Towards the Synthesis of Thiotetronic Acids Found in Groundwater and the Synthesis and Reactions of New 1,4-Oxathiin-\(S,S\)-dioxides

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ABSTRACT

TOWARDS THE SYNTHESIS OF THIOTETRONIC ACIDS FOUND IN GROUNDWATER AND THE SYNTHESIS AND REACTIONS OF NEW 1,4-OXATHIIN-S,S-DIOXIDES

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University of Guelph, 2018
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Project one: Recently, Gabryelski and co-workers identified naturally occurring analogues of thiolactomycin located in groundwater samples. These compounds have not been previously characterized, making identification difficult. To accomplish full elucidation of these thiotetronic acids (TA), as well as providing access to new synthetic analogues, we have established a new synthetic method; allowing the successful synthesis of a TA.

Project two: Extending previously explored chemistry from the Schwan group, a series of 1,4-oxathiin-S,S-dioxides were produced. Using a series of 5-(2-iodo-phenyl)-6-aryl-substituted-1,4-oxathiin-S,S-dioxides, Heck cross-coupling reactions were carried out. A separate selection of 1,4-oxathiins were subjected to iron(III) chloride, which was found as a facile method of ring opening. Two 1,4-oxathiin systems were tested in a series of base catalyzed reactions, and their ultimate stereochemistry was elucidated through a newly devised racemization method. Computational calculations were carried out on several pathways to further the understanding of how the stereochemical outcome might be achieved.
ACKNOWLEDGEMENTS

I would first like to acknowledge Professor Adrian Schwan for being my admirable and patient supervisor. Through him, I was given the opportunity to learn independence in research, and develop my capacity for teaching as well as skill in politics. By allowing me to work under his guidance I have been able to think more logically and more logistically through the moves that the chemistry department endured during my study. These skills will help me in all my future endeavors, rounding me out, no matter where go. I would also like to extend a warm thanks to Dr. Tam and especially Dr. Gabryelski for their council over the three years that they were on my committee, providing invaluable feedback and expertise; and additionally, to Dr. Al-Abdul-Wahid for his aid in NMR support and guidance; and to Dr. Jones for her moral compass.

I would also like to recognize the immeasurable contribution that Dr. Reed has had on me as a person in my time at Guelph. Whether it was allowing me to test a new teaching method, augmenting a course experiment, offering a procedure for my own research, or acting as a sounding board when times were tough; you have acted as the keystone which kept me stalwart. Whether offering your own glassware during the move or helping to dispose of reagents, your actions have inspired a close relationship which has helped me to respect reagents and the knowledge which I aspire to generate and command. Mastery over matter.

I would also like to mention colleagues past and present which have made my time here all the better: Michelle Michalski, Monika Kulak, Erwin Remigio, Tiffany Mills, Joe Findlay, Seren Zevker, Katie Lewis, Nicholas Milutinovic, Michelle Mills, as well as so many others. By sharing our collective knowledge and experiences, I know we each have enriched each other’s
understanding of chemistry and life, especially during the renovations. It has been a pleasure to work with all of you, and I wish you all the best in the future.

Funding for these projects was been provided by NSERC. I remain grateful for their consideration; with the understanding that without them, it is unlikely that this work could ever have been carried out.

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TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................... ii
ACKNOWLEDGEMENTS .................................................................................................................. iii
TABLE OF FIGURES ....................................................................................................................... vi
TABLE OF ABBREVIATIONS ........................................................................................................... viii
LIST OF TABLES ............................................................................................................................... x

Chapter 1: Towards the Synthesis of Thiotetronic Acids Found in Groundwater .............. 1
  1.0 Introduction: ............................................................................................................................... 2
  1.1 Theoretical approach towards the synthesis of the target thiotetronic acids .......... 19
  1.3 Conclusions and future work ............................................................................................... 47
  1.4 Experimental procedures for thiotetronic acids ................................................................. 50

Chapter 2: The Synthesis and Reactions of New 1,4-Oxathiin-SS-dioxides .................. 62
  2.0 Introduction .............................................................................................................................. 63
  2.1 Results and Discussion .......................................................................................................... 83
    2.11 Iron(III) chloride reactions ............................................................................................... 93
    2.12 Heck Cross-coupling Reactions ...................................................................................... 94
  2.2 Base catalyzed ring opening reactions of oxathins ............................................................. 100
  2.3 Computational Calculations for the Base-Catalyzed Ring Opening of Oxathiins .... 118
  2.4 Conclusion and future work of 1,4-oxathiin-SS-dioxides ................................................. 129
  2.5 Experimental procedures for 1,4-oxathiin-SS-dioxides ..................................................... 131
    2.51 General Synthetic Procedures ......................................................................................... 131
    2.52 Bromobenzyl Derivative Synthesis ................................................................................... 131
    2.53 General Method for the synthesis of Thiocyanates ........................................................ 132
    2.54 General Method for Synthesis of Benzyl Alkynyl Sulfides: ....................................... 133
    2.55 General method for synthesis Benzyl Alkynyl Sulfones: .............................................. 133
    2.56 General Method for Preparation of Oxathiin-SS-Dioxides ........................................... 134
    2.57 Reaction of 1,4-oxathiin compounds with FeCl3 ............................................................ 138
    2.58 Heck reactions: .................................................................................................................. 140
    2.59 General procedure for base catalyzed ring openings of oxathiins ......................... 142
  2.6 References .............................................................................................................................. 145
TABLE OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Steps in the development of tuberculosis</td>
<td>4</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Antibiotics: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin</td>
<td>6</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Structure of newest marketed anti-TB drug bedaquiline</td>
<td>7</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Thiolactomycin</td>
<td>7</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Senior's modification of TLM</td>
<td>11</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Relative binding affinity for monoethyl malonate compared to TLM derivatives</td>
<td>12</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Major and minor components found in ground water samples</td>
<td>19</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Identified components found in ground water samples</td>
<td>26</td>
</tr>
<tr>
<td>Figure 9</td>
<td>Structures of Carboxin™ and Oxycarboxin™</td>
<td>64</td>
</tr>
<tr>
<td>Figure 10</td>
<td>Various fungicidal compounds taken from the first patent</td>
<td>65</td>
</tr>
<tr>
<td>Figure 11</td>
<td>All patented herbicidal compounds discovered by Uniroyal in 1975</td>
<td>71</td>
</tr>
<tr>
<td>Figure 12</td>
<td>Quadrants to be modified to increase the inhibition of HIV-I activity</td>
<td>75</td>
</tr>
<tr>
<td>Figure 13</td>
<td>Schwan synthesis of 1,4-oxathiin-S,S-dioxides and several examples</td>
<td>82</td>
</tr>
<tr>
<td>Figure 14</td>
<td>A selection of 1,4-oxathiin-S,S-dioxides produced in the Schwan group</td>
<td>83</td>
</tr>
<tr>
<td>Figure 15</td>
<td>1,4-oxathiin-S,S-dioxides, using benzaldehyde during cyclization</td>
<td>88</td>
</tr>
<tr>
<td>Figure 16</td>
<td>1,4-oxathiin-S,S-dioxides, using other electrophiles during cyclization</td>
<td>88</td>
</tr>
<tr>
<td>Figure 17</td>
<td>Target 1,4-oxathiin-S,S-dioxide starting materials for Iron(III) chloride reactions</td>
<td>89</td>
</tr>
<tr>
<td>Figure 18</td>
<td>Target 1,4-oxathiin-S,S-dioxide starting materials for the Heck reactions</td>
<td>89</td>
</tr>
<tr>
<td>Figure 19</td>
<td>Characteristic meta-iodo peak at 6.9 ppm</td>
<td>90</td>
</tr>
<tr>
<td>Figure 20</td>
<td>Results for the cyclization step producing iron(III) chloride targets</td>
<td>91</td>
</tr>
<tr>
<td>Figure 21</td>
<td>Cyclization step yields for 1,4-oxathiin-S,S-dioxides for Heck targets</td>
<td>92</td>
</tr>
<tr>
<td>Figure 22</td>
<td>Results of Iron(III)chloride and 1,4-oxathiin-S,S-dioxides</td>
<td>94</td>
</tr>
<tr>
<td>Figure 23</td>
<td>NMR of trans/cis isomers 136 and 126, ratio at 4.4 and 4.3 respectively</td>
<td>110</td>
</tr>
<tr>
<td>Figure 24</td>
<td>X-ray structure of DBN-phosphine complex</td>
<td>117</td>
</tr>
<tr>
<td>Figure 25</td>
<td>Comparison of trans diphenyl oxathiin and cis diphenyl oxathiin</td>
<td>120</td>
</tr>
<tr>
<td>Figure 26</td>
<td>Energy diagram and respective energies for anions 145 and 149’</td>
<td>121</td>
</tr>
<tr>
<td>Figure 27</td>
<td>Structures 143, 144, and 145 with corresponding energies and bond distances</td>
<td>121</td>
</tr>
<tr>
<td>Figure 28</td>
<td>Structures 150, 151, and 149’ with respective energies and bond distances</td>
<td>124</td>
</tr>
<tr>
<td>Figure 29</td>
<td>A comparison of trans and cis diphenyl products</td>
<td>125</td>
</tr>
<tr>
<td>Figure 30</td>
<td>Energy diagram for two pathways for the reaction of trans oxathiin with LiOMe</td>
<td>126</td>
</tr>
</tbody>
</table>
Figure 31: Structures 143, 146, 147, 148, 149 with respective energies and bond distances..... 127
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobutyronitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>n-Bu</td>
<td>normal butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
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<tr>
<td>DBN</td>
<td>1,5-Diazabicyclo[4.3.0]non-5-ene</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DFT</td>
<td>density functional theoretical</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>FAB</td>
<td>fatty acid biosynthesis</td>
</tr>
<tr>
<td>FAS</td>
<td>fatty acid synthases</td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Im</td>
<td>imidazole</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>KSCN</td>
<td>potassium thiocyanate</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multidrug-resistance tuberculosis</td>
</tr>
</tbody>
</table>
MS  molecular sieves
μW  microwave
NBS  N-bromosuccinimide
NMR  nuclear magnetic resonance
NNRTIs  non-nucleoside reverse transcriptase inhibitors
NOESY  nuclear Overhauser effect spectroscopy
`OH  hydroxide
Pd  Palladium
PG  protecting group
Ph  phenyl
PMB  para-methoxy benzyl
PMB-SH  4-methoxy-benzenemethanethiol
PMNs  polymorphonuclear leukocytes
PPh₃  triphenyl phosphine
p-tol  para-tolyl
rt  room temperature
TB  tuberculosis
TBAF  tetra-n-butylammonium fluoride
TA  thiotetronic acid
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TLM  Thiolactomycin
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  para-toluenesulfonyl
UV  ultraviolet
WHO  World Health Organization
XDR-TB  extensively drug-resistant tuberculosis
LIST OF TABLES

Table 1: Time lapsed racemization of cis to trans compound over 72 hours.................. 109
Chapter 1: Towards the Synthesis of Thiotetronic Acids Found in Groundwater
1.0 Introduction:

Tuberculosis (TB) is a serious disease that is caused by the pathogen *Mycobacteriaceae tuberculosis*.\(^1\) Other members of the family *Mycobacteriaceae* include species: *M. bovis, M. africanum, M. microti, M. avium*, and *M. leprae*; all of which are intracellular pathogens of higher vertebrates.\(^2\) They can be identified through acid-fast staining, producing Gram-positive results.\(^3\) The family is characterized as non-motile, rod-shaped, obligate aerobic bacteria featuring a cell wall possessing unusually high lipid content. This deadly disease is transmitted from host to host by aerosols,\(^4\) which has led to the infection of over 32% of the world’s population, designating TB as the most prevalent infectious disease worldwide.\(^1\) This method of infection is particularly pernicious, as tiny droplets generated by coughing are able to bypass the defenses of the upper airway\(^4\) and remain suspended in the air for extended lengths of time. When facing this pathogen, we are at a disadvantage when compared to other bacteria, as surfaces cleaned with disinfectants do not remove *M. tuberculosis* from the area.\(^5\) Special air purification filters are required, making the method extremely expensive and not feasible for large scale use.\(^4\)

TB infected hosts generally exhibit symptoms of cough (usually bloody sputum), weight loss, and lack of energy. During the infection, irreversible lung damage develops, allowing the bacterium to travel from the lungs and enter the bloodstream.\(^4\) Interestingly, *M. tuberculosis* can infect any part of the body including bones, joints, liver, spleen, intestines, and brain. When the disease becomes systemic, the result is almost always death.\(^5\) Although this disease can be fatal, it is characterized as slow developing, attacking its host over many years. In cases where the host is immunocompromised, such as AIDS victims, the disease kills much more rapidly, where the fatality rate is nearly 80%.\(^4\) It is estimated that almost 15 million people suffer from the combination TB/AIDS.\(^6\) Hosts that are co-infected generally perished within nine months of active
TB becoming symptomatic, illustrating that the majority of cases occur too quickly to be reported as co-infection. Additionally, the World Health Organization (WHO) estimates that HIV is spreading rapidly in India, where the largest concentrations of TB cases mutually reside.

One of the front-line defenses of the body against airborne pathogens are the alveolar macrophages, found in the lungs. Like other types of macrophages, these white blood cells engulf debris and foreign substances to prevent infection from occurring. M. tuberculosis has evolved to use this defense system as a refuge, surviving and multiplying in unactivated macrophages. However, if the immune system is able to signal that an infection is present, activation of the macrophages can allow for the termination of the bacterium. A host’s ability to activate their immune system and ward off the infection will arbitrate whether exposure to the pathogen will lead to a symptomatic disease or not.

The immune system fends off infection by noticing the initial interaction between a macrophage and the bacterium, which in turn elicits a T-helper (CD4+) and cytotoxic T-cell (CD8+) response. Generally CD4+ helps to fight infection through stimulating antibody production; however this strategy is rendered ineffective as M. tuberculosis is serum resistant and can multiply inside phagocytes. A second outcome of CD4+ production is that it is able to stimulate macrophages into their activated modes, by leading to interferon-γ production. In a cascade, interferon-γ also stimulates endothelial cells to bind to T cells, triggering their movement from blood vessels into the neighbouring tissue to best converge on the infected area. In a healthy adult, exposed to low numbers of the bacterium, this process happens fast enough that the infection is halted before noticeable damage is done to the lung tissue. Should this occur, the patients will become skin test positive, but do not develop symptomatic TB. If, however the host is in an infant
or in an individual whose immune system is compromised, activated macrophages do not appear until the disease has proliferated. In these cases, the bacterium has been able to multiply inside unactivated macrophages, before spreading throughout the area. Because activation of the macrophages did not occur quickly enough to clear the initial infection, new T cells, polymorphonuclear leukocytes (PMNs), and macrophages are attracted to the area and accumulate around the sites where the bacteria are growing. The unactivated macrophages in the vicinity fuse together in large structures called giant cells. With appreciable numbers of macrophages and T cells fused, a layer forms around the epicenter of bacterial growth, encapsulating the bacteria (Figure 1).

Figure 1: Steps in the development of tuberculosis
Sometimes this layer of T cells, PMNs, and macrophages, although unable to kill *M. tuberculosis*, can be successful in walling off the area in a thick fibrin coat, inhibiting the bacterium from spreading. Over time, these lesions calcify, where they can be seen through radiograms.

Unfortunately, even if a patient is able to recover from the disease, the remaining calcified lesions can contain live bacteria. Medications are unable to penetrate the lesions, where *M. tuberculosis* has been known to survive for decades, only appearing after the host becomes immune suppressed.\(^5\) People previously infected with *M. tuberculosis* but are otherwise healthy, face approximately 2-23% chance of reactivation of the TB infection. If the patient however suffers from both TB and AIDS, there is a 5-10% chance per year of developing another infection.\(^9\) When there is no reliable cure for the infection, it becomes evident that more methods of treatment would provide a global benefit.\(^5\)

One of the stumbling blocks in the development of new chemotherapeutic drugs is the cell wall of *M. tuberculosis*. The structural integrity of this feature is paramount, and for bacterial survival any disruption can cause cell death. Unique to this family of bacteria, the cell wall is largely composed of covalently linked mycolic acids, arabinogalactan, and peptidoglycan. Glycolipids such as \(\alpha\)-\(\alpha\)-trehalose monomycolate accompany the mycolic acids forming the foundational cell wall.\(^10\) This matrix offers very selective permeability, sheltering the bacterium from environmental stress and leading to an enduring vitality. This obstacle also impedes the effectiveness of most antibiotics.\(^11\) In recent years, the biosynthetic pathway for cell wall biosynthesis was revealed, offering new inhibition targets. Compounds adept at disrupting these pathways offer hope for the discovery of different chemotherapeutic drugs against *M. tuberculosis*.\(^6\)
Currently there are several classes of drugs that are able to competently inhibit TB infections. These first-line antibiotics: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin (Figure 2) have been used for over half a century for the treatment of TB. However, after decades of use with potent alternative drugs unavailable, many strains of *M. tuberculosis* have developed resistance. Multidrug-resistance tuberculosis (MDR-TB) is a classification for strains of a pathogen when it shows resistance to at least isoniazid and rifampin, the two most potent first-line anti-TB drugs. Clearly, the treatment of MDR-TB infections is far more challenging than TB. In these cases, the prescribed drugs are commonly rendered less effective, duration of treatment increases, side-effects are more pronounced, and the cost is elevated. The WHO estimates that in 2014 over 5% of active TB cases worldwide were MDR-TB infections.  

Frighteningly, extensively drug-resistant TB (XDR-TB) has emerged. Although rare, these strains show resistance to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). These strains have been reported by 105 countries in 2014, accounting for approximately 9.7% of all MDR-TB cases are XDR-TB. Bacteria that show resistance to any of these drugs have evolved specific mechanisms

![Figure 2: Antibiotics: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin](image-url)
or traits that diminish the efficacy of the drugs. Some mechanisms point to deactivation of the antibiotics outside the cells, while other show that the high lipid content makes the natural permeability of the cell wall too difficult for the drug to pass through.

![Figure 3: Structure of newest marketed anti-TB drug bedaquiline](image)

There has however been some headway in the production of new chemotherapeutic agents. Bedaquiline, shown in Figure 3, was discovered by Andries and co-workers and was approved on the global market in 2012, as the first MDR-TB medication to be added to the market since 1966.\textsuperscript{14} Although this drug has helped in the struggle against TB, resistance has already been reported, illustrating that additional drugs are needed to help alleviate the spread of this deadly pathogen. Alternative medications are currently being investigated, in the hopes that moderate activity can be increased through various modifications.

![Figure 4: Thiolactomycin](image)

Thiolactomycin (TLM, Figure 4) is an antibiotic, which was originally isolated from a soil sample collected in Saitama prefecture, Japan in 1982.\textsuperscript{15} Since its discovery, it’s analogues have been found in several locations across the globe, including in groundwater from Guelph Ontario,
Canada.\textsuperscript{16} TLM is produced by soil bacteria \textit{Nordica sp.}, and is structurally unrelated to any other group of known antibiotics.\textsuperscript{15,17} TLM has been found to exhibit moderate \textit{in vivo} activity against many pathogenic bacteria, targeting both Gram-negative and Gram-positive bacteria. Fortuitously, TLM displays promising results against \textit{M. tuberculosis} by inhibiting both plant and bacterial Type II fatty acid synthases (FAS), but not mammalian Type I FAS.\textsuperscript{18} It is unique in that it shares no commonalities with other antibiotics currently employed in treating TB, making it an ideal alternative medication to treat multi-drug resistant TB. In \textit{E. coli}, TLM inhibits both $\beta$-ketoacyl-ACP synthases I,II, III and coenzyme A ACP transcyclase activities for both \textit{in vivo} and \textit{in vitro} conditions.\textsuperscript{1} Complete inhibition of the virulent strain \textit{M. tuberculosis} Erdmman occurred at 25 $\mu$g/mL,\textsuperscript{19} making it approximately 10 times less potent than current front line anti-TB drugs.\textsuperscript{1} Animal studies show that in rodents, TLM can efficiently be absorbed orally, with an LD$_{50}$ of 1.689g/kg,\textsuperscript{20} illustrating its negligible toxicity to mammals. Another interesting attribute of TLM is that it exhibits encouraging antimalarial activity, through the inhibition of type II fatty acid biosynthetic pathway in apicoplasts.\textsuperscript{21,22} Finally, TLM offers significant protection against urinary tract infections, as well as intraperitoneal bacterial infections.\textsuperscript{23}

TLM is known to inhibit Type II dissociable fatty acid synthase, confirmed by Jones and coworkers\textsuperscript{24} through [1-\textsuperscript{14}C] acetate labeling, in pea-leaf chloroplasts. Complementing this, \textit{in vivo} studies using [1,2-\textsuperscript{14}C] acetate labeling,\textsuperscript{24,25} confirm that TLM inhibits the biosynthesis of both fatty acids and mycolic acids.\textsuperscript{26-30} Mycolic acid is a long chain fatty acid that is the major component in the cell wall of \textit{M. tuberculosis}, and is attributed with lending such distinct impermeability to many antibiotics.\textsuperscript{31}

Fatty acid biosynthesis (FAB) in bacteria, plants, and animals is carried out by the fatty acid synthesis (FAS) system.\textsuperscript{32} FAB is a paramount metabolic process that is required for the
majority of cells for both maintaining vitality and allowing for growth. Because this pathway is vital for the health of an organism, it presents an ideal target for inhibitory drug design. Although FAB occurs in most organisms, plants and bacteria use a different system than animals. In the animal FAB pathway, Type I is used. Although Type I and Type II systems are related, sharing function and some structural characteristics, they lack homology. In animals, Type I FAS employs large multifunctional proteins to catalyze FAB. Comparatively, bacteria use multiple enzymes for FAB, and therefore the two systems bear little in common, presenting the FAS Type II system as a prime target for inhibitory drug design. With the emergence of highly resistant strains of bacteria occurring more than ever before, TLM and its derivatives could fill a serious medical need.

Initiating FAB is β-ketoacyl carrier protein synthase FabH, illustrated in Scheme 1. This shows the FAS-II pathway in *M. tuberculosis*, as it produces the longer chain fatty acids from C-18+ acyl-CoAs; initially starting from the FAS-I system. This condensing enzyme catalyzes the first condensation step between acetyl-CoA and malonyl ACP.
The biosynthesis of fatty acids in bacteria uses two sub-systems. FAS-I catalyzes *de novo* FAS and FAS-II, a collection of monofunctional enzymes, which elongate the FAS-I products into long chain mycolic acid precursors. Therefore, the FAS-II system alters C18+ fatty acids, produced from the FAS-I system, to produce a C56+ product; creating a bifunctional system. Of these monofunctionalized FAS-I and FAS-II enzymes, several have been identified as targets for TLM inhibition. β-Ketoacyl carrier protein synthase Kas A and Kas B exhibit IC₅₀ values of 20 μM and 90 μM respectfully. Subsequent rounds of elongation are initiated by either KasA or Kas B, and therefore through multiple visits to these enzymes, extension of the mycolic acids, and ultimately a strong cell wall. Both *in vivo* and *in vitro* results suggest two distinct sites of inhibition for TLM, both KasA/KasB, halting the elongation step in the synthesis of α-mycolates and oxygenated mycolates (Scheme 2). Unfortunately, as interesting as these results are, the promising data does not suggest that TLM is potent enough for use as a marketed antibiotic.

![Scheme 2](image)

Although modern medicine has been successful in the production of a Bacillus Calmette-Guérin vaccine, as well as a range of chemotherapeutic drugs, TB remains one of the most prolific diseases worldwide. In part, this is due to a lack of new medications that have reached the global
market. However the emergence of MDR-TB and XDR-TB strains makes this battle far more
difficult. Some drugs available are potent, but present numerous side effects. As such, new
medications need to be produced that can minimize these often dangerous side effects, but also
reduce treatment duration. One promising drug is the TLM analogues, which offer inhibition of
one of the most integral biosynthetic pathways of *M. tuberculosis*. Through the careful
manipulation of these scaffolds, a range of highly potent and non-toxic drugs is on the horizon, as
an untapped plethora of novel anti-TB drugs.

Several groups have attempted to alter the TLM scaffold to imbue enhanced potency
against *M. tuberculosis*. Senior and co-workers found that increased activity for the inhibition of
*mtFabH* could be induced, through the functionalization of C₅ of TLM. They were able to
produce a biphenyl analogue, (Figure 5) which displayed nearly a four-fold increase in potency.

In a series of modifications, Senior and co-workers found that if the C₅ carbon possessed large
linear π-rich systems enabling hydrogen bonding, an increase in potency was achieved. When
compared to TLM for the inhibition of *mtFabH*, the potency increased from IC_{50} 75μL to 3μL. In
this study it was found that biphenyl analogues with larger and more linear substituents lead to the
increase in activity. Importantly, Besra and co-workers found that these analogues only
possessed high efficacy *in vitro*. When tested *in vivo* it became apparent that the TLM derivative
was ineffective. It was proposed that the mycobacterial cell wall provides a particularly
formidable permeability barrier that protects the organism against various antibiotic and chemical
insults, including the biphenyl derivatives. The disparity between improved *in vitro* performance and loss of antimycobacterial activity is likely related to its inability to traverse this structure. Additionally, Dowd and co-workers suggested that an isoprene unit (such as that found on TLM) is necessary for the activity against condensing enzymes FabH, Kasa, KasB from TB. They concluded that an increase in alkyl chain length or reduction of one or both of the olefins of isoprene resulted in a marked drop in potency.

It is clear that TLM is an inhibitor of the FAS pathway in bacteria. To best gauge this, X-ray analysis was completed on the inhibited system. These studies show that the sulfur containing ring of TLM acts as a malonyl-ACP surrogate. Given Figure 6, it is evident that the relative $pK_a$ of malonyl-ACP and TLM are similar. Model compound 1 possesses a $pK_a = 4.1$, whereas monoethyl malonate has a $pK_a = 3.7$, in water. Dormann suggests that the modest difference implies that the enzyme would likely bind to the deprotonated forms of TLM, rather than the neutral states. Although chemically the differences are apparent, the environment of the active site can dramatically alter these systems, and thus should be only used as supportive evidence in elucidating a proposed method of binding.

![Figure 6: Relative binding affinity for monoethyl malonate compared to TLM derivatives](image)

One method to acquire an array of TLM derivatives, involves purchasing commercially available TLM and subsequently alkylating, to allow for the screening of various modifications at the $C_5$ position. The production of derivatives from the total synthetic models provides fairly low yields, and thus an efficient synthesis must be devised.
One such method was developed by Brückner et al. to provide an efficient pathway to TLM, as shown in Scheme 3. To initiate Brückner’s synthesis of thiolactomycin, the required allyl alcohol was obtained through a Wittig reaction between the corresponding aldehyde and phosphorane followed by ethanolation.\(^{42}\) From here, the pentadienol was subjected to a catalytic Sharpless asymmetric epoxidation, resulting in the epoxy-alcohol that was subsequently protected by tert-butyldiphenylsilyl chloride. The next step was to attach thiopropionic acid to the C\(_2\) position through an S\(_{N}\)2' reaction, as opposed to C\(_3\) conjugate addition. One hurdle to achieve this was the lack of reactivity exhibited by thiopropionic acid. To overcome this, the Lewis acid AlMe\(_3\) was added, producing the desired product with the expected E configuration of the C=C bond. Proceeding towards the desired thiolactomycin, desilylation took place with the addition of HF/pyridine complex, providing the glycol. A reductive vic-didesoxygenderation with PPh\(_3\),
imidazole, and I\(_2\) applied to the glycol produced the diene. The final step was a Dieckmann condensation rendering (+)-thiolactomycin in seven steps. Brückner’s method was further augmented to produce several other synthetic analogues, highlighting the flexibility of the method.\(^{42}\)

In 1984, the first racemic total synthesis of TLM was reported by Salvino et al.\(^ {44}\) To accomplish this, alkylation of a thiotetronic acid dianion with an isoprene cation equivalent had to be executed.\(^ {45}\) As shown in Scheme 4, the synthesis commences with the alkylation of methyl propionylacetate 13, through the addition of the corresponding alkyl or benzyl bromide and potassium carbonate, furnishing alkylated product 14. From here, the \(\beta\)-ketoesters were treated with pyridinium tribromide under acidic conditions, fabricating bromide 15 as a mixture of diastereoisomers. Addition of thiolacetic acid displaced the halogen, forming thioacetate 16. Cyclization was then carried out through treatment of aqueous potassium hydroxide solution, to give the unfunctionalized thiotetronic acid scaffold 17. Modification of these compounds was done through butyl lithium alkylation to generate TLM derivative 20. Although the desired targets were formed, the yields after alkylation were very low, 4-22\%.\(^ {45}\) Additionally, protection of the hydroxyl in preparation for the alkylation step proved unsuccessful. A new synthetic method would allow for the access to these compounds with a much higher efficiency.\(^ {45}\)

In 2003 Gilbert and co-workers modified the procedure to allow for the synthesis of a variety of TLM analogues.\(^ {45}\) Using the same methodology, they were able to perform the alkylation at C\(_5\) before cyclization occurred, thus avoiding the lowest yielding steps. This strategy also applied subsequent alkylations of methyl propionylacetate 21 at the C\(_4\) and C\(_2\) positions, to produce \(\beta\)-ketoester 22. From here bromination at the C\(_4\) position formed bromide 23, which was
proceeded by treatment of thioacetatic acid to manufacture thioacetate 24. Finally, treatment with aqueous potassium hydroxide lead to TLM derivative 25.45

Gilbert and co-workers continued their research, and the following year reported an improved methodology to allow access to other long alkyl chain TLM derivatives (Scheme 5).46
They found that by performing the alkylation step with lithium bis(trimethylsilyl)amide (LiHMDS) as base, they were granted access to yet longer chain TLM derivatives. This step however granted low yields, varying from 10-20 %.\textsuperscript{46}

For a final methodology for the total synthesis of thiolactomycin, Ohata and Terashima proposed a new method employing imide ester exchange to produce the desired chiral product (Scheme 6).\textsuperscript{47} The pathway commenced with a Horner-Wadsworth-Emmons reaction with the corresponding carbonyl, followed by alkaline hydrolysis to produce the hexadieneoic acid. Reaction with pivaloyl chloride then (R)-4-benzyl-2-oxazolidin-2-one installed the chiral auxiliary 28. From here, electrophilic deconjugative asymmetric α-sulfenylation took place, by the addition of S-3,3-dimethoxypropyl methanethiosulfonate in the presence of NaHMDS in THF with 4 equivalents of HMPA, to yield the desired E isomer. Subsequent treatment with titanium isopropoxide in benzyl alcohol effected the removal of the oxazolidinone, supplying the coveted benzyl ester. Acidic hydrolysis of the acetal moiety gave rise to the 2-formylethylthio ester. Next, a retro-Michael reaction followed by acylation produced the thiol functionality. The newly formed aldehyde was treated with cesium carbonate and the formed cesium thiolate was treated with propionyl chloride in the presence of triethylamine without isolation, the desired α-propionylthio
ester was produced in 75% yield. To conclude the pathway, the ketone, underwent a Dieckmann condensation through treatment with LiHMDS, yielding optically pure \((R)-(\beta)-\text{thiolactomycin}\).⁴⁷

Previously, all methodologies used in the production of TLM and its analogues offer little in the way of modification and have limited direction for further derivatization, such as installation of isoprene and methyl functionalities. Recently, the discovery of several naturally occurring analogues have been achieved, thus new synthetic methods will attempt to meet this specific demand.

![Scheme 6](image)

It has previously been established that groundwater contains high levels of organic sulfur. It is speculated that up to 20% of the organics found in groundwater are currently unknown sulfur containing compounds.⁴⁸ Until recently, thorough elucidation of these compounds remained ignored. Recently, Gabryelski and co-workers published an analysis of a series of groundwater samples taken from locations in Canada and the United States, characterizing a variety of these
sulfur containing compounds. Using the field asymmetric waveform ion mobility spectrometry (a variant of mass spectrometry), a variety of TAs were identified. Interestingly, it was also noted that TAs seemed to be the most abundant organic components in groundwater, but no commercially available standards exist, nor is there reference spectra in any database or information in the literature for the synthetic method to produce these new compounds. Analysis of the samples identified 10 TA congeners; however firm structure elucidation could not take place. It was also found that if the groundwater was sourced from the water table, and subsequently underwent ozone purification treatment, residual TAs were detected as well as the decomposed ozonation products of TAs. These compounds are ingested by millions of people each year, either through collecting well-water individually or through naturally sourced, but commercially available bottled water. Shown in Figure 7 is an array of the most prevalent TAs identified by Gabryelski and co-workers. The goal of our work is to supply these previously uncharacterized TAs through a new synthetic method, which will allow for these targets to be efficiently produced and ultimately characterized. In line with the most abundant TAs found, seven synthetic targets were chosen. Fabrication of a new and efficient synthetic method will allow access to some of these naturally occurring TAs, as well as a variety of synthetic analogues. A further goal of this project entails obtaining the various TAs and sending them for further testing to predict binding efficacy; possibly leading to the discovery of new medicines.
1.1 Theoretical approach towards the synthesis of the target thiotetronic acids

Thiotetronic acid 38 will be used as the preliminary target. It is predicted that the nitrile functionality will provide a model system to troubleshoot our synthetic pathway, mimicking the reactivity of ester derivatives, such as modified 33. The electron withdrawing capacity of the cyano group, will aid in nucleophilic attack of a thiol, required towards the end of the synthesis. It was projected that the nitrile functionality would also tolerate the greatest range of our planned chemical treatments.

Our conceptual approach to the new synthetic method is examined in Scheme 7. Looking at the initial target 38, it becomes evident that a tautomer exists with diketone functionality. From here the compound can be dissected to reveal two distinct parts, the first involving two anions, and the second two cations. These conceptual models can be further augmented to ‘mask’ these charges. In this case, removable silane and sulfur protecting group allows for the di-anion charge
to be invoked when needed. These charges could then attack malonyl chloride, producing the first of our targets. It is worth noting that the ethyl and nitrile functionalities play no role in this method, and therefore can be modified to produce a large assortment of the TA targets.

![Scheme 7]

Bringing this theory into practice, the planned retrosynthetic pathway is outlined in Scheme 8. Generalized derivatives of pentynoic acid ester 44 could lead to the production of a variety of TAs. As previously stated, TA 38 is the first target for the elucidation of the proposed synthetic plan. Working in reverse, it is postulated that the ester moiety of 44 can be converted through reductive amination and subsequent dehydration to produce nitrile 43. From here silylation of the triple bond will be carried out to produce the silylated product 42. Addition of a protected thiol leads to the construction of 41. Subsequent deprotection and addition of malonyl chloride will give intermediate 40. The incorporation of a fluorine source will induce the final cyclization step, thereby producing TA 38.
The full synthetic plan to produce TA 38 is described in Scheme 9. The first target in this synthesis is the construction of alkynoic acid ester 44. A simple approach would be to use a short chain alkyne and through deprotonation with butyl lithium followed by addition of a halogenated ester, to provide 44. This method would involve the use of butyne, an expensive and difficult to handle gas. Another method would be the use of a silylated alkyne, to allow for further functionalization to occur. This pathway remains expensive, and therefore is a fallback if need be. Thus, we hope to invoke thermal decomposition of a Wittig reagent to produce alkynoic acid ester 44. This will be accomplished by following the work of Ball-Jones and co-workers. This strategy uses addition of triphenylphosphine and ethyl bromoacetate, followed by a basic work-up to produce the subsequent phosphorane 46. Transylidation will then occur, through the addition of propionyl chloride to produce the keto-ester phosphorane 47.
The next step in synthesis was the pyrolytic cleavage of triphenyl phosphine oxide from 47, liberating the alkyne. Following the procedure developed by Hanack et al, compound 47 will be heated to 260-280 °C under reduced pressure (0.1 mm Hg) for 3 hours. The resulting compound was fractionally distilled off, providing the pure pent-3-ynoic acid derivative 44. Although this reaction will produce a compound with greatly reduced molar mass, the starting materials are more economical than previously described methods. Although this synthetic route depicts the predicted synthesis of TA 38, it should be noted that the generation of the carboxylic acid containing TA 33 could be accomplished by skipping the following functionalization of the ester to the nitrile.
Conversion of the ester moiety 44 to the corresponding nitrile needs to be carried out. This will be accomplished through amination to yield the corresponding amide. Simple amidation through the addition of stock ammonium hydroxide results in the transformation, thereafter dehydration will occur. Phosphorus pentoxide will facilitate the conversion of the amide to nitrile 43.

The next step will be the addition of a silane protecting group to the alkyne. For this transformation phenyldimethylsilane was chosen because of its relative stability to hydration when compared to other less bulky silanes, such as trimethylsilane.52 Looking ahead to later steps, deprotection of the thiol will likely require strongly basic conditions, and thus the phenyldimethylsilane was chosen.52 Following the work of Lipshutz and co-workers, the silylation will employ a boron-silylated agent with catalytic copper(I) acetate and triphenylphosphine to give the desired nitrile 42. It is predicted that the reaction will give the $E$ isomer of the nitrile, in line with other results successfully probed with this silylation system.53 To achieve synthesis of 38, incorporation of a protected sulfur atom must occur. It is proposed that this will be accomplished through the nucleophilic addition of thiolacetic acid. It is expected that attack will occur at the $\beta$-carbon to the nitrile. Although there is a silane present, we predict that the $\beta$-silicon effect will be tempered by the electron withdrawing capacity of the nitrile directing any prospective nucleophilic attack at the $\beta$-carbon to the nitrile. This reaction appears to represent one of the greatest pitfalls in the overall synthesis of TA 38, as nucleophilic attack producing a quaternary centre is generally difficult. Should conditions that allow the addition of thiolacetic acid remain elusive, one way to overcome this hurdle would be through the use of a different thiol, with improved nucleophilicity. As this step exists for the purpose of installing a protected sulfur, there are a variety of options available; 4-methoxy-benzenemethanethiol (PMB-SH) or 2- nitro benzenemethanethiol are
accessible substitutes. Furthermore, an alluring aspect of using PMB-SH as a nucleophile is that obtaining unprotected thiol 41b could be skipped. Addition of malonyl chloride to the PMB protected sulfur, could be accomplished directly. Illustrated in Scheme 10, it is proposed that the sulfur could attack malonyl chloride and form a sulfonium intermediate. Subsequently the lone pair on the para-methoxy group could donate into the ring and at the cost of breaking aromaticity, quench the positive charge on sulfur releasing the PMB in the process. The PMB oxonium then can be attacked by chlorine, driven by the restoration of aromaticity and producing the neutral 1-(chloromethyl)-4-methoxybenzene. Formation of this product could be encouraged through the addition of heat, as well as addition of excess chloride ions. With formation of 40, induced cyclization can then be performed to form final target 38.

A final recourse for the production of compound 40, would be to return to thioacetic acid as the prospective nucleophile and apply different conditions that would favour a homolytic reaction. In this case the use of a radical initiator such as AIBN or benzyl peroxide offers a substitute set of parameters that could lead the desired nitrile 41a. The next step will be the deprotection of the newly installed thiol. Should the reaction proceed with the addition of thioacetic acid, removal may entail the use of 0.2 N NaOH, as described be Greene et al.; though
a variety of options exist for this deprotection. This will produce the thiol required for the final transformation.

With the production of thiol 41b, the final sequence for the formation of thiotetronic acid can begin. This will involve the reaction of the sulfide with malonyl chloride, under basic conditions. It is expected that initial attack but the sulfur will lead to formation of 40. As illustrated in Scheme 11, incorporation of a fluorine source, such as TBAF will lead to removal of the silane, revealing the ‘masked’ anion. The fluoride anion will attack the silane to produce a pentavalent silicon centre. The formation of the Si-F bond is so energetically favourable, in part because of the vacant d-orbitals of silicon that fast cleavage of the Si-C bond occurs. Stabilized by the adjacent sulfur, analogous to DMSO oxidation reactions, the carbon anion will attack the malonyl chloride to produce a variant of 40. Addition of a weak non-nucleophilic base will initiate tautomerization of the ring ultimately leading to the formation of the desired target TA 38. Additionally, malonyl chloride derivatives could be used for production of synthetic analogues.

![Scheme 11](image)

With the completion of this novel method for the synthesis of TAs, it is hoped that additional analogues may be produced to help provide access to previously undiscovered chemotherapeutic agents against M. tuberculosis. Additionally, full characterizations of the TAs found in groundwater samples would offer insight into whether naturally occurring antibiotics are
protecting the population from latent infections. The elucidation of the naturally occurring TAs found by Gabryelski will allow for the antibacterial efficacy of these compounds to be characterized. As these compounds are prolifically produced, it is likely that there is evolutionary pressure leading to their production. These untested analogues may also have other previously unanticipated functions as well. It is also projected that this underexploited method of inhibition could help alleviate the pressures that MDR-TB strains have placed on the world’s populace.

1.2 Results and discussion

As outlined previously, the compounds described by Gabryelski and co-workers, identified from groundwater samples, were previously uncharacterized. Efforts towards the full synthesis of these compounds are discussed in this thesis, and a variety of methods are used to attain a viable pathway to accomplish both the full elucidation of these compounds; and access new ones through a newly developed, efficient method for preparation of thiotetronic acids.

![Figure 8: Identified components found in groundwater samples](image)

Figure 8 depicts the thiotetronic acids identified and will serve as goals for this project. The first TA to be attempted will be the synthesis of 38, as it provides the least complications for side reactions with oxygen. It will also serve as a good model for esters, which can be seen as a
precursor towards the carboxylic acid substituents. As discussed in the introduction of this thesis, the conceptual pathway initially embarked upon will be to synthesize the two substituents at the 5-position of the ring system; then through the addition of a silane group and protected sulfur (embodied in 41, Scheme 10), a precursor is produced.

Scheme 12 illustrates the retrosynthetic strategy initially used to produce TA 38. The product can be cyclized through the addition of a fluorine source or strongly acidic/basic conditions, removing the silane (from 40). Upon production of the fluorine silane bond, the release of the ‘naked anion’ occurs, which attacks the acyl chloride and releases chloride as a leaving group. However, before the addition of malonyl chloride, the deprotection of the precursor, molecule 41, must take place. The quaternary centered bearing molecule (41) will be synthesized through the nucleophilic addition of a protected sulfur nucleophile to the silyl alkene 42; which is generated by boron-silylated agent with catalytic copper(I)acetate and triphenylphosphine to an alkynoic nitrile 43. This can be acquired through a dehydration of the ester variant 44.

If the pathway is successful, then modifications will be carried out to allow for the synthesis of additional TA compounds. Some functional groups represent more challenges than others, such
as installation of α-hydroxyl groups, but with a fully functioning methodology, these modifications can become the focal point.

As noted by the retrosynthetic pathway, the first task carried out was to synthesize the starting alkynoic ester. Ethyl bromoacetate (45) was reacted with triphenylphosphine, and after heat and washes with aqueous base, Wittig reagent 46 was recrystallized and subsequently reacted with propionyl chloride in toluene, to give reagent 47 in 80% yield (Scheme 13). This compound was then subjected to a thermal degradation, under vacuum distillation. At high temperature and pressure, the desired alkynoic ester formed, and quickly distilled through the apparatus, leaving behind the phosphine oxide salts. This step posed several technical issues, requiring repair of the Kugelrohr oven, and eventual optimization of the process using an extended fractional distillation step.

![Scheme 13](image)

However, with the synthesis of 44, conversion of the ester functionality to the nitrile needed to be carried out. This was accomplished (Scheme 14) through the conversion of the ester to the amide with ammonium hydroxide, then dehydration under high temperatures with phosphorus pentaoxide, in a vacuum distillation set-up.
With a stock of ester 44 held in reserves and a production of 43 accomplished, the next step of the synthesis was to use the system developed by Lipshutz and co-workers to silylate the alkyne. As noted previously, we chose a phenyldimethylsilane protecting group (PhMe₂Si-PG) to incorporate a much less acid sensitive PG into our system (Scheme 15). This system uses catalytic copper(I) acetate and triphenylphosphine and is carried out in a surfactant solution of a 2% vitamin E derivative in water. In cases where the starting material was less responsive to reaction conditions, fresh batches of PhMeSiBpin were produced, and increased catalyst loading led to increased yields. Therefore, this reaction worked well and was easy to purify the products, providing a system for the nucleophilic addition of sulfur.

To commence silylation, 42 was subjected to the addition of thioacetic acid as the choice nucleophile. This was because the deprotection strategy for this compound is well known, and methanolation can be achieved in a simple, mild reaction, which can allow for the release of the thiol. Furthermore, it is a common chemical which can be used without preparation; the relatively weak thioacetic acid inhibits degradation of the starting material through desilylation.
Unfortunately, as depicted in Scheme 16, a selection of methods was used to attempt nucleophilic attack to the Michael system by sulfur. All trials involved heating, generally to reflux for 48 hours, under anhydrous and inert conditions (N₂). The graphic shows that many different solvents of varied polarity and acidity were tested. A secondary method of using radical sulfur was used, as per AIBN in benzene; however, no interaction with the double bond could be induced. Even with the presence of a strong Lewis Acid, the reaction was unable to proceed forward. Introduction of a superbase also had no effect in protic or aprotic solvents.

Scheme 16

With so many reactions articulating that this particular acid was an unsuitable nucleophile, the reaction of 42 with potassium thioacetate was carried out in several sets of conditions (Scheme 17). In this case, the conditions would be more encouraging for the addition of sulfur, however even with these modifications; it became apparent that no analogue of thioacetic acid could overcome the steric barrier of nitrile 42.
With a final attempt towards the incorporation of sulfur to this system, \( p \)-methoxybenzyl thiol was used. The electron rich nature of this system, through donation by the methoxy group, designates this nucleophile as much more able to attack the double bond of 42. Unfortunately, there was no reaction under protic-polar solvent or non-protic basic solvent (Scheme 18).

Another compound probed for these reactions was the ester variant of 42. This was created through taking some of the reserved 44 and subjecting it to the silylating conditions discussed previously, to give 48 (Scheme 19). The ester moiety is required because it can be converted to the appropriate groups found in the identified TA assortment.

Having previously attempted and failed to induce nucleophilic attack of sulfur to the Michael system in an analogous system, newly tested methods were generally harsher. Scheme 20 articulates that, although an amine was used in water to attempt a biphasic reaction; the majority
of reactions tested were strong Lewis Acids. It was hoped that coordination of the acids to the ester group would allow for attack at the β-position, however this was not the case. Under such harsh conditions, usually decomposition of the starting material was witnessed.

![Scheme 20](image)

In line with reactions previously tested, 48 was subjected to potassium thioacetate and under separate conditions, PMB-SH. Even with the use of microwaves to heat the reaction, the nucleophilic addition of sulfur to these systems could not be induced (Scheme 21).

![Scheme 21](image)

A final attempt to incorporate sulfur to 48 is illustrated in Scheme 22. This unique strategy utilizes an o-nitro group on the benzyl ring, which, under a deprotection protocol, can coordinate with the sulfur. This sulfide methanolysis occurs to this sulfide, freeing the activated sulfur, which is then theoretically able to attack the Michael system.
Unfortunately, this reaction also failed, and thus left the impression that systems 42 and 48 are likely far too sterically hindered for sulfur to attack, producing a chiral quaternary centre.

Scheme 23

A review of our strategy generated a revision of how the molecule can be assembled. As illustrated in Scheme 24, the first step would be to incorporate the protected thiol, which then would be subjected to the installation of a silane group through a cooperative reagent. Production of 50, would lead to deprotection of sulfur and unmasking of the anion for cyclization to produce 38.
Initial attempts to incorporate the protected sulfur to the scaffold are depicted in Scheme 25, articulated through the reaction of 44 and thioacetic acid. However, no product formed. It was therefore, likely that the nucleophilic ability of thioacetic acid was not great enough to attack this electron deficient alkyne.

![Scheme 25](image)

However, substitution of the nucleophile to PBM-thiol, under basic protic conditions, led to product (51) formation in 53% yield (Scheme 26). The next step would be to silylated this Michael system.

![Scheme 26](image)

Our first attempt to include the silane was to lithiate the reactant through lithium-halogen exchange. This created a highly reactive reagent; however exposure to the Michael system 51 only achieved degradation of the starting material (Scheme 27). Thus tempering the reagent to a cuprate would be required.

![Scheme 27](image)
Generation of the silyl-cuprate reagent (Scheme 28) created a softer nucleophile, which should have been able to attack at the β-position. However this led to the production of complex mixtures, and the complete degradation of the starting materials.

![Scheme 28]

Because of the failure of these methods to incorporate a chiral centre, including protected sulfur, silane, and desired substituents, a simplified system was formulated (Scheme 29). By revisiting the initial method, a system which had less sterical constraints (52) was formed using the previous method of silylation using methyl propiolate.

![Scheme 29]

This system took several attempts, however, as normal reaction conditions yielded 1-5% product formation. Seemingly, the system thrives having an internal alkyne as a starting material. Scheme 30 illustrates the steric difference between materials 48 and 52.

![Scheme 30]
As seen in previous experiments, sulfur was unsuccessfully used to create a chiral centre attacking at the β-position of 48. To best accomplish this, it was proposed that molecule 52 would provide a system with minimized sterics, which could lead to ideal conditions for the addition of sulfur to such a Michael system. Once these conditions had been elucidated, they might be tested on molecule 48. If sulfur addition was only able to occur on alkene 52, then removal of a proton with "BuLi, and subsequent electrophile quench, would offer the desired system.

To start this enterprise, methyl propiolate was subjected to conditions developed by Lipshutz in 2014, to create the unobstructed Michael system 52.53

![Scheme 31](image)

However, it was found that optimization of these systems was needed for our chosen alkyne. Three percent catalyst loading was needed, and the production of freshly distilled PhMe₂SiBpin was chiefly responsible for elevating yields from 1% to 86% (Scheme 31).

With this Michael system, several diverse attempts to induce the nucleophilic addition of sulfur were tested.

![Scheme 32](image)
Using a weak base, several solvents (Scheme 32) (THF, neat, 24-72 hr) were used to help the reaction proceed. However, time and heat did nothing to help the reaction give the desired products. As potassium thioacetate did not proceed with the Michael additions, thioacetic acid was used extensively. After many trials, it was found that excess equivalents could produce the desired product after 96 hours (Scheme 33).

![Reaction Scheme 33](image)

Scheme 33

Additionally, a reagent with increased nucleophilicity was chosen, to try to increase the yields. Therefore, \(p\)-methoxybenzyl mercaptan was reacted with 52 (Scheme 34). It was then found that incorporation of sulfur could be attained with yields of 70%.

![Reaction Scheme 34](image)

Scheme 34

The production of 54 provided an additional benefit, not possessed by 3. This sulfur/silane system would not require a specialized deprotection method, such as methanolysis, to induce the reactivity of sulfur (Scheme 35).
The lone pair on sulfur can attack at a highly reactive electrophilic carbon, producing a sulfonium cation. The para-position methoxy group then is able to push electron density down through the ring and quench the charge, releasing the PMB group. This strategy will later be used to cyclize the thiotetronic ring systems, with removal of the silane.

Incorporation of a fluorine source, such as TBAF would lead to removal of the silane and reveal the ‘masked’ anion. The fluoride anion attacks the silane to produce a pentavalent silicon centre. The formation of the Si-F bond is so energetically favourable, in part because of the vacant d-orbitals of silicon that fast cleavage of the Si-C bond occurs. Naked anions require extremely dry conditions, as the presence of any trace of ‘free’ hydrogen will react with the resulting compound. This also means that any fluorine source, which would be used for the removal of the silane, must be stringently dried. Tetrabutylammonium fluoride is the most commonly used method; however, it is an inherently wet reagent. Therefore, alternative methods to incorporate a source of fluorine were attempted first. An experiment was devised where 54 was reacted with malonyl chloride, and in deuterated THF, to produce of 54a and p-methoxybenzyl chloride; which supports the proposed mechanism (Scheme 35). It was observed that the reaction could not be induced in chloroform.
Another method of cyclization is to add acid, a common method for the removal of silane protecting groups. Therefore 54 was subjected to trifluoroacetic acid, however no change was observed. This articulated that the phenyldimethylsilane protecting group initially chosen for its inherent stability would be much more difficult to remove than previously thought. Without the ability to remove the silane under such conditions, it confirmed our need to investigate a method of desilylation which involved fluoride, in an anhydrous fashion. Cesium fluorine was chosen, as it can be easily dried; therefore. Depicted in Scheme 36, several of the trials undertaken to establish a cyclized product are shown. However, attributed to cesium’s lack of solubility in organic solvents, no fluoride was able to react with 54, and therefore no desired product was observed. An additional factor that may have affected the inability of the ‘naked anion’ to form is the steric hindrance, which is present when using this particular silyl protecting group. It was at this point that our attention shifted to an alternative synthetic pathway.

Unfortunately, even with this modification it was found that the loss of silane was much more difficult than anticipated. It was discovered that dimethylphenylsilylane was too stable of a protecting group to allow for facile removal, revealing a naked anion (Scheme 37). Several
attempts were made, however conditions that allowed for silane removal were too harsh to allow for a naked anion to be formed, and subsequently react with malonyl chloride.

![Scheme 37](image)

A dramatic shift was then taken in methodological approach, completely abandoning previously tested procedures. The original approach produced a system with both ‘R’ groups installed, proceeding thereafter towards creating the ring. The next approach reverses this, starting with the ability to form the TA ring and installing the ‘R’ groups thereafter. This new methodology starts by using protected sulfur and attaching it to a trimethylsilane (Scheme 38). Aside from being a less stable silane, easier for removal later in the synthesis, the scaffold will provide an α-position where subsequent deprotonation(s)/quench(es) can lead to the production of the final molecule.

![Scheme 38](image)

The first part of this synthetic pathway was to employ 2-mercaptobenzothiazole (54), as a protected source of sulfur, and install the silane. Shown in Scheme 39, 54 and potassium carbonate were dissolved in acetone, where upon chloromethyltrimethylsilane was added. The resulting compound 55, could be distilled at 120 °C (0.4 mmHg), providing a scaffold which could be augmented. After several attempts, it was found that optimal conditions demanded LDA at 0 °C to form the α-anion, that could then be quenched with an electrophile; benzyl bromide was chosen so that subsequent transformations could be followed under UV. Therefore, this system acts as a
proof of concept model, rather than a choice towards forming one of the previously described thiotetronic acids.

Scheme 39

With the successful production of 56, efforts towards the synthesis of alternative molecules, which incorporated the protected sulfur, silane, and varied ‘R’ groups, were carried out. However, several interesting results occurred from these investigations. As illustrated in Scheme 40, when p-anisaldehyde was used as the electrophile to quench the reaction, the expected product was not observed. It was postulated that a Brook reaction could have occurred leading to degradation of some starting material, however, this remains an area of further study if employed as a strategy for the installation of alcohols in TAs.

Scheme 40
Although interesting, this means that this method of deprotonation/quenching, is unlikely going to be simple when applied to a variety of systems. This is articulated in Scheme 41, where commonly it is found that degradation of the starting material is observed.

Scheme 41

The method also does not allow for the facile synthesis of a molecule which allows the survival of the trimethylsilane in all cases. It is postulated that a Brook arrangement takes place in some cases with a free hydroxyl, which complicates and limits the electrophiles suitable for this method. The silylated oxygen is then able to be somehow eliminated. However, in the case of 58, additional augmentation would be tested, to create a chiral centre, establishing a method for two ‘R’ groups.

It was postulated that the remaining α-proton could be removed through an equivalent of \(^n\)butyllithium and quenched with an electrophile to producing a chiral centre. This method proved
to create complex mixtures and separation was impossible (Scheme 42). Effort turned to the deprotection of the sulfur. With the removal of such a large protecting group, further augmentations of the system might prove more straightforward.

![Scheme 42](image)

The first attempt for removal of the benzothiazole group warranted the selective methylation of the imine (Scheme 43). Previous research\textsuperscript{55} suggested that with methylation of the nitrogen, a secondary nitrogenous base could attack the thiazole ring, releasing the thiol. Therefore, reaction of 57 and methyl iodide was carried out, however only with heat and pressure was this found to work successfully.

![Scheme 43](image)

Upon formation of the salt, the addition of aniline was carried out to release the thiazole system, and produce the coveted thiol. Unfortunately, this process produced the disulfide in 82\% yield, and thus alternative methods of deprotection were investigated (Scheme 44). As the major product was disulfide, it is unlikely that this method would be gentle enough for the myriad of other thiols needed for the plethora of TA.
The next method chosen appeared to be the most successful, producing the highest yields (Scheme 45). It was found that through the addition of excess LiAlH₄, the benzothiazole system could be removed, allowing for the thiol to be left free in solution. Working up the reaction solution with the Fieser method, quenched all the remaining hydride and allowed the thiol to be isolated through washing the slurry several times with ether. Concentrating the solution and passing the crude through a very short column worked extremely well for attaining pure product.

Metal hydrides such as LiAlH₄, provide very harsh reducing reaction conditions, making some groups for synthesis unsuitable; causing additional chemistry to occur, such as the reduction of an ester group to an alcohol. Proper measures to outmaneuver this issue, and it has been shown in the literature that 'BuLi is able to attach the benzothiazole ring, releasing it. The method used here however, was a clearly simple and efficient method of deprotection, leaving the silane intact that allowed for the cyclization trials to be carried out.
Additional trials with this method were tested (Scheme 46), after the transformation of 55 to 61 through the previously described method, strongly reducing conditions led to the production of 62.

Scheme 46

With thiol 60 in hand (able to be followed by UV), to act as a trial analogue, trials were carried out for the elucidation of an efficient cyclization method for the production of TA. The first test was simply to establish that the free thiol, under basic conditions, would attack malonyl chloride to provide the expected acid chloride derivative (60a)(Scheme 47). The addition of methanol stabilized this compound (60b), illustrating its propensity for nucleophilic attack.

Scheme 47

The initial step shows the product of the thiol attacking the malonyl chloride under basic conditions, to yield intermediate 60a. This reaction occurs quickly, and upon addition of a soluble fluorine source cyclization could occur, from the production of a ‘naked anion’ followed by intramolecular attack. Tetrabutylammonium fluoride (TBAF) is a soluble source of fluorine often used to overcome the poor solubility that conventional sources of dry fluorine possess, however is almost always wet. Scheme 48 shows several attempts that were undertaken to try to overcome
this problem. There was no production of product found in any of the reactions, even when protocols for drying TBAF were employed.

During the 4\textsuperscript{th} method of drying TBAF, (Scheme 49), trace amounts of the desired TA (63) were observed by NMR, but was unable to be isolated. This reaction produced a huge array of side products and less than 1\% of the TA. It became unlikely that the reaction would be suitable for a standard method for the preparation of different TAs.

With this knowledge, a final method was embarked upon for the cyclization of 60 with malonyl chloride. Using concentrated hydrofluoric acid in pyridine, known as Olah’s reagent, a dry source of fluorine was obtained; achieving a large quantity of TA 63.
The reaction was run three times, each showing complete consumption of the starting material, and high reaction yield by NMR. Attempts at purification led to failure however; isolation of pure compound proved to be a huge hurdle, and one that requires further attention. The fluorine produced large amounts of polymeric silane byproducts which could not be easily removed. The coveted compound was found to degrade on silica gel; additionally, the large excess of pyridine required for the reaction, led to changes in polarity when running TLC. This made following the compound extremely difficult, as it behaved unpredictably. Distillation with a Kugelrohr tube oven and sublimation were attempted; however, this had no effect towards purifying the material, and only illustrated its stability at 250 °C at 0.1 mmHg.

1.3 Conclusions and future work

In conclusion, after several explored pathways and difficult investigations, the final pathway has been elucidated towards the synthesis of TA (Scheme 51).
Through as little as 4 steps, the cyclization of a TA can be achieved. Additionally, with the conditions to cyclize the TA known, planning for how to protect the ‘R’ groups can be undertaken. This process can allow for the synthesis of these elusive compounds eventually, leading to the ultimate identification of TAs from groundwater.

The results of this enterprise yielded a novel method towards the synthesis of a thiotetronic acid. Although there were difficulties in the elucidation of the initial pathway, the final choice of 55 proved to work well as a scaffold for the addition of functional groups which could be later incorporated into a TA. The conditions are harsh, however with the pathway realized, protecting groups can be used for the facile installation of various groups. Future work will need to be placed on the purification of these compounds. As they are not stable when placed in silica gel, and are unable to be distilled or sublimated, a gentler means will be required. Deactivated silica gel or basic alumina column might be a means of separating out the silanes, which constitute a large fraction of the organic layer.
It can be postulated however that the pathway forged throughout the investigation leading to the final pathway presented in Scheme 51, can be used to create the TAs found in groundwater. Modification and the use of protecting groups allow for the installation of sensitive and reactive functional groups (such as α-hydroxyl groups). Therefore, it can be concluded that the premise of devising a new methodology and implementing it to create a TA has made this a successful venture. Future work will be needed to use this map to reach the goal of extending original reach of this project, leading to the complete identification of all TAs.
1.4 Experimental procedures for thiotetronic acids

General reaction procedures:

All anhydrous reactions were carried out in flame dried, under vacuum (or dried overnight in a 110 °C oven) glassware. Thin layer chromatography (TLC) was achieved on glass backed plates with Silica Gel 60 (250 µm) containing a fluorescent indicator. Compounds were visualized through UV and I$_2$ indicator. Flash column chromatography was carried out using silica gel supplied by Silicycle (particle size 30–63 (mesh 230–400)). Dry solvents were provided from the anhydrous solvent system, however other solvents and organic reagents were dried/purified using standard procedures found in “Purification of Laboratory Chemicals” by Armarego and Chai. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 300 (300 MHz $^1$H), Bruker Avance 400 (400 MHz $^1$H, 100.6 MHz $^{13}$C), or Bruker Avance 600 (600 MHz $^1$H, 150.6 MHz $^{13}$C). Chemical shift values (δ) are reported in ppm relative to CDCl$_3$ (δ 7.26 ppm) unless otherwise noted. The proton spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), sept, m (multiplet). High-resolution mass spectrometry was carried out using a Q-TOF micro (Queen’s University, ON, Canada).

**Ethyl 2-(triphenylphosphoranylidene)acetate-(46)**$^{49}$ - To a solution of triphenylphosphine (38 mmol, 1.15 eq) in toluene (1M, ~40mL), ethyl bromoacetate (5.75 g, 1eq) was added. The reaction was heated for 12 hours at 80 °C, at which the point the volatiles were removed via rotatory evaporation. The residue was taken up in dichloromethane (200 mL), placed in a large separatory funnel and a solution of KOH (4g in 150mL H$_2$O) was added (~0.5M)) was added. The mixture was shaken vigorously for ten minutes, then the layers were allowed to separate. The organic layer was then separated and dried over
MgSO₄; solvent was removed under reduced pressure. – (46) was obtained as a white solid. Yield: 86%; mp = 122-125 °C (lit. mp = 123.5-125.5 °C); ¹H-NMR (400 MHz) δ: 7.85-7.25 (m 15 H, Ar), 3.88 (2H, q, J = 7.0 Hz), 2.77 (1H br. s.), 1.02 (3H t, J = 7.5 Hz).

**Ethyl 3-oxo-2-(triphenylphosphoranylidene)pentanoate-(47)** - To a solution of propionyl chloride (1eq. 17.2mmol) in toluene (100 mL, ~0.17M), (46) (2 eq., 34.4mmol) was added. The mixture was allowed to stir for 5 hours, after which the solid was filtered off and discarded. The solvent was removed under reduced pressure and the product was recrystallized from EtOAc and hexanes. (47) was obtained as an off white solid from (46) in 77% yield, mp = 123-124 °C; (lit. mp = 124 °C); ¹H-NMR (300 MHz) δ: 7.54 (15 m), 3.72 (2H, q, J= 7.1Hz), 2.90 (2H, q, J= 7.5Hz), 1.08 (3H, t, J= 7.1Hz), 0.66 (3H, t J= 7.1Hz).

**Ethyl 2-pentynoate-(44)** - Wittig (47) is placed in a fractional distillation apparatus with an extended vigreux condenser. The entire apparatus was wrapped in cotton and aluminum and at 0.1 mmHg a distillation slowly took place. The vessel contents were heated in sand bath to 300 °C. As solution approached about 260 °C the degradation product was trapped in a liquid nitrogen cold finger. The process was run for 4-5 hours. Obtained from the thermal degradation of the Wittig reagent (47) in 78% yield, mp = 186-8 °C (lit. mp = 186-188°C); ¹H-NMR (300 MHz) δ: 4.22 (2H, q, J= 7.1Hz); 2.34 (2H, q, J= 7.5Hz), 1.30 (3H, t, J=7.1Hz), 1.21 (3H t, J=7.5Hz); , ¹³C-NMR (75 MHz), δ: 164.32, 89.61, 74.24, 65.36, 12.81, 12.62, 11.21.

**2-Pentynamide-(44b)** - A solution of alkynoic ester (44) was dissolved in stock ammonium hydroxide (27% NH₃/H₂O) and stirred at room temperature for 24 hours. Volatile compounds were removed under reduced pressure, and as this change
occurred the product crashed from solution as a white solid. Obtained through the functionalization of alkynoic ester (44) giving 92% yield; $^1$H-NMR (400 MHz) δ: 5.68, (2H, b.s.), 2.32 (2H, q, J= 5.5Hz), 1.19 (3H, t, J= 7.5Hz); $^{13}$C-NMR (100.6 MHz) δ: 151.24, 79.55, 77.52, 21.21, 11.46; FTIR (neat, cm$^{-1}$): 3310, 2986, 2942, 2881, 2793, 2241, 1663, 1391, 1315, 1133, 1056, 936,810, 720, 590, 540, 443.

2-Pentynenitrile-(43)$^{59}$ - In a 100 mL round bottom flask, 2-pentynamide (50 mmol, 1 eq.) was mixed with sea sand (20g) and P$_2$O$_5$ (52 mmol, 1.1eq). The flask was then fitted to a short column vacuum distillation apparatus and was given two cold fingers between it and the pump. The first chilled to 0 °C, the second to -78 °C. Larger molecular weight impurities will stop at the first finger, and product will condense at the second finger. The apparatus was then heated at 180 °C for 2.5 hours. Caution, P$_2$O$_5$ should be weighed with a mask, as it readily hydrolyzes to make HCl and Phosphoric acid, burning the lungs. (43) was obtained from the reaction of alkynoic amide (44b) and P$_2$O$_5$ for a yield of 68%, as a colourless oil; $^1$H-NMR (300 MHz) δ: 2.37 (2H, q, J= 7.5Hz), 1.24 (3H, t, J= 7.5Hz); $^{13}$C-NMR (75 MHz) δ: 105.11, 88.65, 55.44, 12.71, 11.83.

(Dimethylphenylsilyl)boronic acid pinacol ester-(f)$^{60}$ - Metallic lithium in mineral oil (120 mmol, 4 eq) was washed with hexanes and added to a flask of dry THF (all performed in a glove bag). The solution was then moved to a fume hood, where it was given a nitrogen source of its own and chilled to 0 °C, and chloro(dimethyl)phenylsilane (30 mmol, 1eq) was added dropwise. This mixture stirred overnight, at which point a red solution was witnessed. To this, a second solution of boron reagent (60 mmol, 2 eq) in dry hexanes (30 mL 2.4M) was cannulated; and the mixture was allowed to react overnight at room temperature. The
Volatiles were then removed under reduced pressure; and the residue was taken up in hexanes. This mixture was filtered through a Celite™ plug, to remove unwanted solids; before finally removing the hexanes with a rotary evaporator. This must be done either in a glove bag, or very quickly, as the compound is air sensitive. The final residue was subjected to a vacuum fractional distillation, where the product fraction came off at 120 °C at 0.1 mmHg. Unreacted materials will come off well before this point. Created from the lithiations of chloro(dimethyl)phenylsilane, and quenching with the purchased boron reagent 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [CAS: 61676-62-8] giving an oil, which once distilled gave 64 % yield, bp = 120 °C at 0.1 mmHg; ¹H-NMR (300 MHz)  δ: 7.46 (5H, m), 1.25 (12H, s), 0.33 (6H, s); ¹³C-NMR (75 MHz)  δ: 133.13, 129.54, 129.27, 127.61, 82.26, 24.57, -0.25.

**General procedures for the silylation of alkynes:**

A flask containing Cu(OAc) (1 mol%) and PPh₃ (1 mol%) and surfactant TPGS-750-M 2 wt % in water (1 eq.), under inert conditions, were stirred for 5 minutes with no splashing. At this point, a colour change occurred (yellow). Next, 1eq of the alkyne was added to the solution and stirred for an additional 5 minutes. To this mixture, the silylated boron reagent (f) (1.25 eq.) was added, and the reaction was monitored by TLC. Generally the reactions were less than 30 minutes. In the case of methyl propiolate as the starting alkyne, the catalyst loading was increased to 3%, and reaction time increased to 2 hours. The reaction was ended through pouring onto a silica pad and washing with EtOAc, then the solvent was the removed under reduced pressure. A column employing a hexanes/ethyl acetate system was used to purify the product.
(E)-Ethyl 3-(dimethyl(phenyl)silyl)pent-2-enolate-(48) - prepared from the silylation of alkyne (44) in 75% yield; $^1$H-NMR (300 MHz) δ: 7.4 (5H, m), 6.05 (1H, s), 4.16 (2H, q, J= 7.1Hz), 2.65 (2H,q, J= 7.5Hz), 1.28(3H, t, J= 7.1Hz), 0.95 (3H, t, J= 7.5Hz), 0.43 (6H, s); $^{13}$C-NMR (75 MHz) δ: 165.43, 153.64, 139.82, 134.37, 130.13, 128.21, 128.96, 62.48, 24.64, 15.03, 14.27, 3.75; FTIR (neat, cm$^{-1}$): 2956, 2925, 2856, 1725, 1430, 1304, 1249, 1221, 1165, 839, 996, 840, 817, 730, 698.

3-(Trimethylsilyl)pent-2-enenitrile-(49) - prepared from the silylation of alkynoic nitrile (43) in 88% yield; $^1$H-NMR (400 MHz) δ: 7.43 (5H, m), 5.58 (1H, s), 2.51(2H, q, J= 7.6Hz), 1.01 (3H, t, J= 7.6Hz), 0.45 (6H, s); $^{13}$C-NMR (100.6 MHz) δ: 173.32, 135.14, 134.04, 129.97, 128.92, 115.93, 107.45, 28.2, 14.07, -3.25.

(Methyl 3-(dimethyl(phenyl)silyl)acrylate-(52) - prepared from the silylation of methyl propiolate in 86% yield; $^1$H-NMR (400 MHz) δ: 7.44 (5H, m), 7.36 (1H d, J= 18.9Hz), 6.27 (1H, d, J= 18.5Hz), 3.75 (3H, s), 0.42 (6H, s); $^{13}$C-NMR (75 MHz) δ: 166.73, 146.23, 131.24, 130.96, 130.74, 129.66, 128.27, 61.24, -2.76.

**General procedure for the nucleophilic addition of thioacetic acid to a silylated Michael system:** A silylated Michael system (48,49,52) (0.46mmol, 1 eq.), and two equivalents of base were placed in a flask of solvent (0.1M). To this, thioacetic acid (1.2eq. .55 mmol) was added (in some cases potassium thioacetate was tested or HS-PMB). The reactions were then heated to reflux for 24 hours. The reactions were monitored by TLC, and no changes were found. Shown here is a selection of the attempts:
Ethyl 3-((4-methoxybenzyl)thio)pent-2-enoate (51) - prepared through the addition of HS-PMB to alkynoic ester (44) at room temperature after 96 hours in 57% yield. Product was columned using EtOAc/hexanes system; mp = 102-104 °C; $^1$H-NMR (400 MHz) δ: 7.28 (2H, d, J= 8.7Hz), 6.88 (2H, d, J= 8.7Hz), 5.54 (1H, s), 4.16 (2H, q, J= 7.1Hz), 3.82 (3H, s), 2.82 (2H, q, J= 7.4Hz), 1.30 (3H, t, J= 7.1Hz), 1.22 (3H, t, J= 7.4Hz); $^{13}$C-NMR (100.6 MHz) δ: 174.22, 159.25, 153.86, 128.37, 127.23, 114.02, 113.23, 51.83, 56.14, 42.35, 29.66, 15.67, 12.37.

Metallic lithium in mineral oil (120 mmol, 4 eq) was washed with hexanes and added to a flask of dry THF (all performed in a glove bag). The solution was then moved to a fumehood, where it was given a nitrogen source of its own and chilled to 0 °C, where chloro(dimethyl)phenylsilane was added dropwise (30 mmol, 1eq). This mixture stirred overnight, at which point a red solution was witnessed. This solution was then cannulated to a solution of CuI (2 eq. 60 mmol) in THF and was
allowed to stir for 24 hours. To the silyl cuprate reagent, a solution of the Michael system (1 eq. 30 mmol) in THF (1M) was added. Results show degradation of starting materials and no product formation.

**Methyl 3-(acetylthio)-3-(dimethyl(phenyl)silyl)propanoate-(53)** - prepared from Michael system (48) and the addition of thioacetic acid (1.2 eq, 2.7 mmol) and triethylamine (1.2 eq., 2.7 mmol) into a round bottom flask which was allowed to react for 96 hours; after column chromatography with a 20/80 EtOAc/hexanes system, a 50% yield was obtained; $^1$H-NMR (400 MHz) δ: 7.85 (1H, d, J= 8.1Hz), 7.72 (1H, d, J=7.3Hz), 7.33 (5H, m), 2.75 (1H, s), 2.59 (1H, s), 2.15 (3H, s), 0.18 (6H, s); $^{13}$C-NMR (75 MHz) δ: 194.35, 173.56, 135.66, 128.58, 126.38, 125.29, 63.43, 52.13, 33.96, 31.46, 30.26.

**Methyl-3-(dimethyl(phenyl)silyl)-3-((4-methoxybenzyl)thio)propanoate-(54)** - prepared from Michael system (48) and the addition of HS-PMB (1.2 eq, 2.7 mmol) and triethylamine (1.2 eq., 2.7 mmol) into a round bottom flask which was allowed to react for 96 hours; giving 20% yield; $^1$H-NMR (400 MHz) δ: 7.39 (5H m), 7.18 (2H, d, J= 8.7Hz), 6.81 (2H, d, J= 8.8Hz), 3.80 (3H, s), 3.66 (2H, s), 3.61 (3H, s), 2.52 (3H, m), 0.30 (3H, s), 0.28 (3H, s); $^{13}$C-NMR (100.6 MHz) δ: 179.63, 161.55, 136.26, 130.27, 128.42, 128.27, 127.33, 125.36, 114.29, 73.80, 54.28, 53.17, 42.35, 27.23, 2.82.

**General procedure for the deprotection of phenyldimethylsilane using cesium fluoride:**

Several attempts were carried out and are summarized (vide infra). CsF (1.3 equiv.) was placed in a pre-weighed round bottom flask and the flask was flame dried. 5 mL of solvent was added and to this a solution (54) in solvent was cannulated into the CsF containing flask (fitted
with a condenser). Malonyl chloride was then added to the flask (1.3eq.) and the mixture was stirred and heated to reflux for 48 hours. No removal of silane was observed.

Methyl 3-((3-chloro-3-oxopropanoyl)thio)-3-(dimethyl(phenyl)silyl)propanoate-(54a) - testing the mechanism presented throughout the thesis, suggesting that PMB will be displaced in the presence of malonyl chloride, an equivalent of (54) was placed in THF<sub>d6</sub> and 2 eq. of malonyl chloride were added. The solution was refluxed for 48 hours and the production of (54a) was observed; <sup>1</sup>H-NMR (600 MHz) δ: 7.38 (5H, m), 4.80 (2H, s), 3.56 (3H, s), 2.50 (3H, m), 0.28 (3H, s), 0.26 (3H, s).

2-(((trimethylsilyl)methyl)thio)benzothiazole-(55)<sup>54</sup> - prepared from mercaptobenzothiazole (1eq., 90 mmol) being dissolved in acetone ~100 mL (.9M) and to this (chloromethyl)trimethylsilane (1 eq., 90 mmol) was added. The solution was allowed to stir for 12 hours at room temperature, at which point it underwent gravity filtration to remove waste salts. The solvent was then removed under reduced pressure to produce a yellow oil. Vacuum fractional distillation was then carried out to give of faintly yellow oil. Solids in the fractional apparatus are likely disulfides. (55) can crystalize at room temperature, but remained a
liquid for over a year; giving 77% yield; bp 120 °C at 0.4 mmHg; \(^1\)H-NMR (600 MHz) \(\delta\): 7.86 (1H, d, J=8.6 Hz), 7.75 (1H, d, J=8.0 Hz), 7.40 (1H, t, J=7.6 Hz), 7.27 (1H, t, J=7.6 Hz), 2.61 (2H, s), 0.196 (9H, s); \(^1\)C-NMR (75 MHz) \(\delta\): 170.64, 153.58, 135.29, 125.98, 123.89, 121.30, 120.91, 19.06, -1.72; FTIR (neat, cm\(^{-1}\)): 3062, 2955, 2900, 1458, 1427, 1251, 1075, 991.

**General Procedure for the Lithiation of 55 and Reaction with Electrophiles:**

A solution of (55) (1 eq.) in THF (30 mL/g) was added dropwise to a solution of LDA (1.1 eq. in THF (25 mL) at 0 °C, and the resulting yellow solution was stirred at that temperature for 25 minutes. To this, a solution of the electrophile (1.5 eq.) in THF (1g electrophile in 10 mL solvent) was added, and the resulting solution was stirred for 2 hours. The reaction mixture was then poured into saturated aqueous ammonium chloride, and the layers were separated. The aqueous layer was extracted with ether (3x), and the combined organic extracts were washed with water and dried (MgSO\(_4\)). The solvent was evaporated to give the crude product as an oil, which was purified by column chromatography in 1:1 DCM/hexanes; scalable to 4 g for benzylated product.

![Chemical Structure](image)

**2-((2-Phenyl-1-(trimethylsilyl)ethyl)thio)benzothiazole-(56)** - from (55) in 83% yield as a yellow oil; \(^1\)H-NMR (400 MHz) \(\delta\): 7.84 (1H, d, J=8.0 Hz), 7.70 (1H, d, J=8.0 Hz), 7.26 (5H, m), 3.64 (1H, t, J=7.4 Hz), 3.17 (2H, d, J=7.4 Hz), 0.08 (9H, s); \(^1\)C-NMR (100.6 MHz) \(\delta\): 168.2, 153.3, 140.1, 135.5, 129.3, 128.1, 125.8, 124.0, 120.9, 38.0, 36.1, -2.20; FTIR (neat, cm\(^{-1}\)): 3061, 3026, 2955, 2900, 1603, 1495, 1456, 1427, 1250, 991, 841,754, 698.

![Chemical Structure](image)

**2-((1-(Trimethylsilyl)propyl)thio)benzothiazole-(61)** - produced from (55) in 72% yield as a yellow; \(^1\)H-NMR (400 MHz) \(\delta\): 7.84 (1H, d, J=
2-phenyl-1-(trimethylsilyl)ethanethiol-(60) General procedure for the release of thiol from (56): To a round bottle flask containing dry Et₂O (50 mL solvent for every 1g LiAlH₄), LiAlH₄ (10eq.) was added and stirred for several minutes until no bubbles occurred. Thiol 60 (1 eq.) was then added and the flask was fitted with a condenser. The setup was then purged with argon and fitted with an argon balloon. The solution was vigorously refluxed for 48 hours. The reaction was then allowed to cool to room temperature and was quenched with the Fieser method. (Fieser method: Where reaction contains (x) quantity of LiAlH₄. The reaction was cooled to 0 °C and while stirring, (x) mL H₂O was slowly added. This was followed by the addition of (x) mL 15 % aq. NaOH solution, followed by 3 x mL H₂O. The reaction was then warmed to room temperature and was allowed to stir 15 minutes before MgSO₄ was then added.) Solid aluminum hydroxide was then left stuck to the sides of the flask, and ether was decanted off. Several washes of the gel were done with Et₂O. The combined ether layers were put under reduced pressure to give a yellow liquid. This was then subjected to column chromatography, using 1:1 DCM/hexanes to yield pure thiol (82%).

1H-NMR (400 MHz) δ: 1.17 (1H, d, J=6.7Hz), 2.29 (1H, qd, J= 3.4Hz, 11.6Hz), 2.55 (1H, dd, J= 11.6Hz, 14.0Hz), 3.16 (1H, dd, J= 3.5Hz, 14.0Hz), 7.26 (5H, m; 13C-NMR (100.6 MHz) δ: 3.1, 26.9, 40.1, 126.3, 128.3, 129.0, 140.3; FTIR (neat, cm⁻¹): 3062, 3026, 2956, 2900, 1602, 1494, 1453, 1406, 1250, 841, 753, 698.

1-(trimethylsilyl)propane-1-thiol - (62) - Produced from protected thiol (61) and subjected to LiAlH₄ treatment, giving 36% yield as a colourless oil. 1H-NMR (300
MHz) δ: 3.66 (2H, q, J= 10.7Hz), 0.98 (3H, t, J= 7.2Hz), -0.03 (1H, s); 13C-NMR (100.6 MHz) δ: 33.63, 27.84, 12.65, -2.12; FTIR (neat, cm⁻¹): 3407, 3066, 2956, 2813, 1592, 1504, 1455, 1425, 1318, 1288, 1248, 1169, 869, 695.

General procedure for the unsuccessful cyclization of TAs:
In a round bottom flask, supplied with activated molecular sieves, TBAF (or other fluorinating agent) was introduced to dry MeCN, where it was allowed to stir for several hours to dry. In a separate flask, thiol 60 (1eq.) in MeCN (1g for 100 mL solvent) was introduced to triethylamine (1.1 eq.) followed by malonyl chloride (1.5 eq.). This solution was monitored by TLC for 2 hours until SM was consumed. This solution was then canulated into the flask containing TBAF (or other fluorinating agent), where the solution was then monitored by TLC for the disappearance of the newly produced spot. The crude mixture was then washed with water and extracted with EtOAc. Organic layers were combined and washed with brine and dried with MgSO₄. Solvent was removed under reduced pressure, and the resulting oil was then columned with 1:1 DCM/hexanes. None of the methods provided more than trace product. Some examples are shown below:

\[
\text{HS-Ph} + \text{Cl-OCO-Cl} \xrightarrow{\text{conditions}} \text{NET}_{3}, \text{CsF, THF, N}_{2} \\
\text{NET}_{3}, \text{CsF, MeCN, N}_{2} \\
\text{NET}_{3}, \text{KF, 18-Crown-6, THF, N}_{2} \\
\text{NET}_{3}, \text{TBAF, MeCN, N}_{2} \\
\text{NET}_{3}, \text{dried TBAF, 4Å seives, MeCN, N}_{2}
\]

5-benzyl-4-hydroxythiophen-2(5H)-one-(63) - At 0 °C thiol 60 (1 eq. 0.95 mmol) was added to a side arm flask containing dry THF (0.23M), under constant argon flow. To this pyridine was added (4 eq, 3.8mmol), followed by malonyl
chloride (1.2 eq. 1.14 mmol); the reaction was then allowed to stir for 2 hours, followed by TLC to ensure that the thiol no longer was present in the solution. Next, the argon flow was increased and the rubber septum removed, while Olah’s reagent (70% HF in pyridine) (1.2 eq, 1.14mmol) was added. This solution ate through glass immediately making dispensing it nearly impossible, a Pasteur pipette could not hold a vacuum with it. Therefore, it is likely that excess was added at this step. The only safe method of proper dispensation would be a Teflon syringe. (SAFETY WARNING: Have a saturated bath of calcium chloride handy in case of spills, and calcium gluconate in case of spilling it on yourself. This is EXTREMELY dangerous.) The reaction was stoppered and monitored for 20 mins, by TLC. To this flask, a 6-fold excess (to the fluorine added) of CaCl₂ was dumped into the reaction, to soak up remaining fluorine. This reaction mixture was stirred for 2 hours. Gravity filtration removed inorganic salts, and rotary evaporator removed excess pyridine. Unfortunately, further purification was found to be difficult as the TA (63) was not silica gel column stable, could not be distilled or sublimed, and as an oil, could not be crystallized. Large amounts of pyridine remained overnight on the pump, suggesting complexation occurs. Although 100% consumption of the starting material consumed, no pure product was never obtained; ¹H-NMR (600 MHz) δ: 7.21 (5H, m), 6.15 (1H, s), 3.41 (1H, dd J= 5.8Hz, 9.8Hz), 3.06 (1H, dd, J= 9.8Hz, 14.3Hz), 2.80 (1H, dd, J= 14.3Hz, 5.8Hz), 1.43 (1H, s); ¹³C-NMR (150 MHz) δ: 197.7, 177.2, 140.2, 129.4, 128.4, 126.5, 102.1, 36.9, 30.3; (HSQC was used to determine the carbon peaks among the impure sample) FTIR (neat, cm⁻¹): 3086, 3062, 2956, 2901, 1757, 1620, 1583, 1524, 1410, 1250, 1150, 1089,952, 841, 752, 698.
Chapter 2: The Synthesis and Reactions of New 1,4-Oxathiin-S,S-dioxides
2.0 Introduction

Heterocyclic ring systems are among the most prevalent chemical scaffolds found throughout the natural world, the majority of which contain oxygen, nitrogen, and sulfur. These systems occur in a myriad of both naturally sourced and synthetically produced organic compounds.\textsuperscript{61} Isolation of these unincorporated or unsubstituted systems however presented the synthetic community a greater challenge. The first fully unsaturated compound of this family to be studied and synthesized was 1,4-dioxin (64) in the 1930s, followed by 1,4-dithiin (65) in the 1950s.\textsuperscript{61} It was not however until 1980 that the fully saturated 1,4-oxathiin (66) system was attained.\textsuperscript{61}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{heterocyclic环.png}
\end{figure}

Most enthusiasm in this area is directed towards the synthesis and study of 2,3-dihydro-1,4-dioxin (67), 2,3-dihydro-1,4-dithiin (68), 2,3-dihydro-1,4-oxathiin (69), 2,3-dihydro-1,4-benzodioxin (70), 2,3-dihydro-1,4-benzodithiin (71), and 2,3-dihydro-1,4-benzoxathiin (72). This can be attributed to the bioactivity that analogues of these molecules exhibit; making them excellent targets for applied research, especially in the agrochemical sector.\textsuperscript{61,62}
Contrastingly, saturated systems are commonly known to the chemical community, widely used and studied. Molecule 1,4-dioxane (73) has often been used as a solvent for various chemical processes, whereas replacement of oxygen to sulfur producing 1,4-dithiin (74) and 1,4-oxathiin (75) was achieved at the turn of the past century.\(^{61}\)

In 1966, Von Schmeling and Kulka published a report which showcased the 1,4-oxathiin (69) scaffold, devising two compounds which displayed remarkable fungicidal activity.\(^{63}\) They found 3-carboxanilodo-2-methyl-1,4-oxathiin, later marketed as Carboxin\(^{\text{TM}}\) (76) and its sulfone analogue Oxycarboxin\(^{\text{TM}}\) (77) (Figure 9), were particularly effective against controlling plant pathogenic fungi such as bean rust, leaf rust, and smut of barley.\(^{63}\)

Desirably, after treatment, all fungi were eradicated and symptoms of higher plants were cured after 7 days. This was attributed to good water solubility; credited to the oxathiin functionality, which allowed the plant to readily translocate the compound through the transpirations system (xylem), towards the site of infection. These experiments also showed that the sulfide analogue Carboxin\(^{\text{TM}}\) (76) was more effective and no damage was observed on host plants due to either treatment.\(^{63}\)
This trial however sparked rapid interest in the agrochemical sector, and immediate augmentation of Carboxin™ took place. Von Schmeling found were that functionalization of the amide led to decreased fungicidal activity (carboxylic acids, esters, and N-alkylamides were tested). In 1966, Von Schmeling filed patents for a host of alternative 1,4-oxathiins, a selection of which is shown in Figure 10, however few were marketed as successful fungicides.  

![Figure 10: Various fungicidal compounds taken from the first patent](image)

It was not until several years later that the mode of action of these fungicides was revealed. Until their discovery, fungal treatments possessing the ability to be translocated through plants were rare, limiting the overall effectiveness and measures that could be taken against a given pathogen. Incorporation of oxathiins led to a break from this trend, making them a valuable control for a variety of smuts, rusts, and some seedling diseases. Efficiency of treatment also seems to be governed by the concentration of 1,4-oxathiin derivative able to enter a given cell, making the farmer able to administer the proper dose required for each field, depending on extent of the disease outbreak. Carboxin™ kills pathogens by inhibiting respiration, as shown against fungal cell lines. More specifically, it halts the metabolic
production of acetate, decreasing the pathway’s efficiency, and to a smaller extent glucose production. The study appears to show that the site of action of Carboxin™ appears to be on succinic dehydrogenase and on an inhibitor of complex II of the electron transport system. Whereas tested against mammalian systems, it was shown to be able to inhibit the oxidation of succinate in a noncompetitive manner, but has little overall effect on the system. The sulfide’s (76) superior reactivity towards fungi compared to its oxidized analogue (77) was attributed to its ability to inhibit the oxidation of succinate. However it was noted, that the mono-oxidized variant was able to inhibit succinate-cytochrome reductase. This observation prompted postulation that the oxidation of sulfur may achieve entry into the cell, allowing for alternative pathways to be exploited.

With the discovery of molecules which were able to flow freely throughout the xylem of the plant, and thus be transported directly to the site of infection; a burst of competitive interest in this area has arisen in the past 60 years. Moving beyond the original template of the 1966 patents, several large chemical companies have moved to produce herbicides and fungicides which satisfy the growing and ever-changing demands of the agrochemical industry.

Agrochemicals comprise a vast category of compounds which include insecticides, herbicides, and fungicides and possess the inherent ability to increase the quality of crops, which has ensured their constant use in modern farming methods. Able to reduce labour costs in major fruits, vegetables, corn, and rice, farmers abstain at their own peril. With the constant increase of environmental regulations, coupled with weed and fungal immunity rising over time, the production of safer and more effective agrochemicals is a constant focus of the industry.
Novel agrochemicals are typically discovered through the augmentation of a single bioactive molecule, such as seen in the case of Carboxin™. Optimizations, selecting a particular attribute, come at great cost, time, resources, expertise, and money. Therefore newly derived compounds are rare, and are becoming rarer as shifts in financial investment change. Usually, an integrated team of chemical engineers, computational chemists, toxicological biologists, and chemists, work for several years to derive a usable product. Additionally, simple augmentation of a previous compound allows for governmental regulations to be passed substantially faster than newly described de novo compound, as environmental and biological screening of analogues has likely already occurred.

Commonly employed throughout organic synthesis, pharmaceutical, and agrochemical industry often choose a bioactive molecule and use one of three intermediate derivatization methods. By changing a technique applied or idea applied to an intermediate, in conjunction with biological screening, a patentable compound is often achieved. With the marketing of these chemicals, large quantities of pure products become globally purchasable, and therefore augmentation and the study of intermediates can be carried out by competitors. Embodied in Carboxin™, evolution has led to a range of carboxanilide fungicides. Several alterations have born patents by several large agrochemical companies, and for brevity, a selection has been presented in Scheme 52. Building on the success of another company’s patents, the more recently discovered fungicides have evolved to exclude the 1,4-oxathiin ring entirely.

It was actually the originators of the family, Von Schmeling and Kulka, who initiated the augmentations of Carboxin™ through replacement of the phenyl ring with a biphenyl ring.
it was only several years later that the replacement of the oxathiin group was carried out, to produce mebenil, replacing it with a phenyl ring (Scheme 52).

![Chemical Structures](image)

Scheme 52

This alteration increased the fungicides ability against *Basidiomycetes* and for the control of *Puccinia* spp. on cereals at very low concentrations. In the same vein as the previous example, the oxathiin ring was replaced with a furan ring to achieve compound fenfuram. This was discovered at Shell Research Ltd, and developed by KenoGard Vt Ab (now Bayer AG), a global player in controlling the markets for fungicides targeting smut. Uniroyal Inc. (now Chemtura corp.), the original patent holder, produced metsulfovax, which contained a thiazole ring in place of the oxathiin ring. This change showed broad disease control in the treatment of cereals, cotton, potatoes and ornamentals, lifting the family away from its general focus of controlling smut. The
family could now be marketed against a variety of pathogens and used for landscape, as well as for crop management.69,72

Almost complete detachment from the Carboxin™ scaffold seems to have been achieved when analyzing Benzovindiflupyr (Scheme 53), which has eliminated the oxathiin ring, and replaced it with a pyrazole ring. Syngenta has used modifications of several fungicides, through halogenation to optimize its activity.73 To accomplish this major change, several patented compounds from several individual companies were used, changing a competitor’s molecule to adopt a novel compound in an aggressive race over the past half century.62

While global interest grew in the search for novel fungicides, many of which contained the 1,4-oxathiin functionality, Uniroyal Inc. developed a second class of compounds for the agrochemical sector. Based on an original scaffold from Marshall and Stevenson in the late 50’s,74 a large assortment of functionalized 1,4-oxathiins and their dioxides were probed and patented for their herbicidal activity (78, vide infra).75 This approach diverged from compounds which seemed to be reliant on the amide functionality found in Carboxin™ and Oxycarboxin™. These new
compounds were found to be useful for the selective control of grasses and useful as dwarfing agents; additionally exhibiting inhibition of vegetative and reproductive axillary growth, as well as the ability to increase sugar content in sugar producing species.\textsuperscript{75} Cessation of flowering and inhibition of weed root growth was also an observed effect of the toxin. In short, they changed the 1,4-oxathiin scaffold from a fungicide to a very effective herbicide.\textsuperscript{75}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure11.png}
\end{center}

Crop fungi is a blight, however the presence of weeds can be devastating to agricultural communities as well. Weeds can inhibit the production of foliage, fruit, and seeds of the desired crop, as well as offer huge obstacles during harvesting. Decreased quality is often affiliated with the crops that grow in affected areas, therefore, herbicidal control is essential for maximal production of many horticultural crops, such as corn, rice, and soybeans. In recent years, landscaping has required control of unwanted grasses, for allergy reduction and general aesthetic appeal. This booming industry has made the production of these 2,3-dihydro-1,4-oxathiins especially attractive, as they offer selective control against such unwelcome weeds. As shown in Figure 11, the general form of these compounds is a biphenyl system on an oxathiin ring. Moderate augmentation to these rings of 78, such as selective halogenation and methylation, have made a series of patentable compounds made purchasable by Uniroyal Inc. after 1975.

From this unassuming scaffold,\textsuperscript{74} Uniroyal Inc. was able to assemble an array of 51 patentable compounds (Figure 11).\textsuperscript{75}
These compounds all utilize the 1,4-oxathiin ring, and only show modification on the aryl ring systems, except for the 2-position of the ring. Addition of a methyl or ethyl group was employed, increasing the bank of bioactive compounds.

With the production of so many varied agrochemicals, an industrial synthesis for their mass production was required, which in turn permits distribution, granting viability as a commercial herbicide. Although several methods were patented, one of the general methods employed for the production of these compounds was through the reaction of any substituted benzoin with thionyl chloride, to produce an appropriate α-halo-α-phenylacetophenone. Alternatively, the reaction of 2-phenylacetophenone with elemental bromine would be equally sufficient. The incorporation of cheaply purchased and readily available reagents, makes this synthesis an economically viable option for the production of a commercially produced chemical, required by the multiple kilo scale.\(^75\)
Presented in Scheme 54, 2-chloro-2-phenylacetophenone is placed in benzene where a solution of 1-mercaptoethanol and triethylamine is slowly added. Letting the reaction stir overnight allows for the formation of the thioether, which is then extracted from the mixture. Placed in benzene, $p$-toluenesulfonic acid catalyzes the cyclization of the 1,4-oxathiin under reflux conditions, aided through azeotropic water removal. Washing the crystals with weak base, removes the acid, where after subsequent crystalization from absolute ethanol affords pure 78. The 1,4-oxathiin systems can then be oxidized to a sulfoxide or sulfone through the addition of appropriate equivalents of 30% hydrogen peroxide.75

With synthesis of these chemicals complete, an emulsifiable concentrate must be produced for a farmer to use on a given crop. This was done through dissolving the 1,4-oxathiin in a solvent system such as toluene, octyl phenoxy-poly-ethoxy-ethanol, and chloroform. This concentrate is then purchased by the farmer and added to a water tank of a chemical sprayer, where it can be applied to a field for the control of weeds. The herbicide is frequently applied at rates of 0.10 to 25 pounds per acre.75

There can be little argument of the impact that 1,4-oxathiins have had on the agrochemical sector, having inspired a plethora of novel compounds which exhibit activity against both pathogens and undesirable plants alike. However, the 1,4-oxathiin ring system has proven that it can be used to import additional desirable characteristics in the foods and drug industry.76 Showcasing this, Arnoldi and co-workers produced a molecule which boasts a sweetness 2000 times that of sucrose. Through a novel synthesis of 2,3-functionalized-1,4-benzoxathiins, the installation of an isovanillyl moiety was carried out. It is well understood that isovanillyl elicits a
sweet sensation, however when coupled with the 1,4-oxathiin, it was found that an increase in potency was achieved.\textsuperscript{76}

Their efforts however brought forward an interesting pathway (Scheme 55). Initially, to test their pathway, 2-mercaptophenol (79) reacts with styrene epoxide, where through nucleophilic attack of thiol, at the more reactive benzylic carbon, expected diol 80 is formed. Interestingly, when exposed to an acid catalyst, 80 eliminates water producing product 83 (pathway a). This unexpected product shows that pathway ‘b’ was not observed, and therefore it is likely that the reaction transforms through a rearrangement of an episulfonium ion (81).\textsuperscript{76}

As this pathway would not be viable to produce the isovanillyl desired analogue a secondary pathway was formulated, starting from thiol 84. Additional steps were taken to accomplish final product 85, which possessed striking sweetness (Scheme 56). This synthesis
articulates that incorporation of sulfur can lead to an increase in sweetness, and therefore interaction with a variety of chemical receptors not previously exploited.

One other interesting area of research is that 1,4-oxathiin carboxanilide derivatives have demonstrated an ability to act as non-nucleoside HIV-1-specific reverse transcriptase inhibitors. After the discovery of such inhibitors in the late 1980s, numerous classes of compounds have been identified and are referred to as non-nucleoside reverse transcriptase inhibitors (NNRTIs). These compounds are defined by a high potency and specificity towards the inhibition of HIV-1 strains, however not HIV-2 or other RNA or DNA viruses. However, an omnipresent concern, is the mutation of such viruses, and their ability to gain resistance to any individual treatment, thus prompting the continual search for novel drugs and treatment options.

To circumvent the obstacle presented by drug resistance, the cocktail method developed for the treatment of HIV-1 positive patients, was invented and utilized. With this tactic, a mutant virus may gain resistance to one particular NNRTIs, however it is then wiped out by a secondary inhibitor (drug). This led to 31 different 1,4-oxathiin carboxanilide derivatives to be tested for their ability to inhibit wild-type HIV-1 virus cell lines, resistant to several conventional treatment methods. Articulated in Figure 12, the oxathiin model was split into four quadrants, where structural changes were made and assessed for their ability to inhibit the virus. It was found that minimal changes elicited a marked increase or decrease in virus inhibition, leading the researchers to recommend several of the compounds go forward for drug trials.
These oxathiins were made simply (Scheme 57), from the appropriate methyl or ethyl 2-chloro-3-oxoalkanoate reacting with 2-mercaptoethanol. Under basic conditions, attack by the thiol at the α-position eliminates the chloride. Additional heating and removal of water closes the ring, produces the oxathiin ring system. Hydrolysis led to the acid, and subsequent addition of thionyl chloride produced the acyl chloride derivative.  

Scheme 57

The synthesis of these drugs was generally carried out through the production of an acid chloride-oxathiin that was then reacted with a functionalized amine in toluene, under mildly basic conditions (Scheme 58).  

Scheme 58

Aside from the synthesis of highly functionalized 1,4-oxathiin systems for a direct purpose, whether the agrochemical industry or the pharmaceutical industry, several studies have been directed towards the chemistry of these systems, and the associated by-products. Since the global
production of Carboxin™ and Oxycarboxin™, sourcing of this material has become an economical way to test the chemistry of these systems. Additionally, functionalization became simple, as the 1,4-oxathiin ring was already started with a pre-installed amide functionality (77). Goehmann and co-workers found that under basic conditions, the oxathiin ring system of Carboxin™ could be induced to open, whereupon an acid quench, a vinyl sulfone (86) could be isolated (Scheme 59).

![Scheme 59](image)

Further work was predicated on the additional reactivity of these systems, leading to the synthesis of various products through the addition of both electrophiles and nucleophiles to 86. Expressed in Scheme 60, 77 readily undergoes ring opening at room temperature, however subsequent Michael additions could only be induced with high heat producing 87.

![Scheme 60](image)

This is likely due to the presence of multiple sites of attack on the molecule, however only one of which is irreversible. Several 1,4-oxathiin derivatives underwent similar reactions, however the carboxylic acid derivative was unable to react beyond the production of the vinyl system.
The scope of these reactions was further extended, to encompass the nucleophilic addition of thiols to the Michael system. It was found that ethanolic or alkali hydroxides, as well as heat, were required for reactions to succeed. During the reaction (Scheme 61), 77 reacts with a base, to form the vinyl system 86, where subsequent attack by the thiol produces 88a-c. Here, illustrated is an unsettling side reaction in which an acetyl group is lost, providing only 88a-c.

![Scheme 61](image)

To test the nucleophilic ability of nitrogen nucleophiles on these vinylic systems, 86 was isolated, and in acetic acid, secondary amines were tested. Cleanly progressing Michael additions were observed. Shown in Scheme 62, 86 reacts to give product 89e, expressing again the removal of an acetyl group which is inexplicably lost during reaction conditions.

![Scheme 62](image)

Research probing the reactivity of vinyl sulfones was extended recently by Bulakowska and Konieczny, through base catalyzed ring opening of 2,3-dihydro-1,4-benzoxathiin derivatives (Scheme 63). Vinyl sulfones generally offer interesting biological activity, and boast industrial applications as reactive dyes. Formation of these compounds was achieved through the reaction of 90a-d with excess sodium hydride in DMF.
As seen previously, this system was advanced further, providing a wealth of products (Scheme 64). Under highly basic conditions, with the use of hydroxide, Michael reactions occurred with thiols, secondary amines, and alcohols providing the expected outcome.

Only published in 2015, this study articulates that interest in the area is still present, as are new methods for the synthesis of new derivatives of oxathiins and their byproducts.

Although the large scale synthesis of oxathiins has been covered in some detail by industry, there have been some interesting investigations pertaining to their degradation (vide infra). Upon thermolysis of 2,3-dihydro-1,4-oxathiins, a reaction occurs (a retro-Diels-Alder), forming the corresponding α-oxothiones. This compound can be trapped by reactive compounds such as cyclopentadiene, resulting in a Diels-Alder product. When repeated with a sulfoxide starting material, the expected S-oxide was produced. When trapped with 2,3-dimethyl-1,3-butadiene, product was afforded.
One of the most innovative methods for the generation of chiral 1,4-oxathiins was developed by Capozzi in the late 1990s.

As illustrated in Scheme 65, the application of the Diels-Alder reaction is employed, trapping intermediate α,α’-dioxothione 96 with an electron-ring dienophilic enol ether 97a,b (upper pathway) or activated styrene 98 (lower pathway). Reactive intermediate 96 was created through the addition of a weak base, and loss of the NPhth group. This model system shows the huge variance of substituents and control over the stereochemical outcome. Additional oxidation is carried out to produce 101a,b and 102, by addition of a single equivalent of m-CPBA.
This unique method for the preparation of oxathiins was expanded to incorporate alternative substituents in later studies,\textsuperscript{87,88} each time illustrating a highly regioselective process, whereby no oxygen of the bis-heterodiene links to the substituted olefinic carbon. Additionally, the reaction boasts being chemo-selective, as $\alpha,\alpha'$-dioxothiones react only with the ketonic carbonyl. The most important outcome however is that the stereochemistry of the product is reflected by that of the starting alkene. When a cis alkene was used (97a,b,c), the stereochemistry of the product is shown to be maintained (97b,c)(Scheme 65).\textsuperscript{89}

When sulfoxide 101a was heated in CDCl$_3$ with 2 equivalents of 97b, transformation to 101b was achieved and isolated in 55% yield (Scheme 66). It is likely that sulfoxide 101a undergoes a retro-Diels-Alder reaction, through highly reactive intermediate 103, which is then trapped by 97b. The reverse process was accomplished through heating and a 4 fold excess of 97a, insinuating a flexible equilibrium.

![Scheme 66](image)

Utilizing this chemistry, 101a (Scheme 67) was heated with 2 equivalents of anethole (98) for 40 hours, leading to the expected retro-Diels-Alder reaction/Diels-Alder reaction producing 102 and 104 as two regioisomers. Final oxidation of these products led to fully functionalized 1,4-oxathiin-4,4-dioxides, 105 and 106.\textsuperscript{90}
An interesting caveat for this chemistry is that the only 1,4-oxathiin compounds undergo a retro-Diels-Alder reaction contain a sulfoxide system, articulated by the mechanism shown previously in Scheme 66. This provides wonderful control, where an oxidation of the 1,4-oxathiin could allow for alterations via substitution of the 5-,6-positions of the ring. Cementing stereochemistry can be achieved through a second oxidation to the sulfone.

The Schwan group has also produced a method for the production of novel 1,4-oxathiins, summarized in Figure 13. The synthesis is predicated on the production of aryl sulfonyl alkynes, which are then cyclized through the addition of a strong base and an aldehyde, to form the coveted 1,4-oxathiin-S,S-dioxides. This method was optimized with great care, to formulate a process which would allow for the synthesis of these highly diverse aromatic systems. At first glance, many of these compounds bear a mild similarity to those formulated by Uniroyal Inc. in 1975; however these possess the alkene at the 2-position, and additionally have an aryl group at the 2-position, which was unexplored previously.
Previous efforts were directed into the synthesis of these compounds, as well as probing their reactivity under basic conditions. The scope of this thesis is to extend these efforts and expand the chemical library with the synthesis of new compounds, as well as probe Heck reactions, assess the oxidative ability of FeCl₃ towards these systems, and study the reaction of these compounds under basic media. Through these investigations the facile synthesis of 1,4-oxathiin-S,S-dioxide phenanthrene derivatives will be achieved. Additionally, the reactivity of these compounds under basic media will be studied to further assess their reactivity. To aid in this effort, computational studies will be carried out to understand the role that the alkali base plays during the reaction, ultimately effecting the stereochemical outcome of the ring open product.
2.1 Results and Discussion

Although many varieties of oxathiins have been established since the family’s inception in 1966, there is still a steady flow of additional entries added to the family. Discoveries have been possible through the elucidation of newly devised synthetic pathways which allow for the facile augmentation of the oxathiin ring system. The Schwan group is no exception to this, and has illuminated one such method, producing a variety of oxathiins in a 2013 report (Figure 14).

Although this method does not require the products to have aromatic substituents at the 2,5,6-positions of the 1,4-oxathiin ring, it is a feature that is highly attractive to our research. Using the Schwan method, a variety of oxathiins would be synthesized for further reactions. Previously, oxidations of 1,4-oxathiin-S,S-dioxides had been thoroughly investigated by the Schwan group, testing DDQ, Chloranil, iodobenzene diacetate, cerium ammonium nitrate, and manganese dioxide. Inspired by the newly published work of Maly and co-workers (Scheme 68), coupling of aryl systems found at the 5- and 6-positions through the employment of iron(III) chloride, it was envisioned that a phenanthrene system could be produced.
The first of these pathways to be explored was to probe the oxidative power of iron(III) chloride. It was projected that under similar conditions, a similar coupling could be induced with an oxathiin derivative (Scheme 69). Through closing the ring system, a phenanthrene would be formed through oxidation, while keeping the oxathiin ring intact.

Other coupling reactions are difficult to carry out, and are subsequently more challenging. Reaction conditions are generally harsh and take excessive planning, as it requires prior functionalization of the starting material for intramolecular coupling to occur. The reaction in Scheme 69 offers a simple and elegant method to link these aryl systems to bypass any traditional coupling reactions. To probe the versatility of this reaction, five different oxathiins were used. All of the oxathiins possess functionalized 5,6-diaryl systems and will be presented later in the section.

The next reaction to be probed will be to test these systems under traditional Heck reaction conditions. Previously, this reaction was optimized by the Schwan group; this investigation looks to expand the oxathiins tested and to successfully produce the phenanthrene system (Scheme 70).
Unlike the iron chloride reactions, this reaction takes additional planning, as there will be a 2-iodo moiety on the 5-aryl system. This will serve to initiate coupling, by way of standard Heck conditions. Five 1,4-oxathiins-S,S-dioxide targets will be produced and tested, for the purpose of their coupling reactions.

The pathway invented by the Schwan group to produce these highly variable aromatic oxathiins is given in Scheme 71 (vide infra). This pathway is reliant on producing a benzyl alkynyl sulfone (d), and using a strong base, inducing cyclization with an electrophile such as benzaldehyde. For the synthesis of oxathiin 107, benzyl bromide is subjected to potassium thiocyanate in acetonitrile, displacing the halogen after one hour. Simple gravity filtration and removal of solvent under vacuum allows for sufficiently pure product to be collected for the next step. The next step of the pathway occurs at -78 °C, where a solution of phenylacetylene is deprotonated with n-butyl lithium. Benzyl thiocyanate (ac) is then added dropwise to quench the anionic solution, producing benzyl alkynoic sulfide (ag).
Product **ag** must then be oxidized, which is easily done through the addition of excess *m*-CPBA, generating **ak**. In all attempted examples achieved during this inquiry, phenylacetylene was used in the second step. This obliges a phenyl group to be located at the second position of the ring. In previous trials, other alkynes have been used, however the added stability garnered from the presence of the phenyl group should make deprotonation occur more readily; this outweighed the allure of using additional regents during the cyclization step.

The final and most problematic step in the synthesis of these compounds is the cyclization of the benzyl alkynl sulfone (**ak**) to **107**. During this investigation, many attempts at this reaction were fruitless, from humidity ruining this sensitive reaction. This reaction was optimized at great effort by previous members of the Schwan group, exemplified in Scheme 72.
Because of the sub-stoichiometric quantity of base added to the mixture in order for the reaction to advance, it is likely that the formed anion is able to in turn deprotonate additional material in the reaction pot.

Shown in Scheme 73, is the proposed mechanism for how the anion is able to form the cyclized product 107. Deprotonation is believed to take place at the benzyl position of the benzyl alkynyl sulfone ak, which creates an anion which is then captured by benzaldehyde, to produce an oxyanion. From here the oxygen then intramolecularly attacks the alkynyl system to form the oxathiin ring system, producing an anion, (a) stabilized α to the sulfone. The vinylic α-anion is projected to have the capacity to attack additional molecules of benzyl alkynl sulfone, until the reaction has consumed all starting material. For this reason, highest yields were achieved with one-half equivalents of butyl lithium, and generally short reaction times for initial anion formation to occur (15 minutes). During this series of experiments, difficulties with humidity (in part due to a change in building location), led to several failed trials, as the presence of water hindered the anionic cascade.
Using the Schwan method to synthesize oxathiins, there are two simple ways to achieve variance among the products: by initiating the pathway with a functionalized benzyl group, or to quench the reaction during the cyclization step with a different electrophile from benzaldehyde. Shown below are several previously made oxathiins where the benzyl group possesses a variety of augmentations, and benzaldehyde is used as the electrophile (Figure 15).

Alternatively, if benzyl bromide is the starting compound, leading to the formation of ak (Scheme 73), where no functionalization is added, alternative electrophiles used in the final step can lead to a series of products (Figure 16). This leads to a change in the 6-position of the oxathiin ring system. Theoretically, almost any aldehyde can be used for this purpose.

By interchanging these methods of functionalization, oxathiins illustrated in Figure 17, are proposed targets for the reaction of iron chloride in dichloromethane.
Additionally, oxathiins 107 and 112 would be made in large quantities to be used to probe additional experimental procedures for the base induced ring opening reactions. Furthermore, these larger scale reactions would serve to establish familiarity with this chemistry (Figure 17).

To satisfy the Heck coupling reactions, the oxathiins illustrated in Figure 18 will be produced, using 2-iodobenzyl bromide as the starting compound for the pathway. Varying the electrophile from benzaldehyde to another electrophile will produce our targets, with both electron-rich and poor characteristics.

When working with these iodinated compounds, there is a very distinct means of identification by NMR. There is a doublet of triplets which appears at ~6.9 ppm, corresponding to a proton meta to the iodo-moiety (Figure 19). This simple identification will ensure that after coupling has occurred, it can be followed through the disappearance of this peak, regardless of
how complicated the aromatic region becomes. Of additional significance is the characteristic doublet peaks and singlet peak, indicative of all 1,4-oxathiin targets; thus allowing the simple recognition of these systems.

![Chemical Structures](image)

**Figure 19: Characteristic meta-iodo peak at 6.9 ppm**

In slight contrast to the targets proposed for the iron chloride reactions, Heck targets require an additional step to produce 2-iodobenzyl bromide. As shown in Scheme 74, cyclization towards the Heck target 1,4-oxathiin products, generally had substantially lower yields than previously explored pathways.

![Scheme 74](image)
As the first several steps, leading to the production of the benzyl alkynyl sulfone, are trivial and high yielding, all future yields will be given for the final cyclization step. This step is the most difficult to perform, and purification is the most difficult to carry out.

Although not tested in this investigation, other o-iodophenyl oxathiins that could provide interest in future study would employ pyridine, furan, and pyrrole derivatives on the 6-position of the oxathiin ring; achieved using the corresponding aldehyde during the cyclization step.

![Scheme 75](image)

In 2013, a study by the Schwan group produced a series of oxathiins (Scheme 75). Replication of these compounds led to increased yields for the cyclization step of each oxathiin tested, with the exception of 117. The targets depicted in Figure 20, will serve as the starting materials for the iron chloride reactions.

![Figure 20](image)

**Figure 20: Results for the cyclization step producing iron(III) chloride targets**

Purification of these compounds has always been problematic. It was found by a previous group member that trituration of the products with diethyl ether could yield pure 1,4-oxathiin; however, this method was not universally successful. Oxathiins have a tendency to crystallize inside...
columns when placed in most solvent systems and show minimal differences in $R_f$ compared to starting materials and unwanted byproducts. Using a newly devised method, a compound was placed in a column with 1mL MeOH, 149mL DCM, and 150 mL hexanes. This would crystallize out the 1,4-oxathiin and allow the starting materials and byproducts to slowly pass through. Flushing this column with 30% methanol led to the isolation of pure oxathiin in higher yields than other purification methods. This was particularly important for iodo-analogues, which could not be purified through trituration, or crystallization.

Carrying out the reaction depicted in Scheme 76, the production of oxathiins 110, and 121-4 were produced by using varying aromatic aldehydes (Figure 21). Purification was particularly difficult with these compounds, as the starting material would easily crystallize under most conditions. Only by using the previously mentioned column techniques could pure product be isolated. In the case of 124, two attempts to use $p$-anisaldehyde as an electrophile failed.

Figure 21: Cyclization step yields for 1,4-oxathiin-5,5-dioxides for Heck targets

With the successful isolation of the majority of targeted oxathiins, the iron chloride and Heck reactions were attempted.
2.11 Iron(III) chloride reactions

Shown in Scheme 77, iron(III) chloride, was projected to couple the ring systems together; this however did not occur. It seemed that it was not able to oxidize the ring systems, and therefore coupling was not observed. Instead, breaking of the oxathiin ring system was the only observable product. This is likely due to the coordination of iron and oxygen allowing for α-deprotonation (to the sulfone) by the FeCl₃, presumably playing the role of both Lewis acid activator and Brønsted base. This leads to the breaking of the ring system, after which proton transfer delivers product 125.

When other oxathiin systems were subjected to these conditions, they also showed ring open products in good yield, with complete consumption of the starting material (Figure 22).
Figure 22: Results of Iron(III)chloride and 1,4-oxathiin-5,5-dioxides

2.12 Heck Cross-coupling Reactions

Since the failing of using other oxidation methods to couple the ring systems together to achieve a phenanthrene system, the commonly employed Heck reaction was utilized to couple the 5- and 6-position aryl ring systems together. Shown here in Scheme 78 is the reaction of 110 under standard Heck conditions, previously optimized by a Schwan group member in 2014.

From Scheme 78, it becomes apparent that the proposed oxathiin product of the Heck reaction was not observed. Heck conditions employ potassium carbonate as a base in organic solvent, which may present conditions too basic for the oxathiin to survive. Perhaps the oxathiin

![Scheme 78](image-url)
ring system breaks to allow for the steric of the system to be minimized slightly for the catalytic cycle to couple the 5,6-subsituted rings together. After the reaction, the only observed product is 1-phenyl-2-(phenanthrenyl-9-sulfonyl)-ethanone (131).

Scheme 79 depicts a possible mechanism, starting from the deprotonation of 110 eventually leading to the final product 131. This process occurs by a rearrangement, initialized by a deprotonation alpha to the sulfone. The resulting enolate, would then act as an electron sink as the ring opening process completes. The pKa of a proton α to both a carbonyl group and a sulfone is as low as 10.1 (DMSO), therefore deprotonation is very likely to allow the system to remain in its enolate form, especially under basic conditions. Allylic and benzylic sulfones have a pKa closer to 22 (DMSO), suggesting that the first step would be the rate limiting factor in this sequence. When the reaction has formed the ring opened product, it is likely that the Heck reaction then occurs, generating 131.

Previous experiments utilized this sequence (Scheme 79) to determine the optimized conditions for the Heck reactions. During this time, 131 was also the major product; however a second experiment was run to ensure that the ring open product was formed before the Heck
reaction took place. This was done by repeating the reaction, but monitoring the reaction every 20 minutes by TLC, and at the first appearance of 131, the reaction was halted and an NMR was taken of the mixture. The sample mainly showed the appearance of starting material 110, with only modest quantities of 131, and potential evidence of a ring-open intermediate; this contained iodine peaks and therefore was not the originally anticipated Heck product. This data suggested that such reactions would likely undergo a ring opening step prior to reacting with the palladium system to undergo heterocyclic coupling. This data supports the conclusion that 110a (Scheme 79) is much less sterically hindered compared to starting material 110. In this form, free rotation can occur, allowing the Heck system to react much more easily. The starting material however has a rigid conformation, placing the iodophenyl and phenyl systems trans to each other, yet both in tightly packed adjacent equatorial positions on the ring. This makes the Heck reaction difficult to carry out, as the energy barrier is likely very high, having the ring systems pointed up and down from the plane of the oxathiin ring. By opening the ring, this barrier is lessened, and therefore the Heck reaction can proceed.

With this in mind, we proceeded to perform the Heck reaction on oxathiin 121 (Scheme 80). This however did not provide an NMR with characteristic peaks, which we would attribute to the ring opened product, but observed 132 instead. Upon purification on acidic silica gel, degradation of the oxathiin ring system occurred, producing the predicted ring open product 133.

![Scheme 80]

96
It seems that the thiophene system produces a more reactive candidate for Heck coupling than the previously tested derivative. This means that there is not necessarily a steric barrier that must be crossed before the reaction can proceed, as exhaustively shown by a previous group member.  

The Heck coupled reaction of 123 did not produce the expected phenanthrene product. Articulated in Scheme 81, the starting material for this reaction bears an electron withdrawing substituent at the para position, lowering overall reactivity. It is likely, that under basic conditions, the ring was opened by the carbonate, before the 5-6-position rings could couple. This caused the enolate intermediate, which was able to rotate, and bring the 2-position phenyl ring into close enough proximity to react with the Heck system, producing a 5-membered ring system 134. Purification of this compound was an issue; however, this was the only product of the reaction. This structural assignment is supported through the constant presence of the distinctive ortho-meta peaks found in the NMR, supporting an unaccosted nitro ring system.

![Scheme 81](image_url)

The coupling of 122 was attempted twice with no observed product formation (Scheme 82). Given the difference in features that each product has articulated, this system should have
little problem acting like the first presented system. However, isolation of the 1,4-oxathiin system was difficult, and unsuccessful.

![Scheme 82](image)

As seen from the results, some starting materials are ring-opened before a Heck reaction can occur. Future investigations could pursue weaker bases, as it appears that some starting materials are able to survive these basic conditions. Additionally, some reactions have been successful in base free conditions, taking place in molten tetrabutylammonium bromide. It has been shown that a successful ring coupling can be achieved in electron poor ring systems. Therefore with minimal modifications, 1,4-oxathiin systems are likely able to be coupled without the formation of ring open products, producing the phenanthrene products.
One of the most commonly studied reactions in organic synthesis, the Heck reaction undergoes an anionic catalytic cycle. The phosphine reduces the pd\textsuperscript{II} to pd\textsuperscript{0}.\textsuperscript{96-98} This is the first step of the catalytic cycle, shown in Scheme 83.\textsuperscript{99} This reduced palladium species (Pd\textsuperscript{0}) generated \textit{in situ} is anionic, able to then undergo an oxidative addition with aryl halides through the involvement of a short lived anionic pentacoordinate arylpalladium(II) complex. The result of which is the extrusion of the halide, to produce ArPd(OAc)(PPh\textsubscript{3})\textsubscript{2}, which is involved in an equilibrium with the cationic complex. Subsequent hydride transfer leads to the release of the oxidized catalyst, and the coupled cyclic product.\textsuperscript{99,100}

However it is interesting to note that the addition of acetate ions makes the Heck reaction occur without the addition of base.\textsuperscript{99} This does not lead to an increase in formation of product.
however, but works to liberate sites of coordination on the palladium catalyst. Shown in Scheme 84, a phosphine can transfer to the acetate, allowing for coordination of a potential pi system.

Additionally, should phosphine leave the palladium, due to the potential bidentate character of acetate, it can protect that site of coordination (Scheme 85).

These are some modest accommodations that can be made to try to make a less basic system allow for a phenanthrene system, while keeping the oxathiin ring system unbroken.

2.2 Base catalyzed ring opening reactions of oxathiins
In 1966, Kulka and Von Schmeling published their discovery that 2,3-dihydro-5-carboxanilodo-6-methyl-1,4-oxathiin (76) and its sulfone analogue (77) showed remarkable fungicidal properties against leaf rust, bean rust, and loose smut of barley,\(^6^3\) sparking tremendous interest in the agrochemical sector.

Over the next several decades these compounds would be adapted into a broad family, tapered for specific properties inspiring a plethora of new fungicides.\(^6^2\) Von Schmeling and co-workers produced several compounds, which managed to spur additional interest into this field through functionalization of the 5- and 6-positions of the ring system, deviating from the Guelph based 1966 patent. In 1975, Uniroyal Inc., published a patent for a series of much more potent fungicides, and moreover their industrial production.\(^7^5\) From this, these compounds became accessible and inexpensive to procure; while their fungicidal properties made their exploration of great interest to the international community. This allowed for the facile study of these systems, as cheap materials were easily procured. One of the most well studied compounds in this family is 76, marketed as ‘Carboxin™’ or ‘Vitavax™’(country dependent), both for its effects in biological systems and for its chemical properties as a reagent.

In 1986, Goehmann and co-workers investigated the deprotonation of the oxathiin ring system of Carboxin™ and subsequent nucleophilic addition (Scheme 86).\(^8^1\)
Investigations proved the applicability of the ring opened system to act as a Michael acceptor, given the proper conditions. As such, these systems could undergo a reaction with a variety of nucleophiles, providing a gateway to a large array of new compounds. During their work, they theorized that deprotonation would occur at the 5-position of the oxathiin ring. The deprotonated form then succumbs to an irreversible ring opening. Through a series of subsequent proton transfers, the vinyl product is formed after an acid quench. Reaction intermediates are stabilized through the presence of a counterion, which coordinates with the sulfone. An *in situ* enol formation leads to the creation of a 6-membered ring system. Synthesis with these vinyl systems was then further probed through Michael additions, forming a series of novel compounds; in some cases, loss of the amide functionality was witnessed.\textsuperscript{81}

Since their initial discovery, several new methods for the generation of these compounds have been published, allowing for many newly described substances to be produced. One such method published by the Schwan group in 2013, granted facile generation of 2,5,6-triphenyl-5,6-dihydro-1,4-oxathiin-5,5-dioxide (107). This tri-aryl system was heavily stabilized compared to many previously investigated systems,\textsuperscript{64} and thus base catalyzed ring opening reactions were
showed great promise for an ideal reaction pathway to study. These systems however diverge from the previously illustrated examples, in that they are much more sterically hindered and lack the amide functionality of Carboxin™ (76). Previous studies in the Schwan group found that the ring opening could be problematic during the preparation of these oxathiins. However, since the heterocycles were available, we sought to probe their ring opening chemistry. Moreover, the structure of the actual product of the ring opening had not been firmly established.

As shown in Scheme 87, it is likely that anion b, shifts charge towards the oxygen, this irreversibly opens the ring structure, producing enolate c. Similar to Scheme 86, enol c possesses the ability to form stabilized 6-membered rings, wherein the alkali metal is captured between the sulfonyl group and the enolate. The trans stereochemical outcome is shown in 136 (Scheme 87) (sulfone bears priority). However, our experiments demonstrated that this was not the lone observed outcome, and the chemistry is subject to a variety of conditions. Therefore, this scheme is not meant to definitively show the stereochemistry of d, which can be induced to be cis or trans.

While performing this research previously, the Schwan group developed a method which employed alkynoic sulfone ak (Scheme 104) and butyl lithium to incorporate benzaldehyde in the formation of oxathiin 107. During this reaction, large amounts of a byproduct was found. At the time, it was postulated that deprotonation of the ring system produced the trans product (136). But because of the inherent difficulty that these compounds present in their purification, ultimate identification of the byproduct remained elusive.
Although comparatively, this by-product was not found in the synthesis of any of the oxathiins attempted in the current thesis, the base catalyzed ring opening reactions were attempted to recreate product 136. Through tempering temperature and counterion, the reaction of oxathiin 107 was mapped (Scheme 88). Previous isolation of pure 107, led to x-ray crystal data to be taken of the compound. This synthetic method produces the trans oxathiin (107) exclusively, and thus only the trans oxathiin was studied for all experimental procedures. It was also found that interchanging the reaction parameters would lead to the production of both the trans and the cis product 136 and 126 respectively.

Contrasting the 2,5,6-triphenyl system, compound 112 would be used in an additional reaction series, to show the effect of an electron withdrawing group on the proximal aryl system. This was done through the substitution of a 6-$p$-nitrophenyl group (Scheme 89).
The first reaction conditions to be assessed were performed in THF at -35 °C; reaction conditions similar to the synthesis of oxathiin 107. As denoted in Scheme 90, two separate products were formed; both trans and cis isomers, 136 and 126. Interestingly, at this temperature there was no reaction of LiOMe and the oxathiin ring system. Reaction of 1M NaOH solution in MeOH with 107 produced 90% cis product to 10% trans product. At this temperature, 90% consumption of the starting material was observed by NMR; the reaction led to a yield of 73%. The assignment of relative double bond geometries had not yet been established when these experiments were performed (but are nevertheless presented); the assignments were eventually set through NMR studies (vide infra).

<table>
<thead>
<tr>
<th>Base</th>
<th>trans</th>
<th>cis</th>
<th>Isolated yield</th>
<th>Consumption of starting material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOMe/MeOH (1M)</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
<td>NaOH (1M in MeOH)</td>
<td>10%</td>
<td>90%</td>
<td>73%</td>
<td>90%</td>
</tr>
<tr>
<td>KOtBu</td>
<td>22%</td>
<td>78%</td>
<td>67%</td>
<td>68%</td>
</tr>
</tbody>
</table>

* by NMR

Scheme 90
A larger alkali metal, likely less able to form a six-membered ring stabilized through coordination with a sulfone oxygen and an in situ formed enolate, (as previously shown in Scheme 86) prompts an increase in trans product formation. Potassium 'butoxide however did have a decrease in yield shown in the table of Scheme 91 to be 67%.

The next avenue of pursuit was to increase the consumption of starting material through allowing the reaction to reach room temperature after 3 hours at -35 °C. The table in Scheme 92 illustrates a sharp increase in yield for LiOMe, (82%), however the major product found is the cis product (126).

![Scheme 92](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>trans</th>
<th>cis</th>
<th>Isolated yield</th>
<th>Consumption of starting material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOMe/MeOH (1M)</td>
<td>18%</td>
<td>82%</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>NaOH (1M in MeOH)</td>
<td>8%</td>
<td>92%</td>
<td>75%</td>
<td>94%</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>12%</td>
<td>88%</td>
<td>87%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*by NMR

During initial attempts to produce 107, and establish an optimized protocol, large amounts of byproduct were found. It was postulated that the byproduct was the ring-open product, 126. However, in these trials, both isomers were produced (Scheme 92). The reaction of NaOH with 107 produced similar results seen previously in the table from Scheme 91. It can be noted that the reaction occurs quickly, when allowed to reach room temperature (in the case of LiOMe), however the change in temperature seems to have little effect on the overall stereochemical ratio. Potassium 'butoxide however reacts with 107 to increase the consumption of starting material to 100%, but
decrease the trans/cis ratio from 22/78 previously to 12/88. Since allowing this reaction to achieve room temperature produced a change in the stereochemical outcome of the reaction, it is likely that the ring opening reaction is slower than the reaction with NaOH. It can however be realized that the increase in temperature has dramatically elevated the consumption of starting material by NMR and isolated product yields.

The final reaction series to be investigated utilizing oxathiin 107 occurred at room temperature. There is no change with lithium methoxide, reinforcing that the reaction only occurs when the temperature reaches room temperature.

![Scheme 93](image)

<table>
<thead>
<tr>
<th>Base</th>
<th>trans</th>
<th>cis</th>
<th>Isolated yield</th>
<th>Consumption of starting material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOMe/MeOH (1M)</td>
<td>18%</td>
<td>82%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>NaOH (1M in MeOH)</td>
<td>8%</td>
<td>92%</td>
<td>76%</td>
<td>95%</td>
</tr>
<tr>
<td>KO'Bu</td>
<td>25%</td>
<td>75%</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>KOH (1M in MeOH)</td>
<td>7%</td>
<td>93%</td>
<td>81%</td>
<td>96%</td>
</tr>
</tbody>
</table>

* by NMR

Scheme 93

In the case of sodium hydroxide, there was no change witnessed; articulating that the reaction outcome is stable with minimal cooling. There is however a shift in ratio for the reaction of potassium t-butoxide at room temperature, compared with 3 hours chilling at -35 °C, then 21 hours at room temperature. The previous table in Scheme 92 shows a ratio of 12/88, however, when performed at room temperature for the full 24 hours, an increase of trans (136) to 25/75 was observed (Scheme 93). A final alkali base tested was KOH, which illustrated an even stronger affinity for the production of the cis product over other previously tested bases. The data shows
that the cis product is formed is preferred over the trans product, in all cases. Varying temperature has some effect on this, however no reversal in trend was achieved; in that the trans product was never found to be the major isomer regardless of base or temperature used. It is likely that under the reaction conditions the kinetic product is the cis product.

As previously stated, to assess the electron withdrawing effects of a p-nitro functionality on the aryl system at the 6-position, Scheme 93 illustrates 112 undergoing deprotonation to produce a mixture of trans/cis isomers 137/129 with a series of different alkali bases. In most cases 100% of starting material was consumed, while reaction temperatures were kept at -35 °C over 24 hours. It is logical that the electron withdrawing group makes the system more prone to ring opening than 107, thus the consumption of starting material is increased even at cold temperatures. The cis isomer was the major product of LiOMe, NaOH, and KO\textsubscript{t}Bu. Interestingly, KOH provided the first example of a reversal of the previous trend, wherein the trans product was favoured. A speculative explanation for the contrasting outcomes may be based on solvation of the counterion.

<table>
<thead>
<tr>
<th>Base</th>
<th>trans</th>
<th>cis</th>
<th>Isolated yield</th>
<th>Consumption of starting material*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiOMe/MeOH (1M)</td>
<td>8%</td>
<td>92%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>NaOH (1M in MeOH)</td>
<td>16%</td>
<td>84%</td>
<td>81%</td>
<td>91%</td>
</tr>
<tr>
<td>KO\textsubscript{t}Bu</td>
<td>13%</td>
<td>87%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>KOH (1M in MeOH)</td>
<td>58%</td>
<td>42%</td>
<td>89%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* by NMR

Scheme 94
near the α-sulfonyl anion. A closely affiliated counterion probably has a defined pathway for ring opening, and typically provides the cis product. If the counterion is larger and is sequestered away from the anion, new pathways for opening may become possible, and may lead to an increased preponderance of the trans isomer. Since starting materials were nearly all consumed, additional trials were not attempted with oxathiin 112.

To evaluate what effect of the solvent on the reaction, oxathiin 107 was reacted with 1.2 equivalents of NaOH in methanol (Scheme 95). This increase in polarity led to a change in the trans/cis ratio from 8/92 (Scheme 93) to 40/60. This large change could be due to increased solvation of the counterion as discussed above.

![Scheme 95](image)

At the conclusion of these reactions, it became necessary to separate or distinguish the isomers. As shown in Figure 23, the $^1$H-NMR of the mixture is differentiated by the ratio of peaks at 4.36 ppm and 4.45 ppm. These shifts represent the CH$_2$ protons on the cis and trans products, respectively. Until this point however, there was no direct evidence permitting the ultimate identification of which isomer was cis or trans. Though various solvents for column chromatography were attempted, these compounds could not be separated.
Crystallization, column chromatography, and trituration failed as a means to purify or separate the isomers; thus reacting the compounds, through chemical separation via isomerization was undertaken. The isolation of a single isomer would suffice for the elucidation of stereochemistry of both isomers, as that single isomer’s peaks could be subtracted from that of the mixture.
Our first attempt included the employment of diisopropylamine as a base (Scheme 96). The objective was aimed to identify if the secondary amine possessed the ability to open the ring system, allowing any unreacted starting material to be consumed. This reagent had the benefit of being able to be removed under vacuo, meaning no product loss in a work-up. Unfortunately, the reaction failed, demanding a broader search for an effective base.

All bases used for the base catalyzed ring opening reactions were alkali bases. Going forward, an organobase would be ideal for isomerization, as this would forbid any metal stabilizing coordination from occurring. This normally limits the family to amines, ‘capable of abstracting a proton to produce a carbanion species’.\textsuperscript{102} It is known that incorporation of an imine moiety to an α-carbon of amines increases the general basicity of a species.\textsuperscript{102} When discussing these organobases, the fundamental pK\textsubscript{b} can be related to the number of substituted nitrogens at the same carbon atom; thus amidines with two nitrogen possess good basicity and guanidines with three show the strongest Brønsted basicity among these amine derivatives.\textsuperscript{103} According to Ishikawa, the general strength of guanidine is comparable to the hydroxyl ion (OH). This can be rationalized through the highly effective conjugated system, able to stabilize itself after protonation has occurred under reversible reaction conditions. Fundamentally, these canonical forms, especially isoelectronic forms, can be established, which lends to this exceptional stability of these systems as shown for an amidine (Scheme 97). Choosing an organobase which possessed similar basicity to OH might lead to a better outcome.
As diisopropylamine failed, it is possible that sterically, this amine was unable to abstract a proton, inhibiting the reaction from proceeding. Additionally, the ability of this base to stabilize a charge was limited through lack of conjugation, thus amidine 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was utilized. Although these compounds possess similar pK\(_a\) for their conjugate acids (Et\(_2\)NH = 11.05, DBU = 11.38 in MeCN), under basic conditions in organic nonprotic solvent their pK\(_a\) are dramatically dissimilar. DBU, however is characterized by an intrinsic ability to stabilize charge, a trait not shared by diisopropylamine\(^{102}\). Therefore it was projected that an amidine could be successful for the isomerization. This particular amidine is particularly strong due to ring strain; thus the pK\(_a\) rivals that of simple guanidine systems\(^{102}\). This choice of base would therefore mimic the strength of \(\cdot\)OH however be able to stabilize a formal charge, allowing additional chemistry to occur.

![Scheme 98](image)

Compound 107 (Scheme 98), was subjected to two equivalents of DBU, where it was allowed to stir for 24 hours at room temperature. At this point, a sample was removed and was tested by NMR to determine the isomeric ratio, while the remaining reaction pot was allowed to react for an additional 48 hours. Initial NMR results found 81% cis ring-opening product formation; however after prolonged exposure to DBU the ratio of trans/cis changed from ~1/5 to 1/3. Overall the reaction gave 96% yield. The reaction was also able to completely consume all
starting material, and thus it appeared that isomerization products had been identified, in addition to the anticipated ring opening.

Having established that reaction of 107 and DBU could produce a cis/trans mixture, and over time led to a single isomer, three equivalents of DBU were added to a previously produced mixture which was heated to 50 °C, and monitored for 72 hours (Scheme 99). Initially the mixture contained 3.3% oxathiin 5, 24% trans product, and 72.7% cis product. The first equivalent of DBU is expected to form the enolate, allowing the additional equivalents to proceed with the isomerization. As shown in Table 1, samples were taken every 24 hours and were tested for their isomeric ratio and consumption of oxathiin.

<table>
<thead>
<tr>
<th>Time</th>
<th>Trans product %</th>
<th>Cis product %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hr</td>
<td>24 %</td>
<td>72 %</td>
</tr>
<tr>
<td>24 hr</td>
<td>74 %</td>
<td>26 %</td>
</tr>
<tr>
<td>48 hr</td>
<td>97 %</td>
<td>3 %</td>
</tr>
<tr>
<td>72 hr</td>
<td>100 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Table 1: Time lapsed racemization of cis to trans compound over 72 hours

Complete consumption of oxathiin 107, as well as complete isomerization to the trans product occurred, after 72 hours. This provided a pure sample of one of the isomers for complete NMR
characterization. The only purification required was a water extraction to remove the amine base, making purification extremely fast and straightforward.

With this sample in hand, it was sent to the expertise of Dr. Sameer Al-Abdul-Wahid of the University of Guelph’s NMR centre. Because of the complexity of the aromatic section and lack of distinction among the various aryl and vinyl groups, the stereochemistry could not be assigned with $^{13}$C-, $^1$H-NMR, HSQC alone. Using 2D and 3D techniques, Dr. Al-Abdul-Wahid was able to assign, with reasonable certainty, all the peaks for the trans system and relate them to the mixtures. In doing so, he was able to conclude that the distinctive CH$_2$ peak at 4.37 ppm and the peak at 4.57 pm belong to the cis and trans product, respectively. With this knowledge in hand we can conclude that the cis product forms under kinetic conditions, and after isomerization DBU produces a pure trans product. Stemming from these assignments, preliminary computational calculations were done on the two isomers. It was concluded that the trans product is much more stable once formed (21.3 kcal/mol) in gas phase density functional theory (DFT) calculations. This means that through the reaction of the cis product (126) with DBU, a lower energy product is formed (trans, 136), likely due to hindered rotation. Under the harsher DBU treatment, the thermodynamic product is formed. Additionally, the original presumption (by previous group members), that the byproduct formed was the trans product, was false. From this work, it is likely that the ring open product formed in previous trials was the cis product, as it is the kinetically more favoured product of any given reaction tested.

The next step that was taken was to cool the reaction to -50 °C, and observe the effect on stereochemical outcome of the resulting products. Illustrated in Scheme 100, the reaction at -50 °C, was slow. However NMR results showed that over 24 hours the ratio of products was
approximately the same as would normally occur when the reaction was carried out at room temperature. With this trend established the reaction was halted, as the temperature had little overall effect on the initial production of the cis/trans product.

This supports the conclusion that there is a two-step reaction taking place: first the ring opens to a mixture of cis/trans products, mainly forming the kinetic product (cis, \textbf{126}), and then the trans isomer isomerizes. It also shows that the reaction was unable to be controlled to favour one isomer in the first step.

Displayed in Scheme 101, is a cis/trans mixture which was subjected to isomerization conditions. This showed 100% consumption of cis starting material, and gave 82\% yield. The small scale of the reactions trialed (50-250 mg) dictated that any product loss would have intense after effects. The reaction has however offered a remarkably facile method of isomerization, converting the cis to the trans product with complete conversion of both ring open, and ring closed starting materials with minimal purification required.
The final experiment conducted in this series was the isomerization of the analogous cis/trans products produced from the base catalyzed ring opening of oxathiin 112. As Scheme 102 articulates, this DBU mediated isomerization system is versatile, able to completely consume the cis starting material after 48 hours.

A proposed mechanism for how the general conversion of cis product to trans product would occur is given in Scheme 103. As previously noted, amidines (such as DBU), are able to delocalize charge, by sharing electron density through the pi systems. Other nitrogen bases, such as diisopropylamine, are unable to accommodate this charge density and are therefore not able to fulfill an isomerization mechanism.

The pK\textsubscript{a} of the α-protons to the sulfone is much lower than the pK\textsubscript{b} of DBU, therefore, 3 equivalents of DBU were used for the reaction. Addition of amidine DBU to the double bond of
the cis isomer creates an anionic intermediate that benefits from stabilization of the sulfone. During this state (140), free rotation is able to occur, permitting the formation of the trans product. It is likely that the trans isomer is also prone to a similar attack. Since these conditions are assumed to possess full reversibility, and proceed to eventually form only the trans product, the conclusion is that the trans isomer is the thermodynamically more stable product. Increasing the basicity and the overall unique superbase qualities possessed by DBU is due to its concave structure.\textsuperscript{102} Although it might appear flat, the molecule is actually bent, causing an increase in ring strain and therefore overall basicity of the base.\textsuperscript{104}

Isolated by Reed et al, such structures have been identified.\textsuperscript{104} Figure 24 illustrates a DBN-phosphine bond (related to DBU), and how these large ring systems are able to act nucleophilically to sterically hindered systems, giving optimism to the proposed mechanism. In the case of DBU, the 5-membered ring is planar. However, the 7-membered ring is strained, producing a slightly dome shape, and has been isolated in a similar configuration shown in Figure 24.

![Figure 24: X-ray structure of DBN-phosphine complex](image)

It is this strain that increases the basicity of this compound and allows the mechanism in Scheme 103 to be possible. The three aryl groups on 107 are a hindrance to attack from one side, but this
complexation allows for a higher energy intermediate to be created, discriminately producing the trans isomer.

This investigation towards the identity of the previously formed byproduct of past group member’s reactions, was identified as the kinetic product (cis, 126). The effect of temperature and counterion size was also mapped for two separate reactions under relatively non-polar conditions. These conditions mirrored those that formed the 1,4-oxathiin compounds, however this was extended as well. To finalize stereochemical outcomes and allow for the ultimate elucidation of the stereochemistry of products, an isomerization of products was achieved with the use of DBU. Although this study sheds some light on the role of the counterion in these reactions, additional study is required for the role of solvation of these systems. As probing the reaction in methanol hints, it is likely that a more polar solvent will disallow the counterion to participate in coordination with the enolate, resulting in a substantial change in stereochemical ratio.

2.3 Computational Calculations for the Base-Catalyzed Ring Opening of Oxathiins

To supplement our mechanistic understanding of the base catalyzed reactions of 2,5,6-triphenyl-5,6-dihydro-1,4-oxathiin 4,4-dioxide, computational studies were carried out to elucidate reaction energies and shed light on possible reaction pathways. DFT calculations where run on a series of molecules modeling the following gas phase experiment (Scheme 104):
As reflected in the stereochemistry of the starting material for the reaction shown (107), the trans diphenyl isomer was modeled first, followed by the sister compound, the cis oxathiin (142) (known hereafter as trans/cis oxathiin respectively). Experimentally, only the trans isomer is observed, and is therefore more applicable to the practical applications studied.

For comparative purposes, the cis oxathiin (142) was modeled under the same reaction conditions, to see if alternative mechanisms would lead to a versatile understanding of these pathways and the mechanistic elements which they employ (Scheme 105).

To gather all experimental data, B3LYP functional with the 6-31+G(d) basis set was utilized for all DFT calculations. Experimentally, it should be noted that when the trans oxathiin is subjected to anionic conditions it produces a mixture of both cis and trans product, however is dominated by the cis; generating a compound which has aryl groups trans (sulfone assumes priority). As noted previously, there is no evidence that the cis oxathiin is a corporal compound.

The initial calculation undertaken was to assess which oxathiin isomer was more stable. By arbitrarily setting the minimized structure of trans oxathiin, it was found comparatively that
the cis oxathiin was less stable by 5.2 kcal/mol (Figure 25). This suggests that there must be a higher activation barrier in the formation of this compound which forbids its formation in our synthesis, certainly under the circumstance where the two products arise from protonation of a common anionic intermediate (Scheme 104).

![Figure 25: Comparison of trans diphenyl oxathiin and cis diphenyl oxathiin](image)

From these compounds, minimized structures for the respective deprotonated, lithiated α-sulfonyl anion could be achieved. Setting the energy of the anionic form of trans oxathiin to zero serves as a relative point of reference for all future calculations involving lithiated entities. Thus, based on the anticipated reaction with LiOMe, optimized lithiated structures 143 and 150 were located (143: ΔE = 0 kcal/mol), and assumed to be produced from the reaction of trans oxathiin and cis oxathiin starting materials, respectively.

The energy pathways undertaken by the anions 143 and 150, to develop indentured stereochemistry of their respective products, are shown in Figure 26. Satisfactory transition states were located (suitable irc, one imaginary frequency) for the ring opening processes of each system. Similarly, suitable optimized ring opening products were obtained. Analysis will commence commentary on 143, 144, and 145 before undertaking the account of the reaction of cis oxathiin with LiOMe to lead eventually to 149'. From 143, the anion climbs to a transition state 144 then
falls to a stable anionic product 145. The structures and selected parameters are illustrated in Figure 27.

Figure 26: Energy diagram and respective energies for anions 145 and 149'

<table>
<thead>
<tr>
<th></th>
<th>ΔE (Kcal/mol)</th>
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<th>ΔE (Kcal/mol)</th>
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<tbody>
<tr>
<td>143</td>
<td>0</td>
<td>150</td>
<td>1.77</td>
</tr>
<tr>
<td>144</td>
<td>11.114</td>
<td>151</td>
<td>9.62</td>
</tr>
<tr>
<td>145</td>
<td>-40.742</td>
<td>149'</td>
<td>-36.55</td>
</tr>
</tbody>
</table>

Figure 27: Structures 143, 144, and 145 with corresponding energies and bond distances

ΔE = 0 kcal/mol
Li-Ar = 2.927 Å
Li-O = 3.970 Å
Li-OSR = 1.753 Å

ΔE = 11.1 kcal/mol
Li-Ar = 4.430 Å
Li-O = 2.041 Å
Li-OSR = 1.882 Å

ΔE = -40.7 kcal/mol
Li-Ar = 3.376 Å
Li-O = 1.767 Å
Li-OSR = 1.814 Å
When recognizing the distances between lithium and an aryl system, it is the distance between the exact centre of the aryl ring. This was done through providing a ‘ghost’ atom and measuring the distance from lithium to it; giving the most accurate representation of lithium coordination and any given aryl system. Li-O distances are presented as the distances for the oxygen which would be participating in the enolate formation.

A bond distance of 2.927Å, clearly demonstrated in structure 143, articulates that the lithiated sulfone at this early stage is only able to show slight coordination to the distal aryl system. Additionally, with the oxathiin ring still intact, and a bond distance of 3.970 Å, coordination between the lithium and the 1-oxygen is very weak. However, as the molecule goes through transition state 144, we can see that a nominal input of energy into the system (11.1 kcal/mol). With this transformation, the system has cleaved its ring, forming the enolate whose oxygen is allied with the lithium (Li-O 2.041 Å). Furthermore, there is an increase in the distance from the aryl system, indicating no coordination from this moiety. A slight shift in distance of the lithium away from the sulfone oxygen is witnessed, likely to attempt better coordinate with the enolate. It is likely that the carbanionic species 143 requires lithium nearby, complexing to a sulfone oxygen, but the C-Li interaction is lost in the opening of the ring. Rapid change from 143 to 144 has led to an alteration in the stereochemistry of the aryl systems. From this point, it is clear that the final stereochemical outcome will be trans; meaning that the formation of the enolate, possibly through mild coordination with the lithium, has twisted the rings cis to each other. As the pathway concludes and reaches stable anion 145, there is an implicit release in energy of -40.7 kcal/mol. This anionic state boasts a six-membered ring, formed through the coordination of lithium and the enolate, and is articulated by a Li-O bond distance of 1.767 Å. Additionally, a minute shift away from the sulfone oxygen is seen by the lithium, to best coordinate with the oxygen of the enolate.
Unfortunately, this pathway concluded in the production of a trans product (cis diphenyl) and is not a match for the major product in the experimental trials. Thus, an additional search was performed to seek an alternative pathway, one that accounts for the cis product.

The second pathway from Figure 26, involves the deprotonation of cis oxathiin to produce anion 150, transition state 151, and final stable anionic product 149’ (Vide Infra). In this model, there is only one product. This pathway conceptually follows the same flow as the previously modeled reaction; where the states are shown in detail in Figure 28. As seen in 150, there seems to be weak or no coordination illustrated with a bond distance of 3.156 Å. For rational comparative purposes, the aryl group on the 6-position has been highlighted (called Ar’); as it is not the same aryl group that displays coordination in the alternate system. It should be noted that there is only weak coordination with this distal system (Li-Ar’ = 3.156 Å). From here, the system goes through transition state 151 at a cost of 9.6 kcal/mol, which is able to maintain this level of coordination to the distal aryl group. Additionally, the ring has broken, leading the enolate to decrease the oxygen’s distance from 3.767 Å to 2.393 Å; illustrating a shift towards forming the previously noted six-membered ring. The allure of lithium-enolate coordination seems to be the driving force which twists the molecule, directing the stereochemical outcome of the reaction in the process, producing the cis product (trans diphenyl product). It can be noted that the distal aryl system seems to have maintained its position throughout the entire pathway, due to this slight coordination with lithium.

The final phase of the reaction pathway is 149’, where the lithium ion has been incorporated into the familiar enolate lithium coordinated six-membered ring system. This stable anion has an energy of -36.6 kcal/mol, and exhibits a familiar Li-O bond distance of 1.782 Å. The entire pathway has kept the distal aryl system at approximately the same distance. This is the major
product which was found experimentally; however it is produced from the cis oxathiin, and therefore represents an allowed but not observed pathway.

Figure 28: Structures 150, 151, and 149’ with respective energies and bond distances

In a separate comparison, an isolated study to discover the relative stability of the final products was done. Having completed various pathways towards the final enolates, it was intriguing to see how the final products 136 and 126 compare in relative energies to the products produced upon the addition of acid to the final enolate structures. Shown in Figure 29, the trans product (136) is set to zero energy. By comparing the minimized structures alone, we can assess that the cis product is less stable than the trans, by 21.3 kcal/mol. It is interesting to note that the cis product is the product observed experimentally, and thus the energetic barriers which stand before the compounds, dictates which compound forms, rather than simply their stability.
Previously mentioned, the first pathway expressed employed the correct starting material and anion, however finished with the minimally observed trans product. Although viable, this prompted us to find a more energetically feasible pathway using starting anion 143, in hopes of achieving the alternative stereochemical product.

![Diagram](Image)

**Figure 29: A comparison of trans and cis diphenyl products**

As shown in Figure 30, the newly identified pathway has been laid over the pre-discussed pathway; both using lithiated trans oxathiin as the neutral starting material. It can immediately be noted that the pathway involves more entities than the previously investigated models; lithiated starting material 143 is able to go through transition state 146 then reach energy well 147, before a secondary transition state 148 leads to a final anionic product 149. From this diagram, a mechanistic option is presented to illustrate why the cis product dominates a given reaction; the energy barriers are substantially lower, allowing a facile reaction to take place.
As previously mentioned, 143 has only exhibited weak coordination between the lithium and the aryl system, as articulated with a bond distance of 2.927 Å. From the previously explored models we can compare distances of Li-O bonds and distinguish that it is unlikely that the oxygen of the ring system is coordinating with the lithium at this point. From here, 143 can go through the higher energy pathway previously discussed with an input of 11.1 kcal/mol, however an alternative, lower energy avenue leads to transition state 146. Here, a decrease in the bond distance between the lithium and the aryl system is observed, along with a widening of the distance between the lithium and the ring enolate oxygen. Overall, this system has become heavily dependent on the coordination between the proximal aryl system and the lithium, already coordinated to the oxygen of the sulfone, such as seen particularly strongly in 147 (Figure 31).
On arrival in the energy well, stable lithiated anion 147, is nearly identical to 146. They share similar energy values, Li-Ar bond distances, and Li-O bond distances. All that can be noted is that coordination of Li-Ar is slightly higher, which is exemplified by a minimal increase in stability. Passing through this pathway, the stereochemical outcome of the final product can be visualized as trans. The backbone of the molecule finds itself twisting, throughout the pathway, to accommodate the lithium atom coordination. It can be envisioned that the lithium atom has a profound effect on the overall stereochemical outcome. In transition state 148, the ring system breaks to form the sulfonyl enolate, however no coordination between the enolate and the lithium
is attempted. Instead the coordination between the aryl ring and the lithium atom is maintained heavily throughout 146 and 148. In the final product anion 149, coordination between the impending enolate oxygen and the lithium take place, forming the recognizable lithium bridged six-membered ring. Even still, the interaction with the aryl system is maintained to some degree, with a final bond distance of 2.779 Å. In this lower energy pathway, compared to the initially discussed, the product was cis (trans aryl); thus fulfilling our initial experimental outcomes more accurately. Initially, the Li-Ar bond distance is set at 2.927 Å in structure 143, throughout the series it changes dramatically to decrease its distance to 2.028 Å, as illustrated in 147. It can hardly be contended that coordination between the aryl and lithium systems is an integral part of how the stereochemistry is defined in these systems.

Experimentally, only a small percent of the product appears as the cis aryl product in THF (trans product 136). Products are dominated by the trans aryl product (cis product 126), which is supported by these gas phase calculations. Although the formation of the trans product is allowed, articulated through the first pathway proposed, its initial activation energy is almost four times that of the pathway leading to the cis product (Scheme 106).

![Scheme 106](image)

It should however be noted that these calculations are done in the gas phase, and additional parameters will be done in the future to explore the pathways in different solvent systems.
One striking discovery from the theoretical reactions of cis oxathiin was that $149'$ was the ‘correct’ product, that only varies from $149$ by a sigma bond rotation, supported by an overall energy difference of 0.640 kcal/mol. What is interesting about this is that $149$ and $149'$ exhibit different mechanisms of formation. One relies heavily on the coordination and the proximal aryl group, while the other shows a strong affiliation toward the enolate oxygen. Thus, although the same product was made, through the use of two separate starting materials/anions, two entirely unique mechanisms were identified in the formation of this product.

Later investigations with solvents such as THF, are to be carried out to see if they are in accord with the experimental results, already obtained. Additionally, it would be interesting in the future to see the contribution of sodium or potassium for these systems, especially when compared to lithium. Experimentally, our reactions were done in THF, however one reaction was tested in methanol, achieving nearly 40% trans product. We project that the polar solvent was able to limit the ability of the metal to coordinate with the aryl system and thus, produce a much larger amount of this product. Testing these reactions with different solvent models would help to shed light on these assumptions.

2.4 Conclusion and future work of 1,4-oxathiin-S,S-dioxides

Through the help of previous group members, the pathway for the synthesis of highly and various 1,4-oxathiin-S,S-dioxides were prepared. Building on these sturdy foundations, several novel compounds have been produced and identified. Additionally, their chemistry was explored through the Heck reaction and the iron(III) chloride reactions. The byproduct, once produced in large enough quantities, became a focal point of study through the base catalyzed ring opening
reactions. Supported by theoretical calculations, the byproduct has become an extremely intricate area of investigation, concluding with a method of isomerization.

In future, this work can further pursue the Heck reaction. As outlined in the section 2.3, variations can be carried out which would allow for the reaction to produce phenanthrene systems, in the absence of such highly basic conditions. Molten TBAB or addition of acetate could induce reaction conditions which would allow predicted Heck products. Furthermore, the use of FeCl\textsubscript{3} as a ring opening reagent should be investigated with a plethora of 1,4-oxathiin ring systems. It would be important to see how the mono-oxide derivatives react under the FeCl\textsubscript{3} conditions. To extend the understanding of the base catalyzed reactions, the alteration of solvent past a single reaction is required. Doing a series of reactions with different solvents, changing the polarity, would allow for a transparent understanding of THF’s role in the reaction. Future calculations could be carried out to involve solvation of the enolates with THF, as previous calculations were done in gas phase.
2.5 Experimental procedures for 1,4-oxathiin-SS-dioxides

2.51 General Synthetic Procedures

See general procedures for TA experimental section (pg 48)

2.52 Bromobenzyl Derivative Synthesis

- **p-methoxybenzyl bromide**<sup>105</sup> - (aa) - AIBN (495 mg, 2.76 mmol), N-bromosuccinimide (NBS)(23.7 g, 133 mmol), and 4-methylanisole (14.8 g, 121 mmol) were added to a three-neck flask fitted with a thermometer and water-cooled condenser, containing benzene (200 mL). The mixture was then heated slowly to achieve an internal temperature of 78 °C, inducing gas formation and a colour change. At this time, the flask was removed from the heat, for approximately 10 minutes, before being returned to the heating bath, and allowed to gently reflux for 3 hours. The reaction flask was cooled and 200 mL of ethyl acetate was added, and the organic layer was washed with 100 mL of water four times. The reaction extract was then dried over MgSO₄, and the solvent was removed under reduced pressure;<sup>106</sup> <sup>1</sup>H-NMR (400 MHz) δ: 7.00 (m, 4H) 7.00 (m, 4H), 4.39 (s, 2H), 3.72 (s, 3H).

- **2-iodobenzyl bromide**<sup>105</sup> - (ab) - 88% yield - A solution of 2-iodotoluene (55mmol, 1.0 eq.), NBS (55 mmol, 1 eq.), Br₂ (7.15 mmol, 0.13 eq.), AIBN (13.75 mmol, 0.25 eq.) in benzene (700 mL) was refluxed overnight; the resulting solid was filtered off. 200 mL of EtOAc was added, and the remaining purple/brown solution was then washed with aqueous thiosulfate solution to remove the colour, and then washed with brine to dry the organic layer. MgSO₄ was then used to dry the organic layer further before the solvent was removed under reduced pressure. WARNING!! The crystals can be recrystallized from pentane, however, they pose a huge safety risk as a VERY dangerous lachrymator and sensitizer. The crystals should be
handled with a face shield and in a fume hood at all times. The starting material shows a singlet at 
~2.3 ppm and the product at ~4.6 ppm; therefore there is little need to purify the product further, 
using the crude product in the next step is recommended. Spectral data consistent with Mohammad 

**2.53 General Method for the synthesis of Thiocyanates:¹⁰¹,¹⁰⁵**

A solution of the halogenated benzyl compound (1.0 eq.) was placed in a flask containing 
3 equivalents of KSCN in acetonitrile (20 mL/g). The reaction was allowed to stir at room 
temperature and was monitored by TLC, generally finishing in less than two hours. The solids 
were removed by gravity filtration. The solvent was removed by rotary evaporator, and the 
resulting residue was taken up in EtOAc. The organic layer was then extracted by water 3 times, 
and dried with brine and MgSO₄. Dry solvent was the removed under reduced pressure.

**Benzyl thiocyanate** - (ac) - 92% - $^1$H-NMR (400 MHz) $\delta$: 7.36 (5H, m), 4.15 (2H, s).

**2-Iodobenzyl thiocyanate** - (ad) - 95.9% - Spectral data consistent with M. Hossain’s 2012 Ph.D dissertation.

**4-Methoxybenzyl thiocyanate** - (ae) - 97% - Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**4-Nitrobenzyl thiocyanate** - (af) - 92% - Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.
2.54 General Method for Synthesis of Benzyl Alkynyl Sulfides\textsuperscript{101,105}

Under inert conditions (N\textsubscript{2}), a solution of phenyl acetylene (1.1eq) in dry THF (10 mL/1g of SM) was chilled to -78 °C and \textsuperscript{t}BuLi solution (1.1 eq; 1.6M in hexanes, Aldrich) was added dropwise. The reaction was allowed to stir for 2 hours to allow for anion formation. At this time, a solution of corresponding thiocyanate (1.0 eq) in THF (20mL/1g thiocyanate) was cannulated to the chilled anionic mixture, quenching the reaction. The entire reaction setup was then allowed to reach room temperature and was to stirred overnight, after which NH\textsubscript{4}Cl\textsubscript{(aq.)} was added. Addition of EtOAc occurred, and the organic layer was washed with water, brine, and dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure, and products were generally used without further purification.

**Benzyl 2-phenylethynyl sulfide** - (ag) - 92% - Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**2-Iodobenzyl 2-phenylethynyl sulfide** - (ah) -83% - Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**4-Methoxybenzyl 2-phenylethynyl sulfide** - (ai) - 96% – Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**4-Nitrobenzyl 2-phenylethynyl sulfide** - (aj) - (81%) – Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

2.55 General method for synthesis Benzyl Alkynyl Sulfones\textsuperscript{101,105}

In a large Erlenmeyer flask, \textit{m}-CPBA (assumed to be 72\%, 2.5 eq.) was dissolved in DCM (0.23 M, 25 mL/g), and the undissolved solids (benzoic acid) were filtered off. In a separate flask,
the sulfide was placed in DCM (0.15 M) at -78 °C. The m-CPBA was then cannulated into the chilled sulfide containing flask (addition funnel works well too); after which the cold bath was turned off. The reaction was allowed to stir overnight, then the solids was filtered off with gravity filtration. The flask was then placed into the fridge for an hour, where addition solids formed, and additional gravity filtration was carried out. The filtrate was then washed with aq. sodium carbonate (3x), then with water (3x), brine and dried over magnesium sulfate. The residue was concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel with hexanes/EtOAc and recrystallized from hexanes/EtOAc to yield pure sulfone.

**Benzyl 2-phenylethynyl sulfone** - (ak) - 98% yield; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**2-Iodobenzyl 2-phenylethynyl sulfone** - (al) - 97% yield; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**4-Methoxybenzyl 2-phenylethynyl sulfone** - (am) - 92%; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

**4-Nitrobenzyl 2-phenylethynyl sulfone** - (an) - 75% yield; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

### 2.56 General Method for Preparation of Oxathiin-S, S-Dioxides

Under dry, inert conditions starting sulfone (1.0 eq.) was dissolved in THF (0.05M, freshly distilled from a LiAlH₄ solvent still for this purpose), and chilled to -78 °C. *n*BuLi (1.6 M, 0.5 eq in hexanes), (in some cases 0.5 eq of LDA was used instead) was added and allowed to stir for 15 minutes to allow for anion formation. At this time, in a second flask, a solution of aldehyde (1.5
eq) in THF (1M) was cannulated into the chilled flask. The reaction was allowed to reach -35 °C and stirred for 6 hours, where upon it was stopped with the addition of NH₄Cl. The aqueous layer was then extracted with EtOAc and combined organic layers were washed with brine and dried further with the addition of MgSO₄. The solvent was removed through reduced pressure. Trituration with anhydrous ethyl ether can afford products, however an additional method of purification was to column the resulting residue, using a 1 mL MeOH, 149 mL DCM, 150 mL hexanes solvent system. This system worked to slowly move the starting materials through the column, crystallizing the pure product within the column. A flush with 10-30% MeOH affords pure product. This is especially useful when separating the iodinated compounds, which readily fall from solution.

2,5,6-triphenyl-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (107) - produced from the cyclization of benzyl alkynyl sulfone (ak) and benzaldehyde and was obtained as a white solid in 86% yield; Spectral data consistent with L. Ho’s thesis 2014 M.Sc. dissertation.

2,5-diphenyl-6-(p-nitro-phenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (112) - produced from the cyclization of benzyl alkynyl sulfone (ak) and p-nitro-benzaldehyde and was obtained as a white solid in 62% yield; mp = 146-148 °C; ¹H-NMR (400 MHz) δ: 8.11 (2H, d, J = 8.9Hz), 7.63 (2 H, m), 7.53 (2H, d, J= 8.8Hz), 7.43 (3H, m), 7.31 (5H, m), 6.47 (1H, s), 6.17 (1H, d, J= 11.5Hz), 4.91 (1H, d, J= 11.6Hz); ¹³C-NMR (100.6 MHz) δ: 159.16, 148.26, 141.63, 131.84, 131.51, 130.93, 129.86, 129.05, 128.98, 128.94, 126.29, 124.66, 123.93, 101.91, 67.76; FTIR (neat, cm⁻¹):
2,6-diphenyl-5-(3-chlorophenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (120) - produced from the cyclization of a (meta-chloro)-benzyl alkynyl sulfone provided by previous group members, and benzaldehyde; and was obtained as a white solid in (76%); Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

2,6-diphenyl-5-(2-iodophenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (110) - produced from the cyclization of benzyl alkynyl sulfone (al) and benzaldehyde using LDA and was obtained as a white solid in 27%; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

2-phenyl-5-(4-isopropyl-phenyl)-6-(2-iodophenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (122) - produced from the cyclization of benzyl alkynyl sulfone (al) and cuminaldehyde using LDA and was obtained as a white solid; (8.6% brsm) $^1$H-NMR (400 MHz) $\delta$: 7.77 (1H, m), 7.62 (2H, m), 7.48 (2H, m), 7.45 (3H, d, J= 1.3Hz), 7.29 (3H, m), 6.92 (1H, t, J= 7.0Hz), 6.45 (1H, s), 6.12 (1H, d, J= 11.2Hz), 5.63 (1H, d, J=11.2Hz), 2.82 (1H, sept, J= 6.8Hz), 1.17 (6H, d, J= 6.9Hz); A sample of sufficient purity for $^{13}$C NMR analysis was not obtained; ESI HRMS, calculated for [C$_{25}$H$_{23}$IO$_3$S+H]$^+$: 531.4257; found: 531.0670.

2-phenyl-6-(4-nitrophenyl)-5-(2-iodophenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (123) – produced from the cyclization of benzyl alkynyl sulfone (al) and p-nitro-benzaldehyde using LDA and was
obtained as a white solid in 27%; mp = 185-187 °C; $^1$H-NMR (400 MHz) δ: 8.14 (2H, d, J= 8.8Hz), 7.78 (1H, dd, J= 1.2Hz, 8.0Hz), 7.63 (3H, m), 7.57 (3H, m), 7.46 (2H, m), 7.33 (1H, m), 6.95 (1H, m), 6.51 (1H, s), 6.23 (1H, d, J= 11.3Hz), 5.63 (1H, d, J= 11.3Hz); $^{13}$C-NMR (100.6 MHz) δ: 159.21, 140.95, 140.73, 131.96, 131.93, 131.45, 131.27, 130.88, 129.20, 128.94, 128.64, 128.39, 126.38, 123.86, 104.46, 102.28, 82.66, 69.92; FTIR (neat, cm$^{-1}$): 3055, 2987, 2305, 1600, 1574, 1521, 1447, 1422, 1346, 1322, 1304, 1283, 1223, 1130, 1086, 896, 740; ESI HRMS, calculated for [C$_{22}$H$_{16}$INO$_{5}$S]+: 533.9967; found: 533.9857.

2-phenyl-5-(2-Iodophenyl)- 6-(2-thiofuranyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (121) - produced from the cyclization of benzyl alkynyl sulfone (al) and 2-thiophenecarboxaldehyde using LDA and was obtained as a white solid in 26%; mp = 163-165 °C; $^1$H-NMR (400 MHz) δ: 7.86 (1H, d, J= 8.0Hz), 7.68 (2H, d, J= 8.3Hz), 7.45 (6H, m), 7.06 (1H, d, J= 0.8Hz), 7.01 (1H, m), 6.88 (1H, m), 6.50 (1H, s), 6.48 (1H, d, J= 11.3Hz), 5.61 (1H, d, J= 11.3Hz); $^{13}$C-NMR (100.6 MHz) δ: 159.12, 140.41, 136.75, 131.64, 131.15, 130.84, 129.24, 128.81, 128.61, 128.15, 127.61, 126.84, 126.46, 104.67, 101.71, 78.92, 70.71; FTIR (neat, cm$^{-1}$): 3070, 2953, 2914, 1602, 1573, 1494, 1447, 1307, 1277, 1128, 1066, 706; ESI HRMS, calculated for [C$_{20}$H$_{15}$IO$_{3}$S$_{2}$+H]$^{+}$: 494.9586 found: 494.9586.

2,6-diphenyl-5-(4-methoxyphenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (117) - produced from the cyclization of benzyl alkynyl sulfone (am) and benzaldehyde and was obtained as a white solid in
was obtained as a red solid; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

2,6-diphenyl-5-(4-nitrophenyl)-5,6-dihydro-1,4-oxathiin-S,S-dioxide - (119) - produced from the cyclization of benzyl alkynyl sulfone (an) and benzaldehyde and was obtained as a white solid in 62%; Spectral data consistent with L. Ho’s 2014 M.Sc. dissertation.

2.57 Reaction of 1,4-oxathiin compounds with FeCl₃

To an oven dried flask, an oxathiin (1eq.) was placed with FeCl₃ (6eq.) and under nitrogen, the solids were dissolved in dry dichloromethane (0.1M). The reactions were monitored by TLC, and when the reaction was complete, the solvent was removed under reduced pressure. The residue was taken up in EtOAc and was washed 3 times with water, after which the organic layer was dried with MgSO₄. If needed, a column could be carried out using a EtOAc/hexanes system, but generally crude mixtures were sufficiently pure.

(139) Reaction of provided 2,5-phenyl-6-thiophene-1,4-oxathiin-S,S-dioxide, from a previous group member; 86% yield; ¹H-NMR (400 MHz) δ: 7.99 (2H, d, J= 7.2Hz), 7.87 (1H, s), 7.64 (3H, m, J= 8.6Hz), 7.56 (3H, m, J= 5.0Hz), 7.51 (2H, t, J= 7.9Hz), 7.30 (1H, d, J= 5.0Hz), 7.20 (1H, d, J= 2.9Hz), 6.96 (1H, m, J= 2.9Hz), 4.51 (2H, s); ¹³C-NMR (150 MHz) δ: 188.74, 136.25, 136.13, 134.99, 134.62, 134.57, 134.44, 134.41, 134.33, 131.77, 131.75, 130.38, 130.23, 129.76, 129.36, 128.89, 127.02, 126.90, 57.96, 30.06.

(126) produced from the reaction of 107 under FeCl₃ conditions, providing 100% consumption of SM, 67% yield; ¹H-NMR (600 MHz) δ: 7.25 (16, m), 4.38 (1H, s), 4.38 (2H, s); ¹³C-NMR (100.6 MHz) δ: 198.97, 188.54, 140.73, 139.02, 134.29, 133.92, 131.25, 130.79, 129.85, 129.29, 128.87, 128.70, 128.59, 128.51, 127.79,
57.74; FTIR (neat, cm\(^{-1}\)): 3059, 3028, 2929, 1681, 1596, 1449, 1276, 832, 754; FTIR (neat, cm\(^{-1}\)): 3057, 3025, 2999, 2854, 1681, 1596, 1579, 1492, 1447, 1318, 1275, 1208, 1142, 1125, 1075, 1030, 1000, 771, 698; ESI HRMS, calculated for \([C_{22}H_{18}O_3S+H]^+\) : 361.0893 found: 391.0989.

(130) From the reaction of \textbf{119} under FeCl\(_3\) giving 98\% yield; \(\text{\textsuperscript{1}H-NMR (600 MHz) \(\delta\): 8.23 (2H, d, \(J= 8.7\) Hz), 7.89 (2H, d, \(J= 7.5\)Hz), 7.76 (2H, d, \(J= 8.7\)Hz), 7.69 (1H, s), 7.57 (1H, t, \(J= 7.4\)Hz), 7.44 (2H, t, \(J= 7.7\)Hz), 7.24 (1H, t, \(J= 7.4\)Hz), 7.17 (2H, m), 6.95 (2H, d, \(J= 7.7\) Hz), 4.37 (2H, s); \(\text{\textsuperscript{13}C-NMR (100.6 MHz) \(\delta\): 188.46, 148.61, 142.80, 137.99, 136.11, 135.78, 134.64, 132.73, 131.73, 130.95, 130.71, 129.34, 128.99, 128.84, 124.39, 58.31, 29.7071; FTIR (neat, cm\(^{-1}\)): 3107, 3068, 2927, 2856, 1680, 1598, 1522, 1347, 1144, 731; ESI HRMS, calculated for \([C_{22}H_{17}NO_5S+H]^+\) : 408.1918 found: 408.0900.}

(127) From the reaction of \textbf{117} under FeCl\(_3\) giving 100\% consumption of SM and 68\% yield; \(\text{\textsuperscript{1}H-NMR (400 MHz) \(\delta\): 7.99 (1H, d, \(J= 7.6\)Hz), 7.86 (1H, d, \(J= 7.7\)Hz), 7.60 (1H, m), 7.49 (3H, t, \(J= 7.6\)Hz), 7.43 (2H, m), 7.33 (2H, t, \(J=7.6\)Hz), 7.11 (2H, d, \(J= 8.6\)Hz), 6.74 (2H, d, \(J= 8.6\)Hz), 3.76 (3H, s), 2.64 (2H, s); \(\text{\textsuperscript{13}C-NMR (100.6 MHz) \(\delta\): 198.23, 159.46, 143.48, 137.14, 136.68, 133.59, 133.13, 132.75, 131.31, 130.16, 130.00, 129.78, 129.25, 128.99, 128.59, 128.48, 128.33, 128.24, 127.78, 127.03, 114.18, 55.15, 26.64; FTIR (neat, cm\(^{-1}\)): 3060,3028, 2932, 2857, 1680, 1595, 1449, 1263, 1068, 754.}

(128) From the reaction of \textbf{120} under FeCl\(_3\) giving 100\% consumption of SM and 76\% yield; \(\text{\textsuperscript{1}H-NMR (300 MHz) \(\delta\): 7.97 (2H, m), 7.71 (1H,}
s), 7.65 (2H, m), 7.49 (5H, m), 7.31 (1H, m), 7.22 (2H, m), 7.07 (2H, d, J= 7.2Hz), 4.46 (2H, s);

$^1^3$C-NMR (75 MHz) δ: 188.46, 141.71, 136.72, 135.99, 135.28, 134.43, 132.78, 132.09, 131.15, 130.78, 130.69, 130.63, 130.39, 130.11, 130.08, 129.63, 129.31, 129.09, 128.93, 128.88, 128.67, 57.90; FTIR (neat, cm$^{-1}$): 3062, 2967, 2924, 1679, 1596, 1448, 1319, 1142, 738, 694; HRMS, calculated for [C$_{22}$H$_{17}$ClO$_3$S$^+$]: 397.0660 found: 397.0658.

(129) From the reaction of 112 under FeCl$_3$ giving 100% consumption of SM and 88% yield; $^1$H-NMR (300 MHz) δ: 8.15 (2H, d, J= 8.4Hz), 7.98 (2H, d, J= 8.4Hz), 7.89 (2H, d, J= 8.0Hz), 7.50 (3H, m), 7.32 (3H, m), 7.12 (2H, m), 4.36 (2H, s); $^1^3$C-NMR (100.6 MHz) δ: 197.81, 150.49, 138.21, 137.72, 135.49, 133.14, 130.97, 130.49, 130.24, 130.11, 129.47, 129.29, 129.15, 128.58, 128.32, 127.81, 127.24, 126.59, 124.14, 124.14, 123.85, 123.60, 26.62; FTIR (neat, cm$^{-1}$): 3120, 3069, 2924, 2852, 1676, 1662, 1603, 1526, 1347, 1205, 883; HRMS, calculated for [C$_{22}$H$_{17}$NO$_5$S$^+$]: 408.0900 found: 408.0918.

2.58 Heck reactions:

To a side arm flask, fitted with an argon line, and a greased condenser fresh Pd(OAc)$_2$ (0.037 mmol, 15 mol%), powdered PPh$_3$ (0.113 mmol, 0.5 eq.) and ground K$_2$CO$_3$ (0.736 mmol, 3eq.), were added. The system was purged under argon, and acetonitrile was added (5 mL, 0.037M). The mixture was brought to reflux for one hour to allow for the ligand to dissociate and the palladium catalyst to form. After this time, the red colour turned black, articulating the change. To the black flask, the iodinated oxathiin (100mg, 1eq.) was added, and the reaction was monitored by TLC. Argon was supplied constantly throughout the reaction, ensuring O$_2$ contamination never occurred (ground K$_2$CO$_3$ is very hygroscopic as well). Generally the reaction required 18 hours for completion. The solution was then pipetted onto a Hirsch funnel to remove the palladium and
inorganic salts, washing with acetonitrile if needed (working on this scale, this method is required). Reaction mixtures can be columned by column chromatography using either a 20% EtOAc/hexanes system or 3% MeOH 47% DCM 50% toluene mixture.

(131) Reaction of 110 under Heck conditions for 20% yield; $^1$H-NMR (400 MHz) δ: 8.81 (2H, m), 8.69(d, J = 8.2 Hz), 8.56 (1H, s), 7.97 (1H, dd, J = 1.4Hz, 8.0Hz), 7.81 (5H, m), 7.67 (1H, td, J = 1.1Hz, 8.0Hz), 7.52 (1H, tt, J = 1.2Hz, 7.4Hz), 7.37 (1H, tt, J = 1.1Hz, 7.6Hz), 4.94 (2H, s); $^{13}$C-NMR (100.6 MHz) δ: 187.82, 135.91, 134.73, 134.21, 132.84, 132.41, 131.33, 131.00, 130.55, 129.28, 129.01, 128.74, 128.31, 127.81, 127.73, 126.12, 124.61, 123.81, 122.88, 62.65. FTIR (neat, cm$^{-1}$): 3062, 2996, 2941, 1672, 1596, 1527, 1446, 1312, 1222, 1152, 1119, 1005, 824, 769, 722; HRMS, calculated for [C$_{22}$H$_{16}$O$_3$S+H]$^+$: 361.0893 found: 368.0889.

(134) Reaction of 123 under Heck conditions giving 68% consumption of SM and 9.5% isolated yield; $^1$H-NMR (400 MHz) δ: 8.13 (2H, d, J= 9.0Hz), 7.79 (2H, d, J= 9.0Hz), 7.69 (2H, m), 7.37 (3H, m), 7.21 (3H, m), 6.62 (1H, s), 6.45 (1H, s); $^{13}$C-NMR (100.6 MHz) δ: 156.63, 153.97, 147.43, 141.68, 135.51, 135.21, 134.04, 130.24, 130.00, 129.01, 128.77, 128.51, 128.11, 127.38, 127.28, 127.18, 126.08, 125.59, 123.80, 117.61, 114.39, 29.74; FTIR (neat, cm$^{-1}$): 3056, 2957, 2925, 2853, 1638, 1595, 1516, 1447, 1342, 1267, 1215, 1108, 1053, 908, 839, 754, 734, 694.

Reaction of 121 under Heck conditions for 79% consumption of SM by NMR, however after a column, 50% of the product yielded ring open product as well, not seen in the crude NMR. Thus, the yields are 36% (132) and 37% (133).
(132) $^1$H-NMR (400 MHz) $\delta$: 7.76 (1H, d, J= 7.0Hz), 7.64 (2H, m), 7.50 (2H, m), 7.42 (2H, m), 7.38 (2H,m), 7.28 (2H, m), 6.92 (1H, t, J= 3.4Hz), 6.46 (1H, s), 6.15 (1H, m), 5.70 (1H, m); $^{13}$C-NMR (150 MHz) $\delta$: 159.50, 140.29, 134.36, 133.42, 131.91, 131.56, 131.27, 131.11, 130.69, 129.67, 128.78, 128.67, 128.27, 128.06, 127.31, 126.44, 104.52, 101.70, 83.97, 70.11, 65.19; FTIR (neat, cm$^{-1}$): 3066, 2956, 2925, 2853, 1722, 1608, 1574, 1494, 1447, 1379, 1280, 1219, 1128, 1079, 1028, 909, 734; HRMS, calculated for [C$_{20}$H$_{14}$O$_{3}$S$_{2}$+H]$^+$: 367.0457 found: 367.0449.

(133) $^1$H-NMR (400 MHz) $\delta$: 8.88 (1H, m), 8.68 (1H, s), 8.46 (1H, m), 8.05 (1H, d, J= 5.4Hz), 7.90 (1H, d, J= 5.4Hz), 7.85 (2H, d, J= 8.2Hz), 7.54 (2H, t, J= 7.4Hz), 7.38 (3H, t, J= 7.8Hz), 4.95 (2H, s); $^{13}$C-NMR (150 MHz) $\delta$: 187.90, 140.91, 135.93, 134.72, 134.15, 132.10, 130.50, 129.93, 129.21, 129.16, 128.73, 128.70, 127.64, 127.59, 127.42, 126.06, 124.95, 124.62, 122.82, 122.29, 62.93, 29.76; FTIR (neat, cm$^{-1}$): 3066, 2925, 2854, 1680, 1596, 1579, 1507, 1448, 1360, 1320, 1274, 1192, 1165, 1139, 831, 770, 732; HRMS, calculated for [C$_{20}$H$_{14}$O$_{3}$S$_{2}$+H]$^+$: 367.0457 found: 367.0471.

2.59 General procedure for base catalyzed ring openings of oxathiins

Oxathiin (107 or 112) (1 eq., 0.41 mmol) was dissolved in dry THF (0.041 M, 10mL), after which one equivalent of base was added at -35 °C (monitored by TLC). All reactions were completed in 24 hours, whereupon EtOAc was added and the mixture was poured into NH$_4$Cl. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. Variations of this procedure are discussed in the ring opening chapter, where the temperature was changed. In these cases, reactions were chilled at -35 °C for 3 hours, then allowed to react at room temperature for the rest of the 24 hours. Some experiments
were done at room temperature. Bases used include: LiOMe/MeOH -1 M in MeOH stock solution, KO'Bu, NaOH (1 M in MeOH), KOH (1M in MeOH), NaOH (1M in MeOH).

(136) Through varying temperature and bases used, a mixture of cis/trans ring open products was produced, as discussed in the base catalyzed ring opening reactions chapter. The racemization of the mixture was then carried out. One equivalent (0.37 mmol, of cis/trans products (or oxathiin) were placed in dry THF (0.041 M), and DBU (3 eq., 1.11 mmol) was then added. The reaction was then heated to 50 °C, and monitored for 72 hours. The reaction was then taken up in 15 mL of EtOAc, and the organic layer was washed with water 3 times to remove the amidine. The organic layer was then washed with brine and dried over magnesium sulfate. Volatiles were then removed under reduced pressure. (100% by nmr, 82% yield) Trans only: $^1$H-NMR (400 MHz) δ: 4.44 (2H, s), 7.05 (2H, d, J= 7.5Hz), 7.16 (2H, t, J= 7.6 Hz), 7.25 (1H, t, J= 6.1Hz), 7.47 (5H, m), 7.60 (3H, t, J= 6.7Hz), 7.69 (1H, s), 7.93 (2H, d, J= 7.7Hz). $^{13}$C NMR (150.6 MHz, CDCl3): δ 188.54, 140.73, 138.29, 136.11, 134.32, 132.52, 131.25, 130.95, 130.80, 130.32, 129.86, 129.47, 129.30, 128.89, 128.57, 128.52, 57.74; FTIR (neat, cm$^{-1}$): 3052, 2924, 2853, 1673, 1631, 1594, 1489, 1447, 1408, 1313, 1275, 1212, 1182, 1182, 1133, 822, 700; Trans only ESI HRMS, calculated for [C$_{22}$H$_{18}$O$_3$S+H]$^+$: 363.1037 found: 363.1049; To elucidate the stereochemistry of the cis/trans isomers Dr. Sameer Al-Abdul-Wahid of the University of Guelph’s NMR centre used the following methods: $^1$H-NMR, 1D-NOESY $^{13}$C-NMR, COSY, NOESY, NOE, HSQC, HMBC, and 3D-NMR techniques to quantify the stereochemistry as trans.
(126) refer to page 135; a mixture of isomers (cis/trans) (92% cis product) was measured: ESI HRMS, calculated for \([C_{22}H_{18}O_3S+H]^+\) : 363.1050 found: 363.1049.

(137) Racemization procedure: Oxathiin mixture cis/trans/ring closed (1 eq., 0.28 mmol) was placed in dry THF (0.04M) under inert conditions, and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was then added (2 eq., 0.569 mmol). The reaction was then heated to 50 °C and allowed to stir for 72 hours. The reaction was quenched with the addition of EtOAc, and the organic layer was washed with water 3 times to remove the amine. The organic layer was separated, washed with brine and dried over magnesium sulfate. Volatiles were then removed under reduced pressure. \(^1\)H-NMR (400 MHz) \(\delta\): 8.04 (2H, d, J= 8.9Hz), 7.95 (2H, m), 7.76 (1H, s), 7.65 (1H, m), 7.59 (2H, m), 7.53 (1H, m), 7.50 (4H, m), 7.23 (2H, dd, J= 0.5Hz, 9.0Hz), 4.47 (2H, s); \(^{13}\)C NMR (150.6 MHz, CDCl3): \(\delta\) 188.45, 148.08, 142.44, 138.92, 137.67, 135.88, 135.07, 134.55, 131.20, 131.11, 130.92, 130.48, 130.13, 129.89, 129.80, 129.71, 129.18, 128.99, 128.49, 127.08, 123.62, 57.46; FTIR (neat, cm\(^{-1}\))): 3059, 3007, 2925, 2854, 1681, 1596, 1519, 1491, 1447, 1403, 1346, 1322, 1277, 1143, 883, 699; Trans only: ESI HRMS, calculated for \([C_{22}H_{17}NO_5S+H]^+\) : 408.0893 found: 408.0917

(129) See page 137 for spectra data. Mixtures of the isomers (92% cis) ESI HRMS, calculated for \([C_{22}H_{17}NO_5S+H]^+\) : 408.0893 found: 408.0900; Cis 92% mixture FTIR (neat, cm\(^{-1}\)): 3105, 3066, 2998, 2925, 2853, 1681, 1596, 1519, 1491, 1447, 1403, 1346, 1322, 1277, 1143, 883, 699.
2.6 References


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