
Relax delay 1.000 sec
Pulse 45.0 degrees
Acq time 2.130 sec
Width 20.046 Hz
16 repetitions
Decoupler freq 134.712979 MHz
DATA PROCESSING
FT type 1D
Total time 5 min 9 sec

Plotname: PNI-PB-116 CLEAN.png

Sample Name: PNI-PB-116
Data Collected on: swanlin@chemistry.wisc.edu innova5000
Archive directory:
Sample directory:
File: PNI-PB-116 CLEAN
Pulse Sequence: CARBON (1 pulse)
Solvent: d6-dcc
Data collected on: Jun 30 2015
Temp. 25.0 C / 298.1 K
Operator: ghant
Relax delay 1.000 sec
Pulse 45.0 degrees
Acq time 1.042 sec
Width 19.646 Hz
1300 repetitions
Crossp. 11.7 Hz 13.1050087 MHz
DECOUPLER freq 400.7449705 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Linewidth in hertz 0.5 Hz
FT type 1D
Total time 44 min

Plotname: PNI-PB-116 CARB.png

111
Sample Name: 119

Plotname: P0-000520-21_CAV_apex01

Sample Name: 22g

Plotname: P0-000520-21_CAV_apex01
References


