Shedding Light on Phytochemical Diversity: Photochromism of chromenes isolated from *Piper kelleyi*

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Abstract

The following chapters are focused on understanding the photochromic behavior of naturally occurring chromenes and its role in the biosynthesis of a variety of natural product architectures. Ultimately, chromenes and ortho-quinonemethide derived natural products will be used to understand their role in anti-herbivore activity by exploring the molecular mechanism of photoxicity of chromenes and their synergistic activity with co-occurring natural products. Generation of natural ortho-quinonemethides in this manner for organic synthesis has never been explored before, nor has the role of this mode of reactivity in the composition of plant phytochemical diversity been established. Chapter 2 will establish the nature of the photochemical behavior of a common naturally occurring structural motif, which could be a light activated pharmacophore that could be responsible for its potent toxicity to herbivorous insects and perhaps the diversification of associated insects. This work shows a rapid means to access a large array of natural product scaffolds for the generation of libraries for high throughput screening. Moreover, the results from this study will shed light on the origins of nature’s method of generating natural products diversity and are likely to inspire new reaction discovery. The following work has resulted in the synthesis of a number of natural products, providing material for their full biological investigation. This material will be used to understand the synergistic action of these biosynthetically related and co-occurring natural products mixtures, which could result in a broad framework for discoveries in the health and agricultural sciences.

The last chapter of the thesis will discuss work related to expanding the scope of
reactivity of aza-oxyallyl cations. Previous work in our group sought interest in a modular strategy to prepare these motifs from a formal (3+2) cycloaddition of aza-oxyallylic cations. This work discussed here will focus on the cycloaddition with a carbonyl reactant to deliver 4-oxazolidinone motifs in a one-step pot from simple starting materials.
Dedication

For Cam

Thank you for always being my source of joy.
Thank you Dr. Jeffrey for being more than a PI, but a mentor through out every part of my life while in graduate school. You have pushed me far beyond what I thought I was capable of and supported every dream that I’ve had. Thank you for teaching to how to be an independent scientist and learn to trust my instincts. I am so grateful for you allowing me to join your group and becoming apart of the Jeffrey family.

Thank you to all my committee members for being present and supportive through out this journey. Thank you Dr. Sheridan for always answering my numerous questions on all my light reactions and lending me Cameron when I needed him. Thank you Lora for the wonderful memories we created in Brasil, I had the time of my life out there because of you!

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Chapter 1: Introduction

1.1 Chromene Chemistry Background

Natural products chemistry has originated from mankind’s curiosity about color, taste, odor, and cures for human, animal and plant diseases.\textsuperscript{1} Natural products have been considered the best sources of drugs and drug leads, and this remains true today, from 1981 to date, 80% of small molecule anticancer drugs are natural product-based/inspired, with 53% being either natural products or derived therefrom.\textsuperscript{2} The term natural product is applied to materials derived from plants, microorganisms, and vertebrates, which are biochemical factories for the biosynthesis of both primary and secondary metabolites.\textsuperscript{2} Secondary metabolism produces molecules that are considered important in mediating the interactions of plants with their biotic and abiotic environment.\textsuperscript{3} High genetic plasticity and diversity of secondary metabolites allows plants to adapt that guarantees flexible adaptations of plants to the demands of their changing environment.\textsuperscript{3} The success of a species ultimately depends on their capacity to promote interactions with beneficial organisms while minimizing interactions with non-beneficial organisms such as predators, pathogens and parasites.\textsuperscript{4} Though the chemistry of these biotic interactions is highly complex, multidisciplinary teams of scientists are now beginning to use modern tools in chemistry and biology to understand the molecular nature of these interactions.

The Jeffrey group is part of a large interdisciplinary team of scientists who focus on the causes and consequences of plant natural products diversity. Our group has specifically focused studies on the phytochemistry of the genus, \textit{Piper (Piperaceae)}, a diverse pantropical plant genus that is a rich source of new biologically active natural
products.\textsuperscript{4} Many classes of natural products have been isolated from \textit{Piper}, including phenyl propanoids, amides, imides, lignans, neolignans, terpenoids, pyrones, and flavonoids, many of which have been established to have both ecological and medicinal relevance.\textsuperscript{5} Investigations of the phytochemical mediation of plant insect interactions have led to the isolation and characterization of three geranylated natural products (Figure 1.1.1) from the recently described species, \textit{Piper kelleyi}, (Figure 1.1.2), a mid canopy shrub that grows in the lower montane rain forests in Ecuador and Peru.\textsuperscript{3} These compounds displayed interesting anti-herbivore properties and were found to strongly correlate to the diversification of an associated specialist caterpillar.\textsuperscript{6} Chemically mediated interactions between plants, herbivores and natural enemies have important ecological and evolutionary impacts on biodiversity.\textsuperscript{7} The focus of the following projects is to understand how phytochemistry shapes the composition of insect communities and contributes to diversification of plants and insects.\textsuperscript{8} We propose that there is a relationship between an abiotic factor such as light plays a role in the production of the three isolated metabolites. In order to understand the role of UV light exposure to plants the observed phytochemical variation of the plant metabolites and the photoxicity of these metabolites of herbivores, it is necessary to establish the photochromic properties of naturally occurring chromenes, their reactivity, and its role in the synthesis of these

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Recently isolated prenylated benzoic acid (1), geranylated acid chromene (2), and dimeric chromane (3) from \textit{P. kelleyi}}
\end{figure}
metabolites.\textsuperscript{4}

![Figure 1.1.2 Underside or 'belly' of leaves from tropical shrub Piper kelleyi](image)

### 1.2 Intramolecular (3+2) cycloadditions of aza-oxyallyl cationic intermediates

With a growing concern in the medical community for the need to develop path resistance antibacterials\textsuperscript{9} between 1981-2002 the vast majority of new chemical entities approved for use as antibiotics were natural product derived\textsuperscript{10}, indicating that nature offers highly relevant scaffold for developing therapies in the infectious disease arena.\textsuperscript{11} The Macherla group were the first to isolate substituted oxazolidinones, called lipoxazilidinones A, B & C, (Figure 1.2.1) from an isolated marine actinomycete strain, Marinispora, from Guam that were modeled after Synoxazolidinones.\textsuperscript{11} The lipoxazilidinones A, B & C as well as their hydrolysis product were found to show minimum inhibitory effects against Gram-positive bacteria and against two strains of Haemophilus influenzae.\textsuperscript{11} The antibacterial spectrum and potency were similar to those of the commercially available antibiotic linezolid (Zyvox).\textsuperscript{12} The oxazolidinones are a new class of totally synthetic antibacterials that inhibit protein synthesis in prokaryotes.\textsuperscript{13} This novel method of action results in a lack of cross-resistance between oxazolidinones
and the existing classes of antibacterial agents. The discovery of antibiotics that utilize a unique mechanism of action is of great importance given the emergence of multidrug-resistant bacterial pathogens is a significant and growing problem in hospitals and in the community.\textsuperscript{14,15} Du Pont de Nemours & Company scientists were the first to discover the antimicrobial properties of oxazolidinones while working on plant microbials in the late 1970’s.\textsuperscript{16} Their discovery launched a new chemical space to be explored, and Upjohn Company in Michigan eventually identified linezolid, which ultimately received regulatory approval and went to market in 2000.\textsuperscript{17} While the oxazolidinones heterocycles are a common structural motif shared by the lipoxazilidinones and linezolid, the compounds are clearly distinguished as 4- and 2-oxazolidinones, and each class is uniquely substituted (Figure 1.2.1).\textsuperscript{11} Thus, the 4-oxazolidinones offer a unique scaffold with antibiotic therapeutic potential.\textsuperscript{11}

1.3 References


Chapter 2: Phytochemical diversity in *Piper Kelleyi*

2.1 Chemical Ecology Inspiration

Chemically mediated interactions between plants, herbivores and natural enemies have important ecological and evolutionary impacts, both of which contribute to diversification of plants and insects.¹ There has been a major effort to understand the origins of plant chemical diversity and it’s effects on multitrophic interactions at community and population levels.² Three major compounds that were isolated from the leaves of *Piper kelleyi*-a prenylated benzoic acid (1), chromene (2), and a dimeric chromane (3) (Figure 1.1.1). These three compounds made up 95% of the oil in the crude extract.² Recently, the three secondary metabolites within *P. kelleyi* were found to vary in concentration between individual plants growing up a the mountainside in Ecuador, over a gradient of over 1,500 km (Figure 2.1.1). This study provided evidence for phytochemical variation having an effect on the genotype of the community of specialist herbivores, especially in high elevation with greater UV-B exposure.³ Throughout the study, the concentration of the prenylated benzoic acid, 1 (PBA),
increased with increased elevation. Additionally, the crude plant extract and the individual compounds were found to have potent anti-herbivore properties and that these negative effects were enhanced when the herbivores were exposed to UV light. Variation in phytochemistry as a function of elevation and the phototoxicity of the plant extracts suggests that UV light was playing a role in both these observations. Given the known photochromic properties of chromenes, it is proposed that the chromene isolated from *P. kelleyi* leaves could be responsible for the phototoxicity of the crude extract through the photochromic ring opening to produce the highly reactive *ortho*-quinone methide intermediate. Phototoxicity has been shown to occur in many secondary metabolites when exposed to UV light. Either by being metabolized into more toxic
compounds or generating reactive intermediates that later interfere with DNA or proteins. Evaluation of the antiherbivore activity of the benzoic acid derivatives sparked the interest into how all three derivatives could possibly be related. With the help of visiting scientist, Dr. Kevin McMahon from Carroll University a biosynthetic hypothesis was proposed to account for the relationship between all three metabolites (Scheme 2.1.1). It was proposed that PBA 1, chromene 2, and chromane 3 are biosynthetically linked and the chromane is produced by a hetero-[4+2] cycloaddition reaction of the photogenerated o-quinone methide and its tautomer. This observation is indicative of a subsequent dimerization of 1 to afford 3. Its important to note that compound 3 occurs as a racemic mixture and there are only three other examples of naturally occurring dimeric chromanes with a similar E-olefinic moiety, with two examples of racemic mixtures.

Dimerization of secondary metabolites is a common pathway that can occur via biotic and abiotic

\[ \text{Scheme 2.1.1 Biosynthetic hypothesis of isolated natural products from P. kelleyi} \]
pathways through various reactions types, including Diels-Alder reactions and oxidative aryl-O bond formation. This unique structure of 3 led us to consider the biosynthetic relationship to its presumed chromene monomeric precursor 2. Retrosynthetic analysis of the pyran ring through a hetero Diels-Alder dissection (Scheme 2.1.1) provides ortho-quinone methide hetero diene R6 along with an isoprenylated dienophilic component R8. O-quinone methide intermediates have been long established to undergo facile hetero-[4+2] cycloaddition reactions with tri-substituted alkenes to provide chromanes. Padwa and co-workers established that unsubstituted chromene R5 undergoes a photochemical retro-6π-electrocyclzation to generate the reactive ortho-quinone methide intermediate. In scheme 2.1.2, the photogenerated ortho-quinone methide tautomerized to R9 upon irradiation to give R11. Given this evidence Dr. McMahon proposed that 3, is the result of a [4+2] heterodimerization of quinone methide R6 and butadienyl dienophile R8, which are generated either by a photo-induced retro-electrocyclization of the chromene 2 or by eliminative pathways from benzylic oxidized prenylated phenol R10. Studies of the role, variation, and mechanism of this dimerization will be discussed.
2.2 Understanding the photochromic behavior of naturally occurring chromenes

Chromenes are known to undergo a photochemical retro-6π-electrocyclization to generate a very reactive ortho-quinonemethide (o-quinone methide) intermediate, 4, (Figure 2.2.1).\textsuperscript{12,13} Aware that an abiotic factor, such as light, could be playing a major role in observed phytochemical variation between individual plants, we were interested into how this was occurring and how to mimic this process in a laboratory setting. We hypothesized that the photochemically generated ortho-quinone methide may be responsible for the dimeric chromane, as well as many skeletally related natural products (Figure 2.2.2). Being able to photochemically generate the intermediate opened the door to exploring the photochemistry of chromenes.
Photochemistry is a specialized branch that studies chemical processes that are mediated by the absorption of light by one or more of the reactants.\textsuperscript{14,15} Where a photochemical reaction is initiated by infrared,

\textsuperscript{14,15} Chromenes are known to be photochromic species. Photochromism is photochemical process that is characterized by a molecule that undergoes a reversible color change upon irradiation with light.\textsuperscript{14} Photochromism has been studied for a little over a century\textsuperscript{16} and its relevance to natural products variation and toxicity has yet to be comprehensively studied. Chromenes have the ability to absorb light and undergo a reversible transformation between two forms, A and B.\textsuperscript{16} (Figure 2.2.3) Photochromic molecules have a colorless form A, which converts to a colored form B upon irradiation. In 1972, Padwa and coworkers were the first to report the simple, unsubstituted 2$H$-chromene A can undergo photochemical ring opening to give a reactive
intermediate that provided a variety of photoproducts depending on the conditions.\textsuperscript{17} Quinone methides are readily accessible through reactions of such photochemical excited states.\textsuperscript{18,19} Where absorption of a photon in the UV spectral region may lead to the generation of electrophilic species by fast heterolytic bond cleavage at the photochemically excited state.\textsuperscript{20} More specifically it has been shown that irradiation of 2,2-dimethyl chromene through Pyrex using a 550-W Hanovia lamp generates the reactive ortho-quinone methide intermediate B, which reacts with methanol to form a pair of methyl ethers through nucleophilic attack (Scheme 2.2.5).\textsuperscript{21} As our group had hypothesized, all three compounds could be derived from the ortho-quinone methide intermediate. Dr. Tracy Nguyen initiated the studies of this process further by synthesizing an ethyl ester chromene 5 that served as our “model” chromene. By using a non-substituted, non-acidic chromene a solid understanding of the intermediate could be obtained. We predicted that by gaining a better understanding of the reactivity of the o-quinone methide intermediate, we could use the intermediate as a linchpin for synthesizing a variety natural products (Figure 2.2.2).

Our goal for this project was to try to understand the photochromism of the chromene for the generation of an o-quinone methide intermediate and the reactivity of
the intermediate. This chemical study is directed toward understanding the molecular nature of the intraspecific chemical variation in *P. kelleyi* and the differential toxicity to herbivores at various elevations. To study this we completed a series of photochemical experiments to explore the generation of the intermediate, its inter-and intramolecular reactivity, and the utility of the photochemical products as entryway into various natural products scaffolds.

### 2.3 Synthetic Approach to recently isolated secondary metabolites from *Piper Kelleyi*

A naturally occurring ethyl ester chromene or model chromene was used to explore the reactivity of the chromenes and to understand the behavior of the ortho-quinone methide intermediate. Although geranylated and prenylated chromenes were synthesized and explored, the model chromene 5, did not incorporate the lipophilic side-chains of the chromene isolated from *P. kelleyi*. The model chromene 5, was synthetized in a two-step process performing an O-alkylation of the phenol with the *in-situ* generation of the trifluoroacetate 6, followed by thermal rearrangement of the resulting aryl propargyl ether 7 according to the precedent of Iwai and Ide. (Scheme 2.3.1).\(^{22}\) Quantitative yields were obtained of 5, when installing a propargyl group by *O-*
alkylation of ethyl para-hydroxybenzoate using 2-methylbut-3-yn-2-yl and 2,2,2-trifluoroacetate to install the propargyl ether followed by thermal rearrangement to give the ethyl ester chromene 5. The first studies conducted using the model chromene involved the help of Dr. Robert Sheridan and undergraduate researcher Cameron Berg (University of Nevada, Reno) to qualitatively support if the chromene was undergoing a ring opening. As Becker and Padwa have studied photochromism of chromene systems extensively, we were certain that following their reported procedures would give access to the ortho-quinone methide and methanol adducts of interest. While initial studies used solvolysis with methanol to give the methanol adduct, our lab aimed to determine if the photo-generated o-quinone methide underwent hetero [4+2] to give the chromane. As Scheme 2.3.2 details, the geranylated model chromene 8 NEAT with an excess of acid, TFA was irradiated at 300nm for two hours, while being monitored every thirty minutes by $^1$H NMR spectroscopy. The dimer was formed after two hours, although there was degradation of starting material along with un-characterizable photoproducts. To possibly rid our reaction of any degradation by atmospheric oxygen, we degassed our system before re-running experiments. The degassed system was performed following a standard pump-thaw-freeze protocol using liquid nitrogen. In addition to degassing the system we also used a milder acid, acetic acid. As Scheme 2.3.3 depicts, we irradiated at 300nm for a total of twenty-four hours, initially monitoring every hour for 6 hours then allowed the
reaction to continue overnight without hourly monitoring. With the changes mentioned, the dimer was formed cleaner according to $^1$H-NMR and all starting material was consumed. There are still ongoing studies being done to separate the racemates of the dimer. These set of reactions made way for not only experiments expanding the natural product scaffold as well as the chromene derivatives described later on.

2.4 Expanding the Natural Product Scaffold: Electrophillic Aromatic Substitution (EAS) of o-quinone methide

Figure 2.4.1 Reacting Aryl group with methanol adduct
One of the goals of this project was to explore the reactivity of the intermediate, B and creating a hub of natural product skeleton motifs. The initial hypothesis was to take methanol adduct from the model chromene and add an electron rich aryl substituent and form a pseudo EAS product (Figure 2.4.1)

The first survey of this reaction was performed with the methanol-adduct, 10 and 1 equivalent of dimethoxyphenol, varying acids, solvents, and temperature shown in Table 2.4.1. The product formation ranged from 20-50% yields and both isomeric products were formed. The reaction with the highest and cleanest yields based on $^1$H-NMR spectroscopy was the mixture of PPTS as the acid, deuterated chloroform and at a 50 °C. While starting the reaction with a slight excess of aryl group, we saw a small formation of product. The first adjustment that was made was to allow the reaction to run for a longer period of time. There was only ~20% formation after running the reaction for twenty-four hours. Increasing the amount of excess aryl reactant also increased the yield and decreased the reaction time. Jumping from 1 to 2 to 3 equivalents, a substantial amount of product was formed in a little over an hour. The next derivative of this experiment was changing to a symmetrical aryl group, trimethoxybenzene, making optimization easier.

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>solvent</th>
<th>temp</th>
<th>yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KAM1.69</td>
<td>PPTS</td>
<td>DCM-d$^2$</td>
<td>35 C</td>
<td>21%</td>
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<tr>
<td>KAM1.70</td>
<td>TFA</td>
<td>DCM-d$^2$</td>
<td>35 C</td>
<td>Trace amount</td>
</tr>
<tr>
<td>KAM1.80</td>
<td>PPTS</td>
<td>CDCl$_3$-d$^1$</td>
<td>50 C</td>
<td>49.5%</td>
</tr>
</tbody>
</table>

Table 2.4.1. Results from optimization of EAS reaction varying, solvents, acids, temperature. PPTS= Pyridinium p-toluenesulfonate, TFA= Trifluoroacetic acid, DCM= Dichloromethane, CDCl$_3$= Chloroform
Scheme 2.4.2. This change increased yields to 70% in the trimethoxybenzene case and expanding it to dimethoxyphenol, 11 and phloroglucinol, 13 with yields of 50% and 60% respectively. Qualitative data were obtained from $^1$H NMR as the regioisomers proved almost impossible to separate from with several attempts were performed to isolate phloroglucinol.

The next hypothesis of the o-quinonemethide intermediate was it could be formed *in situ*, allowing us to trap it with the addition of the Aryl group. This would allow formation of the product bypassing the step of trapping with methanol and isolating. The work that follows is in a NEAT degassed system, using standard pump-thaw-freeze protocol. We noticed that running the reaction NEAT, there was no need for such an excess of Aryl substituents, so we reduced the amount of excess from 3.0 equivalents to 1.1 equivalents. The only change to the system was adding 10 equivalents of acetic acid, as previous work

![Scheme 2.4.2 EAS reaction with ethyl ester methanol adduct (10) + trimethoxybenzene to form first EAS analog (12)](image-url)
proved excellent results. The three-aryl groups all gave modest to high yields (Figure 2.4.2). To continue to expand the natural product skeleton hub, two more substrate were tested, figure 2.4.3 both giving low-modal yields. These reactions could use more attention and optimization to improve over all yields, and finding a protocol to purify the more difficult, more polar products as reverse phase column chromatography hasn't proved to be successful.

**Figure 2.4.2 Ethyl Ester Chromene with initial electron rich Aryl groups**

**Figure 2.4.3 Ethyl Ester Chromene with natural and unnatural electron rich Aryl groups**
2.5 Expanding the Natural Product Scaffold: Oxidation of EAS product

Expanding the natural product skeletons, one could envision taking one of the EAS products, and performing an oxidation to form a furan-type ring skeleton. Several attempts were made with each type of oxidation presenting its own challenges and setbacks to work through, which is discussed below. The EAS product we worked with was 11 and subjected it to an oxidation with meta-chloroperbenzoic acid, *m*-CPBA, which would epoxidize the alkene that go on to afford the cyclized furan-type ring product, 14.

Figure 2.5.1 Hypothesized two step process to form furan-type ring, by oxidation and acid workup

Figure 2.5.1. This reaction proved to be much more difficult than literature had led us to believe. The original idea, shown in Figure 2.5.1, was 12 would be oxidized to the furan-type ring product in two-steps, where oxidation to the epoxide was followed by purification and then addition of the acid would lead to the cyclized furan-type ring product. After several screenings of solvents, temperatures, and oxidants (Table 2.5.1) we questioned what was the final product with the addition of *m*-CPBA, the epoxide or the
The cyclized product was characterized by $^1$H, $^{13}$C, HSQC, COSY. After screening several oxidants, $m$-CPBA was the oxidant of choice, but most procedures demonstrated that it was standard to use excess $m$-CPBA. Therefore lengthy screenings were done to find the correct amount of excess oxidant was needed to form the product (Table 2.5.2). Once an agreed upon 4 equivalents reaction was rerun and a yield of 2.1% was obtained for product 14, Figure 2.4.2. The bottle of oxidant that was being used was fairly old and overlooking this could easily lead to low yields. So to be sure we still had a fairly high concentration of oxidant in the bottle, an iodometric titration and NMR test were done to check the purity. The $m$-CPBA comes as a 77% pure...
mixture of the acid, but after the titration it was found to be 20% pure. This would explain why the percent yield was so low, 2%. This small but important piece of information could easily explain the low yields we were obtaining as well as why we needed such an excess of oxidant to form any product. We hope to obtain to a new bottle of \textit{m}-CPBA and see an increase in our yield. Once this issue could be resolved, expanding the oxidation to all EAS products, 11-13 could be subjected to an oxidation, growing the natural product skeleton motifs and showing the versatility of the \textit{ortho}-quinone methide.

![Reactions](image)

\textbf{Figure 2.5.2} Hypothesized two step process to form furan-type ring, by oxidation and acid workup

\section*{2.6 Chromene and Chromane Derivatives}

When doing a literature search for chromene and chromane skeletons there are numerous amounts of natural products that come up. The structurally diverse derivatives are the most enticing not only in a synthetic approach but also provide a biological importance. The Toddalolactones and toddalins of interest contain a skeleton closely related to the acid chromene and dimeric chromane isolated in \textit{P. kelleyi}.

Lin and coworkers isolated and characterized (+)/(-)toddalolactone, toddalins A-D and rediscovered toddacoumalone found in extracts from the roots of \textit{Toddalia asiatica}. Toddacoumalone is the most compelling natural product that could help support the hypothesis of a chromene ring opening upon irradiation and undergoing dimerization to form novel natural products. With the goal of synthesizing toddacoumalone, a
heterodimerization, homodimerization of the parent toddalolactones was the first task to tackle. An example of homodimerization is toddalin D, which is formed by the (-)-toddalolactone undergoing dimerization with itself.

Retrosynthetic analysis of both toddacoumalin and toddalin D give possible parent chromenes and coumarin being: lapachenol, N-methylflyndersine, and seselin. Taking the same approach with respect to performing a retrosynthesis on all three compounds just mentioned, lapachenol and seselin have been shown to undergo the same synthetic approach as the model chromene described previously. N-methylFlyndersine is one of the better-known chromenes thus a synthetic approach had already been established.
2.7 Lapachenole

Lapachenole originally isolated in 1900 and was isolated from a Brazilian white hardwood.\textsuperscript{27,28} Lapachenole has been used as a photochromic agent in protein structure studies\textsuperscript{29} and fluorescent photoaffinity labeling of Cytochrome P450.\textsuperscript{30} The synthesis of Lapachenole (2,2-dimethyl-6-methoxy-7,8-benzo)2H-chromene, \textit{Ch}, 17 shown in Scheme 3.2.1, very similar to the approach taken in model ethyl ester.

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

\textbf{Scheme 2.7.1 Two step synthesis of Lapachenol (17) from 4-methoxy napthol}

chromene. The first step in the two-step synthesis used 2-methylbut-3-yn-2-yl and 2,2,2-trifluoroacetate to install the propargyl ether, as described in chapter 2.2 at 65-80% yields. This synthetic route gave modest yields ranging from 30-40%. During the purification process of Lapachenoles impurities were colored. Before starting any photochemistry, we obtained a UV/VIS spectrum with the help of Dr. Matthew Tucker and graduate student Farzaneh Chalyavi (University of Nevada, Reno, Chemistry Department). In this study, Lapachenole was dissolved in diethyl ether, and UV/VIS spectrum was taken at room temperature. The spectra showed a strong absorption at 310 nm, indicating a layout of the colored intermediate start to appear. Photochemical transformations were performed primarily utilizing similar methods as the model chromene project described earlier. Lapachenole, \textit{Ch}, 17 was insoluble in methanol, so a solvent screen was performed. By irradiating \textit{Ch}, 17 with 300 nm light in five different solvents: methanol-d\textsubscript{4}/water-d\textsubscript{2}, acetonitrile-d\textsubscript{3}/water-d\textsubscript{2}, toluene-d\textsubscript{8}, benzene-d\textsubscript{6}, and dimethylsulfoxide-d\textsubscript{6} (DMSO), and
the results were monitored by \(^1\)H-NMR spectroscopy. Each experiment was conducted in deuterated solvents so qualitative NMR analysis to determine the solvent that dissolved \(Ch, 17\) and provided data for the formation of the dimer. \(Ch, 17\) was dissolved in deuterated solvents at [0.20] Molar (M), and irradiated at 300 nm over a course of 90 minutes. Four solvents consumed starting material but still no clear data to show formation of dimer, methanol-\(d_1\), acetonitrile-\(d_3\), water-\(d_2\), and benzene-\(d_6\). We continued to irradiate \(Ch, 17\) in solvents and at 254 nm over a course of 90 minutes. Benzene-\(d_6\) showed the strongest phototransformation of \(Ch, 17\). It was difficult to characterize the dimer through NMR alone, benzene determined to be the best solvent. A short survey of three acids was performed. Using similar conditions Pyridinium \(para\)-toluenesulfonate (PPTS, 1 eq), trifluoroacetic acid (TFA), \(para\)-toluenesulfonic acid (PTSA), and acetic acid (AcOH). \(Ch, 17\) was dissolved in deuterated benzene at [0.20M], and irradiated at 300 nm over a course of 90 minutes, with 1 equivalent of acid added and then irradiated for another 60 minutes. There was a quick color change when TFA was added, the solution changed from a purple to a dark brown color after second irradiation with complete decomposition of material. PPTS showed no significant difference in consumption of starting material or formation of any new photoproduct via \(^1\)H-NMR spectroscopy. PTSA proved to be the most promising acid with noticeable phototransformation of \(Ch, 17\). In the model system, running the system degassed, NEAT with 10 equiv. of Acetic Acid formation of the dimer happened readily and cleanly. As a last effort to produce the dimer, the same conditions were applied to \(Ch, 17\) and irradiated at 300nm for 24 hours. Unfortunately, no dimer formation was observed under these conditions either, this system still leaves a lot of room to be studied and understood.
2.8 N-methylflindersine

Flindersine, 15 containing a 2\textit{H}-pyran skeletons Becker found it to behave in a similar fashion as the 2\textit{H}-chromenes.\textsuperscript{26} Becker had previously reported the quinoid chromophore appears as a very pale yellow.\textsuperscript{26} With pyranoquinolinones having proved to be more difficult to synthesize with several steps and lower yields, research has focused on improving synthetic methods of pyranoquinolinone derivatives to overcome these problems.\textsuperscript{32} In 2007, Wang and Lee presented a synthetic approach using ethylenediamine diacetate as a catalyst to provide a practice solution to the problems encountered in previous works. The idea behind their approach was that the 2\textit{H}-pyran rings of pyranoquinolinones could be obtained efficiently by formal [3+3]-cycloaddition reaction,

![Figure 2.8.1 Two step synthesis of N-methylflindersine (15)](image)

this reaction may proceed through a tandem process of an aldol-type condensation of 2,4-dihydroquinoline to \(\alpha,\beta\)-unsaturated aldehyde followed by a 6\(\pi\)-electrocyclic ring closure.\textsuperscript{32} Their work used ethylenediamine diacetate to catalyze reactions using resorcinols to \(\alpha,\beta\)-unsaturated aldehydes, (Scheme 2.8.1).\textsuperscript{33} Going forward with the one step reaction, 2,4-dihydroxy-quinoline with crotaonaldehyde in dichloromethane at room temperature for 12 hours afforded flindersine in 60\% yields.\textsuperscript{32} Conversion of flindersine into \(N\)-methylflindersine was carried out in one step. The reaction of compound
flindersine with methyl iodide in the presence of potassium carbonate in $N,N$-dimethylformamide gave $N$-methylflindersine$^{32}$, 15 in modest yields ranging from 67-75% yields. Using the same approach as Lapachenole, we first obtained a UV/VIS spectrum again with the help of Dr. Matthew Tucker. In this study, $N$-methylflindersine, 15 was dissolved in diethyl ether and UV/VIS spectra was taken at room temperature. The spectra obtained showed a $\lambda_{\text{max}}$ at 365nm. $N$-methylflindersine, 15 proved to be a more difficult compound than literature had led on. The first photolysis reaction performed was ran in 0.20M in methanol-d$_1$, and after slight initial solubulity issues after three hours of irradiation at 300nm. $N$-methylflindersine, 15 did dissolve, but unlike previous studies a yellow color photoproduct appeared rather than the expected. Again, knowing acid plays a role in the formation of the dimer in the model chromene, the idea of adding acid was applied here. Based on the appearance of color, the phototransformation appeared to occur. Based on $^1$H NMR it’s hard to definitively determine if any dimer had occurred, further investigation are needed perhaps optimization of irradiation time and solvents.

2.9 Seselin

![Figure 2.9.1 Naturally occurring coumarins in found in nature](image-url)
Coumarins are a class of $O$-heterocyclic natural products widely distributed in high plants (Figure 2.9.1), found in fungi and bacteria and being structurally characterized by the presence of the $2H$-benzopyran-2-one nucleus. Coumarin dyes are widely employed in the chemical industry, medicine, engineering and physics, with widely different applications such as fragrance products or as media to generate laser light in the green-blue spectral region. Coumarins and their derivatives, natural or synthetic, have diverse toxicities and carcinogenicities with the biological activity depending on the constituents of the benzopyrone ring. The coumarin of interest to form toddacoumalone is Seselin 16, a naturally occurring angular pyranocoumarin that exhibits some important biological activities, such as anticancer and antifungal. The synthetic approach was similar to the model chromene (Scheme 2.9.1), started with umbelliferone and quantitative yields were obtained, when installing a propargyl group by $O$-alkylation of ethyl para-hydroxybenzoate using 2-methylbut-3-yn-2-yl-2,2,2-trifluoroacetate to install the propargyl ether followed by thermal rearrangement to give the Seselin 16. Two isomers are formed when thermal rearrangement occurs, 16a and 16b. Isolation of the two isomers were difficult as the $R_f$ are almost identical, thus photolysis reactions proceeded with the mixture of isomers. The first set of photochemical reactions started with the standard procedure for the model chromene, Scheme 3.4.2, and reaction 4A, with a small-scale reaction, irradiating for two hours total and checking phototransformation every fifteen minutes by $^1H$ NMR spectroscopy. Several different attempts were made at altering solvents, concentration of acid, and irradiation time, which are all outlined in Table 3.4.1, no ideal solvent was found as there continues to be
no visible change in the $^1$H spectrums. As the previous chromene and chromene derivatives were subject to the degassed photolysis reactions, so was Seselin, Scheme 3.4.2,

![Scheme 2.9.1 Two step synthetic approach towards mixture of isomers of Seselin (16a, 16b)](image)

reaction 4B. No real progress has been made to being to form a dimer or isolation of any photoproducts as they degrade on silica. As this derivative continues to be studied, isolation procedure needs to be uncovered.

2.10 Cannabichromene

The Pate group did a similar study on Cannabis sativa that Andrea Glassmire and coworkers performed. Pate measured the amount of THC found in higher elevation plants to lower elevation plants. What they found was at higher elevation the concentration increased and at lower elevation it was decreased. Looking at the precursors to THC, and the concentration of cannabinoids at all levels, the cannabichromene is present in all mixtures. This is a very similar to find Andrea found in her work. There is a possibility that the mechanism of forming THC could come from interaction with light, opening the chromen ring and cyclizing to form THC.

Cannabis preparations have been used by man for over 5,000 years. Early use of Cannabis was for medicinal applications, but as newer drugs were discovered, the use of plant extracts such as cannabis diminished. Today, THC is used in treatment of patients undergoing cancer chemotherapy because of its antinauseant effect, but also used for its antiemetic, antiglaucoma, and analgesic properties. The total number of compounds
known to occur in *Cannabis* is 421 with new compounds constantly being discovered and reported.\(^{36}\) Compounds found in the female flowering parts of *Cannabis sativa* are named cannabinoids (Figure 2.10.1)\(^{38}\) which belong to the chemical class of terpenophenolics.

Cannabichromene, *CBC* (22), referred to as the cannabichromene-type and one of the four major cannabinoids found in *Cannabis*\(^{39,36}\) The first two reported extracts of *CBC* were reported by Claussen\(^{40}\) and Gaoni\(^{41}\) in 1966. Claussen reported *CBC* as a complex with dimethylformamide, where Gaoni used a hexane extract of hashish and fluorisil column chromatography. While a number of groups have reported the isolation of active constituents\(^{42}\), most are not fully characterized, and comparisons with or between groups are difficult.\(^{43}\) There are only a few papers on the synthesis of the four major cannabinoids, and even less on synthesis of \((-\)-\(\Delta^9\)-trans-tetrahydrocannabinol, THC, (21) which is currently used for the treatment of anorexia,\(^{44,45}\) and for the management of neuropathic pain and spasticity,\(^{46,47}\) with side effects including motor impairment and psychosis. After obtaining the cannabichromene from Toronto Research

\[\text{Figure 2.10.1 Four major types of cannabinoids isolated from *Cannabis sativa*}\]
Initially when starting this project the model chromene was still being optimized with deuterated methanol as the solvent, which is the solvent used to run the experiments. All experiments were conducted in deuterated solvents so qualitative NMR analysis could be used to understand the solvent that dissolved \textit{CBC}, and provided data for the exact time consumption of starting material had occurred. The experiments were monitored after every fifteen minutes of irradiation by $^1$H NMR spectroscopy. \textit{CBC}, was dissolved in 0.6M solution of methanol-d$_1$ with trial 1 having a catalytic amount of acetic acid and trial 2 without, each experiment ran for 30 minutes. Though no confident characterization could be interpreted from the initial trials, it was apparent that there was some change with the acid, so the next two trials performed included acid. The second set of experiments that used TFA as the acid source and deuterated solvents were explored. \textit{CBC}, was dissolved in a 1.0M solution of either ethyl ether-d$_2$ or methanol-d$_1$ with a catalytic amount of acid added. Reactions were irradiated at 300 nm over a course of 30 minute, monitored by $^1$H NMR spectroscopy every 15 minutes. The \textit{CBC}, dissolved in methanol-d1 with TFA, was most promising with an apparent phototransformation to what was believed to be the epimer of THC. To support the hypothesis that the formation of THC was going through the $o$-quinonemethide, irradiation was done with the help of Dr. Robert Sheridan and Cameron Berg. Dissolving \textit{CBC}, in a small amount of ether in a quartz NMR tube. The sample was cooled to roughly -78°C and irradiated for no
more than 30 seconds and the colorless \textit{CBC}, \textbf{22} turned to a pale purple and after 2 minutes of irradiating, (Figure 2.10.2). This color transformation would indicate that indeed the phototransformation occurring is going through the photocolored intermediate, the \textit{ortho}-quinone methide \textbf{23}, then forming our product, THC \textbf{21}, (Scheme 2.10.2). With these data, a large-scale reaction was conducted to give the opportunity to isolate the product and begin characterization. 20mg of \textit{CBC}, \textbf{22}, dissolved in 0.7mL of acetic acid was then irradiated at 300nm for 15 minutes. This was enough to see complete consumption of the \textit{CBC} and form a THC epimer, \textbf{21}. The product formed appeared as a mixture of both THC and an epimer of it. Ongoing studies are being done to characterize the epimer as well as separating the two epimers from one another to collect full characterization of the two products. As mentioned in the beginning of this section, very few studies have been done on the synthesis of THC and very few reports on full characterization of the cannabinoids have been reported, making characterization of the phototransformed product that much more difficult. Though a small amount of information is known on the chemistry of \textbf{21}, we believe that the endo-cyclization
produces the epi-THC isomer and exo-cyclizations produces THC.

2.11 Discussion

This project demonstrated that the quinone methide can be accessed by irradiation of UV light while providing evidence of the reactivity of the intermediate. By varying conditions we were able to show the intermediate may be responsible for a variety of natural product scaffolds. We have yet to determine if the reactivity of the quinone methide in our experiments are similar to the conditions in leaves. Additionally, how does the plant regulate or control the reactivity of the intermediate to not intercalate the plants DNA? Is it controlled? How the reactivity occur? Can we recreate those conditions in a laboratory setting?

As we reached the final optimized reaction conditions for trapping the quinone methide, we learned that the reaction proceeded far more quickly when moving from wavelengths of 350nm to 300nm and increasing the concentration of acid to full 10 equivalents. This guaranteed conversion to the light generated ortho-quinone methide.
We also found that the concentration of the chromene was insignificant. When expanding the reactivity of the quinone methide and performing the EAS reactions, we found that the best yields were obtained when using 1.1 equivalents of the reagents and letting the reaction irradiate for full 24 hours.

Research efforts are focused on expanding natural product motifs (Figure 2.2.5) and efforts in optimizing yields. Although previous literature demonstrated trapping the $o$-quinone methide with alkenes to form Diels-Alder products with hydrogen gas, we have yet to report any data to support this. Efforts have been focused on using two alkenes, cyclohexene and dihydropyran (Scheme 2.6.1). However, no conclusive data has been accumulated. More extensive studies would need to be performed to establish the Diels-Alder reaction, and should test different alkenes. These research efforts will promote collaboration with the Biochemistry department to investigate the biological activity of these compounds. The bioassays will compliment the observed patterns that intraspecific chemical variation between individual host plants could give rise to geographically variable selection with unique herbivores assemblages being adapted to specific concentrations of individual secondary compounds. By fully characterizing and understanding the photochromism of these secondary metabolites it has implications to understanding how chemical diversity is promotes insect diversity. Closing out these projects will also continue to show evidence of how phytochemical variation across host plant populations might shape the composition of herbivore assemblages, and could give rise to geographically divergent selection on herbivore populations.

This chapter also focused heavily on chromene derivatives that are prevalent in nature. The roles of these chromene derivative classes can be thought to be as precursors
to synthesis of more complex molecules through the photochemical production of a reactive colored form.\(^2\) While adding to the library of synthetic routes to these derivatives, our approach is simple, high yielding and encourages further to exploration of the reactivity of the photocolored product that is formed in all three cases. While the approach works well with the model chromene system, the conditions fail to work for all three derivatives. Now that we have exhausted the conditions that worked well for the model chromene it is now time to do the same for each of three derivatives. When taking a look at the absorption spectra, the seselin and lapachenol show two peaks in the absorption spectra, where the first is a peak at \(\sim300\text{-}320\text{nm}\), we expected that they would be able to react to irradiation at or near this wavelength to follow the conditions that were used on the model chromenes. However, no reaction occurred at these wavelengths. By monitoring the reaction via \(^1\)H NMR we concluded that little to no reactivity was occurring to form the reactive intermediate. Different acids were screened, concentrations were varied, as well different solvents (whether they were deuterated or not), we took time screening different conditions to see if we could generate any of the quinone methide intermediate before succumbing to the result of the wavelength wasn't correct. Thought the idea of just switching wavelengths is a simple jump, this begs the question that maybe the reactivity of these chromene skeletons are enzymatic? The result of no visible change was occurring leads me to believe that there is something more involved than just light playing a role. The next step would be to support this hypothesis would be of course to treat each derivative as an individual and use the greatest absorption peak in their UV/VIS spectra to find the appropriate light source for irradiation. Lapachenole, 17 is known to have great biochemical use, and thus continuing to study the appearance of
the intermediate and not only trapping it but finding conditions to form the dimer begs the question, could the natural product scaffold laid out for the model chromene system be applied to Lapachenole as well? \(N\)-methylflindersine, 15 showed to have the lowest yields of all three chromene derivatives, where optimization would need to be performed during the second step of the synthetic approach, which is the methylation of Flindersine to \(N\)-methylflindersine, 15. Though \(N\)-methylflindersine, 15 and Seselin, 16 showed no distinctly clear transformation to the dimer, hopes are that future studies will be able to optimize the conditions for these to be produced. If in fact, there is optimization to either trap the intermediate or form the dimer, this would open a new avenue to synthesizing another class of natural products, the Toddalolactones.

The Toddalolactones are a heterodimerization of the \(N\)-methylflindersine, 15 and Seselin, 16, Scheme 3.6.1. These would be challenging as a mixture of products could be produced, both homo- and hetero-dimerization could occur. Which is why the possibility of trapping the intermediates of both would allow greater structural control of the end product. This project warrants further investigations into photolysis to optimize current conditions and exploring new avenues into accessing the Toddalolactones.

2.12 Experimental

Reactions were carried out under inert atmosphere of nitrogen (\(N_2\)) gas in clean, oven-dried glassware (Pyrex) with magnetic stirring, unless otherwise specified. All reagents and solvents were purchased from Sigma-Aldrich Chemical Company and used without further purifications. TLC was recorded and performed using Silicycle glass 60 F254 plates or on Sorbtech alumina N TLC plates, w/UV254, polyester backed (200 nm) and visualized observed
using UV light (254 nm) or developed by staining with KMnO4 or CAM. Each reaction was purified using flash chromatography with Silicycle Siliaflash® P60 (230-400 mesh) or basic alumina. \(^1\)H-NMR spectra were measured on Varian 400 (400 MHz) or Varian 500 (500 MHz) spectrometers and are reported in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; integration); coupling constant(s) in Hz; using d-CDCl3 (7.26 ppm, with 0.01% TMS at 0.00 ppm). \(^1^3\)C-NMR spectra were measured on Varian 400 (101 MHz) or Varian 500 (126 MHz) spectrometers and are reported in ppm using d-CDCl3 (77.16 ppm, with 0.01% TMS at 0.00 ppm). Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR with a diamond ATR and the bands reported in cm\(^{-1}\) (br = broad, st = strong). High-resolution mass spectra were obtained using an Agilent 6230 TOF LC/MS with an atmospheric pressure photoionization (APPI, with C60 and anthracene internal standards) or electrospray (ESI, with purine and HP-0921 internal standards)

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2-methylbut-3-yn-2-yl)-2,2,2-trifluoroacetate (6) and Ethyl 4-(1,1-dimethyl-2-propynloxy)benzoate (7):

\[
\begin{align*}
\text{O} & \text{O} \\
\text{O} & \text{O} \\
\text{OH} & \text{OH}
\end{align*}
\]

\begin{align*}
\text{Part 1: DBU (1.34 mL, 9.0 mmol) was added to a solution of 2-methyl-3-butyn-2-ol (0.67 mL, 6.9 mmol) in anhydrous CH3CN (3.5 mL, 2M) and cooled in an ice bath (0° C). Trifluoroacetic anhydride (1.0 mL, 7.0 mmol) was added drop-wise and stirred for an additional 30 minutes to produce the propargyl-trifluoroacetate derivative in situ, 6.}

\text{Part 2: In a second reaction, DBU (1.16 mL, mmol) and CuCl}_2\cdot2\text{H}_2\text{O (1.5 mg, mmol) was added to a solution of ethyl p-hydroxybenzoate (1.0 g, mmol) dissolved in anhydrous CH}_3\text{CN (10 mL, 0.3M), cooled in an ice bath under nitrogen, and the propargyl-trifluoroacetate solution (6) was}
\end{align*}

added drop-wise via cannulation addition. After 5 hours at 0°C, the mixture was concentrated at reduced pressure. The crude mixture was dissolved in toluene (50 mL) and washed with 1 M HCl (3x25mL), aqueous NaHCO₃ (2x25mL) and saturated aqueous brine (2x25 mL) and dried with anhydrous Na₂SO₄. The solvent was removed at reduced pressure to give a crude product that was purified by column chromatography using 4:1 (hexanes:ethyl acetate) to give the desired white solid product (1.24 g, 90%); The experimental melting point was determined to be 50.2 51.6 °C; The Rf was calculated = 0.6 using 4:1 (hexanes:ethyl acetate); 1H NMR (500 MHz, chloroform-d) δ 7.99 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 9.0 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.63 (s, 1H), 1.70 (s, 6H), 1.39 (t, J = 7.1 Hz, 3H), 16b 13C NMR (126 MHz, chloroform-d) δ 166.35, 159.68, 130.86, 124.19, 119.40, 85.26, 74.59, 72.32, 6.65, 29.57, 14.37; 16b IR (neat): 3290.95, 3075.10, 2986.96, 2938.09, 2899.83, 2111.28, 1709.52 (st), 1603.16, 1505.46, 1271.98, 1245.64, 1098.99; HR-MS (ESI) calcd' for C₁₄H₁₆O₃ (M+H)+ 232.1099, observed 232.1103.

6-ethoxycarbonyl-2,2-dimethyl-2H-chromene (5):

Compound 7 (1.1 g, 4.7 mmol) was dissolved in N, N-diethylaniline (5 mL, 1 M) and stirred at reflux (210°C) for two hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with Et₂O (50 mL), washed (highly exothermic) with 6 M aqueous HCl (4x25 mL), followed by saturated NaHCO₃ solution (2x20 mL), saturated NaCl solution (2x20 mL) and dried over anhydrous Na₂SO₄. The solvent was removed giving crude amber oil that was flushed through a plug of silica yielding a light yellow oil (0.98 g, 90%). Rf = 0.6, 4:1 (hexanes:ethyl acetate); 1H NMR (500 MHz, chloroform-d) δ 7.82 (dd, J = 8.4, 2.2 Hz, 1H), 7.69
(d, J = 2.1 Hz, 1H), 6.78 (dd, J = 8.6, 0.6 Hz, 1H), 6.36 (d, J = 9.8 Hz, 0H), 5.65 (d, J = 9.9 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.46 (s, 6H), 1.38 (t, J = 7.1 Hz, 3H). \( ^{13} \)C NMR (126 MHz, chloroform-d) \( \delta \) 166.31, 157.05, 131.01, 130.95, 127.99, 122.86, 121.72, 120.59, 116.08, 77.29, 60.57, 28.27, 14.37; IR (neat): 3025.10, 2972.06, 2924.16, 2850.93, 1715.83 (st), 1433.31, 1310.90, 1245.72, 1195.77, 1163.39; HR-MS (ESI) calcd’ for C\textsubscript{14}H\textsubscript{16}O\textsubscript{3} (M+H)+ 232.1099, observed 232.1099.

4-bromo 2-[(2E)-3,7-dimethyl-2,6-octadien-1-yl]phenol (8):

\[
\text{Br} \quad \text{ger} \\
\text{O}
\]

p-Bromophenol (4.00 g, 23.1 mmol) was dissolved in dry toluene (80 mL, 0.3M), and NaH (60% dispersion in mineral oil, 2.1.00 g, 25.0 mmol) was slowly added. After five minutes of stirring, geranyl bromide (13.8 g, 63.6 mmol) was added and the mixture was stirred at room temperature for 1.5 hours. The reaction was carefully diluted with DI water (50 mL) and acidified with 2 M acetic acid (pH 4-5). The toluene layer was separated. The aqueous layer was partitioned with diethyl ether (2x100 mL). The combined organic layer was washed with saturated NaHCO\textsubscript{3}, followed by saturated NaCl, dried with anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude oil was purified via flash column chromatography (9:1 hexanes:ethyl acetate) and 5.64 g of product was isolated (79.1%) as a pale yellow oil. Yields varied (60-79%) due to competitive di-geranylation. Rf = 0.25 (9:1 hexanes:ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 7.25 – 7.16 (m, 2H), 6.68 (dd, J = 8.0, 0.7 Hz, 1H), 5.27 (tq, J = 7.2, 1.3 Hz, 1H), 5.10 – 5.03 (m, 2H), 3.32 (d, J = 7.2, 1H), 2.16 – 2.06 (m, 4H), 1.75 (d, J = 1.2 Hz, 1H), 1.69 (d, J = 1.1, 1H), 1.60 (d, J = 0.55, 1H); \(^{13} \)C NMR (126 MHz, CDCl\textsubscript{3}): ! 153.55, 139.39, 132.45, 132.12, 130.18, 129.14, 123.66, 120.69, 117.54, 112.69, 39.64, 29.56, 26.33, 25.70, 17.72, 16.22; FT-IR (neat):
4-ethoxycarbonyl-2-(3-methoxy-trans-isopenten-1-yl)phenol (10):

![Chemical structure](image)

Compound 5 (1.0 g, 4.3 mmol) was dissolved in methanol (0.1 M) and TFA (0.40 mL, 5.2 mmol) was added. The solution was purged under nitrogen and irradiated at 300 nm for 3.5 hours. The solution was neutralized with aqueous sodium bicarbonate and methanol was removed under reduced pressure. The resulting solution was extracted with ethyl acetate (4x25mL), dried with anhydrous sodium sulfate and concentrated. The crude mixture was recrystallized using hexanes provided an off-white solid (0.80 g, 70 %). MP = 137.3-139.1 °C; Rf = 0.20, 4:1 (hexanes:ethyl acetate); \(^1\)H NMR (500 MHz, methanol-d4) δ 8.06 (d, J = 2.2 Hz, 1H), 7.75 (dd, J = 8.5, 2.2 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.26 (d, J = 16.5 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.22 (s, 3H), 1.39 – 1.35 (m, 9H); \(^13\)C NMR (126 MHz, methanol-d4) δ 166.80, 159.13, 135.12, 129.79, 128.19, 123.85, 123.67, 121.28, 114.85, 75.49, 60.37, 49.33, 24.87, 24.86; HRMS (ESI) calcd’ C\(_{15}\)H\(_{20}\)O\(_4\) (M+H) - 264.1362, observed 264.1367

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General Procedure for the Electrophilic Aromatic Substitution (DEGASSED) reaction (11-13) with ethyl ester model chromene (5):

To a solution of ethyl ester chromene (5) (1 equiv) was added 1.1 equiv of Aryl group and 10 equiv of Glacial Acetic Acid. The reaction was degassed by using the “pump-thaw-freeze” method and irradiated at 300 nm for 3 – 12 hours. The solution was neutralized with aqueous...
sodium bicarbonate. The resulting solution was extracted with ethyl acetate (4x25mL), dried with anhydrous sodium sulfate and concentrated. The reaction progress was monitored by $^1$H NMR, every half-hour for the first 2 hours then every hour after. The volatiles were concentrated under reduced pressure and the residue was purified via flash column chromatography (20% hexanes: ethyl acetate) to provide desired EAS products.

Prepared in 34-60% yields (102 mg, 0.34 mmol) as an oil from the reaction of ethyl ester chromene 5 (1.0 equiv) was added and 3,5-dimethoxy phenol (1.1 equiv) via the general procedure. Rf = 0.35, 20% hexanes:ethyl acetate. Major product: $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.16 (t, $J = 1.7$ Hz, 1H), 7.79 (dt, $J = 8.5$, 1.8 Hz, 1H), 6.84 (dd, $J = 8.4$, 1.3 Hz, 1H), 6.26 – 5.85 (m, 3H), 5.39 (d, $J = 8.0$ Hz, 1H), 4.53 – 4.22 (m, 2H), 4.22 – 4.03 (m, 2H), 3.84 (d, $J = 1.3$ Hz, 3H), 3.71 (d, $J = 1.3$ Hz, 3H), 2.06 (d, $J = 1.3$ Hz, 3H), 1.81 (s, 3H), 1.64 (d, $J = 1.4$ Hz, 3H), 1.38 (d, $J = 1.3$ Hz, 2H), 1.36 – 1.20 (m, 2H). Minor Product: $^1$H NMR (500 MHz, Chloroform-$d$) δ 8.11 (d, $J = 2.2$ Hz, 1H), 7.76 (dd, $J = 8.4$, 2.3 Hz, 1H), 7.11 (s, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 5.87 (s, 0H), 5.37 (d, $J = 8.2$ Hz, 1H), 3.80 (s, 7H), 2.18 (d, $J = 0.4$ Hz, 1H), 2.06 (s, 7H), 1.79 (s, 3H), 1.62 (d, $J = 1.3$ Hz, 3H), 1.56 (s, 15H).
Prepared in 34-60% yields (102 mg, 0.34 mmol) as an oil from the reaction of ethyl ester chromene 5 (1.0 equiv) was added and 1,3,5-trimethoxy benzene (1.1 equiv) via the general procedure. Rf = 0.35, 20% hexanes:ethyl acetate; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.27 – 7.89 (m, 1H), 7.84 – 7.57 (m, 1H), 7.12 (q, $J = 0.5$ Hz, 1H), 6.77 (dd, $J = 8.5$, 1.1 Hz, 1H), 6.13 (d, $J = 1.1$ Hz, 2H), 6.10 (dq, $J = 8.5$, 1.5 Hz, 1H), 5.35 (d, $J = 8.3$ Hz, 1H), 4.32 (ddd, $J = 6.9$, 5.5, 1.2 Hz, 2H), 3.78 (dd, $J = 19.3$, 1.2 Hz, 10H), 1.77 (d, $J = 1.6$ Hz, 4H), 1.60 (d, $J = 1.4$ Hz, 4H), 1.36 (d, $J = 1.2$ Hz, 2H).

Prepared in 34-60% yields (102 mg, 0.34 mmol) as an oil from the reaction of ethyl ester chromene 5 (1.0 equiv) was added and phloroglucinol (1.1 equiv) via the general procedure. Rf = 0.35, 20% hexanes:ethyl acetate; $^1$H NMR (500 MHz, CDCl3) $\delta$ 8.06 (d, $J = 2.2$ Hz, 1H), 7.75 (dd, $J = 8.5$, 2.2 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.26 (d, $J = 16.5$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H),
3.22 (s, 3H), 1.39 – 1.35 (m, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 166.80, 159.13, 135.12, 129.79, 128.19, 123.85, 123.67, 121.28, 114.85, 75.49, 60.37, 49.33, 24.87, 24.86;

6-ethoxycarbonyl-2,2-dimethyl-2H-chromene (14)

![Chemical Structure]

To a solution of mCPBA (.528g, 42.3mmol) in CH$_2$Cl$_2$ (.2M) was added to a solution of the olefin (.5mL,14.2 mmol) in CH$_2$Cl$_2$ (.2M). The reaction was stirred for 12 hours and cooled to 0°C. 2-methyl-2-butene (76.9 mmol) was added to quench the reaction and the resulting mixture was slowly warmed to room temperature and stirred for an additional 4 hours. The mixture was diluted with saturated NaHCO$_3$ and extracted my DCM. The combined DCM extracts were washed with saturated Na$_2$SO$_4$, 5% NaOH, and water and dried with MgSO$_4$. The crude mixture was purified via flash column chromatography (8:1 hexanes:ethyl acetate) and product was isolated as a white solid. (14.7mg, 2.01 %); Rf = 0.27, 4:1 (hexanes:ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.07 (s, 1H), 7.79 (dd, J = 8.5, 1H), 7.68 (dd, J= 2.5, 1H), 6.91 (d, J = 8.5 Hz, 1H), 6.19 (s, 2H), 4.45 (d, J=8.93Hz, 1H), 4.24 (m, 3H), 3.86 (d, J=7.3Hz, 1H), 3.82 (s, 3H), 3.76 (s, 6H); 13C NMR (101 MHz, Chloroform-d) δ 166.71, 160.70, 159.86, 158.76, 130.97, 129.69, 126.59, 121.98, 116.65, 107.16, 91.34, 67.07, 61.47, 60.24, 55.72, 55.28, 37.13, 24.80, 18.31, 14.34.

Methylation to N-methylFlindersine (15):
Methyliodide in DMF was added to a solution of flyndersine and K2CO3 in DMF. The mixture was stirred at room temperature for 10 hours. The solvent was evaporated under pressure. The residue was treated with water, acidified with 1M HCl, extracted with ethyl acetate. The organic layers were combined and washed with Brine, dried MgSO4, filtered and evaporated under reduced pressure. The crude mixture was purified via flash column chromatography (50:50 hexanes:ethyl acetate) and product was isolated as a golden brown solid. (0.3362g, 67%); Rf = 0.67, 1:1 (hexanes:ethyl acetate); 1H NMR (400 MHz, Chloroform-d) δ 7.87 (ddd, J = 8.1, 1.5, 0.5 Hz, 1H), 7.45 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 6.72 (d, J = 9.9 Hz, 1H), 5.53 (d, J = 9.9 Hz, 1H), 4.10 (d, J = 7.2 Hz, 0H), 2.03 (d, J = 4.9 Hz, 2H), 1.52 (s, 6H), 1.24 (s, 0H).

Seselin (16): Intermediate

Part 1: DBU (0.6 mL, 2.312 mmol) was added to a solution of 2-methyl-3-butyn-2-ol (0.34 mL, 3.54 mmol) in anhydrous CH3CN (1.0 mL, 2M) and cooled in an ice bath (0°C). Trifluoroacetic anhydride (0.49 mL, 1.77 mmol) was added drop-wise and stirred for an additional 30 minutes to produce the propargyl-trifluoroacetate derivative in situ.
Part 2: In a second reaction, DBU (0.6 mL) and CuCl$_2$·2H$_2$O (.6 mg) was added to a solution of 7-hydroxy coumarin (0.5 g) dissolved in anhydrous CH$_3$CN (1.5 mL), cooled in an ice bath under nitrogen, and the propargyl-trifluoroacetate solution (Part 1) was added drop-wise via cannulation addition. After 5 hours at 0°C, the mixture was concentrated at reduced pressure. The crude mixture was dissolved in toluene (50 mL) and washed with 1 M HCl (3x25mL), aqueous NaHCO$_3$ (2x25mL) and saturated aqueous brine (2x25 mL) and dried with anhydrous Na$_2$SO$_4$. The solvent was removed at reduced pressure to give a crude product that was purified by column chromatography using 4:1 (hexanes:ethyl acetate) to give the desired pale yellow solid product (0.556 g, 50-73%); The Rf was = 0.56 using 4:1 (hexanes:ethyl acetate); H NMR (500 MHz, Chloroform-$d$) δ 7.65 (dd, $J$ = 9.4, 0.8 Hz, 1H), 7.36 (d, $J$ = 8.6 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.05 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.28 (d, $J$ = 9.4 Hz, 1H), 2.66 (s, 1H), 1.72 (s, 7H).

Seselin (16a): major product

![16a](image)

Compound 16 intermediate (1.1 g, 4.7 mmol) was dissolved in N, N-diethylaniline (5 mL, 1 M) and stirred at reflux (210°C) for two hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with Et2O (50 mL), washed (highly exothermic) with 6 M aqueous HCl (4x25 mL), followed by saturated NaHCO$_3$ solution (2x20 mL), saturated NaCl solution (2x20 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed giving crude amber oil that was flushed through a plug of silica to
give the desired pale yellow solid product (0.556 g, 73-90%); The Rf was = 0.56 using 4:1 (hexanes:ethyl acetate); $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.59 (d, $J = 9.4$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H), 6.88 (dd, $J = 10.1$, 0.8 Hz, 1H), 6.72 (dd, $J = 8.4$, 0.8 Hz, 1H), 6.23 (d, $J = 9.4$ Hz, 1H), 5.73 (d, $J = 10.1$ Hz, 1H), 1.48 (s, 6H), 1.47 (s, 1H).

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**Seselin (16b): minor product**

![Image of Seselin (16b)]

Compound **16 intermediate** (1.1 g, 4.7 mmol) was dissolved in N, N-diethylaniline (5 mL, 1 M) and stirred at reflux (210°C) for two hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with Et2O (50 mL), washed (highly exothermic) with 6 M aqueous HCl (4x25 mL), followed by saturated NaHCO$_3$ solution (2x20 mL), saturated NaCl solution (2x20 mL) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed giving crude amber oil that was flushed through a plug of silica to give pale yellow solid. Based off of NMR yields range from (20-25%); The Rf was = 0.56 using 4:1 (hexanes:ethyl acetate); 1H NMR (500 MHz, chloroform-d) $\delta$ 7.99 (d, $J = 9.0$ Hz, 1H), 7.25 (d, $J = 9.0$ Hz, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 2.63 (s, 1H), 1.70 (s, 6H), 1.39 (t, $J = 7.1$ Hz, 3H),$^{13}$C NMR (126 MHz, chloroform-d) $\delta$ 166.35, 159.68, 130.86, 124.19, 119.40, 85.26, 74.59, 72.32, 6.65, 29.57, 14.37; 16b IR (neat): 3290.95, 3075.10, 2986.96, 2938.09, 2899.83, 2111.28, 1709.52 (st), 1603.16, 1505.46, 1271.98, 1245.64, 1098.99; HR-MS (ESI) calcd’ for C$_{14}$H$_{16}$O$_3$ (M+H)$^+$ 232.1099, observed 232.1103.
**Lapachenol (17): Intermediate**

![Chemical Structure of Lapachenol](image)

*Part 1:* DBU (0.456 mL, 3.20 mmol) was added to a solution of 2-methyl-3-butyn-2-ol (0.37 mL, 3.3 mmol) in anhydrous CH$_3$CN (1mL) and cooled in an ice bath (0°C). Trifluoroacetic anhydride (0.54 mL, 4.30 mmol) was added drop-wise and stirred for an additional 30 minutes to produce the propargyl-trifluoroacetate derivative *in situ*.

*Part 2:* In a second reaction, DBU (0.6 mL) and CuCl$_2$·2H$_2$O (1.3 mg) was added to a solution of 4-methoxy napthol (0.5060 g) dissolved in anhydrous CH$_3$CN (2.0 mL), cooled in an ice bath under nitrogen, and the propargyl-trifluoroacetate solution (*Part 1*) was added drop-wise *via* cannulation addition. After 5 hours at 0°C, the mixture was concentrated at reduced pressure. The crude mixture was dissolved in toluene (50 mL) and washed with 1 M HCl (3x25mL), aqueous NaHCO$_3$ (2x25mL) and saturated aqueous brine (2x25 mL) and dried with anhydrous Na$_2$SO$_4$. The solvent was removed at reduced pressure to give a crude product that was purified by column chromatography using 4:1 (hexanes:ethyl acetate) to give the desired white solid product (0.8 g, 90%); The experimental melting point was determined to be 50.2–51.6 °C; The Rf was = 0.47 using 4:1 (hexanes:ethyl acetate); $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 8.34 – 7.93 (m, 1H), 7.57 – 7.36 (m, 2H), 6.72 (d, $J = 8.3$ Hz, 1H), 3.98 (s, 2H), 2.53 (s, 0H), 2.17 (s, 0H), 1.72 (s, 4H), -0.00 (s, 3H).
Laphanenol (17):

Compound 17 intermediate (1.1 g, 4.7 mmol) was dissolved in N, N-diethylaniline (5 mL, 1 M) and stirred at reflux (210°C) for two hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with Et2O (50 mL), washed (highly exothermic) with 6 M aqueous HCl (4x25 mL), followed by saturated NaHCO₃ solution (2x20 mL), saturated NaCl solution (2x20 mL) and dried over anhydrous Na₂SO₄. The solvent was removed giving crude amber oil that was flushed through a plug of silica yielding a light yellow oil (0.98 g, 90%). Rf = 0.6, 4:1 (hexanes:ethyl acetate); 1H NMR (400 MHz, Chloroform-d) δ 8.37 – 7.98 (m, 1H), 7.57 – 7.27 (m, 1H), 6.50 (s, 1H), 6.39 (d, J = 9.6 Hz, 1H), 5.64 (d, J = 9.6 Hz, 1H), 3.94 (d, J = 0.3 Hz, 2H), 1.48 (s, 4H).
2.13 References


Chapter 3: Expanding reactivity and scope of the aza-oxyallyl cations

3.1 Introduction

4-Oxazolidinones are unique heterocyclic motifs present in a number of recently discovered anti-microbial natural products (Figure 3.1.1).\textsuperscript{1-5} These natural products have been isolated from a variety of marine sources and share the common potent ability to inhibit the group of MRSA (Methicillin-resistant \textit{Staphylococcus aureus}) strains of staph. MRSA is an infectious disease that plagues approximately 80,000 people per year and is commonly found to infect post-operative hospital patients.\textsuperscript{6} Unfortunately, most current antibiotics are ineffective for the treatment of MRSA, stimulating research toward the discovery of new anti-MRSA small molecules to combat this infectious disease. The bioactivity of these 4-oxazolidinone containing natural products has stimulated recent interest from the synthetic community.\textsuperscript{6} In 2010, Ye and co-workers established that 4-oxazolidinones could be prepared in enantiopure form through an organo-catalyzed reaction of and a ketene, Scheme 4.1.1.\textsuperscript{7} Later, Pierce and co-workers developed the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.1.1.png}
\caption{4-Oxazolidinones recently discovered natural products}
\end{figure}
methods to prepare 4-oxazolidinones from α-ketoacid chlorides or amides with imines or aldehydes, respectively (Scheme 3.1.2).

While the aim was to synthesize and derivativize the oxazolidinones to target anti-MRSA analogues, we found that they are also of interest to those targeting *Mycobacterium tuberculosis*, Tuberculosis. Tuberculosis (TB) is one of most ancient diseases of mankind, with molecular evidence going back to over 17,000 years. TB is among the top 10 killer infectious diseases and a worldwide pandemic according to the World Health Organization. Developing nations are most affected by TB, although there has been resurgence in the first world due largely due to the spread of HIV/AIDS. There are approximately 8.5 million new active cases and 2 million deaths annually from TB, most of which are preventable with antibiotic treatment. Described below is a convergent method enabled the synthesis of a variety of potential anti-MRSA and anti-TB analogs.
3.2 Access to 4-Oxazolidinones: A (3+2) Cycloaddition Approach

Previous work done in our group has shown that aza-oxyallylic cations can be generated in-situ from α-halohydroxamates through a dehydrohalogenation reaction\(^\text{14}\) or diaza-oxyallylic cations through an oxidative generation using hypervalent iodide reagents.\(^\text{15}\) In both cases, the reactive aza- or diazoxyallylic cations efficiently react with an indole reactant in a (3+2) manner\(^\text{7,16}\) or a diene reactant through a (4+3) pathway.\(^\text{13,14}\) The Wu group and then the Liao group recently uncovered that aza-oxyallylic cations efficiently undergo a formal (3+2) heteroannulation with 1,3-disubstituted indoles to afford pyrroloindolines.\(^\text{7}\) Lin and co-workers also demonstrated a similar approach for the construction of 4-oxazolidinone using aldehyde reactants.\(^\text{17}\) The discovery of (3+2) heteroannulations of indoles with aza-oxyallyl cations prompted us to consider a cycloaddition reaction with different carbonyls to produce 4-oxazolidinone motifs in a one-step reaction from simple starting materials. With continuing interest in oxazolidinones, and previous work on a formal (3+2) cycloaddition of aza-oxyallylic cation recently published, we explored the possibility of undergoing a formal (3+2) heteroannulation. The proposed synthesis would generate the aza-oxyallylic cation from dehydrohalogenation in the presence of a carbonyl reactant to provide a 4-oxazolidinone structural motif. The proposal lies on the polarity of the carbonyl and the efficiency to r

![Scheme 3.2.1 Basic approach to synthesizing 4-oxazolidinones](image-url)
react with the highly electrophilic aza-oxyallylic cation. We surveyed a variety of
aldehydes, ketones, esters, and amide reactants for the modular synthesis to give the
bioactive heterocyclic motif. Although our group had published on the reactivity of the
aza-oxyallylic cation, initial studies began with the optimization of the reaction of α-
halohydroxamate 1 and benzaldehyde 2 (Scheme 3.2.1). Working side by side with
recent graduate student, Dr. Arjun Acharya (Texas A & M University) first attempts
provided trace amount of 3 of the product after 24 hours with solvolysis by
Trifluoroethanol (TFE) as the major product (Table 3.2.1).  

By switching the solvent to a less bulky one, Hexafluoroisopropanol (HFIP) led to
the isolation of the 4-oxazolidinone in good yield (Table 3.2.1, row 5). A screen of
inorganic bases was performed using Sodium carbonate (Na₂CO₃), Potassium carbonate
(K₂CO₃) and Cesium carbonate (Cs₂CO₃) with all three provided moderate-good yields.
With optimized conditions, we explored the substrate scope of the reaction with different
aldehydes. The reactions of aromatic (3, 6a-j) and heteraromatic aldehydes 6k-l
efficiently provided the 4-oxazolidinone products in good to excellent yields, Figure 3.2.2.
Electron withdrawing groups in the para position substantially reduced the rate of
reaction, however electron-donating groups in ortho position enhance the reactivity.

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Table 3.2.1. Results from optimization of (3+2) cyclodaddition, varying solvent and base
56

Figure 3.2.2 Reaction scope with various aldehydes
Saturated 6m, unconjugated 6n, and conjugated 6o–p aldehydes were also found to be compatible with the reaction conditions, providing functionalized 4-oxazolidinones in good to excellent yield. A study of the reaction with esters, amides and ketones demonstrated the versatility of this reaction (Figure 3.2.3). The reaction with ethyl acetate efficiently provided the cyclic ortho-amide 8a in good yield. Reactions with unsaturated lactones provided unique spirocyclic 4-oxazolidinones 8b and 8c in fair to good yield. DMF proved to be an excellent reactant, giving the amino ortho-amide in good yield. The reaction with acetone provided the stable imidate 8e in excellent yield. Attempts to convert this imidate to the oxazolidinone under forcing conditions such as

\[
\begin{align*}
\text{O} & \quad \text{OBn} \\
\text{Br} & \quad \text{H} \\
\text{1} & + \quad \text{Et}_3\text{N} (2 \text{ equiv}) \\
\text{R}^1 \text{O} & \quad \text{R}^2 \text{O} \\
\text{7} & \quad \text{HFIP} \\
\text{8a-g} & \\
\text{O} & \quad \text{OBn} \\
\end{align*}
\]

*Figure 3.2.4* Reaction scope with amides, esters, ketones
heat or acid (formic acid, trifluoroacetic acid and concentrated Hydrochloric acid, HCl) only resulted in decomposition. Further exploration of the reactions (Table 3.2.3) with the cyclohexyl substituted hydroxamate 9 reactions are found to be accelerated to provide fair to excellent yield of products with aromatic, heteroaromatic, non-conjugated and aliphatic aldehydes. Although, primary amides 11 and 13 required elevated temperature and longer reaction time to provided 4-oxazolidinones products with moderate diastereoselectivity (Figure 3.2.2 entry 5 and 6) gave good yields. The isolation of the imidate products 4 and 8e from the reactions and the apparent rearrangement to the 4-oxazolidinone products led to the following mechanistic hypothesis (Scheme 3.2.3).

Consistent with the reports of Wu and co-workers on oxyallyl cation\(^{16}\) and aza-oxyallyl cation intermediates,\(^{7b}\) we believe that the aza-oxyallylic cation undergoes a C-O annulation reaction to directly provide the imidate 4. Wu and co-workers computationally provided support that the (3+2) reaction of oxyallylic and aza-oxyallylic cations with indoles first cyclizes with the oxygen of the carbonyl followed by a rearrangement to the
pyrroloindoline. Their computational results\textsuperscript{7b,17a} were further supported experimentally by the isolation of an $O$-alkylated cycloadduct of the reaction of a 1,3-disubstituted indole with the haloketone, which provided the carbocycle fused indoline product, through an $O$ to $C$ rearrangement.\textsuperscript{16} We therefore propose that the initial cycloaddition of aza-oxyallyl cation occurs via $C$ and $O$ bond formation to provide the imidate 4. This imidate then rearranges to the 4-oxazolidinone 3 upon extended exposure to the reaction conditions or via acid catalysis in the work-up. It is apparent that substitution of the carbonyl reactant greatly changes how facile this rearrangement is. We observed that substituents that provide resonance stabilization to the cation rapidly rearrange to the 4-oxazolidinone products 3, whereas, less stabilizing substituents form more stable imidates, which

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<td>70 (4.2:1)</td>
</tr>
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</table>

\textbf{Figure 3.2.3} Scope with cyclohexyl amide starting material
require an acid catalyzed work up to force rearrangement (6g-I,m-s, 10c-d, 12, 14). The failed rearrangement of the acetone adduct 8e suggests that the stability of the product dramatically slows the rearrangement. Additionally, consistent with our previous reports, substrates without electron releasing groups on nitrogen failed to stabilize aza-oxyallyl cation and trapped by carbonyl functionality.

With a handle on the aza-oxyallyl intermediate reactivity giving the ability to produce a handful of analogs that fit the profile for anti-TB targets, the compounds were sent to collaborator professor James Sacchettini (Texas A&M University) to test activity against the *M. tuberculosis* mc²7000 strain. With the help of graduate student, Juan Shao (Texas A&M University) bioassays were performed on all analogs that were synthesized. *M. tuberculosis* mc27000 were grown as biofilms and treated each analog sent and the percent inhibition of growth was recorded. The assay that was performed was the MIC50, which measures the minimal inhibitory concentration (MIC) affecting 50% of the biofilm. Which is a great bioassay for initial potency testing to find potential active compounds. The three compounds that came back showing any inhibition were three compounds. Results of the MIC50 are shown in Figure 4.2.5 for the three compounds. These three compounds showed inhibition against the mc27000 strain, with the last compound with the smallest concentration showing the same percentage of inhibition. These results of these three compounds are promising, showing that the 4-oxazolidinones are valuable not only as anti-MRSA candidates but for TB as well. Further bioactivity assays are currently being performed on the three compounds of interest.
3.3 Discussion

The synthesis of the 4-oxazolidinones has been a continuation of work previously reported by our group of the versatility of the (3+2)-cycloadditions. This recently published work has shown the growing scope of the (3+2)-cycloaddition reactions of simple α-halohydroxamates and carbonyl compounds. With aldehydes, ketones, esters and amides provide 4-oxazolidinones products in good to excellent yields. Although there were a handful of compounds that were synthesized the few that did not leave room for optimization of the reaction conditions. The alkynes that were performed such as benzonitrile, showed no reaction with initial conditions with only allowing reaction to run 24 hours. As we’ve seen in other cases some reactions take up to 72 hours to be produced, this reaction could possibly fall into that category. Future work on this project is ongoing towards not only expanding the versatility to alkynes, but methods towards a total synthesis to natural products. Bioactivity tests are continuing to be performed with a see

![Figure 3.2.5. MIC50 bioassay of compounds (1-3) at varying concentrations against M. tuberculosis mc²7000](image)
how well these oxazolidinones motifs behave as possible anti-MRSA and anti-TB drug candidates.
3.4 Experimental

All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring, unless otherwise specified. Hexafluoroisopropanol (HFIP) and 2,2,3,3-tetrafluoropropanol (TFP) were purchased from SynQuest. All other reagents and solvents were purchased from Sigma-Aldrich Chemical Company and used without any further purification. TLC information was recorded on Silicycle glass 60 F254 plates and developed by staining with KMnO₄ or ceric ammonium molybdate (CAM). Purification of reaction products was carried out by flash chromatography using Silicycle Siliaflash® P60 (230-400 mesh). ¹H NMR spectra were measured on Varian MR400 (400 MHz), or Varian 500 (500 MHz) spectrometers and are reported in ppm (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad; integration; coupling constant(s) in Hz), using TMS as an internal standard (TMS at 0.00 ppm) in CDCl₃. ¹³C NMR spectra were recorded on V400 or V500 spectrometer and reported in ppm using solvent as an internal standard (CDCl₃ at 77.16 ppm). Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR with a diamond ATR and data are reported as cm⁻¹ (br = broad, s = strong). High-resolution mass spectra (HRMS) were obtained using an Agilent 6230 TOF LC/MS with an electrospray (ESI) source with purine and HP-0921 as an internal calibrants.

General Procedure for the (3+2)-cycloaddition of with α-halohydroxamates with carbonyl compounds:

To a solution of α-haloamide (1 equiv) in HFIP (1.0 M) was added 1.1 equiv carbonyl compound (2 equiv for 8b, 8c, 8e, 12 and 14, 10 equiv. for 8a, 8d and 0.65
equiv for 8f, 8g) and triethylamine (2 equiv) and stirred at room temperature until complete consumption of starting material. The reaction progress was monitored by TLC (8:2 or 2:1 hexanes : ethyl acetate). TFA (1.4 to 2 equiv) was added and stirred for another 10-20 min only for 6d-e,h-j,n-t, 10c-d, 12 and 14. The volatiles were concentrated under reduced pressure and the residue was purified via flash column chromatography (8:2 to 7:3, hexanes: ethyl acetate) to provide desired cycloadducts.

3-(Benzyloxy)-5,5-dimethyl-2-phenyl-1,3-oxazolidin-4-one (3)

Prepared in 93 % yield (102 mg, 0.34 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with benzaldehyde (45 µL, 0.40 mmol) via the general procedure. R_f = 0.69 (3:1, hexanes: ethyl acetate); mp 69.4 – 71.9 °C; 1H NMR (500 MHz, CDCl_3): δ 7.51 – 7.47 (m, 2H), 7.43 – 7.36 (m, 5H), 7.34 – 7.30 (m, 2H), 7.29 – 7.25 (m, 1H), 6.33 (s, 1H), 5.01 (s, 2H), 1.59 (s, 3H), 1.54 (s, 3H); 13C NMR (126 MHz, CDCl_3): δ 157.69, 137.64, 134.91, 130.34, 128.48, 128.33, 128.20, 127.72, 127.03, 104.21, 80.24, 76.47, 26.16, 24.09; FT-IR (neat): 3062, 3036, 2981, 2931, 2871, 1680 cm⁻¹; HRESI-MS: calculated for C_{18}H_{19}NO_{3}Na (M+Na)^+ 320.1257, observed 320.1252.
**N-(Benzyloxy)-5,5-dimethyl-2-phenyl-1,3-dioxolan-4-imine (4)**

![Chemical structure of N-(Benzyloxy)-5,5-dimethyl-2-phenyl-1,3-dioxolan-4-imine (4)](image)

Prepared in 18 % yield (19 mg, 0.07 mmol) as a white solid from the reaction of 2-bromo-2-methyl-\(N\)-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with benzaldehyde (45 µL, 0.40 mmol) *via* the general procedure. \(R_f = 0.73\) (8:2, hexanes: ethyl acetate); mp 110.1 – 112.5 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.48 – 7.41 (m, 5H), 7.33 – 7.27 (m, 3H), 7.19 – 7.16 (m, 2H), 5.61 (s, 1H), 4.92 (d, \(J = 10.1\) Hz, 1H), 4.42 (d, \(J = 10.1\) Hz, 1H), 1.56 (s, 3H), 1.42 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 172.5, 135.9, 134.4, 130.4, 129.1, 129.0, 128.7, 128.4, 127.9, 87.7, 78.2, 78.2, 25.4, 22.7; FT-IR (neat): 3065, 3034, 2978, 2931, 2883, 1726 cm\(^{-1}\); HRESI-MS: calculated for C\(_{18}\)H\(_{19}\)NO\(_3\)Na (M+Na\(^+\)) 320.1257, observed 320.1252.

**3-(Benzyloxy)-5,5-dimethyl-2-(2-methylphenyl)-1,3-oxazolidin-4-one (6a)**

![Chemical structure of 3-(Benzyloxy)-5,5-dimethyl-2-(2-methylphenyl)-1,3-oxazolidin-4-one (6a)](image)

Prepared in 88 % yield (100 mg, 0.32 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-\(N\)-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 2-methylbenzaldehyde (45 µL, 0.40 mmol) *via* the general procedure. \(R_f = 0.42\) (8:2,
hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.37 – 7.24 (m, 5H), 7.21 – 7.19 (m, 1H), 7.16 (dd, $J = 7.8$, 1.6 Hz, 2H), 5.93 (s, 1H), 4.94 (d, $J = 10.2$ Hz, 1H), 4.46 (d, $J = 10.2$ Hz, 1H), 2.39 (s, 3H), 1.54 (s, 3H), 1.43 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.5, 137.4, 134.2, 133.0, 130.8, 129.7, 129.4, 128.8, 128.2, 127.9, 126.2, 84.8, 78.0, 77.9, 24.8, 22.4, 18.6; FT-IR (neat): 3064, 3032, 2977, 2931, 1727 cm$^{-1}$; HRESI-MS: calculated for C$_{19}$H$_{21}$NO$_3$Na (M+Na)$^+$ 334.1414, observed 334.1406.

3-(Benzyloxy)-2-(2-hydroxyphenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6b)

Prepared in 89 % yield (102 mg, 0.33 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with salicyaldehyde (43 µL, 0.40 mmol) via the general procedure. $R_f = 0.50$ (7:3, hexanes: ethyl acetate); mp 158.3 – 159.9 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36 (ddd, $J = 8.1$, 7.5, 1.7 Hz, 1H), 7.32 – 7.23 (m, 5H), 7.21 – 7.13 (m, 2H), 6.98 (td, $J = 7.5$, 1.1 Hz, 1H), 6.94 (dd, $J = 8.2$, 1.1 Hz, 1H), 5.90 (s, 1H), 4.84 (d, $J = 9.8$ Hz, 1H), 4.37 (d, $J = 9.9$ Hz, 1H), 1.60 (s, 3H), 1.44 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.5, 156.4, 134.0, 131.8, 129.8, 129.7, 129.3, 128.9, 128.8, 128.6, 128.4, 120.2, 119.1, 117.2, 86.5, 78.9, 78.7, 78.2, 24.8, 21.9; FT-IR (neat): 3253, 3036, 2881, 2928, 2890, 1700, 1605 cm$^{-1}$;
HRESI-MS: calculated for $\text{C}_{18}\text{H}_{19}\text{NO}_4\text{Na} (\text{M+Na})^+ 336.1206$, observed 336.1205.

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**3-(Benzyloxy)-2-(2-bromophenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6c)**

![Chemical structure](image)

Prepared in 83 % yield (114 mg, 0.34 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-$N$-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 2-bromobenzaldehyde (47 µL, 0.40 mmol) via the general procedure. $R_f = 0.35$ (8:2, hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58 (dd, $J = 8.0$, 1.1 Hz, 1H), 7.50 (dd, $J = 7.8$, 1.7 Hz, 1H), 7.36 (td, $J = 7.6$, 0.9 Hz, 1H), 7.31 – 7.21 (m, 6H), 6.20 (s, 1H), 4.99 (d, $J = 10.3$ Hz, 1H), 4.65 (d, $J = 10.3$ Hz, 1H), 1.53 (s, 3H), 1.43 (s, 3H); $\delta^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.2, 134.6, 134.2, 133.2, 131.4, 129.5, 129.5, 129.0, 128.5, 127.9, 124.1, 86.1, 78.3, 78.0, 25.1, 23.1; FT-IR (neat): 3064, 3032, 2978, 2930, 1726 cm$^{-1}$; HRESI-MS: calculated for $\text{C}_{18}\text{H}_{18}\text{BrNO}_3\text{Na} (\text{M+Na})^+ 398.0368$, observed 398.0346.
3-(Benzylxy)-2-(3-bromophenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6d)

Prepared in 85 % yield (117 mg, 0.35 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 3-bromobenzaldehyde (47 µL, 0.40 mmol) via the general procedure. 

\[ R_f = 0.35 \] (8:2, hexanes: ethyl acetate);

\[
{^1}H \text{ NMR (500 MHz, CDCl}_3\) : } \delta 7.60 - 7.53 (m, 2H), 7.40 - 7.24 (m, 5H), 7.22 - 7.17 (m, 2H), 5.53 (s, 1H), 4.96 (d, \( J = 10.3 \) Hz, 1H), 4.51 (d, \( J = 10.3 \) Hz, 1H), 1.56 (s, 3H), 1.42 (s, 3H);
\]

\[
{^{13}}C \text{ NMR (101 MHz, CDCl}_3\) : } \delta 172.6, 138.2, 134.2, 133.3, 130.8, 130.2, 129.6, 129.1, 128.5, 126.4, 122.7, 86.9, 78.3, 78.3, 25.3, 22.7; FT-IR (neat): 3064, 3032, 2931, 2884, 1728 cm\(^{-1}\); HRESI-MS: calculated for C\(_{18}\)H\(_{18}\)BrNO\(_3\)Na (M+Na)\(^+\) 398.0368, observed 398.0352.

3-(Benzylxy)-2-(4-bromophenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6e)

Prepared in 89 % yield (122 mg, 0.33 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 4-
bromobenzaldehyde (74.7 mg, 0.40 mmol) via the general procedure. \( R_f = 0.51 \) (3:1, hexanes: ethyl acetate); mp 87.2 – 88.6 °C; \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\):} \( \delta \) 7.55 – 7.52 (m, 2H), 7.35 – 7.28 (m, 5H), 7.19 – 7.17(m, 2H), 5.54 (s, 1H), 4.95 (d, \( J = 10.4 \) Hz, 1H), 4.52 (d, \( J = 10.4 \) Hz, 1H), 1.55 (s, 3H); \(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\):} \( \delta \) 172.65, 134.97, 134.34, 131.88, 129.62, 129.47, 129.05, 128.50, 124.46, 87.08, 78.23, 78.19, 25.37, 22.71; FT-IR (neat): 3060, 3032, 2980, 2929, 2895, 1709 cm\(^{-1}\); HRESI-MS: calculated for C\(_{18}\)H\(_{18}\)BrNO\(_3\)Na (M+Na\(^+\)) 398.0368, observed 398.0355.

3-(Benzyloxy)-2-(4-chlorophenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6f)

![Chemical Structure of 3-(Benzyloxy)-2-(4-chlorophenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6f)](image)

Prepared in 91 % yield (110 mg, 0.33 mmol) as a white solid from the reaction of 2-bromo-2-methyl-\(N\)-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 4-chlorobenzaldehyde (57 mg, 0.40 mmol) via the general procedure. \( R_f = 0.51 \) (4:1, hexanes: ethyl acetate); mp 69.0 – 71.1 °C; \(^1\text{H} \text{NMR (500 MHz, CDCl}_3\):} \( \delta \) 7.39 – 7.26 (m, 7H), 7.19 – 7.17(m, 2H), 5.55 (s, 1H), 4.94 (d, \( J = 10.4 \) Hz, 1H), 4.51 (d, \( J = 10.4 \) Hz, 1H), 1.55 (s, 3H), 1.41 (s, 3H); \(^{13}\text{C} \text{NMR (126 MHz, CDCl}_3\):} \( \delta \) 172.66, 136.19, 134.43, 134.33, 129.61, 129.20, 129.05, 128.93, 128.49, 87.02, 78.24, 78.20, 25.35, 22.68; FT-IR (neat): 3093, 3063, 3029, 2881, 2931, 2890, 1738 cm\(^{-1}\); HRESI-MS: calculated for
\[ \text{C}_{18}\text{H}_{18}\text{ClNO}_3\text{Na} (\text{M+Na})^+ \text{ 354.0867, observed 354.0857.} \]

4-[3-(Benzyloxy)-5,5-dimethyl-4-oxo-1,3-oxazolidin-2-yl]benzonitrile (6g)

Prepared in 75 \% yield (96.6 mg, 0.30 mmol) as a pale yellow solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 4-cyanobenzaldehyde (42 \mu L, 0.40 mmol) via the general procedure. \( R_f = 0.26 \) (8:2, hexanes: ethyl acetate); mp 75.9 – 77.8 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.70 – 7.64 (m, 2H), 7.52 – 7.46 (m, 2H), 7.35 – 7.32 (m, 1H), 7.31 – 7.26 (m, 2H), 7.18 – 7.15 (m, 2H), 5.58 (s, 1H), 4.97 (d, \( J = 10.6 \) Hz, 1H), 4.57 (d, \( J = 10.6 \) Hz, 1H), 1.55 (s, 3H), 1.43 (s, 3H); \( \delta \) \(^13\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 172.7, 140.8, 134.2, 132.4, 129.6, 129.2, 128.5, 128.5, 118.2, 114.0, 86.7, 78.5, 78.1, 25.3, 22.8; FT-IR (neat):3099, 3064, 2985, 2935, 2887, 2231, 1739 cm\(^{-1}\); HRESI-MS: calculated for \( \text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3 \) (M+H)^+ 323.1390, observed 313.1395.
3-(Benzyloxy)-5,5-dimethyl-2-(4-nitrophenyl)-1,3-oxazolidin-4-one (6h)

![Chemical Structure]

Prepared in 77 % yield (96.6 mg, 0.28 mmol) as a pale yellow solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 4-nitrobenzaldehyde (61 mg, 0.40 mmol) via the general procedure. $R_f = 0.27$ (8:2, hexanes: ethyl acetate); mp 91.7 – 93.9 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.25 – 8.18 (m, 2H), 7.58 – 7.51 (m, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.25 (m, 2H), 7.19 – 7.14 (m, 2H), 5.62 (s, 1H), 4.99 (d, $J = 10.7$ Hz, 1H), 4.60 (d, $J = 10.7$ Hz, 1H), 1.57 (s, 3H), 1.45 (s, 3H); $\delta$ $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.8, 149.0, 142.6, 134.2, 129.6, 129.1, 128.7, 128.5, 123.7, 86.4, 78.5, 78.1, 25.3, 22.8 FT-IR (neat): 3116, 3087, 2980, 2920, 2894, 2850, 1734 cm$^{-1}$; HRESI-MS: calculated for C$_{18}$H$_{18}$N$_2$O$_5$Na(M+Na)$^+$ 365.1113, observed 365.1103.
3-(Benzyloxy)-2-(3,5-dimethoxyphenyl)-5,5-dimethyl-1,3-oxazolidin-4-one (6i)

Prepared in 70 % yield (91.7 mg, 0.26 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 3,5-dimethoxybenzaldehyde (56 µL, 0.40 mmol) via the general procedure. $R_f = 0.35$ (8:2, hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.33 – 7.27 (m, 3H), 7.26 – 7.22 (m, 2H), 6.61 (d, $J = 2.3$ Hz, 2H), 6.53 (t, $J = 2.3$ Hz, 1H), 5.53 (s, 1H), 4.96 (d, $J = 10.2$ Hz, 1H), 4.52 (d, $J = 10.2$ Hz, 1H), 3.80 (s, 6H), 1.55 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.3, 161.0, 138.2, 134.4, 129.6, 129.0, 128.4, 105.6, 102.1, 87.6, 78.2, 78.1, 55.4, 25.3, 22.7; FT-IR (neat): 2975, 2934, 2840, 1727, 1598 cm$^{-1}$; HRESI-MS: calculated for C$_{20}$H$_{23}$NO$_5$Na (M+Na)$^+$ 380.1468, observed 380.1458.
3-(Benzyloxy)-5,5-dimethyl-2-(naphthalen-2-yl)-1,3-oxazolidin-4-one (6j)

![Chemical Structure](image)

Prepared in 85% yield (108 mg, 0.31 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 2-naphthaldehyde (63 mg, 0.40 mmol) via the general procedure. $R_f = 0.31$ (8:2, hexanes:ethyl acetate); mp 120.0 – 121.1 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.91 (d, $J = 8.4$ Hz, 1H), 7.90 – 7.87 (m, 3H), 7.61 – 7.52 (m, 3H), 7.28 – 7.17 (m, 3H), 7.14 – 7.08 (m, 2H), 5.78 (s, 1H), 4.92 (d, $J = 10.3$ Hz, 1H), 4.43 (d, $J = 10.3$ Hz, 1H), 1.61 (s, 3H), 1.47 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.7, 134.4, 134.3, 133.1, 132.8, 129.6, 128.9, 128.9, 128.5, 128.4, 128.3, 127.9, 127.1, 126.6, 124.0, 88.0, 78.3, 78.2, 25.4, 22.8; FT-IR (neat): 3058, 3030, 2935, 2892, 1732 cm$^{-1}$; HRESI-MS: calculated for C$_{22}$H$_{21}$NO$_3$Na ($M+Na$)$^+$ 370.1419, observed 370.1407.

3-(Benzyloxy)-5,5-dimethyl-2-(5-methylfuran-2-yl)-1,3-oxazolidin-4-one (6k)

![Chemical Structure](image)

Prepared in 77% yield (44 mg, 0.15 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (53 mg, 0.19 mmol) with 5-
methylfurfural (25 µL, 0.21 mmol) via the general procedure. \( R_f = 0.43 \) (8:2, hexanes: ethyl acetate); mp 73.5 – 75.2 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.37 – 7.32 (m, 3H), 7.32 – 7.28 (m, 2H), 6.44 (d, \( J = 3.2 \) Hz, 1H), 6.00 (dq, \( J = 2.8 \), 0.9 Hz, 1H), 5.56 (s, 1H), 5.01 (d, \( J = 10.4 \) Hz, 1H), 4.63 (d, \( J = 10.4 \) Hz, 1H), 2.32 (s, 3H), 1.54 (s, 3H), 1.40 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 171.5, 154.4, 146.4, 134.5, 129.6, 129.0, 128.4, 113.6, 106.7, 81.1, 78.2, 78.0, 25.1, 23.7, 13.7; FT-IR (neat): 3134, 3033, 2978, 2933, 2900, 2866, 1729 cm\(^{-1}\); HRESI-MS: calculated for C\(_{17}\)H\(_{19}\)NO\(_4\)Na (M+Na)\(^+\) 324.1206, observed 324.1199.

**tert-Butyl 2-(3-benzyloxy-5,5-dimethyl-4-oxo-1,3-oxazolidin-2-yl)-1H-pyrrole-1-carboxylate (6l)**

![Structure of 6l](image)

Prepared in 91 % yield (129 mg, 0.33 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with N-Boc-pyrrole-2-carbaldehyde (48 µL, 0.40 mmol) via the general procedure. \( R_f = 0.38 \) (8:2, hexanes: ethyl acetate); mp 98.8 – 100.5 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.33 - 7.31 (m, 5H), 7.30 (dd, \( J = 3.3 \), 1.8 Hz, 1H), 6.47 (ddd, \( J = 3.5 \), 1.8, 0.6 Hz, 1H), 6.35 (s, 1H), 6.19 (t, \( J = 3.4 \) Hz, 1H), 5.10 (d, \( J = 10.4 \) Hz, 1H), 4.84 (d, \( J = 10.4 \) Hz, 1H), 1.53 (s, 9H), 1.40 (s, 3H), 1.39 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta \) 171.3, 148.5, 134.6, 130.5, 129.5, 129.0, 128.4, 123.4, 114.6, 110.4, 84.6, 80.6, 77.8, 77.6, 27.8, 25.2, 24.3; FT-IR
(neat): 2884, 2936, 1740, 1726 cm$^{-1}$; HRESI-MS: calculated for $C_{21}H_{26}N_2O_5Na$ (M+Na)$^+$ 409.1734, observed 409.1728.

3-(Benzyloxy)-2-cyclohexyl-5,5-dimethyl-1,3-oxazolidin-4-one (6m)

![Chemical Structure of 3-(Benzyloxy)-2-cyclohexyl-5,5-dimethyl-1,3-oxazolidin-4-one (6m)]

Prepared in 76 % yield (84.5 mg, 0.28 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with cyclohexanecarboxaldehyde (49 µL, 0.40 mmol) via the general procedure. $R_f = 0.51$ (8:2, hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 – 7.42 (m, 2H), 7.41 – 7.36 (m, 3H), 5.17 (d, $J = 10.5$ Hz, 1H), 4.97 (d, $J = 10.5$ Hz, 1H), 4.55 (d, $J = 2.1$ Hz, 1H), 1.82 – 1.73 (m, 2H), 1.70 – 1.60 (m, 2H), 1.59 – 1.52 (m, 2H), 1.38 (s, 3H), 1.29 (s, 3H), 1.26 – 1.10 (m, 5H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.0, 134.7, 129.7, 129.1, 128.6, 89.5, 77.3, 77.2, 39.4, 27.4, 26.3, 25.7, 24.7, 24.6, 23.3; FT-IR (neat): 3032, 2977, 2928, 2854, 1722 cm$^{-1}$; HRESI-MS: calculated for $C_{18}H_{25}NO_5Na$ (M+Na)$^+$ 326.1727, observed 326.1720.
3-(Benzyloxy)-2-(cyclohex-3-en-1-yl)-5,5-dimethyl-1,3-oxazolidin-4-one (6n)

Prepared in 73 % yield (80.6 mg, 0.27 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with cyclohex-3-ene-1-carbaldehyde (48 µL, 0.40 mmol) via the general procedure. $R_f = 0.48$ (8:2, hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.47 – 7.42 (m, 5H), 7.41 – 7.36 (m, 5H), 5.70 – 5.65 (m, 4H), 5.19 (d, $J = 2.5$ Hz, 1H), 5.17 (d, $J = 2.5$ Hz, 1H), 4.99 (d, $J = 8.7$ Hz, 1H), 4.97 (d, $J = 8.8$ Hz, 1H), 4.65 (d, $J = 2.4$ Hz, 1H), 4.64 (d, $J = 1.8$ Hz, 1H), 2.12 – 1.86 (m, 10H), 1.70 – 1.60 (m, 2H), 1.48 – 1.39 (m, 2H), 1.39 (s, 3H), 1.39 (s, 3H), 1.31 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.2, 172.0, 134.6, 134.6, 129.7, 129.2, 129.2, 128.6, 128.6, 127.2, 126.7, 125.7, 125.7, 89.0, 88.7, 77.3, 77.3, 77.3, 35.9, 35.7, 26.2, 25.3, 24.9, 24.8, 24.7, 23.5, 23.4, 23.4, 23.3, 21.0; FT-IR (neat): 3025, 2977, 2929, 2842, 1722 cm$^{-1}$; HRESI-MS: calculated for C$_{18}$H$_{23}$NO$_3$Na (M+Na)$^+$ 324.1576, observed 324.1564.
3-(Benzyloxy)-2-ethenyl-5,5-dimethyl-1,3-oxazolidin-4-one (6o)

Prepared in 72 % yield (65 mg, 0.26 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with acrolein (27 µL, 0.40 mmol) via the general procedure. $R_f = 0.52$ (8:2, hexanes: ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.43 – 7.33 (m, 5H), 5.70 (ddd, $J = 17.3$, 10.0, 7.7 Hz, 1H), 5.52 – 5.42 (m, 2H), 5.09 (d, $J = 10.4$ Hz, 1H), 5.01 (d, $J = 7.7$ Hz, 1H), 4.93 (d, $J = 10.4$ Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 172.2, 134.6, 134.2, 129.8, 129.1, 128.5, 123.2, 87.7, 78.3, 77.7, 25.5, 23.2; FT-IR (neat): 3056, 3033, 2979, 2932, 2882, 1726 cm$^{-1}$; HRESI-MS: calculated for C$_{14}$H$_{18}$NO$_3$ (M+H)$^+$ 248.1287, observed 270.1286.

3-(Benzyloxy)-5,5-dimethyl-2-(2-methylprop-1-en-1-yl)-1,3-oxazolidin-4-one (6p)

Prepared in 92 % yield (93 mg, 0.34 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 3-
methylbut-2-enal (39 µL, 0.40 mmol) via the general procedure. \( R_f = 0.53 \) (8:2, hexanes: ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.42 - 7.33 \) (m, 5H), \( 5.43 \) (d, \( J = 8.6 \) Hz, 1H), \( 5.09 \) (d, \( J = 10.6 \) Hz, 1H), \( 5.04 \) (ddt, \( J = 8.6, 2.7, 1.4 \) Hz, 1H), \( 4.92 \) (d, \( J = 10.6 \) Hz, 1H), \( 1.77 \) (d, \( J = 1.3 \) Hz, 3H), \( 1.70 \) (d, \( J = 1.3 \) Hz, 3H), \( 1.43 \) (s, 3H), \( 1.34 \) (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta 172.4, 143.6, 134.8, 129.7, 128.9, 128.4, 121.1, 82.8, 78.3, 77.4, 26.1, 25.5, 22.9, 18.2; \) FT-IR (neat): 3032, 2977, 2932, 2882, 1726 cm\(^{-1}\); HRESI-MS: calculated for C\(_{16}\)H\(_{21}\)NO\(_3\)Na (M+Na)+ 298.1421, observed 298.1406.

3-(Benzyloxy)-2,5,5-trimethyl-1,3-oxazolidin-4-one (6q)

\[
\begin{align*}
\text{O} & \quad \text{N-OBn} \\
\text{O} & \quad \text{CH}_3
\end{align*}
\]

Prepared in 70 % yield (60 mg, 0.26 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with acetaldehyde (42 µL, 0.73 mmol) via the general procedure. \( R_f = 0.36 \) (8:2, hexanes: ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 7.48 - 7.34 \) (m, 5H), \( 5.13 \) (d, \( J = 10.6 \) Hz, 1H), \( 4.99 \) (d, \( J = 10.6 \) Hz, 1H), \( 4.84 \) (q, \( J = 5.3 \) Hz, 1H), \( 1.42 \) (s, 3H), \( 1.31 \) (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \( \delta 172.5, 134.7, 129.7, 129.1, 128.6, 83.5, 78.1, 77.5, 77.4, 25.4, 22.7, 20.0; \) FT-IR (neat): 3033, 2982, 2933, 2882, 1726 cm\(^{-1}\); HRESI-MS: calculated for C\(_{13}\)H\(_{17}\)NO\(_3\)Na (M+Na)+ 258.1106, observed 258.1093.
3-(Benzylmethyl)-5,5-dimethyl-2-propyl-1,3-oxazolidin-4-one (6r)

Prepared in 64% yield (61.7 mg, 0.23 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with butanal (37 µL, 0.40 mmol) via the general procedure. 

\( R_f = 0.60 \) (8:2, hexanes: ethyl acetate); \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.46 – 7.41 (m, 2H), 7.41 – 7.37 (m, 3H), 5.15 (d, \( J = 10.6 \) Hz, 1H), 4.97 (d, \( J = 10.6 \) Hz, 1H), 4.71 (dd, \( J = 6.3, 2.8 \) Hz, 1H), 1.75 – 1.67 (m, 1H), 1.56 – 1.47 (m, 1H), 1.40 (s, 3H), 1.45 – 1.32 (m, 3H), 1.30 (s, 2H), 0.91 (t, \( J = 7.4 \) Hz, 3H); \( ^{13}\text{C} \) NMR (101 MHz, CDCl\(_3\)): \( \delta \) 172.20, 134.71, 129.68, 129.13, 128.58, 86.26, 77.79, 77.38, 35.18, 25.16, 23.02, 16.05, 13.84; FT-IR (neat): 3033, 2961, 2934, 2874, 1724 cm\(^{-1}\); HRESI-MS: calculated for C\(_{15}\)H\(_{21}\)NO\(_3\)Na (M+Na)\(^+\) 286.1419, observed 286.1406.

2-Heptyl-3-(benzyloxy)-5,5-dimethyl-1,3-oxazolidin-4-one (6s)

Prepared in 71% yield (83 mg, 0.26 mmol) as a ## from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with octanal (63 µL, 0.40 mmol) via the general procedure. 

\( R_f = 0.65 \) (8:2, hexanes: ethyl acetate); \( ^1\text{H} \) NMR
(500 MHz, CDCl₃): δ 7.45 – 7.41 (m, 2H), 7.41 – 7.36 (m, 3H), 5.14 (d, J = 10.6 Hz, 1H), 4.97 (d, J = 10.6 Hz, 1H), 4.71 (dd, J = 6.3, 2.7 Hz, 1H), 1.72 (dddd, J = 14.1, 9.5, 6.0, 2.8 Hz, 1H), 1.56 – 1.45 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.27 (br.s, 10H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 172.2, 134.7, 129.7, 129.1, 128.6, 86.4, 77.8, 77.4, 33.1, 31.7, 29.3, 29.1, 25.2, 23.0, 22.7, 22.6, 14.0; FT-IR (neat): 2926, 2856, 1725 cm⁻¹; HRESI-MS: calculated for C₁₉H₂₉NO₃Na (M+Na)⁺ 342.2045, observed 342.2033.

3-(Benzyloxy)-2-ethoxy-2,5,5-trimethyl-1,3-oxazolidin-4-one (8a)

\[
\begin{align*}
\text{O} & \quad \text{N-OBn} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

Prepared in 77 % yield (85 mg, 0.28 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with ethyl acetate (0.36 mL, 3.7 mmol) via the general procedure. Rᵢ = 0.45 (8:2, hexanes: ethyl acetate); ¹H NMR (500 MHz, CDCl₃): δ 7.49 – 7.44 (m, 2H), 7.41 – 7.33 (m, 3H), 5.14 (d, J = 9.9 Hz, 1H), 5.06 (d, J = 10.0 Hz, 1H), 3.60 (dq, J = 9.0, 7.1 Hz, 1H), 3.43 (dq, J = 9.0, 7.1 Hz, 1H), 1.55 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 170.8, 134.5, 129.5, 129.0, 128.5, 109.0, 78.4, 77.3, 57.5, 25.7, 24.6, 24.6, 14.8; FT-IR (neat): 3033, 2980, 2935, 2892, 1735 cm⁻¹; HRESI-MS: calculated for C₁₅H₂₁NO₄ (M)⁺ 279.1470, observed 279.1470.
4-(Benzyloxy)-2,2,7,9-pentamethyl-1,6-dioxa-4-azaspiro[4.5]dec-9-en-3-one

(8b)

Prepared in 49 % yield (0.18 g, 0.54 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (0.3 g, 1.1 mmol) with 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.29 mL, 2.2 mmol) via the general procedure. $R_f = 0.43$ (8:2, hexanes: ethyl acetate); $^1H$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.45 – 7.40 (m, 2H), 7.39 – 7.33 (m, 3H), 5.12 (d, $J = 10.3$ Hz, 1H), 5.05 (d, $J = 10.3$ Hz, 1H), 4.32 (s, 1H), 1.77 (d, $J = 1.0$ Hz, 3H), 1.59 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 171.6, 156.5, 135.0, 129.7, 128.7, 128.3, 104.2, 101.4, 94.6, 78.6, 76.7, 28.4, 25.5, 25.4, 23.2, 19.8; FT-IR (neat): 3033, 2985, 2940, 1734, 1681 cm$^{-1}$; HRESI-MS calculated for C$_{18}$H$_{23}$NO$_5$Na (M+Na)$^+$ 356.1468, observed 356.1467.

3'-(Benzyloxy)-5',5'-dimethyl-4'H-spiro[1-benzopyran-2,2'-[1,3]oxazolidin]-4'-one (8c)

3'-(Benzyloxy)-5',5'-dimethyl-4'H-spiro[1-benzopyran-2,2'-[1,3]oxazolidin]-4'-one (8c)
Prepared in 79 % yield (98 mg, 0.29 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with coumarin (107.3 mg, 0.73 mmol) via the general procedure. \( R_f = 0.44 \) (8:2, hexanes: ethyl acetate); mp 111.6 – 113.9 °C; \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 7.36 – 7.22 (m, 6H), 7.19 (dd, \( J = 7.5, 1.5 \) Hz, 1H), 7.01 (td, \( J = 7.5, 1.0 \) Hz, 1H), 6.96 (d, \( J = 8.2 \) Hz, 1H), 6.86 (d, \( J = 9.7 \) Hz, 1H), 5.36 (d, \( J = 9.7 \) Hz, 1H), 5.13 (d, \( J = 10.2 \) Hz, 1H), 5.01 (d, \( J = 10.2 \) Hz, 1H), 1.62 (s, 3H), 1.46 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}): \( \delta \) 171.2, 151.3, 134.4, 130.9, 130.1, 129.8, 129.0, 128.4, 127.2, 122.0, 117.9, 117.8, 116.1, 106.8, 78.8, 78.1, 25.9, 25.5; FT-IR (neat): 3076, 2979, 2930, 1742, 1649 cm\(^{-1}\); HRESI-MS: calculated for C\textsubscript{20}H\textsubscript{19}NO\textsubscript{4}Na (M+Na)\(^+\) 360.1206, observed 360.1200.

\[ \text{3-}(\text{Benzyloxy})-2-(\text{dimethylamino})-5,5-\text{dimethyl-1,3-oxazolidin-4-one \ (8d)} \]

Prepared in 72 % yield (76 mg, 0.26 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with DMF (0.28 mL, 3.7 mmol) via the general procedure. \( R_f = 0.30 \) (8:2, hexanes: ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 7.48 – 7.46 (m, 2H), 7.40 – 7.37 (m, 3H), 5.23 (s, 1H), 5.15 (d, \( J = 10.4 \) Hz, 1H), 5.01 (d, \( J = 10.4 \) Hz, 1H), 2.39 (s, 6H), 1.41 (s, 3H), 1.31 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}): \( \delta \) 171.24, 134.73, 129.65, 129.06, 128.49, 98.70,
77.44, 76.61, 36.78, 24.69, 24.49. FT-IR (neat): 3064, 3033, 2979, 2946, 2879, 2852, 2992, 1728 cm\(^{-1}\); HRESI-MS: calculated for C\(_{14}\)H\(_{21}\)N\(_2\)O\(_3\)(M+H)\(^+\) 265.1547, observed 265.1537.

\[N-(\text{Benzyloxy})-2,2,5,5\text{-tetramethyl-1,3-dioxolan-4-imine (8e)}\]

Prepared in 84 % yield (77.5 mg, 0.31 mmol) as a white solid from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with acetone (30 µL, 0.40 mmol) via the general procedure. R\(_f\) = 0.69 (8:2, hexanes: ethyl acetate); mp 53.5 – 55.6 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.40 – 7.37 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 1H), 5.01 (s, 1H), 1.55 (s, 3H), 1.47 (s, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 158.7, 137.9, 128.2, 128.1, 127.6, 113.2, 79.9, 77.3, 28.7, 28.3; FT-IR (neat): 2889, 2934, 2877, 1682 cm\(^{-1}\); HRESI-MS: calculated for C\(_{14}\)H\(_{19}\)NO\(_3\) (M+H)\(^+\) 250.1443, observed 250.1434.

\[3-(\text{Benzyloxy})-2,5,5\text{-trimethyl-2-phenyl-1,3-oxazolidin-4-one (8f)}\]
Prepared in 69 % yield (52.2 mg, 0.17 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with acetophenone (30 µL, 0.24 mmol) via the general procedure. $R_f = 0.62$ (8:3, hexanes: ethyl acetate); mp ### °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 – 7.57 (m, 2H), 7.42 – 7.36 (m, 3H), 7.35 – 7.30 (m, 5H), 5.04 (d, $J = 9.6$ Hz, 1H), 4.61 (d, $J = 9.6$ Hz, 1H), 1.81 (s, 3H), 1.53 (s, 3H), 1.44 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 170.3, 141.5, 134.3, 129.6, 129.0, 128.8, 128.4, 125.8, 92.3, 78.6, 77.2, 26.4, 26.2, 25.8; FT-IR (neat): 2981, 2931, 1728, 1450 cm$^{-1}$; HRESI-MS: calculated for C$_{19}$H$_{21}$NO$_3$Na (M+Na)$^+$ 334.1419, observed 334.1411.

3-(Benzyloxy)-2-(4-methoxyphenyl)-2,5,5-trimethyl-1,3-oxazolidin-4-one (8g)

Prepared in 62 % yield (51.2 mg, 0.15 mmol) as a colorless oil from the reaction of 2-bromo-2-methyl-N-(phenylmethoxy)propanamide (100 mg, 0.37 mmol) with 4-methoxyacetophenone (40 µL, 0.24 mmol) via the general procedure. $R_f = 0.6$ (8:3, hexanes: ethyl acetate); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.52 – 7.47 (m, 2H), 7.36 – 7.29 (m, 5H), 6.93 – 6.87 (m, 2H), 5.01 (d, $J = 9.7$ Hz, 1H), 4.61 (d, $J = 9.7$ Hz, 1H), 3.82 (s, 3H), 1.79 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 170.3, 160.0, 134.4, 134.0, 129.6, 128.9, 128.4, 127.4, 113.7, 92.2, 78.6, 77.2 55.3, 26.4, 26.1,
26.0; FT-IR (neat): 2981, 2931, 1724, 1612 cm\(^{-1}\); HRESI-MS: calculated for C\(_{20}\)H\(_{24}\)NO\(_4\) (M+H)\(^+\) 364.1519, observed 342.1511.

3-(Benzyloxy)-2-phenyl-1-oxa-3-azaspiro[4.5]decan-4-one (10a)

[Structure image]

Prepared in 96 % yield (105.5 mg, 0.35 mmol) as a white solid from the reaction of N-(benzyloxy)-1-bromocyclohexane-1-carboxamide (100 mg, 0.32 mmol) with benzaldehyde (36 \(\mu\)L, 0.35 mmol) via the general procedure. \(R_f = 0.62\) (8:2, hexanes: ethyl acetate); mp 103.6 – 105.3°C; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.51 – 7.41 (m, 2H), 7.31 – 7.24 (m, 2H), 7.17 – 7.15 (m, 1H), 5.63 (s, 1H), 4.89 (d, \(J = 10.0\) Hz, 1H), 4.37 (d, \(J = 10.1\) Hz, 1H), 1.94 (ddd, \(J = 13.4, 11.9, 4.5\) Hz, 1H), 1.89 – 1.82 (m, 1H), 1.78 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H); \(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 172.34, 136.24, 134.37, 130.26, 129.57, 128.91, 128.65, 128.38, 127.96, 87.88, 79.28, 78.26, 33.88, 30.40, 24.77, 21.06, 20.98; FT-IR (neat): 3033, 2944, 2924, 2853, 1705 cm\(^{-1}\); HRESI-MS: calculated for C\(_{21}\)H\(_{23}\)NO\(_3\)Na (M+Na)\(^+\) 360.1570, observed 360.1566.

3-(Benzyloxy)-2-(furan-2-yl)-1-oxa-3-azaspiro[4.5]decan-4-one (10b)

[Structure image]
Prepared in 73% yield (76.3 mg, 0.23 mmol) as a white solid from the reaction of  

$N$-(benzyloxy)-1-bromocyclohexane-1-carboxamide (100 mg, 0.32 mmol) with furfural (32 µL, 0.39 mmol) via the general procedure. $R_f = 0.50$ (8:2, hexanes: ethyl acetate); mp 80.6 – 82.8 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.51 – 7.51 (m, 1H), 7.34 – 7.32 (m, 3H), 7.27 (dd, $J = 6.6$, 3.3 Hz, 2H), 6.57 (dd, $J = 3.3$, 0.8 Hz, 1H), 6.43 (dd, $J = 3.3$, 1.8 Hz, 1H), 5.66 (s, 1H), 4.97 (d, $J = 10.3$ Hz, 1H), 4.56 (d, $J = 10.3$ Hz, 1H), 1.87 (dd, $J = 8.2$, 4.0 Hz, 2H), 1.77 – 1.65 (m, 5H), 1.65 – 1.55 (m, 2H), 1.39 – 1.29 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ 171.5, 148.9, 144.1, 134.5, 129.6, 129.0, 128.5, 112.2, 110.7, 81.3, 79.3, 78.4, 33.5, 31.6, 24.7, 21.1, 21.0; FT-IR (neat): 2946, 2936, 2854, 1711, 1601 cm$^{-1}$; HRESI-MS: calculated for C$_{19}$H$_{21}$NO$_4$Na (M+Na)$^+$ 350.1368, observed 350.1357.

3-(Benzyloxy)-2-cyclohexyl-1-oxa-3-azaspiro[4.5]decan-4-one (10c)

Prepared in 52% yield (57.0 mg, 0.17 mmol) as a colorless oil from the reaction of  

$N$-(benzyloxy)-1-bromocyclohexane-1-carboxamide (100 mg, 0.32 mmol) with cyclohexanecarboxaldehyde 42 µL, 0.39 mmol) via the general procedure. $R_f = 0.53$(8:2, hexanes: ethyl acetate); mp 67.6 – 69.3 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 – 7.43 (m, $J = 6.5$, 2.9 Hz, 2H), 7.38 – 7.37 (m, $J = 5.5$, 1.6 Hz, 3H), 5.15 (d, $J = 10.4$ Hz, 1H), 4.96 (d, $J = 10.4$ Hz, 1H), 4.57 (d, $J = 1.8$ Hz, 1H), 1.83 – 1.49 (m, 15H), 1.33 – 1.11 (m, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 172.2, 134.8, 129.7, 129.1, 128.6, 89.7, 78.1, 77.3,

3-(Benzyloxy)-2-propyl-1-oxa-3-azaspiro[4.5]decan-4-one (10d)

\[
\begin{align*}

\text{O} & \quad \text{N-OBn} \\
\text{O} & \quad \text{n-C\(_3\)H\(_7\)}
\end{align*}
\]

Prepared in 47 % yield (48.6 mg, 0.15 mmol) as white solid from the reaction of \(N\)-benzyloxy-1-bromocyclohexane-1-carboxamide (100 mg, 0.32 mmol) with butyraldehyde (31 µL, 0.39 mmol) via the general procedure. \(R_f = 0.65\) (8:2, hexanes: ethyl acetate); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.43 – 7.40 (m, 2H), 7.39 – 7.37 (m, \(J = 5.1, 1.8\) Hz, 3H), 5.12 (d, \(J = 10.5\) Hz, 1H), 4.96 (d, \(J = 10.5\) Hz, 1H), 4.74 (dd, \(J = 6.1, 2.8\) Hz, 1H), 1.75 – 1.33 (m, 14H), 0.92 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 172.3, 134.8, 129.7, 129.1, 128.5, 86.5, 78.4, 77.8, 35.3, 33.7, 30.9, 24.8, 21.1, 21.0, 16.1, 13.9; FT-IR (neat): 2929, 2855, 1710, 1601 cm\(^{-1}\); HRESI-MS: calculated for C\(_{18}\)H\(_{25}\)NO\(_3\)Na (M+Na)\(^+\) 326.1732, observed 326.1739.
3-(Benzyloxy)-5-methyl-2-phenyl-1,3-oxazolidin-4-one (12)

N-(benzyloxy)-2-bromopropanamide (100 mg, 0.36 mmol) with benzaldehyde (197 µL, 1.94 mmol) via the general procedure. Major diastereoisomer: $R_f = 0.38$ (8:2, hexanes: ethyl acetate; mp 105.2 – 106.7 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.49 – 7.44 (m, 5H), 7.31 – 7.25 (m, 3H), 7.16 – 7.13 (m, 2H), 5.65 (d, $J = 1.5$ Hz, 1H), 4.90 (d, $J = 10.1$ Hz, 1H), 4.42 – 4.38 (m, 2H), 1.59 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 171.1, 135.7, 134.4, 130.5, 129.5, 128.9, 128.7, 128.4, 128.0, 89.6, 78.4, 72.8, 17.7; FT-IR (neat): 3062, 3032, 2978, 2951, 2899, 1747, 1649 cm$^{-1}$; HRESI-MS: calculated for C$_{17}$H$_{17}$NO$_3$Na (M+Na)$^+$ 306.1106, observed 306.1108. Minor diastereoisomer (Characterized as a mixture of isomers): $R_f = 0.38$ (8:2, hexanes: ethyl acetate; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.50 – 7.41 (m, 5H), 7.34 – 7.26 (m, 3H), 7.24 – 7.22 (m, 2H), 5.63 (d, $J = 2.0$ Hz, 1H), 4.96 (d, $J = 10.5$ Hz, 1H), 4.62 – 4.56 (m, 2H), 1.47 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 170.1, 136.1, 134.5, 130.3, 129.6, 129.1, 128.8, 128.5, 127.5, 89.0, 78.2, 72.1, 17.7; FT-IR (neat): 306.65, 3034, 2980, 2930, 2884, 1739, 1649 cm$^{-1}$; HRESI-MS: calculated for C$_{17}$H$_{17}$NO$_3$Na (M+Na)$^+$ 306.1106, observed 306.1108.
3-(Benzyloxy)-5-ethyl-2-phenyl-1,3-oxazolidin-4-one (14)

Prepared in 69 % yield (77 mg, 0.26 mmol) as a colorless oil from the reaction of N-(benzyloxy)-2-bromobutanamide (200 mg, 0.73 mmol) with benzaldehyde (0.37 mL, 3.68 mmol) via the general procedure. Characterized as a mixture of diastereoisomers: $R_f$ = 0.27 (8:2, hexanes: ethyl acetate); $^1$H NMR (400 MHz, CDCl3): $\delta$ 7.52 – 7.12 (m, 20H), 5.65 (d, $J$ = 1.5 Hz, 1H), 5.62 (d, $J$ = 2.1 Hz, 1H), 4.95 (d, $J$ = 10.5 Hz, 1H), 4.86 (d, $J$ = 10.1 Hz, 1H), 4.58 (d, $J$ = 10.5 Hz, 1H), 4.47 (ddd, $J$ = 6.8, 4.5, 2.2 Hz, 1H), 4.42 (d, $J$ = 10.1 Hz, 1H), 4.30 (ddd, $J$ = 6.0, 4.3, 1.5 Hz, 1H), 2.07 – 1.74 (m, 4H), 1.09 (t, $J$ = 7.4 Hz, 3H), 1.04 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl3): $\delta$ 170.9, 169.4, 169.3, 136.4, 135.7, 134.5, 134.3, 134.3, 130.5, 130.2, 129.6, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.0, 127.5, 89.6, 89.6, 78.4, 78.3, 77.3, 76.7, 24.8, 24.7, 9.0, 8.9; FT-IR (neat): 3063, 3033, 2970, 2936, 2921, 2888, 2878, 1729, 1497, 1457 cm$^{-1}$; HRESI-MS: calculated for $C_{18}H_{19}NO_3Na$ (M+Na)$^+$ 320.1257, observed 320.1272.
5,5-Dimethyl-2-phenyl-1,3-oxazolidin-4-one (15)

To a solution of 3 (100 mg, 0.34 mmol) in anhydrous THF (0.1 mL) added 0.1 SmI$_2$ solution in THF (10.2 mL) and stirred at room temperature for 3 h under nitrogen. The reaction was quenched with saturated solution of ammonium chloride (10 mL) and extracted with ethyl acetate (10 mL x 3). The volatiles were removed under reduced pressure and the residue was purified via flash column chromatography (6:4 hexanes: ethyl acetate) to provide title compound as a white solid in 77 % yield (50 mg, 0.26 mmol). $R_f = 0.6$ (1:1, hexanes: ethyl acetate); mp 121.3 – 122.7 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.05 (s, 1H), 7.51 – 7.34 (m, 5H), 6.03 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 178.1, 138.3, 129.7, 128.7, 126.6, 85.0, 79.7, 25.0, 23.0; FT-IR (neat): 3060, 3037, 2974, 2930, 2869, 1704 cm$^{-1}$; HRESI-MS: calculated for C$_{11}$H$_{13}$NO$_2$Na (M+Na)$^+$ 214.0844, observed 214.0839.
3.5 References


Chapter 4: Conclusions

4.1 Conclusions

Investigations of the phytochemical mediation of plant-insect interactions have led to the isolation and characterization of three geranylated natural products from the recently described species, *Piper kelleyi*. Two of the three secondary metabolites were hypothesized to dimerize and form the third compound. Dimerization of secondary metabolites is a common pathway that can occur via biotic and abiotic pathways through various reaction types, including the Diels-Alder reaction and oxidative aryl-O bond formation. This work helps support this hypothesis by showing the studies on role, variation, diastereoselectivity and mechanism of this dimerization. After concluding some these studies, further tests were done to show the diversity of the intermediates that were formed. These could show support for the screening hypothesis. The screening hypothesis suggests that phytochemical diversity is maintained because it increases a plants’ likelihood of containing a potent compound or a precursor to a potent compound that is effect against a particular type of natural enemy. As work continues to be done on expanding the natural product skeletons that made available through a host of reactions involving the ortho-quinone methide, there is still a lot of room for the chromene derivatives to be explored.

As recent literature has shown, 4-oxazolidinones are becoming much more prevalent in the pharmaceutical industry, a growing interest of accessing the skeleton has grown. Our group has shown through several publications in the last 5 years of the ability to start from simple starting materials such as the α-halohydroximate to form the oxazoallylic cation and various aldehydes, amines, ketones to form 4-oxazolidinone
derivatives. With such an easily accessible method of forming these derivatives, an interest in expanding the substrate scope with alkynes has become a priority.

4.2 References

