NEW ANIONIC ANNULATION REACTIONS

AND

ANION ACCELERATED AMINO-COPE REARRANGEMENT

by

Isaac Chogii

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<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>Hfacac</td>
<td>hexafluoroacetylacetonate</td>
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<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
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<td>lithium diisopropylamide</td>
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<td>N-chlorosuccinimide</td>
</tr>
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</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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ABSTRACT

New Anionic Annulation Reactions and Anion Accelerated Amino-Cope Rearrangement

This dissertation compiles asymmetric anionic reactions of chiral Ellman sulfinyl imines and dienolates to access diverse nitrogen-containing compounds. Chiral sulfinimines and dienolates derived from γ-bromocrotonates reacted diastereoselectively forming 3-pyrrolines and cis-vinyl aziridines via a formal [3+2]-annulation and vinylogous aza-Darzens reactions respectively. Concise asymmetric syntheses of three natural products have been achieved demonstrating the power of the [3+2]-methodology. Reaction of conjugated sulfinimines with enolates derived from non-halogen containing crotonates, were found to undergo a tandem diastereoselective α,α-addition, and anionic [3,3]-rearrangement affording vinylogous amide products. Synthesis of aromatic imines via 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) initiated oxidative aromatization highlights the synthetic value of the accelerated anion amino-Cope rearrangement.
CHAPTER 1

INTRODUCTION
1.1 The aza-Darzens Reaction

The aza-Darzens reaction is a useful [2+1]-anionic strategy which is commonly used to synthesize the smallest nitrogen-containing heterocycle, the aziridine. The development of the aza-Darzens reaction was necessitated by efforts to extrapolate application of the Darzens\textsuperscript{[1]} approach towards oxiranes to the nitrogen analogue.\textsuperscript{[2]} The duality in functionalities of the reaction components allows formation of cyclic structures as a result of displacement of a leaving group by an \textit{in situ} generated anion. In the Darzens reaction (\textbf{Scheme 1.1}, \(X=O\)), aldehyde carbonyl group is converted to an alkoxide upon a 1,2-addition by a nucleophilic component. The oxy-anion subsequently displaces a leaving group at the initial nucleophilic carbon atom. Therefore, the consequence of the addition step is that the oxy-anion ‘bites’ back displacing the leaving group to afford the oxirane. In general, the Darzens reaction employs stabilized \(\alpha\)-halocarbonyl anions and aldehydes to form oxiranes.

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

\textbf{Scheme 1.1.} The Darzens and aza-Darzens reactions

The application of Darzens reaction conditions for the synthesis of dichloro aziridines\textsuperscript{[3]} by reaction of trichloromethyl anion and imines led to the discovery of the aza-Darzens synthesis of aziridines. In one of the earliest efforts, Deyrup reported that the reaction of benzalaniline with ethyl chloroacetate and potassium \(t\)-butoxide (\textbf{Scheme 1.2}) afforded aziridine products.\textsuperscript{[2]}
Following the discovery of the *aza*‐Darzens reaction, a variety of modified racemic and asymmetric strategies have since been reported.[4] These approaches include the use of alternative chiral[5] and achiral anion stabilizing groups (benzylic, alkenyl, nitro, heteroaryl).[6] Most asymmetric approaches employ chiral imines derived from chiral pool sources.[7]

### 1.2 Asymmetric *aza*‐Darzens approaches utilizing chiral enolates

Gennari and co‐worker reported a two‐step synthesis of chiral aziridines using chiral boron reagents. The chiral boron enolates were generated *in situ* from α‐bromo‐ or chloro‐thioacetate and menthone‐based bromoborate. The addition of the enolates to trimethylsilyl *N*‐protected imines affords amino esters, which required additional cyclization step using lithium aluminum hydride (LiAlH₄) to afford the *cis*‐aziridine products shown in Scheme 1.3.[5c]
Sweeney’s one-pot asymmetric approaches derive asymmetry from camphor and oxazolidinone based α-bromoenolates (Scheme 1.4).\textsuperscript{[5a, 8]} Both chiral enolates provide a diastereoselective access to cis-aziridines. The researchers report poor reactivity when employing oxazolidinone-based enolates whereas good product yields and diastereoselectivities were observed in the case of the enolates derived from camphor-sultam.

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

**Scheme 1.4.** Sweeney’s asymmetric \textit{aza}-Darzens approaches

Ruano employed a one-pot double asymmetric induction strategy using chiral tolyl sulfinimines and chiral bromo or iodo-benzyl nucleophile precursors (Scheme 1.5). Their approach has broad substrate scope, and affords \textit{trans}-aziridine products in high yields.

\begin{center}
\includegraphics[width=0.5\textwidth]{ruano_diagram.png}
\end{center}

**Scheme 1.5.** Ruano’s asymmetric \textit{aza}-Darzens synthesis
1.3 Asymmetric aza-Darzens approaches utilizing chiral imines

Professor F.A. Davis pioneered the use of chiral sulfinimines for asymmetric construction of aziridines and their azirine derivatives. His extensive research in this area forms the basis of sulfinimine-based synthesis of chiral nitrogen-containing compounds including aziridines. The Davis group has widely reported a robust asymmetric access to aziridines from commonly used α-bromo-enolates to phosphonate-substituted aziridines obtained from chiral imines and anions derived from halomethylphosphonates (Scheme 1.6). Other researchers have adapted this approach for other nucleophile sources to access asymmetric aza-Darzens products such as mono-substituted aziridines.

![Scheme 1.6. Davis’ asymmetric chiral sulfinimine based-aza-Darzens approach](image)

Encouraged by the stereodirecting benefits of the p-toluenesulfonyl group, the groups of Njardarson and Stockman have used Ellman’s sulfinimines (Scheme 1.7). Njardarson and co-workers subjected conjugated tert-butanesulfinimines to aza-Darzens nucleophiles which afforded cis and trans-vinyl aziridines. Stockman’s contributions range from syntheses of 2,3-di-, and 2,2’,3-tri-substituted aziridines to synthesis of vinyl aziridines using non-substituted and vinyl substituted bromoacetate enolates respectively.
Savoia and co-workers reported asymmetric synthesis of 2-pyridylaziridines starting with chiral imines deriving asymmetry from chiral pool sources (Scheme 1.8). Chiral imines containing trimethylsilyl protected S-valinol, and those obtained from S-valine methyl ester, reacted with chloromethylolithium to afford chiral aziridines.\(^{[15]}\) In the case of the imines derived from the methyl ester of valine, the aziridination did not occur selectively but rather, the organolithium reagent reacted with both the imine and the ester providing chloromethyl keto-aziridines. However, this approach is limited to 2-pyridyl-containing imines. The 2-pyridyl CN double bond and the \textit{exo}-cyclic imine constitutes a bidentate ligand system which is a critical directing group, and also serves to enhance the nucleophilic character of the organolithium reagent.

**Scheme 1.7.** tert-Butanesulfinimine based asymmetric \textit{aza}-Darzens approaches

**Scheme 1.8.** Savoia’s asymmetric \textit{aza}-Darzens approaches
Apart from the *aza*-Darzens modification of the original Darzens reaction, synthetic efforts are currently underway in our laboratories to access the dihydrofuran motifs using a similar approach.\(^{16}\) The first example of vinylogous Darzens reaction reported by Koppel,\(^{17}\) aimed at the synthesis of dihydrofuran products (Scheme 1.9) unexpectedly afforded the vinyl oxirane. In this reaction, the γ-enolate of methyl 4-bromocrotonate (1.9b) generated using potassium \(t\)-butoxide reacted with benzaldehyde (1.9a) in \(t\)-butanol affording vinyl oxirane (1.9c) instead of the expected dihydrofuran compound (1.9d). No product was formed from reaction of alkyl aldehydes with the γ-enolate.

**Scheme 1.9.** Koppel’s vinylogous Darzens observation

The ready availability of the precursor aldehydes and the simplicity of the synthetic operations required for preparation of the imines and resulting aziridine products, ranks the *aza*-Darzens reaction as one of the most applied and dependable strategy towards the aziridinyl motif, among reported aziridinations.\(^{7, 18}\) In addition, the *aza*-Darzens approach is assembles two components whose overall union gives rise to highly functionalized and synthetically useful products.

Asymmetric syntheses using chiral nucleophiles for the *aza*-Darzens transformation are limited by steps required for their preparation. Therefore, the ease of access to chiral imines from
commercially available chiral auxiliaries makes this approach more attractive for aziridine synthesis.

Current research in Njardarson’s laboratories seeks to contribute to asymmetric syntheses of three and five-membered nitrogen containing heterocycles by reacting chiral Ellman-type sulfinimines with γ-halocrotonates. The applications of γ-halodienolates as Darzens and/or aza-Darzens nucleophiles have not received much attention and there is need to investigate the synthetic opportunities that could be unraveled by testing their potential reactivity, and determine the scope thereof. Koppel’s vinyl oxirane synthesis (Scheme 1.9) is limited to the reaction of γ-anion with aromatic aldehydes. Surprisingly, while investigating the scope of our anionic [3+2]-annulation strategy, we found literature reports of one racemic synthesis of 3-pyrroline employing similar nucleophile used by Koppel from Steel’s group (Scheme 1.10).[19] Since the leaving group is positioned such that the subsequent anionic displacement would occur via a 5-exo-tet pathway, the overall cascade constitutes a formal [3+2]-annulation towards 3-pyrrolines.

Scheme 1.10. Steel’s racemic vinylogous aza-Darzens example

These examples of modified Darzens and aza-Darzens reactions clearly depict the untapped potential of the original [2+1]-anionic cascade. The objective of our research was designed to be able to asymmetrically deliver products from the vinylogous aza-Darzens, and the extended aza-Darzens approaches, using a common chiral starting material. We envisioned that the β-substitution of the γ-bromocrotonate would disrupt conjugation of the γ-anion thereby allowing addition of the γ-enolate leading to formation of vinyl aziridine. On the other hand, the
enolate derived from unsubstituted γ-bromocrotonate would provide an α-addition intermediate which would proceed via an extended *aza*-Darzens pathway to provide the 3-pyrroline (**Scheme 1.11**).

**Scheme 1.11.** Nucleophile tuning to afford diverse *aza*-Darzens products
CHAPTER 2
ASYMMETRIC [3+2] ANNULATION APPROACH TOWARDS 3-PYRROLINES
2.1 Introduction

The Pyrrolidine ring system is an important five-membered nitrogen heterocycle that is featured widely in natural and pharmaceutical products.\textsuperscript{[20],[21]} Representative examples of pyrrolidine-containing natural products are illustrated in Figure 2.1.

![Figure 2.1 Examples of natural and pharmaceutical products containing pyrrolidine motif](image)

The 3-pyrroline core is a useful synthetic intermediate whose reactive functional groups can facilitate further transformations to access higher order alkaloids. Examples of total syntheses employing the pyrroline motif are shown in Figure 2.2. The 3-pyrroline enabled syntheses of (+)-ibophyllidine\textsuperscript{[22]} and trachelamidine,\textsuperscript{[23]} employed chiral phosphine [3+2]-annulation, tandem cationic aza-Cope/Mannich cyclization, aza methine ylide cycloaddition, and ring closing metathesis as the key step in their syntheses, respectively.
Owing to their synthetic value in accessing pyrrolidine substructures of complex natural product or biologically important compounds, synthetic chemists have devised a variety of reaction strategies for synthesis of 3-pyrrolines. As reported by Njardarson,[16, 24] judicious selection of a synthetic method is normally influenced by a number of factors such as ease of access to reaction intermediates and tolerance of the functional groups to various reaction conditions. It is therefore imperative for synthetic chemists to develop a variety of good methods. Other useful pyrrolidine ring forming strategies including those shown in Figure 2.2 include the McMurry coupling of dicarbonyl compounds, vinyl phosphonium cascade,[25] dipolar cycloadditions[26] and Birch reduction of pyrroles.[27]

Application of these methods face efficiency challenges due to the need to construct chiral synthons prior to the key transformations aimed at introducing asymmetry. Our contribution is focused on designing scalable new approaches towards chiral 3-pyrrolines in good yields and excellent diastereoselectivity.
The Njardarson group’s contributions toward the synthesis of five-membered heterocyclic compounds is an ongoing program that includes copper catalyzed ring expansions of vinyl oxiranes, aziridines and thiiranes (Scheme 2.1) to access furan, pyrrolidine and thiophene compounds, respectively.[28]

Scheme 2.1 Njardarson’s copper-catalyzed ring expansion endeavors

Vinyl aziridines are well suited for ring expansion to higher order nitrogen containing heterocycles via a variety of approaches, including rearrangements to 3-pyrroline derivatives.[29] The copper hexafluoroacetylacetone (Cu(hfacac)₂) catalyzed ring expansion of chiral vinyl aziridines[12] stereo-specifically affords 3-pyrrolines (2.2c) in a two-step procedure that includes a non-productive yet synthetically necessary sulfur oxidation (2.2b) operation (Scheme 2.2).

Scheme 2.2 Stereo specific copper catalyzed ring expansion of chiral aziridines to pyrrole

In the Njardarson’s synthesis of 2,5-cis and trans-3-pyrrolines (Scheme 2.2), vinyl aziridines were obtained using the aza-Darzens reaction of conjugated sulfinimines (2.2a) and tert-butyl bromoacetate. To access vinyl aziridines from non-conjugated imines, we envisioned delivery the vinyl group by a vinylogous aza-Darzens nucleophile. [17][30] This approach could open the door to a variety of 3-pyrrolines upon ring expansion.
2.2 Results and Discussion

In our initial efforts, we utilized chiral benzyloxyacetaldimine (2.3b), which was obtained using a modified Ellman’s protocol,[31] and commercially available ethyl 4-bromocrotonate (2.3a). The dienolate generated from 2.3a using LDA in THF at -78 °C, reacted with 2.3b affording a single diastereomer of the 3-pyrroline product 2.3f in 22% yield. Upon careful analysis of the ¹H NMR of the crude reaction mixture, the expected aziridine product was not observed.

We proposed a mechanism (Scheme 2.3) to rationalize the reaction pathway that resulted in the formation of 2.3f. We expected that the enolate (nucleophile), which is first generated when 2.3a is treated with LDA, would react regio-selectively with the imine via its α or γ-positions, or both. Our original proposition was that the imine would trap the γ-enolate (2.3g), and then the resulting aziridination did not occur. Instead, the enolate was selectively trapped at the α-position (2.3c), followed by an inter and/or intra-molecular deprotonations by the LDA or the aziridination to give the more stable conjugated ester (2.3e).
Scheme 2.3. Proposed mechanism of the anionic [3+2] approach towards chiral 3-pyrroline

As to whether in the initial addition step the \( E \) or \( Z \) enolate adds to the imine, we predicted that the \( E \) enolate would be preferentially formed, and the addition would produce a syn adduct. Due to rapid double bond isomerization (2.3d to 2.3e), we could not determine the mode of addition. However, our findings from related projects, involving reaction of enolates with conjugated and non-conjugated imines, confirmed to us the formation of syn addition intermediates en route to cis chiral vinyl aziridines (Chapter 5). The excellent diastereoselectivity of our reaction is in agreement with a model developed by Professor Davis\(^{[32]} \) postulating that the initial addition of the imine proceeds via a closed chair transition state with the \( R \) substituent being at the pseudo-axial position. It is important to note that the proton shuffling leading to the conjugated ester can yield the cis or trans olefin (Scheme 2.3). For the cyclization to occur, the terminal brominated carbon must be cis to the aza-anion. Finally, under the kinetic conditions, a 5-exo-tet cyclization irreversibly afforded one diastereomer of the 2-substituted-3-pyrroline (2.3f).
Using X-ray crystallography, we were able to unambiguously assign the absolute configuration of the C2 position (Figure 2.3). Our assignment of the C2 position is predictable from the enantiomer of the Ellman’s sulfinimine used. For example, the S enantiomer affords 3-pyrrolines whose C2 center can be safely assigned as S by simply assigning the nucleophilic component the second priority following the Cahn-Ingold’s rule. This example serves as a general model for determining the stereochemistry at the C2 center of the 3-pyrroline products including those derived from the R-enantiomer of the Ellman’s auxiliary.

![Figure 2.3 X-ray structure of 2-naphthyl 3-pyrroline 2n.](image)

In order to optimize the reaction conditions towards the 3-pyrroline product, we carried out base, solvent and temperature optimization studies. Using THF, we compared the effectiveness of LDA, lithium hexamethyldisilylazide (LiHMDS) sodium hexamethyldisilylazide (NaHMDS) and potassium tert-butoxide (KOrBu) in generating the enolate and eventually completing the overall cascade. As evident from the results summarized in Table 2.1, LDA emerged as the best base for our cascade.

Another important parameter is the order of addition of the reaction components. In our order of addition studies, we established that it is important to generate the dienolate by adding the ethyl 4-bromocrotonate first into the LDA solution followed by addition of the sulfinimine. When
a mixed solution of the sulfinimine and 2.3a is added to the pre-cooled LDA solution (Table 2.1, entry 11) product was obtained in 58% isolated yield. When this order is reversed, adding LDA (via cannula) into pre-cooled mixture of the ethyl-4-bromocrotonate and sulfinimines (Table 2.1, entry 12), the 3-pyrroline was obtained in 55% isolated yield. While adding the sulfinimine as the last component, it is important that the solution be added at a slower rate. Comparison of the isolated yields from 1.0 mL/h, 2.0 mL/h and 0.5 mL/h addition rates show improved yields when the sulfinimine solution is added slowly. Slow addition of imine (0.5 mL/hr) helps suppress potential self-condensation of alkyl imines.\textsuperscript{[33]} According to the optimization data for this reaction using benzyloxyacetaldimine summarized in Table 2.1, our favorable reaction conditions and procedure required addition of 1.2 equivalents of the ethyl 4-bromocrotonate to a cooled LDA solution (3.0 eq.) in THF at -78 °C to first generate the enolate. This is followed by slow addition of a 1.0 M THF solution of imine (1.0 eq; 0.5 mL/h) and the reaction maintained at this temperature for four hours after complete addition of the imine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>equiv</th>
<th>time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>2</td>
<td>6</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>NaHMDS</td>
<td>2</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>2</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>KOtBu</td>
<td>2</td>
<td>6</td>
<td>&lt;10</td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>3</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>7</td>
<td>LDA, Et₂O</td>
<td>3</td>
<td>4</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>LDA, 6°</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>LDA</td>
<td>3</td>
<td>4</td>
<td>60°</td>
</tr>
<tr>
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<td>3</td>
<td>4</td>
<td>52°</td>
</tr>
<tr>
<td>11</td>
<td>LDA</td>
<td>3</td>
<td>4</td>
<td>58°</td>
</tr>
<tr>
<td>12</td>
<td>LDA</td>
<td>3</td>
<td>4</td>
<td>55°</td>
</tr>
</tbody>
</table>

Table 2.1. Optimized reaction conditions for the 3-pyrroline asymmetric cascade
**Optimal reaction conditions:** Crotonate (1.2 equiv.) added to base in THF at -78 °C followed by slow addition of a 1.0m THF solution of imine (1.0 equiv; 0.5 mL/h). A single diastereomer is observed by $^1$H NMR analysis. [a] 1.0 mL/h addition of imine. [b] 2.0 mL/h addition of imine. [c] Imine and crotonate added simultaneously to a cooled LDA solution. [d] LDA added to solution of imine and crotonate at -78 °C

Using LDA as base of choice, our study then focused on the equivalents of base required to generate the enolate and eventually effect the 5-**exo trig** cyclization. Three equivalents of LDA afforded better yields when compared to two equivalents (Table 2.1, entries 2 and 6). Two equivalents of LDA and 1.2 equivalents of the ethyl-4-bromocrotonate under our slow addition protocol afforded a 77% yield of the desired 3-pyrroline product (Table 2.1, entry 6).

Having screened for the conditions using the benzyloxyacetaldimine, the reaction was tested on a variety of imines to determine the scope of our formal [3+2]-annulation reaction. Sulfinimines bearing aryl, vinyl and enolizable alkyl substituents were employed and they successfully afforded the 3-pyrroline in good yields. This indicated the general applicability and compatibility of this versatile strategy. We have also established that the diastereoselectivity ($<99\%$) of the reaction is uniformly excellent for both $R$ and $S$ enantiomeric series of the sulfinimines. Chiral column separation using HPLC confirmed that enantiopure 3-pyrrolines are obtained using this strategy. With the absolute stereochemistry determined, we were able to asymmetrically access either enantiomer of the 3-pyrroline by simply changing the Ellman’s auxiliary of the sulfinimine. A variety of chiral sulfinimines with alkyl, aryl and hetero-aromatic substituents were synthesized following Ellman’s protocol (Table 2.2).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonimine</th>
<th>3-pyrrole</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td>2a, 77%</td>
</tr>
<tr>
<td>1b</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td>2a ent., 75%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
<td>2b, 52%</td>
</tr>
<tr>
<td>2b</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td>2b ent., 50%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td>2c, 53%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
<td>2d, 55%</td>
</tr>
<tr>
<td>4b</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
<td>2d ent., 56%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
<td>2e, 52%</td>
</tr>
<tr>
<td>5b</td>
<td><img src="image17" alt="Image" /></td>
<td><img src="image18" alt="Image" /></td>
<td>2e ent., 55%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
<td>2f, 69%</td>
</tr>
<tr>
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<td><img src="image21" alt="Image" /></td>
<td><img src="image22" alt="Image" /></td>
<td>2f ent., 68%</td>
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<tr>
<td>7</td>
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<td><img src="image24" alt="Image" /></td>
<td>2g, 59%</td>
</tr>
<tr>
<td>8</td>
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<td><img src="image26" alt="Image" /></td>
<td>2h, 58%</td>
</tr>
<tr>
<td>9</td>
<td><img src="image27" alt="Image" /></td>
<td><img src="image28" alt="Image" /></td>
<td>2i, 75%</td>
</tr>
<tr>
<td>9b</td>
<td><img src="image29" alt="Image" /></td>
<td><img src="image30" alt="Image" /></td>
<td>2i ent., 74%</td>
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<td>2j, 56%</td>
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<td>11</td>
<td><img src="image33" alt="Image" /></td>
<td><img src="image34" alt="Image" /></td>
<td>2k, 63%</td>
</tr>
<tr>
<td>11b</td>
<td><img src="image35" alt="Image" /></td>
<td><img src="image36" alt="Image" /></td>
<td>2k ent., 56%</td>
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<tr>
<td>12</td>
<td><img src="image37" alt="Image" /></td>
<td><img src="image38" alt="Image" /></td>
<td>2l, 63%</td>
</tr>
<tr>
<td>13</td>
<td><img src="image39" alt="Image" /></td>
<td><img src="image40" alt="Image" /></td>
<td>2m, 56%</td>
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<tr>
<td>14</td>
<td><img src="image41" alt="Image" /></td>
<td><img src="image42" alt="Image" /></td>
<td>2n, 63%</td>
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<tr>
<td>15</td>
<td><img src="image43" alt="Image" /></td>
<td><img src="image44" alt="Image" /></td>
<td>2o, 51%</td>
</tr>
<tr>
<td>16</td>
<td><img src="image45" alt="Image" /></td>
<td><img src="image46" alt="Image" /></td>
<td>2p, 56%</td>
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<tr>
<td>17</td>
<td><img src="image47" alt="Image" /></td>
<td><img src="image48" alt="Image" /></td>
<td>2q, 56%</td>
</tr>
</tbody>
</table>

**Table 2.2.** Substrate scope of asymmetric [3+2]-annulation reaction
We imagined that a 3-pyrroline ester with tethered diene and dienophile moieties could undergo an intra-molecular Diels-Alder cycloaddition to form a fused tricyclic nitrogen and oxygen containing heterocycles (2.4c). We prepared a derivative of bromocrotonate with a diene (2.4b) motif and when it was submitted to our optimal reaction conditions, the 3-pyrroline compound was not formed. Instead, uncyclized α-adduct was obtained. Exposure to sodium hydride (NaH) in THF enabled the 5-exo-tet cyclization to the 3-pyrroline, 2.4a (Scheme 2.4). The cyclization challenge faced in this example indicated that our annulation strategy is sensitive to steric hindrance.

![Scheme 2.4 Attempted intra-molecular Diels-Alder cycloaddition](image)

Attempts to perform intra-molecular cycloaddition have proved unsuccessful to date. Both thermal and Lewis acid catalyzed Diels-Alder conditions did not afford the desired product. Refluxing in dry toluene lead to recovery of the starting material, whereas Lewis acid catalyzed reaction resulted in hydrolysis of the ester functionality.

Our interest in accessing fused hetero-tricyclic ring systems (2.5b) inspired us to extend the inter-molecular [3+2]–annulation cascade to an intra-molecular annulation. We designed a substrate (2.5a) whereby the nucleophilic and the electrophilic moieties are tethered in one scaffold. However, our optimal reaction conditions afforded a complex mixture that could not be
analyzed or separated for analysis. When we resorted to LiHMDS, we surprisingly obtained a nitrile (2.7c) whose spectral data matched literature reports (Scheme 2.5).[^34]

![Scheme 2.5 Attempted intra-molecular (3+2)-Annulation](image)

Grayson and co-worker reported regioselective γ-alkylation of aldehydes by γ-anions generated from γ-chloro phenyl sulfone[^35] to give the respective vinyl oxirane. Interestingly, no dihydrofuran compound was observed.[^36] Application of γ-halo-vinylic phenylsulfone as nucleophile precursor for our cascade would provide synthetically useful 3-pyrroline products. The known (E)-((3-bromoprop-1-en-1-yl) sulfonyl) benzene (2.6a)[^35] was reacted with benzyloxyacetaldimine(2.3b) using our reaction conditions which resulted in the 2-substituted 3-phenylsulfonyl pyrr line (2.6b) in a good yield. The sulfonyl group affords additional synthetic opportunities, for example desulfurization would result in a traceless asymmetric synthesis of 2-substituted 3-pyrrolines (Scheme 2.6).

![Scheme 2.6 Sulfone as an alternative ester-stabilizing group](image)
Our success in the [3+2]-annulation of imines prompted us to wonder whether we could apply the methodology to synthesize 2,5- dihydrofurans from aldehydes. Since Koppel’s report is limited to only one example of the aromatic aldehyde shown, our current observations (Scheme 2.7) have motivated us to further study the potential of this reaction to selectively afford 2-substituted 2,5-dihydrofurans. Application of our [3+2] annulation strategy to aldehyde substrates would enable access to the 2-substituted 2,5-dihydrofurans. Our preliminary investigation using benzyloxyacetaldehyde (2.7a) and ethyl 4-bromocrotonate (2.3a) afforded the 2,5-dihydrofuran (2.7b) as the only product. Interestingly, when we subjected benzaldehyde (1.9a) to the reaction, we did not observe the desired 2,5-dihydrofuran. Instead, the vinyl oxirane (2.7c) was formed as the only product. Spectral data for 2.7c matches literature reports of vinyl oxirane 1.9c obtained via vinylogous Darzens approach using γ-halo enolate and aldehydes (Scheme 1.9).[17] Investigations are currently underway to determine the scope of the vinylogous Darzens reaction.

Scheme 2.7 Application of the [3+2]-annulation to synthesis of 2,5-dihydrofurans

2.3 Conclusion

We have developed a new asymmetric [3+2] annulation reaction to form chiral 3-pyrrolines. The reaction has a wide substrate scope (aryl, alkyl, conjugated and hetero-aryl sulfinimines) and provides the synthetic community with important asymmetric tool to access 2-substituted 3-pyrrolines with robust synthetic handles for further modifications to higher order pyrrolidine-containing organic compounds. From the furan example, we postulate application of this
methodology to the synthesis of 2,5-dihydrofuran compounds. We also envision the utility of this cascade as a traceless route to mono-substituted pyrrolines following desulfurization of the sulfone. The power of the methodology is showcased through the syntheses of natural products (+)-elacomine, (-)-supinidine and (+)-isoretronecanol is discussed in Chapter 3.

2.4 HPLC Analysis of Pyrroline Enantiomers

![Graphs showing HPLC analysis of pyrroline enantiomers](image)

mixture of 2a and 2a ent.
Compounds 2e and 2e ent.

mixture of 2e and 2e ent.

2.5 Crystal data for 3-pyrroline 2n (CCDC 1062144)

X-ray data were collected at the University of Arizona X-ray Diffraction Facility. Colorless plate-like crystals were mounted onto a Cryoloop under a film of Paratone oil. Diffraction data for all crystals were collected at 100° (2) K using a Bruker Kappa APEX II DUO diffractometer. Data were integrated and structure solved using Bruker SAINT and SHELXT and/or Olex2 respectively.
Ethyl (S)-1-((S)-tert-butylsulfanyl)-2-(naphthalen-2-yl)-2,5-dihydro-1H-pyrrrole-3-carboxylate

Crystal data and structure refinement for pyrrole (CCDC 1062144)

Formula: C_{20}H_{22}NO_3S
Formula weight: 371.48
Crystal morphology: Colorless
Temperature: 100(2) K
Wavelength: 1.54178 Å [Cu-Kα]
Crystal system: Orthorhombic
Space group: P2_12_12_1
Unit cell dimensions:
\[ a = 9.0728(8) \text{ Å} \quad \alpha = 90° \]
\[ b = 12.2573(11) \text{ Å} \quad \beta = 90° \]
\[ c = 17.6356(16) \text{ Å} \quad \gamma = 90° \]
Volume: 1961.2(3) Å³
Z: 4
Density (calculated): 1.258 Mg/m³
Absorption coefficient: 1.623 mm⁻¹
\( F(000) \): 792
Crystal Size: 0.59 x 0.29 x 0.21 mm
Data collection range: 4.39 ≤ θ ≤ 68.11°
Index ranges: -10 ≤ h ≤ 10, -14 ≤ k ≤ 14, -21 ≤ l ≤ 21
Reflections collected: 35679
Independent reflections: 3568 [R(int) = 0.0252]
Observed reflections: 3465 [I > 2σ(I)]
Absorption correction: multi-scan
Max. and min. transmission: 0.7531 and 0.6101
Refinement method: Full
Data / restraints / parameters: 3568 / 0 / 239
Goodness of fit: 1.043
Final R indices [I > 2σ(I)]: \( R_1 = 0.0332, \text{wR}_2 = 0.0866 \)
R indices (all data): \( R_1 = 0.0339, \text{wR}_2 = 0.087 \)
Largest diff. peak and hole: 0.169 and -0.343 e Å⁻³
Absolute structure parameter: 0.020(14)
2.6 Experimental procedure for synthesis of chiral 3-pyrrolines

General Information:

All the reactions were performed using flame dried glassware under nitrogen atmosphere. All reagents from commercial sources were used without further purification unless otherwise specified. \(n\)-Butyllithium was titrated using menthol following reported protocol.\(^{[37]}\) Reaction solvents; dichloromethane (\(\text{CH}_2\text{Cl}_2\)), diethyl ether (\(\text{Et}_2\text{O}\)) and tetrahydrofuran (THF) were dried by passage through activated alumina. Flash chromatography was performed with Silicycle SiliaFlash® F60 silica, and thin layer chromatography (TLC) was performed with EMD 250μm silica gel 60-F254 plates. \(^1\)H and \(^{13}\)C NMR spectral data were acquired on Bruker DRX 400 MHz, Bruker DRX 500 MHz and or Bruker DRX 600 MHz spectrometer. Infrared spectra were recorded on Shimadzu Prestige FT-IR spectrometer. High-resolution mass spectrometry was performed at the University of Arizona Mass Spectrometry Facility. Optical rotations were recorded on Rudolph Autopol IV polarimeter.

X-ray data were collected at the University of Arizona X-ray Diffraction Facility. Colorless plate-like crystals were mounted onto a Cryoloop under a film of Paratone oil. Diffraction data for all crystals were collected at 100° (2) K using a Bruker Kappa APEX II DUO diffractometer. Data were integrated and structure solved using Bruker SAINT and SHELXT and/ or Olex2 respectively.

2.7 General Procedure 1 (GP1) for the Synthesis of 3-Pyrrolines:

To a flask equipped with magnetic stir bar and diisopropyl amine (3.0 eq. in THF, -78 °C) was added \(n\)-butyl lithium (3.0 eq.) after which the solution was warmed to 0 °C and allowed to stir for
15 minutes. The resulting lithium diisopropyl amide (LDA) solution was then cooled to -78 °C and additional THF was added to reach an overall concentration of 0.1 M based on the sulfinimine. Neat ethyl 4-bromocrotonate (75%, 1.2 eq.) was added to the LDA solution at -78 °C and stirred for 30 minutes. A solution of the respective sulfinimine (1.0 eq., 1M in THF) was then added using a syringe pump (0.5 mL/h) while the reaction temperature was maintained at -78 °C and allowed to stir for additional 4 to 8 hours after addition was complete. The reaction was then quenched with saturated ammonium chloride and allowed to warm to room temperature, extracted using ethyl acetate (3 times) and washed with brine. The combined organic extracts were dried using anhydrous sodium sulfate (Na₂SO₄) and solvent evaporated. Crude material was purified by flash column chromatography (silica gel, 20-40% EtOAc in hexanes) to afford the respective compound.
2.8 Characterization and spectral data for chapter 2 (Table 2.1)

2a: Colorless oil, 77% yield. \([\alpha]^{23}_D = -78.8^{\circ} (c\ 1.0, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz,) \(\delta 7.35 - 7.23\) (m, 5H), 6.83 (dd, \(J = 4.0, 1.8\) Hz, 1H), 4.86(dt, \(J = 17.1, 2.2\) Hz, 1H), 4.67 (ddd, 1H), 4.50(d, \(J =3.3\) Hz, 2H), 4.17 (q, \(J = 7.1, 2H\)), 3.69 (ddd, \(J = 17.1, 5.5, 1.7\) Hz 1H), 3.67 - 3.61 (m, 2H), 1.25 (t, \(J = 7.1\) Hz, 3H), 1.19 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 162.52, 140.68, 138.14, 132.93, 128.23, 127.53, 127.51, 72.99, 72.25, 72.00, 60.61, 57.78, 47.64, 23.44, 14.14\); IR (thin film) 2980, 2926, 2864, 1716, 1643, 1363, 1280, 1174 cm\(^-1\); HRMS (ESI\(^+\)) \(m/z\) 366.1730 [calculated mass for C\(_{19}\)H\(_{28}\)NO\(_4\)S (M+H)\(^+\) 366.1734].
**2a ent.** Colorless oil, 75% yield. \([\alpha]_{23}^D = +37.9^\circ \ (c \ 4.9, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.23 (m, 5H), 6.83 (dt, \(J = 2.6, 1.8\) Hz, 1H), 4.90 (m, 1H), 4.68 (ddd, \(J = 17.1, 2.6, 1.8\) Hz, 1H), 4.50 (d, \(J = 3.3\) Hz, 2H), 4.17 (m, 2H), 3.72 – 3.67 (m, 1H), 3.67 – 3.61 (m, 2H), 1.25 (t, \(J = 7.1\) Hz, 3H), 1.19 (s, 9H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 162.47, 140.63, 138.08, 128.18, 127.48, 127.46, 72.93, 72.19, 71.94, 60.55, 57.73, 47.61, 23.38, 14.08; IR (thin film) 2981, 2925, 2903, 2864, 2864, 1716, 1652, 1454, 1364, 1261, 1075 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 366.173 [calculated mass for C\(_{19}\)H\(_{28}\)NO\(_4\)S (M + H\(^+\)] 366.1733].
2b Colorless oil, 52% yield. $[\alpha]^{23}_{D} = -43.1^\circ$ ($c$ 1.4, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 – 7.28 (m, 2H), 7.26 – 7.22 (m, 3H), 6.90 (dt, $J = 2.4$, 1.8 Hz, 1H), 5.67 (dt, $J = 5.6$, 2.0 Hz, 1H), 4.78 (dt, $J = 17.2$, 2.5 Hz, 1H), 4.13 – 3.91 (m, 2H), 3.83 (ddd, $J = 17.2$, 5.6, 2.0 Hz, 1H), 1.12 (t, $J = 7.2$ Hz, 3H), 1.00 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.23, 141.63, 138.40, 136.12, 128.28, 127.70, 127.45, 75.19, 60.54, 57.41, 47.81, 23.11, 13.92; IR (thin film) 3030, 2980, 2958, 2870, 1720, 1456, 1365, 1263, 1074, 761 cm$^{-1}$; HRMS (ESI$^+$) m/z 322.1473 [calculated mass for C$_{17}$H$_{24}$NO$_3$S (M+H)$^+$ 322.1471].
2b ent Colorless oil, 50% yield. $[\alpha]^{23}_{D} = +66.1^\circ$ (c 3.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 6.90 (dt, $J = 2.5, 1.8$ Hz, 1H), 5.67 (dt, $J = 5.6, 2.1$ Hz, 1H), 4.78 (dt, $J = 17.2, 2.4$ Hz, 1H), 4.10 – 3.97 (m, 2H), 3.83 (ddd, $J = 17.2, 5.6, 2.0$ Hz, 1H), 1.12 (t, $J = 7.1$ Hz, 3H), 1.00 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.24, 141.63, 138.40, 136.13, 128.28, 127.70, 127.45, 75.19, 75.19, 60.55, 57.42, 47.81, 23.12, 13.92; IR (thin film) 2980, 2960, 2870, 1720, 1643, 1456, 1365, 1263, 1074, 761 cm$^{-1}$; HRMS (ESI$^+$) m/z 344.1292 [calculated mass for C$_{17}$H$_{23}$NNaO$_3$S (M+Na)$^+$ 344.1291].
2c: Colorless oil, 53% yield. [α]$_D^{23}$ = -72.9° (c 1.4, CHCl$_3$) $^1$H NMR (500 MHz, CDCl$_3$) δ 6.74 (q, $J$ = 2.0 Hz, 1H), 4.85 (dtt, $J$ = 5.6, 3.8, 1.7 Hz, 1H), 4.65 (ddd, $J$ = 17.2, 2.6, 1.9 Hz, 1H), 4.27 - 4.11 (m, 2H), 3.63-3.56 (m, 3H), 1.90 – 1.83 (m, 1H), 1.75 – 1.63 (m, 1H), 1.61 – 1.49 (m, 1H), 1.46 – 1.37 (m, 1H), 1.28 (t, $J$ = 7.1 Hz, 3H), 1.21 (s, 9H), 0.87 (s, 9H), 0.2 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.62, 139.18, 135.11, 71.68, 63.06, 60.58, 57.61, 47.77, 31.27, 27.05, 25.95, 23.63, 18.36, 14.21, -5.3; IR (thin film) 2955, 2929, 2857, 1719, 1257, 1085 cm$^{-1}$; HRMS (ESI$^+$) m/z 440.2264 [calculated mass for C$_{20}$H$_{39}$NNaO$_4$Si (M+Na)$^+$ 440.2261].
2d: Colorless oil, 55% yield. $[\alpha]^2_D = -53.6^\circ$ (c 1.16, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.70 (dd, $J = 3.9, 1.9$ Hz, 1H), 4.77 (m, 1H), 4.61 (dt, $J = 17.2, 2.3$ Hz, 1H), 4.25 – 4.12 (m, 2H), 3.57 (ddd, $J = 17.2, 5.3, 1.9$ Hz, 1H), 1.77 (m, 1H), 1.68 – 1.58 (m, 1H), 1.29-1.18 (m, 20H), 0.84 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.72, 138.90, 135.42, 71.95, 60.52, 57.63, 47.71, 34.90, 31.72, 29.18, 23.66, 23.62, 22.55, 14.18, 14.01; IR (thin film) 2954, 2924, 2854, 1720, 1643, 1458, 1257, 1072 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 352.1923 [calculated mass for C$_{17}$H$_{31}$NNaO$_3$S (M+Na)$^+$ 352.1917].
2d ent Colorless oil, 56% yield. [α]$_2^D$ = +79.8° (c 3.46, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.73 (q, $J$ = 2.0 Hz, 1H), 4.80 (tdt, $J$ = 5.2, 3.5, 1.7 Hz, 1H), 4.65 (dt, $J$ = 17.2, 2.3 Hz, 1H), 4.23 – 4.18 (m, 2H), 3.61 (ddd, $J$ = 17.2, 5.3, 1.9 Hz, 1H), 1.87 – 1.76 (m, 1H), 1.69 – 1.59 (m, 1H), 1.31 – 1.22 (m, 20H), 0.86 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.71, 138.89, 135.40, 71.94, 60.50, 57.61, 47.70, 34.88, 31.70, 29.16, 23.64, 23.61, 22.54, 14.16, 14.00; IR (thin film) 2956, 2927, 2854, 1718, 1643, 1263, 1097, 1074 cm$^{-1}$; HRMS (ESI$^+$) m/z 330.2103 [calculated mass for C$_{17}$H$_{32}$NO$_3$S (M+H)$^+$ 330.2097].
2e: Yellow oil, 52% yield. \([\alpha]^{22}_D = -53.6^\circ (c \ 1.1, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.76 (dt, \(J = 2.9, 1.6\) Hz, 1H), 4.71 (m, 1H), 4.65 (ddd, \(J = 17.1, 2.8, 1.3\) Hz, 1H), 4.19 (m, 2H), 3.56 (ddd, \(J = 17.2, 5.0, 1.8\) Hz, 1H), 2.17 (m, 1H), 1.29 (t, \(J = 7.1\) Hz, 3H), 1.27 (s, 9H), 1.01 (d, \(J = 6.9\) Hz, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 162.83, 139.32, 135.44, 77.65, 60.51, 58.74, 48.66, 32.30, 24.27, 19.89, 15.52, 14.14; IR (thin film) 2978, 2931, 1720, 1651, 1458, 1365, 1257, 1180, 1041 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 288.1624 [calculated mass for \(\text{C}_{14}\text{H}_{26}\text{NO}_3\text{S}\) (M+H)\(^+\) 288.1628].
**2e ent** Yellow oil, 55% yield. $[\alpha]_D^{23} = +103.2^\circ$ (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.76 (dt, $J = 3.0$, 1.6 Hz, 1H), 4.72 (m, 1H), 4.65 (ddd, $J = 17.2$, 2.8, 1.3 Hz, 1H), 4.22 - 4.17 (m, 2H), 3.56 (ddd, $J = 17.2$, 5.0, 1.8 Hz, 1H), 2.17 (m, $J = 6.9$, 2.1 Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.27 (s, 9H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.80 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.86, 139.34, 135.47, 77.68, 60.53, 58.77, 48.68, 32.33, 24.30, 19.91, 15.55, 14.16; IR (thin film) 2964, 2933, 2906, 1720, 1645, 1446, 1367, 1253, 1072, 1018 cm$^{-1}$. HRMS (ESI$^+$) $m/z$ 310.1449 [calculated mass for C$_{14}$H$_{25}$NNaO$_3$S (M+Na)$^+$ 310.1447].
2f Colorless oil, 69% yield. \([\alpha]_D^{23} = -94.2^\circ (c 1.0, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29-7.24 (m, 7.6 Hz, 2H), 7.14-7.12 (m, 3H), 6.78 (dd, \(J = 2.0\) Hz, 1H), 4.89 (tdd, \(J = 5.3, 3.6, 1.8\) Hz, 1H), 4.70 (dt, \(J = 17.2, 2.3\) Hz, 1H), 4.20 (m, 2H), 3.68 (ddd, \(J = 17.2, 5.3, 1.9\) Hz, 1H), 2.61 (dddd, \(J = 44.8, 13.6, 11.4, 5.3\) Hz, 2H), 2.18 (dddt, \(J = 14.0, 11.4, 5.1\) Hz, 1H), 2.00 (m, 1H), 1.32-1.28 (m, 12H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 162.58, 141.71, 139.34, 134.98, 128.34, 125.26, 71.65, 60.60, 57.71, 47.80, 36.66, 30.21, 23.69, 14.16; IR (thin film) 3026, 2978, 2929, 2866, 1716, 1647, 1456, 1363, 1261, 1074 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 350.1783 [calculated mass for C\(_{19}\)H\(_{28}\)NO\(_3\)S (M+H\(^+\))] 350.1784.
**2f ent** Colorless oil, 68% yield, [α]$_{D}^{23}$ = +107.2° (c 2.0, CHCl$_3$). ¹H NMR (500 MHz, CDCl$_3$) δ 7.28 – 7.25 (m, 2H), 7.19 – 7.12 (m, 3H), 6.78 (q, $J = 2.0$ Hz, 1H), 4.89 (ttd, $J = 5.2$, 3.5, 1.8 Hz, 1H), 4.70 (dt, $J = 17.4$, 2.3 Hz, 1H), 4.23 – 4.18 (m, 2H), 3.67 (ddd, $J = 17.2$, 5.3, 1.9 Hz, 1H), 2.66 (ddd, $J = 13.5$, 11.4, 5.4 Hz, 1H), 2.57 (ddd, $J = 13.7$, 11.5, 5.2 Hz, 1H), 2.18 (ddt, $J = 14.0$, 11.6, 5.1 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.30 – 1.26 (m, 12H); ¹³C NMR (125 MHz, CDCl$_3$) δ 162.57, 141.71, 139.34, 135.00, 128.34, 128.26, 125.83, 71.67, 60.62, 57.73, 47.82, 36.69, 30.24, 23.72, 14.20; IR (thin film) 3026, 2978, 2929, 1716, 1647, 1456, 1261, 1074 cm$^{-1}$; HREMS (ESI$^+$) m/z 350.1785 [calculated mass for C$_{19}$H$_{28}$NO$_3$S (M+H)$^+$ found 350.1784].
2g: Colorless oil, 59% yield. $[\alpha]^2_D = -9.7^\circ$ (c 1.51, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.70 (dt, $J = 2.8$, 1.6 Hz, 1H), 5.05 (dddt, $J = 7.1$, 5.7, 2.8, 1.4 Hz, 1H), 4.77 (dddt, $J = 7.9$, 4.6, 3.0, 1.4 Hz, 1H), 4.64 (dddt, $J = 17.3$, 2.7, 1.3 Hz, 1H), 4.21 – 4.17 (m, 2H), 3.63 (dddt, $J = 17.3$, 4.8, 1.8 Hz, 1H), 1.95 (q, $J = 7.5$ Hz, 2H), 1.72 – 1.68 (m, 1H), 1.66 (d, $J = 1.3$ Hz, 3H), 1.58 (d, $J = 1.3$ Hz, 3H), 1.55 – 1.49 (m, 2H), 1.28 (t, $J = 7.6$, 3 H), 1.23 (m, 11H), 0.96 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.71, 138.56, 137.13, 131.18, 124.65, 70.80, 60.53, 58.24, 47.46, 43.47, 38.08, 28.56, 25.72, 25.30, 23.91, 18.77, 17.61, 14.15; IR (thin film) 2960, 2926, 1720, 1668, 1259, 1076 cm$^{-1}$; HRMS (ESI$^+$) m/z 370.2406 [calculated mass for C$_{20}$H$_{36}$NO$_3$S (M+H)$^+$ 370.2410].
2j: Yellow oil, 58% yield. [α]$_D$ = +66.1° (c 4.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.79 (dt, $J = 7.8$, 0.8 Hz, 1H), 7.27–7.25 (m, 2H), 6.90–6.85 (m, 1H), 6.82 (dt, $J = 2.7$, 1.4 Hz, 1H), 5.16 (dddt, $J = 9.2$, 5.0, 4.0, 1.0 Hz, 1H), 4.62 (dddd, $J = 17.5$, 2.8, 0.9 Hz, 1H), 4.13 (qd, $J = 7.2$, 3.6 Hz, 1H), 4.02 (dq, $J = 10.8$, 7.1 Hz, 1H), 3.73 (dddd, $J = 17.6$, 4.1, 1.7 Hz, 1H), 3.28 (dd, $J = 14.0$, 5.0 Hz, 1H), 2.97 (dd, $J = 14.0$, 9.3 Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H), 0.94 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.74, 140.68, 140.30, 139.47, 137.30, 130.73, 128.23, 128.14, 102.37 72.91, 60.68, 57.77, 47.60, 46.97, 23.21, 14.12; IR (thin film) 2959, 2928, 1722, 1465, 1367, 1259, 1075, 750 cm$^{-1}$; HRMS (ESI$^+$) m/z 462.0594 [calculated mass for C$_{18}$H$_{25}$INO$_3$S (M + H)$^+$ 462.0594].
**2k ent** Yellow oil, 56 % yield. $[\alpha]_{D}^{23} = -59.8^\circ$ (c 2.7, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.67 (dt, $J = 2.9, 1.7$ Hz, 1H), 4.75 – 4.70 (m, 1H), 4.61 (ddd, $J = 17.2, 2.8, 1.5$ Hz, 1H), 4.19 – 4.13 (m, 2H), 3.60 (ddd, $J = 17.3, 4.9, 1.8$ Hz, 1H), 1.83 – 1.72 (m, 1H), 1.53 – 1.48 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.19 (s, 9H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.76, 138.55, 136.94, 70.97, 60.53, 58.09, 47.44, 45.15, 24.32, 23.84, 23.79, 21.89, 14.16. IR (thin film) 2978, 2931, 2870, 1728, 1450, 1242, 1180, 1095, 1041 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 324.1600 [calculated mass for C$_{15}$H$_{27}$NNaO$_3$ (M+Na)$^+$ 324.1604].

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**$^1$H NMR (500 MHz, CDCl$_3$):**

- $\delta$ 6.67 (dt, $J = 2.9, 1.7$ Hz, 1H)
- $\delta$ 4.75 – 4.70 (m, 1H)
- $\delta$ 4.61 (ddd, $J = 17.2, 2.8, 1.5$ Hz, 1H)
- $\delta$ 4.19 – 4.13 (m, 2H)
- $\delta$ 3.60 (ddd, $J = 17.3, 4.9, 1.8$ Hz, 1H)
- $\delta$ 1.83 – 1.72 (m, 1H)
- $\delta$ 1.53 – 1.48 (m, 2H)
- $\delta$ 1.25 (t, $J = 7.1$ Hz, 3H)
- $\delta$ 1.19 (s, 9H)
- $\delta$ 0.92 (d, $J = 6.6$ Hz, 3H)
- $\delta$ 0.85 (d, $J = 6.6$ Hz, 3H)

**$^{13}$C NMR (125 MHz, CDCl$_3$):**

- $\delta$ 162.76
- $\delta$ 138.55
- $\delta$ 136.94
- $\delta$ 70.97
- $\delta$ 60.53
- $\delta$ 58.09
- $\delta$ 47.44
- $\delta$ 45.15
- $\delta$ 24.32
- $\delta$ 23.84
- $\delta$ 23.79
- $\delta$ 21.89
- $\delta$ 14.16

**IR (thin film):**

- 2978 cm$^{-1}$
- 2931 cm$^{-1}$
- 2870 cm$^{-1}$
- 1728 cm$^{-1}$
- 1450 cm$^{-1}$
- 1242 cm$^{-1}$
- 1180 cm$^{-1}$
- 1095 cm$^{-1}$
- 1041 cm$^{-1}$

**HRMS (ESI$^+$):**

- $m/z$ 324.1600 [calculated mass for C$_{15}$H$_{27}$NNaO$_3$ (M+Na)$^+$ 324.1604]
2I: White solid, 63% yield. $[\alpha]_{D}^{23} = +87.4^\circ$ (c 2.8, CHCl$_3$) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.24 (ddd, $J = 5.0$, 3.0, 0.4 Hz, 1H), 7.16 (ddd, $J = 3.0$, 1.3, 0.5 Hz, 1H), 6.96 (dd, $J = 5.0$, 1.3 Hz, 1H), 6.87 (dt, $J = 2.5$, 1.8 Hz, 1H), 5.81 (dt, $J = 5.3$, 1.9 Hz, 1H), 4.75 (dt, $J = 17.2$, 2.4 Hz, 1H), 4.15 - 4.06 (m, 2H), 3.80 (ddd, $J = 17.2$, 5.3, 2.0 Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.06 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.32, 142.82, 138.51, 135.84, 126.31, 125.92, 122.18, 70.47, 60.66, 57.61, 47.49, 23.17, 14.06; IR (thin film) 2979, 2962, 1721, 1369, 1261, 1178, 1074 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 350.0856 [calculated mass for C$_{15}$H$_{21}$NNaO$_3$S$_2$ (M+Na)$^+$ 350.0855].
2m: White solid, 56% yield. \([\alpha]^{23}_D = +21.9^\circ (c 2.6, \text{CHCl}_3)\) \(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.37 (d, J = 1.4, 0.6 \text{ Hz}, 1\text{H}), 7.33 (t, J = 1.7 \text{ Hz}, 1\text{H}), 6.84 (dt, J = 2.5, 1.8 \text{ Hz}, 1\text{H}), 6.29 (dd, J = 1.9, 0.9 \text{ Hz}, 1\text{H}), 5.70 (dt, J = 5.1, 1.9 \text{ Hz}, 1\text{H}), 4.72 (dt, J = 17.2, 2.3 \text{ Hz}, 1\text{H}), 4.16 – 4.11 (m, 2\text{H}), 3.76 (ddd, J = 17.2, 5.2, 1.9 \text{ Hz}, 1\text{H}), 1.21 (t, J = 7.2 \text{ Hz}, 3\text{H}), 1.11 (s, 9\text{H}); \(^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 162.28, 143.26, 139.67, 138.65, 135.48, 126.42, 109.06, 66.94, 60.66, 57.55, 47.37, 23.25, 14.05; \text{IR (thin film)} 2981, 1720, 1366, 1261, 1179, 1072 \text{ cm}^{-1}; \text{HRMS (ESI') } m/z 312.1267 \text{ [calculated mass for C}_{15}\text{H}_{22}\text{NO}_{4}\text{S (M+H)}^+ 312.1264].
2n: White solid, 63% yield. [α]$_D^{23}$ = +188.9° (c 2.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 – 7.78 (m, 3H), 7.74 – 7.73 (m, 1H), 7.49 – 7.45 (m, 2H), 7.36 (dd, $J$ = 8.5, 1.8 Hz, 1H), 6.96 (dt, $J$ = 2.0, 1.6 Hz, 1H), 5.86 (dt, $J$ = 5.5, 2.1 Hz, 1H), 4.85 (dt, $J$ = 17.2, 2.5 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.91 (dd, $J$ = 17.2, 5.6, 2.0 Hz, 1H), 1.10 (t, $J$ = 7.1 Hz, 3H), 0.99 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.25, 138.90, 138.59, 136.07, 133.16, 133.01, 128.25, 128.04, 127.64, 126.68, 126.08, 125.94, 125.15, 75.39, 60.60, 57.49, 47.97, 23.18, 13.94; IR (thin film) 3056, 2979, 2930, 1721, 1643, 1367, 1262, 1073, 749 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 372.1627 [calculated mass for C$_{21}$H$_{26}$NO$_3$S (M+H)$^+$ 372.1628].
20: Yellow oil, 51% yield. [$\alpha$]$^\text{D}$_2$ = +45.7° (c 1.74, CHCl$_3$) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.72 (dt, $J$ = 2.5, 1.8 Hz, 1H), 5.69 (dq, $J$ = 15.2, 6.6, 0.9 Hz, 1H), 5.39 – 5.33 (m, 1H), 5.11 – 5.06 (m, 1H), 4.62 (dt, $J$ = 17.1, 2.3 Hz, 1H), 4.21 – 4.13 (m, 2H), 3.65 (ddd, $J$ = 17.0, 5.2, 1.9 Hz, 1H), 1.68 (dd, $J$ = 6.4, 1.7 Hz, 3H), 1.26 (t, 1.9 Hz, 3H), 1.18 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.61, 138.31, 135.50, 130.72, 127.86, 73.35, 60.50, 57.45, 47.18, 23.44, 17.59, 14.14; IR (thin film) 2980, 2934, 2906, 1722, 1447, 1367, 1262, 1176, 1076 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 286.1471 [calculated mass for C$_{14}$H$_{24}$NO$_3$S (M+H)$^+$ 286.1471].
**2p:** Yellow oil, 56% yield. \([\alpha]_{D}^{23} = +17.4° (c 3.42, CHCl_3)\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.35 (m, 2H), 7.31 (ddd, \(J = 7.7, 6.8, 1.2\) Hz, 2H), 7.26 – 7.22 (m, 1H), 6.80 (dt, \(J = 2.5, 1.8\) Hz, 1H), 6.64 – 6.59 (d, \(J = 15.8,\) Hz, 1H), 6.10 (dd, \(J = 15.7, 7.7\) Hz, 1H), 5.33 (dddt, \(J = 7.8, 5.0, 2.1, 1.0\) Hz, 1H), 4.71 (dt, \(J = 17.2, 2.4\) Hz, 1H), 4.20 – 4.15 (m, 2H), 3.75 (ddd, \(J = 17.2, 5.2, 2.0\) Hz, 1H), 1.25 (t, \(J = 7.1\) Hz, 3H), 1.20 (s, 9H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 162.44, 138.77, 136.60, 135.23, 131.65, 128.91, 128.54, 127.72, 126.52, 73.47, 60.66, 57.65, 47.44, 23.47, 14.14; IR (thin film) 3060, 2980, 2906, 1725, 1447, 1180, 1075 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 370.1447 [calculated mass for \(\text{C}_{19}\text{H}_{25}\text{NNaO}_{3}\) \((\text{M+Na})^+\) 370.1447].

![NMR Spectra](image-url)
2q: Yellow oil, 58% yield. $[\alpha]^{23}_{D} = +119.6^\circ$ (c 0.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.67 (dt, $J = 2.6, 1.9$ Hz, 1H), 6.13 (dd, $J = 15.1, 10.4$ Hz, 1H), 5.97 – 5.91 (m, 1H), 5.69 – 5.61 (m, 1H), 5.37 (ddq, $J = 15.2, 7.9, 0.7$ Hz, 1H), 5.09 (dd, $J = 7.4, 5.0, 2.3$ Hz, 1H), 4.58 (dt, $J = 17.0, 2.3$ Hz, 1H), 4.13 – 4.08 (m, 2H), 5.63 – 3.58 (m, 1H), 1.69 – 1.67 (m, 3H), 1.20 (t, $J = 7.1$ Hz, 3H), 1.12 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.48, 138.41, 135.37, 132.11, 130.62, 130.35, 129.55, 73.24, 60.58, 57.56, 47.29, 23.47, 18.14, 14.16; IR (thin film) 2978, 2931, 1728, 1369, 1178, 1072 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 334.1447 [calculated mass for C$_{16}$H$_{25}$NNaO$_3$S (M+Na)$^+$ 334.1447].
2.4a: colorless oil, 43% yield. $[\alpha]_D^{25} = +51.923$ (c, 0.52, CHCl$_3$). $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.35 – 7.23 (m, 5H), 6.85 (dt, $J = 2.4$, 1.7 Hz, 1H), 6.24 (ddd, $J = 15.2$, 10.4 Hz, 1H), 6.09 – 5.99 (m, 1H), 5.81 – 5.70 (m, 1H), 5.58 (dddd, $J = 15.3$, 7.5, 6.0, 0.9 Hz, 1H), 4.85 (m, 1H), 4.68 (ddd, $J = 17.2$, 2.6, 1.8 Hz, 1H), 4.62 (d, $J = 6.6$ Hz, 2H), 4.50 (d, 2H), 3.71 (dd, $J = 5.2$, 1.9 Hz, 1H), 3.69 – 3.61 (m, 3H), 1.76 (m, 3H), 1.18 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 162.3, 141.0, 138.2, 135.1, 132.8, 131.5, 130.3, 128.2, 127.53, 127.50, 123.3, 73.0, 72.3, 72.0, 65.1, 57.8, 47.7, 23.4, 18.1. IR (thin film): 2959, 2927, 1718, 1454, 1364, 1180, 1074, 913 cm$^{-1}$. HRMS (ESI$^+$) $m/z$ 418.20503 [calcd for C$_{23}$H$_{33}$NO$_4$S (M + H)$^+$ 418.20466].
2.5c; Colorless oil, 23% yield. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.61 (d, $J = 16.8$ Hz, 1H), 7.36 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.28 (ddd, $J = 8.1, 7.4, 1.7$ Hz, 1H), 6.95 (td, $J = 7.6, 1.1$ Hz, 1H), 6.83 (dd, $J = 8.1, 1.0$ Hz, 1H), 6.15 (d, $J = 16.8$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.95, 146.70, 132.15, 129.39, 121.16, 121.01, 118.98, 116.42, 97.02; IR (thin film) 3346, 2220, 1706, 1458, 1253, 914 cm$^{-1}$; LRMS (ESI$^+$) $m/z$ 145.05[calculated mass for C$_9$H$_7$NO (M$^+$)].
2.5a: White solid, 73% yield. \([\alpha]_D^{24} = +233.4^\circ (c1.2, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.71 (s, 1H), 8.04 (dd, \(J = 7.8, 1.7\) Hz, 1H), 7.58 (ddd, \(J = 8.1, 7.4, 1.7\) Hz, 1H), 7.39 (dddd, \(J = 7.8, 7.3, 1.2, 0.6\) Hz, 1H), 7.28 – 7.22 (m, 2H), 6.32 (dt, \(J = 15.3, 1.3\) Hz, 1H), 4.12 (dd, \(J = 7.2, 1.3\) Hz, 2H), 1.27 (s, 9H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 163.61, 158.00, 150.30, 144.70, 133.30, 129.91, 126.54, 126.32, 123.29, 123.24, 57.92, 28.71, 22.66; IR (thin film): 2956, 2923, 2878, 1720, 1682, 1367, 1259, 1088 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 394.0087 [calcd for \(\text{C}_{15}\text{H}_{18}\text{BrNO}_3\text{S} (\text{M+Na})^+\) 394.0083].
2.6b: white solid, 51% yield. $[\alpha]^2_\text{D}_{2} = +3.7^\circ$ (c 1.4, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.91 – 7.88 (m, 2H), 7.63 – 7.60 (m, 1H), 7.53 – 7.49 (m, 2H), 7.31 (tt, $J$ = 6.8, 1.2 Hz, 2H), 7.27 – 7.23 (m, 3H), 6.98 (dt, $J$ = 2.7, 1.4 Hz, 1H), 4.71 (dtt, $J$ = 4.0, 2.6, 1.2 Hz, 1H), 4.43 (ddd, $J$ = 17.2, 4.3, 1.7 Hz, 1H), 4.33 (s, 2H), 4.08 (ddd, $J$ = 17.2, 2.6, 1.1 Hz, 1H), 3.75 (dd, $J$ = 10.4, 2.6 Hz, 1H), 3.70 (dd, $J$ = 10.4, 2.9 Hz, 1H), 1.11 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 142.85, 141.76, 139.70, 138.01, 133.67, 129.15, 128.18, 127.70, 127.44, 127.42, 73.06, 69.80, 61.88, 58.18, 57.99, 22.77; IR (thin film) 2959, 2924, 2855, 1307, 1150, 1084 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 434.1461 [calculated mass for C$_{22}$H$_{28}$NO$_4$S$_2$(M+H)$^+$ 434.1454].
2.7b: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37 – 7.27 (m, 5H), 6.95 (q, $J$ = 1.9 Hz, 1H), 5.14 (ddddd, $J$ = 8.2, 4.3, 3.5, 2.1 Hz, 1H), 4.86 (dd, $J$ = 15.7, 6.2, 1.8 Hz, 1H), 4.75 (dd, $J$ = 15.7, 3.5, 1.9 Hz, 1H), 4.64 – 4.52 (m, 2H), 4.18 (q, $J$ = 7.1 Hz, 3H), 3.79 (dd, $J$ = 10.7, 2.2, 0.5 Hz, 1H), 3.73 (dd, $J$ = 10.7, 4.5 Hz, 1H), 1.26 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.4, 140.1, 138.4, 132.5, 128.3, 127.50, 127.46, 84.8, 75.0, 73.4, 71.3, 60.6, 14.3; IR (thin film): 2980, 2926, 2870, 1716, 1367, 1259, 1097 cm$^{-1}$; HRMS (ESI*) $m/z$ 263.1290 [calcd for C$_{15}$H$_{19}$O$_4$ (M+H) $^+$ 263.1288].
2.7c: Colorless oil, 62% yield. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.38 (m, 3H), 7.31 (m, 2H), 6.83 (dd, $J = 15.7, 6.9$ Hz, 1H), 6.21 (dd, $J = 15.7, 0.8$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.86 (d, $J = 1.8$ Hz, 1H), 3.50 (ddd, $J = 6.9, 1.9, 0.8$ Hz, 1H), 1.33 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.55, 143.49, 136.02, 128.60, 125.46, 124.05, 61.01, 60.67, 14.21; IR (thin film) 2981, 2925, 2903, 2864, 1716, 1652, 1454, 1364, 1261, 1075 cm$^{-1}$; HRMS (ESI$^+$) m/z 218.0933 [calculated mass for C$_{13}$H$_{14}$O$_3$S (M + H)$^+$ 218.0943].
CHAPTER 3
APPLICATION OF THE ANIONIC [3+2]-ANNULATION APPROACH TOWARD NATURAL PRODUCT ALKALOIDS
3.1 Asymmetric total synthesis of (+)-elacomine

Elacomine is a hemiterpene spirooxindole alkaloid isolated in 1968 by Slykwa from the roots of *Elaeagnus commutate* as a racemate. Borschberg and co-workers confirmed its structure and absolute configuration through isolation, synthesis and X-ray crystallographic analysis. Although there is no biological activity associated with elacomine, the 3, 3'-pyrrolidinyl-spirooxindole unit forms the core of a large family of biologically active natural products. In addition, its structural complexity has attracted the attention of synthetic chemists as a target for total synthesis to showcase new synthetic strategies. To date, three racemic total syntheses by Borschberg, Horne, White and a recent formal synthesis by Takemoto have been reported.

3.1.1 Prior syntheses of elacomine

The first total synthesis of elacomine was reported by Borscheberg and co-workers in 1996. Their racemic and enantioselective (Scheme 3.1) approaches towards elacomine employed tryptamine-based starting compounds (6-methoxytryptamine, l-tryptophan and isovaleraldehyde) to introduce the indole and the alkyl units respectively. A Pictet-Spengler reaction of the condensation product of the amine and the aldehyde enabled construction of the spiro-pyrrolidine core through N-bromosuccinimide mediated oxidative rearrangement of β-carbol ine. Borschberg’s racemic five-step sequence used an advanced starting compound, 6-methoxytryptamine. enantioselective synthesis (Scheme 3.1) using l-tryptophan delivered (+)-elacomine in eleven steps in 76% ee.
Scheme 3.1. Borschberg’s enantioselective total synthesis of (+)-elacomine

Horne’s\textsuperscript{[40]} strategy (Scheme 3.2) used tryptamine, a similar but achiral source of the indole unit as Borschberg’s group. The commercially available tryptamine hydro-bromide was converted to 2,6-dibromotryptamine which was then reacted with isovaleraldehyde to afford the imine (3.2a). Trifluoroacetic acid catalyzed intramolecular iminium ion spiro-cyclization produced the spirooxindole system (3.2b), which was advanced to the natural product.

Scheme 3.2. Horne’s total synthesis of (+)-elacomine

White’s\textsuperscript{[41]} synthesis (Scheme 3.3) utilized a tandem intramolecular photo-cyclization of 3.3a and a retro-Mannich fragmentation of 3.3b to access a tetra-hydro β-carboline system (3.3c) which was then subjected to an oxidative spiro-cyclization affording the core of the natural product (3.3d) with the desired stereocenters. Hydrogenolysis of the amino and phenolic groups afforded (+)-elacomine.
Scheme 3.3. White’s total synthesis of (+)-elacomin

A recent formal synthesis from the lab of Takemoto (Scheme 3.4) began with commercially available iodoaniline. The key step in their synthesis utilized a one pot intramolecular palladium catalyzed Heck-cyclization of the carbamoyl chloride (3.4a) followed by a Lewis acid-mediated hydro-amination cascade of 3.4b to construct the spirooxindole core (3.4c). To complete the total synthesis, hydrogenolysis of the benzyl group afforded a known methoxy elacomin carbamate (Scheme 3.4).

Scheme 3.4 Takemoto’s total synthesis of (+)-elacomin

The key step in Borschberg’s, Horne’s and White’s syntheses require oxidative conditions to access the spirooxindole core. The consequence of these aggressive equilibrating conditions is
isomerization of chiral centers leading to poor enantioselectivity. We have proposed a concise synthesis commencing from an optically pure 3-pyrroline ester with the requisite C2 substituent of the natural product’s pyrrolidine unit. Borrowing lessons of the discussed syntheses, we carefully planned for mild introduction of the aryl motif and formation of the spiro-oxindole core to retain the stereochemical integrity of starting compound in our approach (Scheme 3.7). We recently reported the shortest (six-step) asymmetric synthesis of (+)-elacomine.[16] A substrate controlled asymmetric installation of the spirooxindole scaffold was enabled by a chiral pyrrolidine core, which was accessed using our methodology.

3.1.2 Results and Discussion

Starting from commercially available isovaleraldehyde (Scheme 3.7), the resulting chiral sulfinimine was synthesized using Ellman’s procedure.[31] The asymmetric [3+2] annulation strategy afforded the 3-pyrroline ester 3.7c with the required substituent and stereochemistry in 63% yield. The 3-pyrroline ester was then converted directly to the halo-aryl amide (3.5a and 3.7c) following a trimethyl aluminum-mediated amidation[43] of the ester 3.7c with the halo-aniline (Scheme 3.7).

In our first approach, attempts to perform intra-molecular Heck and radical cyclizations on a bromo aryl amide 3.5a were not successful (Scheme 3.5). No reaction was observed with respect to the Heck conditions (starting material was recovered). The lack of reactivity of bromo compound 3.5a under mild conditions (60 °C), and our failed attempt to effect the transformation at higher reaction temperature (110 °C) due to decomposition of 3.5a meant that we had a narrow window for optimization of the cyclization. Our experience with the radical approach was more deleterious because the radical species from 3.5a was readily reduced to the de-halogenated
undesired product 3.5b. We postulate that the reactivity of the radical species coupled with the orientation due to the congestion favored the reduction pathway as opposed to the desired cyclization event.

Scheme 3.5. Unsuccessful radical and palladium mediated spiro-cyclizations

Undeterred by the failure to cyclize the bromo substrate under the radical or Heck conditions, we turned to the relatively simpler 2-iodoaryl 3-pyrroline 3.6a for our pilot studies. To our satisfaction, the palladium and radical conditions (Scheme 3.6) that did not work with the bromoaryl amide provided the tricyclic indeno-type structures (3.6b and 3.6c respectively) in good yields. This achievement indicated to us that the more reactive iodo analogue 3.7e (Scheme 3.7) would undergo spiro-cyclization under the Heck or radical approaches.

Scheme 3.6. Palladium and radical approaches towards rigid tricyclic motifs.

The iodoaryl amide 3.7e was prepared as previously described from the 3-pyrroline 3.7c and iodoaniline 3.7d (Scheme 3.7). Substrate-controlled intra-molecular Heck reaction using Overman’s conditions proceeded with excellent selectivity via 5-exo-cyclization to afford
enamine 3.7f. X-ray analysis of a crystal of the enamine confirmed the absolute configuration of the all-carbon quaternary stereocenter (Figure 3.1).

Scheme 3.7. Njardarson’s asymmetric total synthesis of (+)-Elacomine

Figure 3.1. X-ray crystal structure of 3.7f

With enamine 3.7f in hand, we needed to reduce the double bond of the C4-C5 system of the natural product. Attempts using palladium catalyzed hydrogenations to reduce the enamine in ethyl acetate and methanol were not successful. In one instance, isomerization was observed when the hydrogenation was performed in methanol (overnight). To circumvent this challenge, the methoxy elacomine (3.7g) was obtained through a concomitant cleavage of the sulfoxide and
reduction of the resulting iminium species in acetic acid-zinc (powder) conditions in one pot. Demethylation using boron tribromide reagent afforded (+)-elacomine in six steps from the commercially available isovaleraldehyde 3.7a.

In addition to excellent substrate stereo-controlled construction of sterically encumbered quaternary centers, we have shown that the radical pathway can be terminated with a carbon electrophile further enabling formation of more carbon-carbon bonds (Scheme 3.8). The configuration of the allylated 3.8c was determined by 2D NOE experiment. The facial selectivity of the radical allylation leading to 3.8c is substrate controlled, allowing the allylation from the less sterically hindered convex face of the compound. Our attempts to cyclize and trap the palladium complex in situ with a vinyl group were not successful. The vinylation of the iodo-palladium oxidative addition complex occurred prior to cyclization affording the styrenyl product 3.8b.

Scheme 3.8. Cyclization and Carbon-carbon bond forming adventures

The architectures of the radical and Heck-cyclization products (Scheme 3.6 and Scheme 3.8) have common features in pharmaceutical and biologically active natural products. As an entry to our medicinal chemistry program, we were interested in demonstrating further synthetic modifications targeting the amine and ester functionalities of the tricyclic compounds. The summary of the transformations is presented in Scheme 3.9. First, we demonstrate the ease of removal of the sulfoxide protecting group using HCl to afford 3.9a. The deprotected nitrogen was then N-acylated, alkylated and sulfonylated to afford 3.9b-d. We have also shown access to chiral
cyclic amino alcohols (3.9e) by a tandem reduction of the ester carbonyl and acid-catalyzed removal of the sulfoxide protecting group.

![Scheme 3.9. Functionalization of tricyclic products](image)

### 3.2 Asymmetric Total Syntheses of (-)-Supinidine and (-)-Isoretronecanol

Pyrrolizidine alkaloids (-)-supinidine and (-)-isoretronecanol, among other necine bases, have a characteristic aza-bicyclo [3.3.0] core. Most of these compounds are commonly isolated as pyrrolizidine esters. For example, (+)-amabiline (Figure 3.2) is naturally obtained as an ester of (-)-supinidine and viridifloric acid.\(^{[46]}\) The attractive structural architecture and the diverse biological activities exhibited by some of the pyrrolizidine compounds including anti-tumor, hypotensive, anesthetic, anti-bacterial, anti-inflammatory, carcinogenic, and hepatotoxic activities continue to elicit synthetic interest.\(^{[47]}\)
Pyrrolizidine alkaloids have been a subject of wide synthetic campaign with a number of both racemic\cite{48} and asymmetric strategies having been developed\cite{49}. Most of the reported asymmetric syntheses of (-)-supinidine and (-)-isoretronecanol and their respective enantiomers derived enantioselectivity from chiral pool sources, such as L-proline and carbohydrate based building blocks, as well as the use of chiral auxiliaries and reagents to induce chirality. In the context of our asymmetric approach, a brief summary of asymmetric syntheses of these pyrrolizidine alkaloids are discussed\cite{50}.

### 3.2.1 Prior Asymmetric Syntheses of (-)-Supinidine

Robbin’s synthesis (Scheme 3.10) of (+)-supinidine and (+)-isoretronecanol was the first asymmetric approach to the pyrrolizidine alkaloids\cite{47a}. The key step towards the pyrrolizidine core is the conversion of the diformylated hydroxyl-L-proline to the azomethine ylide which undergoes 1,3-dipolar cycloaddition with the ethyl propiolate to form the dihydropyrrolizine ester. This strategy previously afforded racemic isoretronecanol in Albonico’s synthesis of pyrrolizidine alkaloids in which L-proline is the starting compound\cite{51}. Robbin’s anticipated directed hydrogenation by the formylated hydroxyl group is key in setting up the two stereocenters C1 and C8.
Scheme 3.10. Robin’s asymmetric total syntheses of (-)-supinidine and (-)-isoretronecanol

Nagao and co-workers\textsuperscript{[52]} employed an Evans-type chiral auxiliary to diastereoselectively alkylate an iminium ion using the \textit{in situ} generated chiral enolate (Scheme 3.11). The diacetoxy lactam derived from succinic anhydride was alkylated using the chiral tin (II) enolate giving the desired diastereomer as the major product. The auxiliary and acetoxy groups were hydrolyzed, the ensuing acid converted to the methyl ester and the primary alcohol to a methane sulfonate respectively. LDA mediated enolate formation and displacement of the methane sulfonylate formed the pyrrolizidine ring with the desired stereochemistry at the C8 center.

Scheme 3.11. Nagao’s asymmetric total synthesis of (-)-Supinidine
Pilli’s synthesis used Evan’s type-chiral auxiliary to asymmetrically synthesize (+)-isoretronecanol (Scheme 3.12). Addition of the chiral titanium (IV) enolate of 3.12a to the acyl iminium derived from 3.12c proceeded diastereoselectively (10:1), setting the two stereocenters in a single operation.[53] Overall, (+)-isoretronecanol was obtained in four linear steps starting from the advanced substrates 3.12a and 3.12c in 32% overall yield.

Scheme 3.12. Pilli’s total synthesis of (+)-isoretronecanol

Hassner’s asymmetric synthesis of (−)-supinidine derives chirality from L-proline (Scheme 3.13). The pyrrolizidine core was constructed using an intra-molecular oxime-olefin cycloaddition of the N-acetoximino-2-vinylpyrrolidine (3.13a). The natural product was finally obtained through a lithium aluminum hydride reductive cleavage of the N-O bond of the oxazolidine (3.13b) to an amino alcohol. The double bond of the natural product was installed by a tandem conversion of the amino group to a diazonium using nitrous acid followed by elimination.

Scheme 3.13. Hassner’s asymmetric total synthesis of (−)-supinidine
Takahata and co-workers introduced asymmetry in their approach by reagent controlled Katsuki-Sharpless epoxidation of the hydroxyl urethane 3.14a (Scheme 3.14). The pyrrolidine core (3.14c) was constructed using an amidomercuration which was advanced to the amino ester 3.14d. Trimethylaluminum amidation of the ester afforded the pyrrolizidine lactam (3.14e), which was subsequently transformed to the natural product in six steps.

Scheme 3.14. Takahata’s total synthesis of (-)-supinidine

Benn’s divergent asymmetric approach starting from N-Cbz protected L-proline (3.15a) afforded both (-)-supinidine and (-)-isoretronecanol (Scheme 3.15). The carboxy group of the L-proline derivative was homologated followed by alkylation of the nitrogen. Dieckmann cyclization of the diester 3.15b afforded hydroxyl pyrrolizidine ester 3.15c, which they divergently transformed to the natural products (-)-supinidine and (-)-isoretronecanol in three and two steps respectively.
Scheme 3.15. Benn’s asymmetric syntheses of (-)-supinidine and (-)-isoretronecanol

Hewson’s formal synthesis of (-)-supindine employed the known (L)-N-benzyloxycarbonylpyroglutamic acid derived from L-glutamic acid as the chiral source (Scheme 3.16). The pyrrolizidine core was accessed by a tandem Wittig olefination and a vinyl phosphonium cyclization of (3.16b) affording the known acetoxy-protected supinidine (3.16c).

Scheme 3.16. Hewson’s asymmetric formal synthesis of (-)-supindine

3.2.2 Prior Asymmetric Syntheses of (-)-Isoretronecanol

Starting from unsaturated amino ester derived from D-glucosamine, Tatsuta and co-workers reported a 13-step asymmetric synthesis of (-)-isoretronecanol (Scheme 3.17). Hydrogenation of the double bond of 3.17a proceeded with formation of the lactam setting up the C8 stereocenter (3.17b). Reduction of the lactam carbonyl followed by a tandem cyclization afforded the pyrrolidizine core with the required stereochemistry of (-)-isoretronecanol.
Scheme 3.17. Tatsuta’s asymmetric total synthesis of \((-\)-isoretronecanol

Lhommet’s asymmetric synthesis of \((-\)-isoretronecanol employed a substrate-controlled diastereoselective olefin reduction using (S)-methylbenzyl amine as the chiral auxiliary (Scheme 3.18).\cite{58} Reaction of the cyclopropane keto-ester with (S)-methylbenzyl amine afforded the pyrroline diester (3.18b) with an endocyclic double bond. In setting up the requisite stereochemistries of the bridge center and that of the \(\text{CH}_2\text{OH}\), stereo-selective reduction of the olefin proceeded with high diastereoselectivity. Hydrogenolysis of the auxiliary and a reflux in toluene afforded the pyrrolizidine lactam along with its enantiomer. The lactam was converted to a thiolactam using Lawesson’s reagent to enable recrystallization and separation of enantiopure 3.18d, which was advanced to the natural product.

Scheme 3.18. Lhommet’s asymmetric total synthesis of \((-\)-isoretronecanol

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Ley’s enantioselective synthesis\textsuperscript{[59]} of the cyclic allyl carbamate derives asymmetry from L-proline. The commercially available 3.19a was advanced to carbamate 3.19b. Conversion of 3.19b to allyl tricarbonyliron complex 3.19c (\textbf{Scheme 3.19}) followed by exhaustive carbonylation of the iron-complex afforded pyrrolidizine lactam 3.19d, which was then converted to the natural product.

\textbf{Scheme 3.19.} Ley’s synthesis of (-)-isoretronecanol

Davies and co-workers recently reported asymmetric synthesis of (-)-isoretronecanol employing (S)-N-benzyl-N-methylbenzyl)-amide, a source of chiral nitrogen (\textbf{Scheme 3.20}).\textsuperscript{[60]} An \textit{aza}-Michael on the conjugated ester and trapping of the resultant enolate with allyl bromide installed the required allyl group. Ring-closing metathesis gave 4,5-disubstituted cycloheptene which was followed by isomerization of the ester group to give the required chirality of the CH$_2$OH in the natural product. To construct the pyrrolizidine system, the triol was obtained via \textit{in situ} epoxidation in acidic media followed by hydride ring opening of the lactone. Oxidative cleavage of the 1,2-diol followed by reductive amination provided the natural product.
Scheme 3.20. Davies total synthesis of (-)-isoretronecanol

Szymoniak asymmetric synthesis employed a chiral phenylglycinol derived imine 3.21a. A Babier mediated diastereoselective allylation afforded 3.21c. Hydrozirconation-aminocyclization afforded pyrrolidine 3.21d (Scheme 3.21).[61] The N-protected pyrrolidine was subjected to hydrogenolysis to remove the phenylglycinol group. Desilylation and bromination of the resultant hydroxyl group enabled a nucleophilic displacement by nitrogen to yield the pyrrolizidine core with the desired C1 and C8 chiral centers. Debenzylation of 3.21f afforded the natural product in seven steps.

Scheme 3.21. Szymoniak’s total synthesis of (-)-isoretronecanol

Most of the above asymmetric approaches employ L-proline or hydroxyl L-proline chiral pool starting materials to introduce half of the pyrrolizidine core. Other asymmetric strategies
include substrate and reagent controlled facial bias by chiral auxiliaries most of which require a number of steps to prepare the key intermediate.

Our synthetic design focused on assembling all the required carbon framework with the requisite stereochemistry at the C-8 position using our new annulation strategy (Figure 3.3). We would then need to perform a few functional group interconversions to complete the synthesis. For example, nucleophilic displacement of a leaving group by the nitrogen atom would deliver the pyrrolizidine core.\[24]\] Another attractive cyclization approach is reductive amination of a masked terminal aldehyde.\[46]\] With these two approaches in mind, (-)-supinidine was envisioned via asymmetric construction of the [3.3.0] aza-bicyclo ring system by displacement of a leaving group pre-installed at the terminal carbon of the n-butyl C2-substituent of the 3-pyrroline. Alternatively, a protected hydroxyl group could be converted to a leaving group such as tosylate or bromide at an advanced stage of the synthesis. Another option would be condensation of an aldehyde with the amine group. Lindsley and co-workers demonstrated a tandem deprotection of the sulfoxide and an acetal allowing condensation of the liberated amine and aldehyde giving the pyrrolizidine core while preserving the C-8 stereocenter.\[62]\] This synthetic sequence would then be extended to (-)-isoretronecanol following saturation of the olefin in a substrate controlled hydrogenation.\[63]\]

**Figure 3.3.** Our retrosynthesis of the pyrrolizidine alkaloids
3.2.3 Results and Discussion

Since the key step in our synthetic plan is the synthesis of the 2-substituted 3-pyrroline ester using our [3+2]-annulation approach, we first focused on synthesis of the 3-pyrroline compounds with the desired C2 sidechain. In the first approach, we synthesized the (S)-sulfinimine with the protected aldehyde functionality as shown in Scheme 3.22. The monoprotected aldehyde was prepared by partial ozonolysis of 2,5-cyclooctadiene, which was protected as an acetal by reaction with the 1,3-propane diol. Complete ozonolysis of the remaining double bond afforded dioxolane aldehyde 3.22a, which was converted to the sulfinimine 3.22b using modified Ellman’s conditions.

Our key step towards the natural product afforded the desired 3-pyrroline ester 3.22c, but yield was poor, rendering this approach synthetically impractical. The poor reactivity of 3.22b is associated with two oxygen atoms of the dioxolane ring chelating with the lithium and imine nitrogen.

![Scheme 3.22](image)

**Scheme 3.22.** Our first approach towards (-)-supinidine

Our next plan focused on synthesis of sulfinimines with a pre-installed leaving group or with a functionality that would allow installation of a leaving group at a later stage. A common starting point for this route is commercially available 1,4-butandiol which was mono-protected as a tert-butyldimethylsilyl ether (TBS) 3.23b and the tosylate 3.23a (Scheme 3.23). The respective mono-protected alcohol was oxidized to an aldehyde using Dess-Martin periodinane (DMP). Conversion of the aldehydes to sulfinimines (3.23a and b) was performed following the
reported Ellman’s protocol using the tert-butanesulfinamide as the source of chiral nitrogen handle. We formed both the TBS (3.23d) and the tosyl (3.23c) 3-pyrrolines using our methodology. We were excited that the tosylate survived the reaction conditions, once again exhibiting the robustness of this strategy in conversion of sulfinimines to the pyrroline ester in a good yield. Because the TBS protected substrate (3.23d) required deprotection and installation of a leaving group for the cyclization step essentially adding more steps to our sequence, we chose to pursue the tosyl ester whose terminal C2-sidechain contained a leaving group.

Formation of the pyrrolizidine ester required that the protected nitrogen be unmasked to allow the planned intra-molecular amination. A mild deprotection of the Ellman’s auxiliary\[^{31}\] was performed using HCl generated from trimethylsilyl chloride (TMSCl) and deionized water. The chloride salt of the cyclic amine 3.23c was treated with triethyl amine (Et\(_3\)N) in its crude form which allowed the intramolecular nucleophilic displacement of the tosyl group affording the aza bicyclo [3.3.0] octane core of the pyrrolizidine ester. Hydride delivery using diisobutylaluminum hydride (Dibal-H) reduced the pyrrolizidine ester (3.23d)\[^{64}\] completing the asymmetric synthesis of (-)-supinidine whose spectral data and optical rotation are in agreement with published literature reports.\[^{54,65}\]

![Scheme 3.23. Njardarson’s asymmetric total synthesis of (-)-supinidine and (-)-isoretronecanol](image)

Scheme 3.23. Njardarson’s asymmetric total synthesis of (-)-supinidine and (-)-isoretronecanol
With (-)-supinidine in our hands, the natural product (-)-isoretronecanol required a simple but stereochemically challenging hydrogenation of the C1-C2 double bond. Scrutiny of the conformation of (-)-supinidine suggested the potential of a substrate-controlled hydrogenation of the convex face of the molecule. Stereoselective hydrogenation of (-)-supinidine using palladium on carbon afforded (-)-isoretronecanol.

3.2.4 Conclusion

We have developed a concise asymmetric approach towards (-)-supinidine and (-)-isoretronecanol that represents one of the shortest (five-step) asymmetric approach from the known aldehyde 3.23a toward the pyrrolidine natural products. The key step in our synthesis is the diasteoselective [3+2]-pyrroline synthesis using chiral sulfinimines. This approach enables access to the opposite enantiomeric series of the natural products, the (+)-supinidine and (+)-isoretronecanol due to the availability of the R-enantiomer of the chiral nitrogen source.

3.3 Progress towards the Total Synthesis of (-)-Kainic Acid

The kainoid alkaloids (Figure 3.4) are generally characterized by a 2,3,4-trisubstituted pyrrolidine motif with three contiguous stereocentres respectively. The (-)-Kainic acid is the first member of the kainoid family isolated in 1953 from sea weed *Digenea simplex*. Other biologically important kainoids include (+)-allokainic acid, acromelic acid and domoic acid. This family of natural products are popular synthetic targets due to their important biological activities. The structure-activity relationship of these compounds is an important factor for consideration in their synthesis. For example, the *cis* relationship of the C3 and C4 substituents is very critical for potency as demonstrated by relative activities of the (-)-kainic acid with greater potency compared to its epimer, the allokainic acid due to its C3-C4 *trans* relationship. The neuro excitatory
activity of the kainoids is also attributed to the similarity in functionalities to those L-glutamic acid and their binding site, the kainate receptor which is one of the glutamate receptors.\cite{70}

![Kainoid alkaloids](image)

**Figure 3.4.** Kainoid alkaloids

Comprehensive accounts of syntheses of kainic acid and its epimer, the allokainic acid\cite{71} have been presented in a number of reviews.\cite{68-69,72} To date, there exist over 35 total syntheses of kainic acid including three gram-scale approaches. Examination of these syntheses revealed that the main challenge is stereoselective installation of the three contiguous asymmetric centers within the relatively small five-membered heterocycle.\cite{68} Apart from structural challenge, there is a need to address the scalability of the synthetic method to allow mass production\cite{73} due to the high demand by biologists and to mitigate the high costs of the kainoids.

Our synthetic plan (Scheme 3.24) envisioned a concise synthesis of (−)-kainic acid starting from 3-pyrroline ester 3.25b. The isopropenyl group could be introduced by 1,4-addition. The power of this synthetic design is its flexibility to provide access other kainoids by simply changing the nucleophile or the enantiomer of 3-pyrroline. Homologation of the ester carbonyl would allow installation of the acyclic carboxy group. The C2 carboxy group is readily available by oxidation of the protected primary alcohol.
3.3.1 Results and Discussion

Our approach commenced with synthesis of the TBS ether of 2-hydroxy acetaldimine (3.25a) and using our [3+2]-annulation strategy, the pyrroline 3.25b was formed in good yield. Conjugate addition of the organo-copper reagent, prepared in situ from commercially available isopropenyl magnesium bromide (3.25c) and copper (I) iodide in anhydrous ether, provided the C2, C3 and C4 tri-substituted pyrrolidine 3.25d. To homologate the ester, diisobutylaluminum hydride (Dibal-H) smoothly converted the ester (3.25d) to the primary alcohol (3.25e), which was quickly converted to the methanesulfonate using methanesulfonyl chloride and triethyl amine as an acid scavenger. With the mesylate (3.25f) in hand, nucleophilic displacement of the mesylate by the cyano group afforded the nitrile (3.25g). Thus, we had all the carbon framework of the natural product assembled. We decided to target the known cyclic carbamate previously synthesized by Evans en route to the (-)-kainic acid.[74] Acid catalyzed methanolysis of nitrile 3.25g to the methyl ester proceeded with concomitant global deprotection of the primary alcohol and the nitrogen atom. Using the crude hydrochloride salt of the intermediate amino alcohol (3.25h), the cyclic carbamate was then obtained via acylation using N,N'-carbonyldiimidazole (CDI). When we compared our spectral data (1H and 13C NMR) to the reported data from Evan’s synthesis of (-)-kainic acid, we were disappointed that the spectral data did not match.
Scheme 3.25. Asymmetric annulation approach towards (-)-kainic acid

Luckily, we were carrying out a parallel synthetic sequence (Scheme 3.26) using the enantiomer of 3.25b. Through this approach, we were able to obtain an X-ray quality crystal of the corresponding enantiomer of the mesylate (3.26e). Unambiguous assignment of the mesylate 3.26e lead to the discovery that the relationship of the three contiguous centers were unexpectedly all cis. Our current postulate explaining this occurrence is existence of a co-operative/associative effect of the cuprate reagent, the sulfoxide and the sulfur, which dominantly impact facial selectivity. Fortunately, using the latter sequence (Scheme 3.26), we were able to construct the pyrrolidine scaffold of the (-)-kainic acid with the desired C3 and C4 configurations. Our challenge is to isomerize the epimerizable C2 stereo-center, of which there are successful epimerization examples\textsuperscript{[75]} of the C2 which rescued an advanced intermediate like ours.
Scheme 3.26. Our second generation approach towards (-)-kainic acid

3.3.2 Conclusion

We have developed a feasible synthetic design towards (-)-kainic acid. Synthetic efforts are now underway to convert compound 3.26f to a cyclic carbamate, a key intermediate towards the natural product. We envision epimerization of the C2 center and subsequent oxidation of the CH$_2$OH to complete the asymmetric total synthesis of (-)-kainic acid.
3.4 X-ray structural data for 3.7f (CCDC 1062146)

Crystal data and structure refinement (CCDC 1062146)

Empirical formula \( \text{C}_{23}\text{H}_{32}\text{N}_{2}\text{O}_{3}\text{S} \)
Formula weight 376.50
Temperature/K 100.01
Wavelength 0.71073 Å (MoK\(\alpha\))
Crystal system triclinic
Space group P1

Unit cell dimensions
\[ a = 9.6001(12) \text{ Å} \quad \alpha = 94.148^\circ \] (4)
\[ b = 9.6006(12) \text{ Å} \quad \beta = 106.962^\circ \] (4)
\[ c = 12.7209(16) \text{ Å} \quad \gamma = 109.951^\circ \] (4)

Volume 1034.7(2) Å\(^3\)
\( Z \)
2
Density (calculated) 1.208 Mg/m\(^3\)
Absorption coefficient 0.177 mm\(^{-1}\)
\( F(000) \)
404
Crystal size 0.52 × 0.31 × 0.18 mm
Data collection data
3.42 ≤ θ ≤ 52.76°

Index ranges
-11 ≤ h ≤ 11, -11 ≤ k ≤ 12, -15 ≤ l ≤ 15

Reflections collected 8201
Independent reflections 8201 \([R_{int} = 0.0407]\)
Data/restraints/parameters 8201/3/481
Goodness of fit 1.028

Final R indexes \([I>2\sigma(I)]\)
\( R_I = 0.0455, wR_2 = 0.1146 \)

Final R indexes [all data]
\( R_I = 0.0482, wR_2 = 0.1169 \)

Largest diff. peak and hole
0.73 and -0.88 e Å\(^{-3}\)

Flack parameter 0.01(6)
3.5 Characterization and spectral data (+)-elacomine and tricyclic compounds

Ethyl (3aR,8aR)-1-((S)-tert-butylsulfinyl)-8,8a-dihydroindenol[2,1-b]pyrrole-3a(1H)-carboxylate (3.6b).

Palladium (II) acetate (2.5 mg, 0.011 mmol) and triphenylphosphine (11.6 mg, 0.044 mmol) was dissolved in THF (10.0 mL) and the solution purged with nitrogen for 10 min. Solution of the iodo ester (50.0 mg, 0.11 mmol) in THF was added followed by silver carbonate (23.6 mg, 0.086 mmol) and reaction was refluxed at 60 °C under nitrogen atmosphere for 3 h. Reaction was cooled to r.t., filtered over celite pad, solvent evaporated and purified by flash chromatography (30% EtOAc in Hexanes) to afford the enamine, white solid, (29.6 mg, 82%); [α]$_{23}^{D}$ = +183.1° (c 0.96, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.36 (m, 1H), 7.25-7.20 (m, 3H), 6.31 (d, J = 4.2 Hz, 1H), 5.56 (d, J = 4.2 Hz, 1H), 5.23 (dd, J = 6.9, 1.9 Hz, 1H), 4.2 – 4.14 (m, 2H), 3.53 (ddd, J = 17.1, 6.9, 1.2 Hz, 1H), 3.13 (dd, J = 17.1, 1.9 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 1.24 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.68, 142.21, 140.37, 131.66, 128.29, 127.41, 125.18, 124.19, 110.86, 71.33, 69.79, 61.47, 58.30, 39.99, 23.17, 14.11; IR (thin film) 2978, 2926, 1724, 1238, 1078, 914, 742 cm$^{-1}$; HRMS (ESI$^+$) m/z 334.1471 [calcd for C$_{18}$H$_{24}$NO$_3$S (M + H)$^+$ 334.1470]
Ethyl (3aR,8aR)-1-((S)-tert-butylsulfanyl)-2,3,8,8a-tetrahydroindeno[2,1-b]pyrrole-3a(1H)-Carboxylate (3.6c)

To a solution of the iodo ester (50.0 mg, 0.11 mmol) in benzene (10.0 mL) was added AIBN (1.8 mg, 0.011 mmol) in 0.5 mL benzene and tributyltin hydride (0.22 mmol, 60 µL). The reaction refluxed at 80 °C for 2 h, cooled to r.t., solvent evaporated and crude product purified by flash chromatography (30% EtOAc in Hexanes) to provide the title compound, a white solid (23.6 mg, 64% yield). [α]D = +62.4° (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.34 (m, 1H), 7.27 – 7.24 (m, 2H), 7.22 (m, 1H), 4.76 (d, 6.0 Hz, 1H), 4.14 – 4.07 (m, 2H), 3.82 (ddd, J = 10.5, 7.7, 2.1 Hz, 1H), 3.44 (ddd, J = 16.5, 6.0, 1.0 Hz, 1H), 2.94 (d, J = 16.6 Hz, 1H), 2.51 (td, J = 10.5, 6.3 Hz, 1H), 2.44 – 2.30 (m, 2H), 1.21 (t, 7.0 Hz, 3H), 1.13 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 172.60, 142.42, 142.09, 128.50, 127.20, 124.96, 124.06, 72.34, 65.88, 61.26, 57.22, 41.90, 41.10, 37.17, 23.42, 14.06; IR (thin film) 2958, 2926, 1724, 1259, 1074, 750 cm⁻¹; HRMS (ESI⁺) m/z 336.1622 [calcd for C₁₈H₂₆NO₃S (M + H)⁺ 336.1628]
**3-pyrroline (3.7c)**

Yellow oil, 63 % yield, $[\alpha]_{D}^{23} = +54.5^\circ$ (c 2.2, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.66 (dt, $J = 2.9, 1.6$ Hz, 1H), 4.72 (dt, $J = 8.4, 4.9, 1.5$ Hz, 1H), 4.60 (ddd, $J = 17.3, 2.7, 1.5$ Hz, 1H), 4.18 – 4.13 (m, 2H), 3.60 (ddd, $J = 17.2, 4.9, 1.8$ Hz, 1H), 1.77 (m, 1H), 1.50 (ddd, $J = 6.7, 4.5, 3.1$ Hz, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.19 (s, 9H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.66, 138.47, 136.85, 70.88, 60.43, 57.99, 47.37, 45.06, 24.23, 23.75, 23.71, 21.82, 14.08. IR (thin film) 2978, 2931, 2870, 1728, 1450, 1242, 1180, 1095, 1041 cm$^{-1}$; HRMS (ESI$^+$) m/z 324.1605 [calculated mass for C$_{15}$H$_{27}$NNaO$_3$S (M+Na)$^+$ 324.1604].

![1H NMR (500 MHz, CDCl3)](image1)

![13C NMR (125 MHz, CDCl3)](image2)
(S)-1-((S)-tert-butylsulfanyl)-N-(2-iodo-5-methoxyphenyl)-2-isobutyl-2,5-dihydro-1H-pyrrole-3-carboxamide (3.7e). To a cooled CH$_2$Cl$_2$ (10.0 mL, 0 °C) solution of 2-iodo-5-methoxyaniline$^{18}$ (246.6 mg, 0.99 mmol), was added trimethylaluminum (2.0 M in hexanes, 0.54 mL, 1.08 mmol), warmed to r.t and stirred for 2 h. Solution of the ester (100.0 mg, 0.33 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added at 0 °C and the reaction warmed to r.t and stirred for 12 h after which reaction mixture was slowly quenched with ice-cold solution Rochelle’s salt (10.0 mL) and stirred for 1 h. The CH$_2$Cl$_2$ layer was collected, the aqueous layer extracted using CH$_2$Cl$_2$ (3*10.0 mL) and the organic extracts dried using anhydrous Na$_2$SO$_4$. The solvent was evaporated and crude product purified by column chromatography (30% EtOAc in Hexanes) affording product as white solid (118.1 mg, 71%). [α]$^2_23$D = -8.6° (c 1.7, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.01 (d, $J = 2.9$ Hz, 1H), 7.84 (s, 1H), 7.60 (dd, $J = 8.8$ Hz, 1H), 6.56 (dt, $J = 2.8$, 1.5 Hz, 1H), 6.48 (dd, $J = 8.8$, 3.0 Hz, 1H), 4.93 (dddd, $J = 8.0$, 4.6, 3.0, 1.6 Hz, 1H), 4.72 (ddd, $J = 16.9$, 2.7, 1.4 Hz, 1H), 3.81 (s, 3H), 3.73 (dd, $J = 16.9$, 4.8, 1.8 Hz, 1H), 1.87 (m, 1H), 1.69 – 1.57 (m, 2H), 1.25 (s, 9H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.75, 160.55, 140.90, 138.52, 138.50, 132.75, 113.16, 107.06, 78.11, 71.48, 58.20, 55.47, 47.66, 45.03, 24.31, 23.80, 23.78, 21.81.; IR (thin film) 2956, 2933, 1674, 1577, 1519, 1456, 1170, 1141, 1051; HRMS (ESI$^+$) m/z 527.0840 [calculated mass for C$_{20}$H$_{30}$N$_2$NaO$_3$S (M + Na)$^+$ 527.0836].
(2'S,3R)-1'-(S)-tert-butyldimethylsilyl)-2'-isobutyl-6-methoxy-1',2'-dihydrospiro[indoline-3,3'-pyrrol]-2-one (3.7f).

To a solution of palladium (II) acetate (3.6 mg, 0.016 mmol), triphenylphosphine (16.8 mg, 0.064), and the iodo amide (80.0 mg, 0.16 mmol) in 10.0 mL THF was added silver carbonate (88.2 mg, 0.32 mmol) and the reaction heated to reflux for 3 h. The reaction mixture was cooled to r.t., filtered over a celite and solvent evaporated. Crude product was purified by column chromatography (40% EtOAc in Hexanes) affording the enamine as white solid (46.4 mg, 78%).

[α]$_{23}^{D}$ = -288.6° (c 1.72, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.28 (s, 1H), 7.24 (d, $J$ = 8.3 Hz, 1H), 6.74 (d, $J$ = 4.2 Hz, 1H), 6.57 (dd, $J$ = 8.3, 2.3 Hz, 1H), 6.45 (d, $J$ = 2.3 Hz, 1H), 4.91 (dd, $J$ = 4.2, 0.6 Hz, 1H), 4.36 (dd, $J$ = 10.0, 4.8 Hz, 1H), 3.80 (s, 3H), 1.95 (ddd, $J$ = 14.2, 10.0, 4.4 Hz, 1H), 1.55 (m, 1H), 1.32 (s, 9H), 1.21 (m, 1H), 0.74 (d, $J$ = 6.6 Hz, 3H), 0.59 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 178.59, 160.34, 141.06, 134.83, 125.18, 124.56, 111.65, 107.31, 97.27, 71.27, 60.78, 58.61, 55.48, 40.68, 24.48, 23.66, 23.30, 21.59; IR (thin film) 3084, 2954, 2848, 1712, 1633, 1458, 1219, 1051 cm$^{-1}$; HRMS (ESI$^+$) m/z 399.1714 [calculated mass for C$_{20}$H$_{28}$N$_2$O$_3$S (M + Na)$^+$ 399.1712].
(2'S,3R)-2'-isobutyl-6-methoxyspiro[indoline-3,3'-pyrrolidin]-2-one (3.7g). To a solution of the enamine (20.0 mg, 0.053 mmol) dissolved in 2 mL acetic acid, was added zinc powder (10.0 mg) and the vial tightly capped. The reaction was stirred for 15 min, filtered over celite, then acetic acid was evaporated. Purification by column chromatography (10% MeOH in CH₂Cl₂) afforded the product, as a white solid (9.5 mg, 66%). [α]²³D = +5.8° (c 0.7, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.67 (s, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 8.2, 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 3.81 (s, 3H), 3.42 (ddd, J = 11.8, 8.8, 5.7 Hz, 1H), 3.22 (td, J = 11.8, 10.8, 5.0 Hz, 2H), 2.35 – 2.29 (m, 1H), 2.20 – 2.15 (m, 1H), 1.61 (m, 1H), 1.36 (m, 1H), 0.92 (m, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 182.03, 159.78, 141.85, 123.19, 122.99, 107.19, 97.05, 68.50, 57.65, 55.51, 45.99, 38.20, 37.84, 25.82, 23.53, 21.74; IR (thin film) 3084, 2856, 1712, 1259, 1157, 748 cm⁻¹; HRMS (ESI⁺) m/z 275.1761 [calculated mass for C₁₆H₂₃N₂O₂ (M + H)⁺ 275.1754]. Spectral data matches reported data.³⁸
(+)-Elacomine. To a CH₂Cl₂ (1.0 mL) solution of the spirooxindole methyl ether (10.0 mg, 0.036 mmol) cooled to -78 °C was added boron tribromide (6.9 µL, 0.072 mmol) and the reaction warmed to 0 °C then stirred for 4 h. Reaction mixture was quenched with H₂O (1.0 mL), product extracted with CH₂Cl₂ (3 x 1.0 mL) and washed with 1.0 mL saturated NaHCO₃. Combined organic extracts were dried using Na₂SO₄, solvent evaporated and product purified by preparatory T.L.C (5% MeOH in CHCl₃) obtained as white powder (4.3 mg, 46%). [α]²³D = +4.3° (c 0.2, MeOH) ¹H NMR (500 MHz, CD₃OD) ¹H NMR (500 MHz, MeOD) δ 7.07 (d, J = 8.1 Hz, 1H), 6.47 (dd, J = 8.1, 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 3.46 (m J = 11.8, 7.7 Hz, 1H), 3.37 (dd, J = 9.2, 4.3 Hz, 1H), 3.24 (dt, J = 11.7, 7.2 Hz, 1H), 2.26 (m, 2H), 1.54 – 1.47 (m, 1H), 1.46 – 1.38 (m, 1H), 1.00 (ddt, J = 12.6, 8.2, 4.0 Hz, 1H), 0.79 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H); ¹³C NMR (125 MHz, MeOD) δ 182.51, 158.33, 143.36, 123.27, 120.63, 109.15, 98.28, 66.44, 57.39, 44.97, 38.10, 36.60, 25.55, 22.60, 21.16; IR (thin film) 3297, 2957, 2930, 1694, 1631, 1468, 1338 cm⁻¹; HRMS (ESI⁺) m/z 261.1596 [calculated mass for C₁₅H₂₁N₂O₂ (M + H)⁺ 261.1597]. Spectral data matches reported data.^[38]
Ethyl(3R,3aR,8aR)-3-allyl-1-((S)-tert-butylsulfinyl)-2,3,8,8a-tetrahydroinden[2,1-b]pyrrole-3a(1H)-carboxylate (3.8c).

To a solution of the iodo ester (50.0 mg, 0.11 mmol) in benzene (10.0 mL), was added AIBN (1.8 mg, 0.011 mmol) in 0.5 mL benzene and allyltributyltin (0.22 mmol, 70 µL) and the reaction refluxed at 80 °C for 3 h. Reaction was cooled to r.t., solvent evaporated and crude product purified by flash chromatography (20% EtOAc in Hexanes) to provide the title compound, white solid (32.3 mg, 78% yield). [α]23D = +16.1° (c 1.5, CHCl3). 1H NMR (500 MHz, CDCl3) δ 7.49 (m, 1H), 7.30 – 7.17 (m, 3H), 5.82 (ddt, J = 16.9, 10.1, 6.9 Hz, 1H), 5.25 (dq, J = 17.0, 1.5 Hz, 1H), 5.10 (ddt, J = 10.0, 2.0, 1.0 Hz, 1H), 4.78 (d, J = 4.6 Hz, 1H), 4.16 (m, 2H), 3.62 (dd, J = 10.4, 1.2 Hz, 1H), 3.31 (dd, J = 16.2, 4.8 Hz, 1H), 2.91 (d, J = 16.2 Hz, 1H), 2.63 (m, 1H), 2.54 (m, 1H), 2.16 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.09 (s, 9H). 13C NMR (125 MHz, CDCl3) δ 170.79, 142.04, 141.99, 136.07, 128.60, 127.13, 125.16, 124.66, 117.58, 69.95, 69.26, 61.08, 57.15, 46.62, 45.44, 40.80, 32.94, 23.58, 14.10; IR (thin film) 2956, 2925, 2855, 1729, 1641, 1223, 1073 cm⁻¹; HRMS (ESI⁺) m/z 376.1940 [calcd for C21H30NO3S (M + H)⁺ 376.1941]
Styrenal compound 3.8b

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 7.6$ Hz, 1H), 7.17 (m, 2H), 7.08 (dd, $J = 17.3, 11.0$ Hz, 1H), 6.76 (dt, $J = 2.9, 1.5$ Hz, 1H), 5.65 (dd, $J = 17.3, 1.4$ Hz, 1H), 5.32 (dd, $J = 11.0, 1.4$ Hz, 1H), 5.07 (m, 1H), 4.58 (ddd, $J = 17.5, 2.8, 1.0$ Hz, 1H), 4.19 – 4.08 (m, 3H), 3.57 (ddd, $J = 17.5, 4.2, 1.7$ Hz, 1H), 3.29 (dd, $J = 14.1, 4.1$ Hz, 1H), 2.82 (dd, $J = 14.1, 8.9$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.97 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.86, 140.04, 137.51, 137.26, 135.71, 134.69, 131.37, 127.37, 126.89, 125.85, 115.82, 73.48, 60.71, 57.81, 47.62, 39.84, 23.45, 14.15. HRMS (ESI$^+$) m/z 384.1608 [calcd for C$_{20}$H$_{27}$NO$_3$S (M+H)$^+$ 384.1603].

[Chemical structures and spectra images]
**Sulfone 3.9b**

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.84 – 7.78 (m, 2H), 7.29 – 7.19 (m, 4H), 7.02 – 6.97 (m, 2H), 4.73 (dd, $J =$ 6.7, 1.9 Hz, 1H), 4.07 – 3.96 (m, 2H), 3.88 (s, 3H), 3.52 (dd, $J =$ 17.2, 6.7 Hz, 1H), 3.46 (ddd, $J =$ 11.1, 7.5, 3.6 Hz, 1H), 3.36 (ddd, $J =$ 17.1, 1.8 Hz, 1H), 3.12 (ddddd, $J =$ 12.7, 9.5, 6.0 Hz, 1H), 2.15 (ddddd, $J =$ 12.7, 5.9, 3.6 Hz, 1H), 2.07 (ddddd, $J =$ 12.7, 9.6, 7.5 Hz, 1H), 1.12 (t, $J =$ 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.29, 162.97, 142.35, 141.02, 129.91, 129.45, 128.70, 127.21, 125.16, 123.63, 114.25, 67.15, 66.49, 61.34, 55.59, 48.61, 40.78, 35.30, 13.96; IR (thin film) 2956, 2925, 2855, 1698, 1630, 1223 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 402.1366 [calcd for C$_{21}$H$_{24}$NO$_5$ (M + H)$^+$ 402.1370]
Urea 3.9c
white solid, 87%. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.38 (dq, $J = 8.1, 1.3$ Hz, 3H), 7.29 – 7.26 (m, 4H), 7.24 – 7.21 (m, 1H), 7.06 – 6.96 (m, 1H), 6.17 (s, 1H), 4.97 (dq, $J = 6.1, 1.3$ Hz, 1H), 4.20 – 4.08 (m, 2H), 3.73 (dd, $J = 9.8, 8.1, 1.9$ Hz, 1H), 3.51 (dd, $J = 17.0, 6.1, 1.0$ Hz, 1H), 3.27 (d, $J = 16.8$ Hz, 1H), 3.09 (dd, $J = 10.6, 9.5, 6.2$ Hz, 1H), 2.60 (ddd, $J = 12.7, 10.6, 8.2$ Hz, 1H), 2.45 (ddd, $J = 12.7, 6.2, 1.9$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.57, 153.24, 142.60, 141.19, 138.72, 128.87, 128.84, 128.72, 127.25, 125.28, 123.70, 123.07, 119.68, 64.81, 61.44, 45.77, 39.34, 34.49, 14.05. IR (thin film) 2956, 2925, 2855, 1698, 1630, 1223 cm$^{-1}$; HRMS (ESI$^+$) m/z 351.1703 [calcd for C$_{21}$H$_{23}$N$_2$O$_3$ (M + H)$^+$ 351.1703]
Benzyl 3.9d
H NMR (500 MHz, Chloroform-<i>d</i>) δ 7.30 – 7.19 (m, 10H), 4.17 – 4.06 (m, 2H), 4.02 (d, J = 13.1 Hz, 1H), 3.61 (dd, J = 6.7, 1.1 Hz, 1H), 3.43 (d, J = 13.1 Hz, 1H), 3.25 – 3.14 (m, 1H), 3.01 – 2.92 (m, 1H), 2.89 (dd, J = 9.2, 7.2, 1.9 Hz, 1H), 2.74 (ddd, J = 12.7, 6.8, 1.9 Hz, 1H), 2.39 (ddd, J = 10.4, 9.2, 6.8 Hz, 1H), 2.05 (ddd, J = 12.7, 10.4, 7.3 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl<sub>3</sub>) δ 174.75, 145.67, 142.36, 138.86, 128.99, 128.24, 128.17, 127.67, 126.95, 125.15, 124.36, 72.42, 65.98, 61.00, 58.56, 53.81, 37.21, 36.26, 14.12; IR (thin film) 2954, 2927, 2855, 178, 1642, 1223 cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>) m/z 322.1804 [calcd for C<sub>21</sub>H<sub>24</sub>NO<sub>2</sub> (M + H)<sup>+</sup> 322.1802]
**Amino alcohol 3.9e**

$^1$H NMR (500 MHz, Methanol-$d_4$) δ 7.30 – 7.17 (m, 4H), 4.28 (d, $J = 7.4$ Hz, 1H), 3.74 (d, $J = 11.2$ Hz, 1H), 3.62 (d, $J = 11.1$ Hz, 1H), 3.44 (dd, $J = 18.1$, 7.5 Hz, 1H), 3.38 – 3.32 (m, 1H), 3.20 (d, $J = 18.1$ Hz, 1H), 2.98 – 2.90 (m, 1H), 2.41 (dt, $J = 13.2$, 8.2 Hz, 1H), 2.18 (ddd, $J = 13.2$, 6.6, 4.3 Hz, 1H); $^{13}$C NMR (125 MHz, MeOD) δ 144.79, 141.52, 129.55, 129.05, 125.90, 124.72, 66.50, 66.24, 63.95, 46.81, 36.59, 34.44; IR (thin film) 3300, 2956, 2925, 2855, 1628, 1223 cm$^{-1}$; HRMS (ESI$^+$) m/z 190.1227 [calcd for C$_{12}$H$_{16}$NO (M + H)$^+$ 190.1226]
3.6 Characterization and spectral data for (-)-supinidine and (-)-isoretronecanol

3-pyrroline (3.23c)
Yellow oil, 58 % yield. [α]$^23_D = +43.1^\circ$ (c 1.4, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 6.74 (q, $J = 2.0$ Hz, 1H), 4.79 (ttd, $J = 5.3$, 3.6, 1.8 Hz, 1H), 4.63 (dt, $J = 17.3$, 2.4 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.02 – 3.97 (m, 2H), 3.57 (ddd, $J = 17.3$, 5.3, 1.9 Hz, 1H), 2.45 (s, 3H), 1.90 – 1.81 (m, 1H), 1.72 – 1.58 (m, 3H), 1.26 (t, $J = 7.2$ Hz, 3H), 1.19 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.36, 144.67, 139.58, 134.42, 132.98, 129.75, 127.76, 71.09, 70.16, 60.66, 57.64, 47.70, 30.67, 23.54, 21.57, 14.11; IR (thin film) 2954, 2926, 2868, 1720, 1436, 1359, 1176, 1070, 964, 815 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 480.1480 [calculated mass for C$_{21}$H$_{33}$NNaO$_6$S$_2$ (M+Na)$^+$ 480.1485].

![NMR spectrum of 3-pyrroline (3.23c)](image-url)
Ethyl (S)-2,3,5,7a-tetrahydro-1H-pyrrolizine-7-carboxylate (3.23e). To a solution of the tosylate (100.0 mg, 0.22 mmol) in 5.0 mL methanol was added 5.0 eq. of HCl (TMSCl-H2O; 2:1) and stirred at r.t. for 15 minutes after which the solvent was evaporated, the crude salt diluted with 2.0 mL CH2Cl2 and washed with saturated 1.0 mL NaHCO3. The CH2Cl2 layer was collected and the aqueous layer extracted using EtOAc (3×2.0 mL). All the organic extracts were dried with anhydrous Na2SO4 and the solvent evaporated. To the crude suspended in CH2Cl2 (5.0 mL, 0 °C), was added triethyl amine (92.0 µL, 0.66 mmol,) and the reaction allowed to stir at 0 °C for 1 hour after which CH2Cl2 was evaporated and product purified by column chromatography (5% MeOH in CH2Cl2) to give the pyrrolidizine ester as colorless oil (29.6 mg, 75%). [α]23D = -20.9° (c 0.85, CHCl3). 1H NMR (500 MHz, CDCl3) δ 6.67 (m, 1H), 4.38 (bs, J = 7.3, 3.5, 1.7 Hz, 1H), 4.23-4.18 (m, 2H), 4.01 (ddd, J = 18.2, 3.6, 2.0 Hz, 1H), 3.50 (ddd, J = 18.2, 5.1, 2.3 Hz, 1H), 3.13 (dt, J = 10.1, 5.2 Hz, 1H), 2.51 (dt, J = 9.7, 7.2 Hz, 1H), 2.26 – 2.04 (m, 1H), 1.88 – 1.70 (m, 2H), 1.61 (dt, J = 12.4, 8.0, 6.7 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); 13C NMR (125 MHz, CDCl3) δ 163.56, 138.30, 136.69, 70.49, 61.96, 60.43, 56.97, 31.22, 25.71, 14.24; IR (thin film) 2958, 2925, 2902, 1719, 1643.4, 1219, 1177 cm⁻¹; HRMS (ESI⁺) m/z 182.1181 [calculated mass for C10H16NO2 (M + H)+ 182.1176]. Spectral data matches reported data. [64]
(-)-Supinidine. To a solution of the ester (20.0 mg, 0.11 mmol) in CH$_2$Cl$_2$ (1.0 mL, -78 °C) was added DibalH (1.0 M in CH$_2$Cl$_2$, 0.33 mL) and the reaction stirred at -78 °C for 2 h. The reaction was diluted with 1.0 mL CH$_2$Cl$_2$, quenched with a solution of 10% Rochelle’s salt (1.0 mL) and the mixture stirred at r.t for 1 h, after which the CH$_2$Cl$_2$ layer was collected and the aqueous layer extracted with CH$_2$Cl$_2$ (3 × 2.0 mL). All organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and solvent evaporated to give a colorless oil (14.1 mg, 92% yield) without further purification. [α]$^2_{\text{D}}$ = -11.9° (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.45 (bs, 1H), 4.22 – 4.18 (m, 2H), 4.13 – 4.04 (m, 1H), 3.85 (dp, $J$ = 15.2, 2.1 Hz, 1H), 3.29 (ddq, $J$ = 15.2, 4.2, 2.0 Hz, 1H), 3.06 (dt, $J$ = 10.3, 5.8 Hz, 1H), 2.53 (dt, $J$ = 10.3, 6.7 Hz, 1H), 1.96 (ddt, $J$ = 12.2, 7.6, 6.1 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.50 (dq, $J$ = 12.0, 7.2 Hz, 1H); IR (thin film) 3480, 2925, 2902, 1643, 1219, 1177 cm$^{-1}$; $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.24, 120.66, 71.07, 61.86, 59.63, 56.47, 30.32, 25.72; HRMS (ESI$^+$) m/z 140.1071 [calculated mass for C$_8$H$_{14}$NO (M + H)$^+$ 140.1070]. Spectral data matches reported data.\[^{[54]}\]
(−)-Isorettraceanol. To a solution of (−)-supinidine (10.0 mg, 0.07 mmol) in 1.0 mL CH₂Cl₂ was added palladium on carbon (10 wt%, 7.7 mg, 0.007 mmol) and the reaction mixture stirred under hydrogen atmosphere (balloon) at r.t. for 8 h. The reaction mixture was then filtered over celite and concentrated to give the product as a colorless oil (9.8 mg, 97% yield) without further purification. \([\alpha]_{D}^{23} = -56.1^\circ (c 0.7, \text{EtOH})\). ¹H NMR (500 MHz, CDCl₃) δ 4.36 (m, 1H), 3.90 – 3.80 (m, 2H), 3.69 – 3.58 (m, 2H), 3.06 (m, 1H), 2.81 – 2.70 (m, 2H), 2.20 – 2.07 (m, 4H), 1.87 – 1.80 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 69.05, 60.98, 55.52, 53.79, 42.71, 26.72, 26.29, 25.64; IR (thin film) 3386, 2958, 2919, 2849, 1055 cm⁻¹; HRMS (ESI⁺) m/z 142.1228 [calculated mass for C₈H₁₆NO (M + H)⁺ 142.1226]. Spectral data matches reported data.⁶¹
3.7 X-ray crystal data for mesylate 3.26e (CCDC 1478415)

Crystal data and structure refinement for 3.26e (CCDC 1478415)
Formula \( \text{C}_{20}\text{H}_{13}\text{NO}_{3}\text{S}_{2}\text{Si} \)
Formal weight 467.75
Size \( 0.5 \times 0.22 \times 0.16 \text{ mm} \)
Crystal morphology Colorless fragment
Temperature 100 K
Wavelength MoK\(\alpha \) (\( \lambda = 0.71073 \))
Crystal system monoclinic
Space group \( P_{2} \)
Unit cell dimensions
\( a = 6.5079(3) \text{ Å} \quad \alpha = 90^\circ \)
\( b = 18.7654(8) \text{ Å} \quad \beta = 103.7110(10)^\circ \)
\( c = 10.8888(6) \text{ Å} \quad \gamma = 90^\circ \)
Volume 1291.88(11) \( \text{Å}^3 \)
\( Z \)
2
Density (calculated) 1.202 \( \text{Mg/m}^3 \)
Absorption coefficient 0.280 mm\(^{-1} \)
\( F(000) \)
508.0
Data collection range 3.85 to 52.87\(^{\circ} \)
Index ranges -8 \( \leq h \leq 8, -23 \leq k \leq 23, -13 \leq l \leq 13 \)
Reflections collected 19113
Independent reflections 5309 [\( R_{\text{int}} = 0.0358, R_{\text{sigma}} = 0.0358 \)]
Absorption correction multi-scan
Max. and min. transmission 0.7459 and 0.660
Refinement method Full
Data / restraints / parameters 5309/1/277
Goodness of fit 1.021
Final R indices \([ I > 2 \sigma (I) ]\)
\( R_{1} = 0.0278, \ wR_{2} = 0.0662 \)
R indices (all data)
\( R_{1} = 0.0310, \ wR_{2} = 0.0678 \)
Largest diff. peak and hole 0.27 and -0.22e.\( \text{Å}^{-3} \)
Absolute structure parameter 0.01(2)
3.8 Experimental procedures and characterization data for Kainic acid (first approach)

3-pyrroline 3.25b
Colorless oil, 74% yield. $[\alpha]_{D}^{23} = -52.6^\circ$ (c 8.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.80 (q, $J = 2.0$ Hz, 1H), 4.71 (dd, $J = 5.4$, 3.8, 2.3, 1.3 Hz, 1H), 4.64 (ddd, $J = 17.0$, 2.6, 1.7 Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 3H), 3.83 (dd, $J = 10.4$, 3.9 Hz, 1H), 3.73 (dd, $J = 10.4$, 2.4 Hz, 1H), 3.65 (ddd, $J = 17.0$, 5.2, 1.9 Hz, 3H), 1.28 (s, 3H), 1.22 (s, 9H), 0.85 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.63, 140.76, 132.94, 73.86, 64.96, 60.51, 57.71, 47.93, 25.72, 23.47, 18.09, 14.21, -5.50, -5.65; IR (thin film) 2956, 2930, 2902, 2857, 1717, 1645, 1472, 1371, 1257, 1111, 1081, 836 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 390.2132 [calculated mass for C$_{13}$H$_{36}$NO$_2$Si (M + H)$^+$ 390.2128].
Isopropenyl ester 3.25d

To a suspension of copper (I) iodide (255.0 mg, 1.34 mmol) in Et₂O (10.0 mL, cooled to -78 °C) was added isopropenylmagnesium bromide (0.5M in THF, 5.36 mL) and the solution stirred for 30 min. Solution of the ester (350.0 mg, 0.89 mmol) in 1.0 mL Et₂O was added and the reaction stirred for 2 h after which the reaction was quenched with saturated ammonium chloride and warmed to RT. The Et₂O layer was separated, aqueous layer extracted with Et₂O (3*10.0 mL), the combined organic extracts were washed with brine and dried over anhydrous MgSO₄. Evaporation of the solvent followed by purification of the crude by column chromatography (15% EtOAc in hexanes) provided the product as a yellow oil (318.6 mg, 83% yield). [α]$_{23}^{23}$D = -38.6° (c 1.53, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 4.81 (s, 1H), 4.67 (s, 1H), 4.11 (dq, J = 10.8, 7.1 Hz, 1H), 4.00–3.91 (m, 2H), 3.81 (dd, J = 10.0, 7.2 Hz, 1H), 3.72–3.64 (m, 2H), 3.39 (t, J = 6.5 Hz, 1H), 3.28 (dd, J = 11.6, 10.1 Hz, 1H), 2.69 (dt, J = 11.9, 7.0 Hz, 1H), 1.78 (s, 3H), 1.19 (m, 12H), 0.85 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.78, 140.97, 111.37, 67.56, 63.64, 59.95, 57.41, 49.35, 48.59, 43.19, 25.69, 23.65, 23.00, 18.06, 14.15, -5.53, -5.65; IR (thin film); 2956, 2930, 1717, 1645, 1257, 1081, 836 cm$^{-1}$; HR-MS (ESI$^+$) m/z 432.2600 [calculated mass for C$_{21}$H$_{32}$NO$_3$Si (M+H)$^+$ 432.2598].
Alcohol 3.25e
To a solution of the ester (300.0 mg, 0.69 mmol) in CH$_2$Cl$_2$ (7.0 mL, -78 °C), was added Dibal-H (1.0 M in CH$_2$Cl$_2$, 2.1 mL) and the reaction stirred for 3 h after which the reaction was quenched with a solution of 10% Rochelle’s salt (1.0 mL). The mixture warmed to RT., stirred for 1 h. and the CH$_2$Cl$_2$ layer separated and the aqueous layer extracted with EtOAc (3 * 5.0 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered, solvent evaporated and purified by column chromatography (30% EtOAc in hexanes) to give a colorless oil (231.2 mg, 86% yield). [$\alpha$]$_{D}^{23}$ = 74.8° (c 1.45, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.91 (s, 1H), 4.64 (s, 1H), 3.87 (m, 1H), 3.83 (s, 1H), 3.82 – 3.77 (m, 2H), 3.66 (t, $J$ = 8.6 Hz, 1H), 3.54 – 3.43 (m, 2H), 2.86 (t, $J$ = 10.4 Hz, 1H), 2.64 – 2.54 (m, 2H), 1.79 (s, 3H), 1.18 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.12, 111.59, 67.34, 63.40, 58.83, 57.29, 48.49, 44.55, 43.05, 25.71, 23.78, 23.04, 18.09, -5.42, -5.58; IR (thin film); IR (thin film); 3410, 2954, 2928, 2857, 1253, 1072 cm$^{-1}$; HR-MS (ESI$^+$) $m/z$ 390.2492 [calculated mass for C$_{19}$H$_{29}$NO$_3$SSi (M+H)$^+$ 390.2492].
Methanesulfonate 3.25f
To a solution of the alcohol (200.0 mg, 0.51 mmol) in CH₂Cl₂ (5.0 mL, cooled to 0 °C), was added Et₃N (0.14 mL) and methanesulfonyl chloride (59 µl, 0.77 mmol) and reaction kept at 0 °C for 2 h. The reaction was diluted with 5.0 mL CH₂Cl₂, washed with saturated NaHCO₃ and the organic layer collected. The aqueous layer was extracted with CH₂Cl₂ (3*10.0 mL) and combined organic extracts dried over anhydrous Na₂SO₄ and solvent evaporated. Purification of the crude by chromatography (30% EtOAC in hexanes) afforded the mesylate as white solid (217.1 mg, 91%). [α]<sup>23</sup>D = -42.6° (c 2.0, CHCl₃).<sup>1</sup>H NMR (500 MHz, CDCl₃) δ 4.96 (s, 1H), 4.76 (s, 1H), 4.31 (dd, J = 10.0, 4.9 Hz, 1H), 4.25 (dd, J = 10.0, 4.3 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.87 – 3.82 (m, 1H), 3.76 (dd, J = 10.5, 5.5 Hz, 1H), 3.68 (dd, J = 10.4, 9.4 Hz, 1H), 2.94 (m, 4H), 2.78 – 2.71 (m, 1H), 2.71 – 2.63 (m, 1H), 1.80 (m, 3H), 1.18 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H);<sup>1</sup>³C NMR (125 MHz, CDCl₃) δ 141.21, 112.04, 67.22, 66.17, 63.08, 57.38, 48.16, 42.82, 40.68, 37.00, 25.81, 23.71, 23.35, 18.12, -5.44, -5.49; IR (thin film); 2954, 2929, 2857, 1359, 1176, cm⁻¹; HR-MS (ESI⁺) m/z 468.2260 [calculated mass for C₂₀H₂₄N₂O₅S₂Si (M+H)⁺ 468.2268].
Nitrile 3.25g

To a solution of the mesylate (200.0 mg, 0.43 mmol) in dimethyl sulfoxide (4.0 mL) was added KCN (84.9 mg, 1.29 mmol) and the reaction stirred at 80 °C for 12 h after which the reaction was cooled to r.t., diluted with Et₂O (20.0 mL) and H₂O (20.0 mL). The organic layer was washed with brine, dried over anhydrous MgSO₄, filtered and solvent evaporated. Purification by column chromatography (15% EtOAc in hexanes) gave the product as white solid (123.2 mg, 72% yield). [α]²³ D = -28.6° (c 2.6, CHCl₃). ¹H NMR (500MHz, CDCl₃) δ 5.06 (s, 1H), 4.88 (s, 1H), 3.90 – 3.85 (m, 2H), 3.84 (t, J = 5.1 Hz, 1H), 3.70 (t, J = 10.0 Hz, 1H), 3.15 (t, J = 10.8 Hz, 1H), 2.74 – 2.66 (m, 2H), 2.45 (dd, J = 17.1, 5.1 Hz, 1H), 2.32 (dd, J = 17.1, 4.6 Hz, 1H), 1.79 (s, 3H), 1.19 (s, 9H), 0.89 (s, 9H), 0.09 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 140.25, 119.60, 113.28, 67.08, 62.88, 57.50, 48.80, 41.77, 38.50, 25.79, 23.67, 23.37, 18.10, 12.37, -5.44, -5.53; IR (thin film): 2954, 2928, 2338, 1225, 1072 cm⁻¹; HR-MS (ESI⁺) m/z 421.2315 [calculated mass for C₂₀H₃₈N₂O₂Si (M+Na)⁺ 421.2315].
Cyclic carbamate 3.25i

To a solution of the nitrile (30.0 mg, 0.094 mmol) in methanol (1.0 mL) was added a solution of acetic acid in methanol (1:2, 0.5 mL) and the reaction stirred at 60 °C for 72 h after which the reaction was cooled to RT., and solvent was evaporated on vacuo. All volatiles were further removed on high vac. The crude product was dissolved in dichloromethane then a solution of 1,1'-carbonyldiimidazole (36.6 mg, 3.0 eq.) was added dropwise and the reaction stirred at r.t., for 4 hours. The reaction was then quenched with DI water (0.5 mL), then the organic layer collected, dried over Na$_2$HSO$_4$, filtered and solvent evaporated. Purification by column chromatography (15% EtOAc in hexanes) gave the product as colorless oil (11.8 mg, 68% yield). [α]$^2$D = +36.1° (c 0.4, CHCl$_3$). $^1$H NMR (400MHz, CDCl$_3$) δ 5.02 (d, $J = 1.9$ Hz, 1H), 4.77 (s, 1H), 4.45 (dd, $J = 10.8, 9.6$ Hz, 1H), 4.24 (dt, $J = 9.3, 3.8$ Hz, 2H), 3.68 (s, 3H), 3.44 (t, $J = 10.9$ Hz, 1H), 3.35 (dd, $J = 10.7, 8.0$ Hz, 1H), 3.07 (dt, $J = 12.1, 6.5$ Hz, 1H), 2.75 (dq, $J = 9.3, 4.6$ Hz, 1H), 2.19 (dd, $J = 17.9, 3.2$ Hz, 1H), 1.99 (dd, $J = 17.8, 9.5$ Hz, 1H), 1.76 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 173.23, 161.11, 140.33, 113.58, 64.41, 63.22, 52.08, 51.24, 46.03, 38.22, 27.33, 23.37; IR (thin film): 2957, 2926, 2338, 1736, 1621, 1350, 1072 cm$^{-1}$; HR-MS (ESI$^+$) $m/z$ 262.1053 [calculated mass for C$_{13}$H$_{17}$NNaO$_4$ (M+Na)$^+$ 262.1049].
3.9 Characterization and spectral data for Kainic acid approach 2

3-pyrroline 3.26b
Colorless oil, 75% yield. [α]$_D^{23}$ = +65.2$^\circ$ (c 4.01, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.80 (q, J = 2.0 Hz, 1H), 4.70 (ddq, J = 6.8, 3.8, 1.8 Hz, 1H), 4.63 (ddd, J = 17.0, 2.7, 1.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.82 (dd, J = 10.4, 3.9 Hz, 1H), 3.72 (dd, J = 10.4, 2.4 Hz, 1H), 3.64 (ddd, J = 17.0, 5.2, 1.9 Hz, H), 1.27 (t, J = 7.1 Hz, 3H), 1.21 (s, 9H), 0.83 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.64, 140.78, 132.96, 77.25, 77.00, 76.75, 73.87, 64.98, 60.52, 57.72, 47.94, 25.74, 23.49, 18.11, 14.23, -5.49, -5.63; IR (thin film) 2956, 2930, 2902, 2857, 1717, 1645, 1472, 1371, 1257, 1081, 836 cm$^{-1}$; HRMS (ESI$^+$) m/z 390.2135 [calculated mass for C$_{18}$H$_{36}$NO$_4$SSi (M + H)$^+$ 390.2128].

![NMR and IR spectra images]

120
Isopropenyl ester 3.26c
Yellow oil (318.6 mg, 79% yield). \([\alpha]_{D}^{23} = +55.1^\circ (c 0.7, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.81 (p, \(J = 1.4\) Hz, 1H), 4.67 (q, \(J = 1.2\) Hz, 1H), 4.11 (dq, \(J = 10.8, 7.1\) Hz, 1H), 4.00 - 3.91 (m, 2H), 3.81 (dd, \(J = 10.1, 7.1\) Hz, 1H), 3.72 - 3.64 (m, 2H), 3.39 (t, \(J = 6.5\) Hz, 1H), 3.28 (dd, \(J = 11.6, 10.1\) Hz, 1H), 2.69 (dt, \(J = 12.6, 7.0\) Hz, 1H), 1.78 (dd, \(J = 1.5, 0.8\) Hz, 3H), 1.19 (d, \(J = 8.2\) Hz, 12H), 0.85 (s, 9H), 0.02 (s, 3H), -0.01 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.78, 140.97, 111.37, 67.56, 63.64, 59.95, 57.41, 49.35, 48.59, 43.19, 25.69, 23.65, 23.00, 18.06, 14.15, -5.53, -5.65; IR (thin film): 2956, 2930, 2857, 1717, 1645, 1257, 1081 cm\(^{-1}\); HR-MS (ESI\(^+\)) \(m/z\) 454.2413 [calculated mass for C\(_{21}\)H\(_{41}\)NNaO\(_4\)SSi (M+Na)+ 454.2417].
**Alcohol 3.26d**
Colorless oil 87% yield. \([\alpha]^{23}_D = +6.2^\circ\) (c 2.1, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 4.91 (q, \(J = 1.4\) Hz, 1H), 4.64 (d, \(J = 1.5\) Hz, 1H), 3.87 (dt, \(J = 8.9, 5.1\) Hz, 1H), 3.83 (s, 1H), 3.82 – 3.78 (m, 2H), 3.66 (dd, \(J = 9.0, 7.6\) Hz, 1H), 3.51 – 3.44 (m, 2H), 2.86 (t, \(J = 10.5\) Hz, 1H), 2.63 – 2.56 (m, 2H), 1.79 (d, \(J = 1.3\) Hz, 3H), 1.18 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 142.12, 111.59, 67.34, 63.40, 58.83, 57.29, 48.49, 44.55, 43.05, 25.71, 23.78, 23.04, 18.09, -5.42, -5.58; IR (thin film); IR (thin film); 3410, 2954, 2928, 2857, 1253, 1072 cm⁻¹; HR-MS (ESI⁺) \(m/z\) 412.2308 [calculated mass for C₁₉H₃₉NNaO₃SSi (M+Na)⁺ 412.2312]
Methanesulfonate 3.26e
White solid, 91%. [α]$_{23}^D$ = +15.8° (c 5.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 4.97 (p, J = 1.4 Hz, 1H), 4.76 (q, J = 1.2 Hz, 1H), 4.31 (dd, J = 10.0, 4.9 Hz, 1H), 4.25 (dd, J = 10.0, 4.3 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.87 – 3.82 (m, 1H), 3.76 (dd, J = 10.5, 5.5 Hz, 1H), 3.68 (dd, J = 10.5, 9.4 Hz, 1H), 2.94 (s, 4H), 2.74 (ddd, J = 10.8, 6.2, 4.6 Hz, 1H), 2.67 (dt, J = 13.0, 7.0 Hz, 1H), 1.80 (q, J = 0.8 Hz, 3H), 1.18 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 141.21, 112.04, 67.22, 66.17, 63.08, 57.38, 48.16, 42.82, 40.68, 37.00, 25.81, 23.71, 23.35, 18.12, -5.44, -5.49; IR (thin film); 2954, 2929, 2857, 1359, 1097, cm$^{-1}$; HR-MS (ESI$^+$) m/z 468.2256 [calculated mass for C$_{20}$H$_{42}$NO$_5$S$_2$Si (M+H)$^+$ 468.2268].
Nitrile 3.26f
White solid 73% yield. \([\alpha]^{23}_D = +27.6^\circ (c \ 0.9, \text{CHCl}_3)\). \(^1\)H NMR (500MHz, CDCl\(_3\)) \(\delta 5.07 (h, J = 1.3 \text{ Hz}, 1\text{H}), 4.89\) (q, \(J = 1.1 \text{ Hz}, 1\text{H}), 3.91 - 3.86 (m, 2H), 3.84 (t, \(J = 5.1 \text{ Hz}, 1\text{H}), 3.73 - 3.67 (m, 1\text{H}), 3.16 (t, J = 10.9 \text{ Hz}, 1\text{H}), 2.75 - 2.66 (m, 2H), 2.45 (dd, \(J = 17.1, 5.2 \text{ Hz}, 1\text{H}), 2.33 (dd, \(J = 17.1, 4.6 \text{ Hz}, 1\text{H}), 1.80 (p, J = 0.6 \text{ Hz}, 3\text{H}), 1.19 (s, 9\text{H}), 0.90 (s, 9\text{H}), 0.09 (s, 6\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 140.26, 119.62, 113.30, 67.10, 62.89, 57.52, 48.81, 41.79, 38.51, 25.80, 23.69, 23.39, 18.11, 12.39, -5.42, -5.51; IR (thin film); 2954, 2928, 2857, 2338, 1652, 1225, 1072 cm\(^{-1}\); HR-MS (ESI\(^+\)) \(m/z 399.2495 \text{ [calculated mass for C}_{20}H_{39}N_2O_2S_i (M+H)^+ 399.2496]}\)
CHAPTER 4
ANIONIC ACCELERATED
AZA-COPE REARRANGEMENT
4.1 Introduction

The Cope rearrangement, first observed by Arthur C. Cope and Elizabeth M. Hardy in 1940,[76] is an important carbon-carbon bond forming reaction (Figure 4.1). This transformation, involves a concomitant migration of the allyl and vinyl groups of a 1,5-hexadiene system relative to the C3 position. The traditional Cope reaction requires high reaction temperatures and relatively long reaction times to accomplish a [3,3]-rearrangement. These harsh reaction conditions make this strategy unattractive when planning synthetic operations. Synthetic chemists have cleverly designed ways to carry out Cope-type transformations under mild reaction conditions.

![Figure 4.1. General Cope and oxy-Cope rearrangements](image)

Generally, modified Cope reactions are known to be accelerated by presence of a cationic[77],[78] or hetero-anionic centers within the molecule.[79] The cationic-Cope reaction, usually accompanied by the intra-molecular Mannich reaction, is a versatile chemical tool for synthetic organic chemists, particularly when constructing structurally complex organic compounds such as natural products.[80] The initiation of follow-up reaction/s after the sigmatropic rearrangements enables complex transformations in a single reaction vessel. This phenomenon elevates the value of the Cope reaction especially in cases where tertiary and quaternary stereo centers are being constructed. An example of the power of this tandem rearrangement is showcased in Overman’s total synthesis of actinophylic acid where a combined [3,3]-oxy-Cope and 2-azonia-Cope rearrangements (4.1a-4.1b) regenerates an iminium which is subsequently trapped in an aza-Mannich reaction (Scheme 4.1).[80-81]
Scheme 4.1. Overman’s synthesis of actinophylic acid

The anionic accelerated [3,3]-sigmatropic rearrangements unleashed the potential of Cope type reactions. Substitutions at the 3-position of the 1,5-hexadiene with an amino or hydroxyl group gives rise to more facile aza- and oxy-Cope variants, respectively. The benefits of these discoveries enabled aza- and oxy-Cope reactions to be carried out at milder reaction temperatures.\[^{82}\] Synthetic utility of the anionic accelerated aza-Cope reaction was realized when MacDonald and co-workers observed that lithium amide anions allowed the [3,3]-rearrangement to be carried out at very low temperatures (-50 °C) and the reaction times were dramatically shortened.\[^{83}\] In comparison, the temperature necessary for the anionic aza-Cope rearrangement is 65 °C lower than that for the anionic oxy-Cope.

Mechanistically, the anion accelerated aza-Cope rearrangement has been the subject of debate. Based on theoretical calculations,\[^{84}\] and some limited experimental data,\[^{85}\] it is now believed that it proceeds through a dissociation and re-association pathway as opposed to the known concerted nature of the anionic oxy-Cope transformation. An example of synthetic evidence supporting the fragmentation-recombination pathway is shown using the bicyclic amine system (Scheme 4.2). In the amino system, both the endo (4.2b) and exo (4.2a) vinyl motifs participate in the rearrangement to afford the same [3,3]-sigmatropic rearrangement product.\[^{83a}\] When the hydroxyl analogue with an exo vinyl group was subjected to the same conditions, the anionic oxy-Cope did not occur,\[^{79}\] confirming the non-concerted and concerted pathways for the
anionic \textit{aza}-Cope and anionic oxy-Cope respectively. Loss of enantioselectivity upon fragmentation-recombination in the anionic \textit{aza}-Cope probably could help explain why this type of reaction is underutilized in organic synthesis.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {4.2a};
\node (b) at (3,0) {4.2c};
\node (c) at (6,0) {4.2b};
\draw[->] (a) -- (b) node[midway,above] {\text{fBuOK, nBuLi}};
\node at (2,0) {50 \degree \text{C}};
\draw[->] (b) -- (c) node[midway,above] {\text{fBuOK, nBuLi}};
\node at (4,0) {50 \degree \text{C}};
\end{tikzpicture}
\end{center}

Scheme 4.2. An example of dissociation-association amino $[3,3]$-rearrangement pathway

Prior to introduction of asymmetric amino-Cope rearrangement by Allin,[86] the anionic \textit{aza}-Cope rearrangement was underutilized. The synthetic value of the asymmetric \textit{aza}-Cope is demonstrated through modifications of the intermediate enamine anion as a candidate for alkylation to forge carbon-carbon bonds and to introduce additional stereocenters in addition to the classic enamine–imine tautomerization and subsequent hydrolysis to respective aldehydes.[87] Borrowing from the above synthetic discoveries and advancements, we have sought to demonstrate the value of a newly discovered facile asymmetric \textit{aza}-Cope reaction.

The discovery of the accelerated anionic \textit{aza}-Cope reaction resulted from our desire to access \textit{cis}-di-vinyl aziridines from conjugated sulfinimines using our vinylogous \textit{aza}-Darzens protocol (Chapter 5). Following unsuccessful attempts to synthesize \textit{cis}-di-vinyl aziridines using non-conjugated sulfinimines and 4-bromobutenolide, we wondered whether a simpler vinylogous \textit{aza}-Darzens nucleophile such as methyl (\textit{E})-4-bromo-3-methylbut-2-enoate (4.3b) would afford the desired aziridine products (Scheme 4.3). When cinnamaldimine (4.3a) was subjected to the enolate of 4.3b, we were surprised that the cyclopropane-containing amino ester (4.3c) was formed instead of the desired \textit{cis} di-vinyl aziridine (4.3d). The unexpected product (4.3c) has been
structurally elucidated by 1and 2D NMR analysis (COSY, DEPT-90, DEPT-135, HMBC and HSQC.). Our current efforts are geared towards absolute assignment of 4.3c by x-ray analysis.

Scheme 4.3. Discovery of asymmetric anionic accelerated aza-Cope rearrangement

Our mechanistic explanation of the above transformations leading to formation 4.3c is presented in Scheme 4.4. We propose that the α-enolate of 4.3b adds to the imine to form the α,α-adduct 4.4a. The 3-aza anion 4.4a constitutes a Cope system, which rearranged to enamide anion 4.4b. A tandem intra-molecular trapping of this enamide via the β-carbon led to displacement of the bromide affording 4.4c along with regeneration of the imine functionality. A second α,α-addition on the newly formed imine provided 4.3c. All four transformations are facile, taking place at -78 ºC in less than one hour.

Scheme 4.4. Proposed mechanism for formation of cyclopropane 4.3c
4.2 Results and Discussion

Our brief experience with the cyclopropanation example informed us of the significance of reaction temperature and that we need at least two equivalents of the nucleophilic agent. We therefore decided to simplify the reaction, by using an approach that would suppress the competing 3-\textit{exo}-tet cyclization (Scheme 4.4). Our studies commenced by subjecting a cooled (-78 °C) solution of (S)-2-methyl-N-((1\textit{E},2\textit{E})-3-phenylallylidene)propane-2-sulfinamide (4.3a) and methyl 3-methylbut-2-enolate (4.5a) in THF to LiHMDS upon which the kinetic product of the enolate and the imine, the β-amino ester (4.5b) was isolated after 2 hours in 77% yield (Scheme 4.5). The isolated α,α-adduct (4.5b) structurally resembles 4.4a with its 3-\textit{amino} Cope system perfectly set for a [3,3]-sigmatropic rearrangement. In preliminary experiments, 4.5b proved to be a versatile intermediate when subjected to sodium hydride (NaH) or butyl lithium (\textit{n}BuLi) at 0 °C, affording the vinylogous amide (4.5c).

Scheme 4.5. Discovery of the anionic [3,3]-rearrangement cascade

We predicted the mode of addition to be predominantly \textit{syn} as observed from our previous \textit{cis} vinyl aziridines studies, and literature reports.\cite{88} Overall, this transformation proceeded via tandem stereospecific [3,3]-sigmatropic rearrangement followed by reaction of the lithium enamide anion with the ester to afford the vinylogous amide. The discovery of the two-step anionic
aza-Cope cascade prompted us to entertain the idea that we could perform the addition, and the entire rearrangement cascade, in one reaction vessel.

We began by using established conditions similar to those of our vinylogous aza-Darzens endeavors (Chapter 5), but we were curious to know the temperature at which the rearrangement would occur. Based on the TLC profile and crude proton NMR of reactions carried out at -78, -40 and -20 °C, the rearranged product is formed at -40 °C in about 10% after 2 hours. Upon warming the reaction to -20 °C, we observed over 80% conversion of the addition product to the desired product after stirring for 3 hours. We therefore selected the serendipitously established protocol of first forming the α,α-adduct at -78 °C (2 hours) followed by the facile [3,3]-rearrangement at 0 °C for 30 minutes.

From our design, a slight excess of base would be required to fully convert the α,α-adduct to the vinylogous amide. Using 2.0 eq. of LiHMDS, 1.5 eq. of methyl (E)-3-phenylbut-2-enolate and 1.0 eq. of S-2-methyl-N-((1E,2E)-3-phenylallylidene)propane-2-sulfinamide, full conversion of the imine to the α,α-adduct was observed after 2 hours (by TLC). Warming of the reaction to 0 °C allowed formation of the vinylogous amide in 10 minutes. Crude proton NMR showed full consumption of the imine and formation of a single diastereomer of the rearranged product. Purification by silica gel column chromatography afforded a single diastereomer of the vinylogous amide in excellent yield (Table 4.1, entry 1) on our first attempt.

Among the bases investigated, LDA seemed too aggressive when the reaction is warmed to 0 °C whereas NaH was only useful for rearrangement of the intermediate amino ester. We therefore chose LiHMDS for its effectiveness in affording the intermediate amino ester at lower temperatures and its mildness at 0 °C to complete the cascade.
We were also interested to understand how electronic and steric properties of the reacting components would affect the reaction and the yields thereof. Our study of electronic effects was performed using \textit{para}-substituted electron rich and electron deficient aromatic sulfinimines. The differences in isolated yield and respective reaction time are minor for any conclusion to be drawn in regard to the electronic nature of the substrates. Both electron-rich and poor imine substrates are tolerated in equal measure affording high product yields.

The main factor affecting the progress of the reaction is steric size of the substituent at the \(\beta\)-position of both the imine and the nucleophile. Our studies showed excellent yields for the substrates that have bulky substituents at the \(\beta\)-position irrespective of the nature of the substituent (aryl or alkyl). When the less steric hindering groups were employed, we obtained low product yields for both the methyl substituted imine (\textit{Table 4.1, entry 14}) and nucleophile (\textit{Table 4.1, entries 11-14}). The low product yield obtained with the \(\beta\)-methyl substituents could also be attributed to the presence of enolizable protons, rendering the products unstable.

To further probe substituent effects, we used the unsubstituted imine synthesized from acrolein from which \(\alpha\) and \(\gamma\)-addition addition intermediates were formed. The \(\alpha\)-adduct proceeded to provide the desired products albeit in a poor yield (\textit{Table 4.1, entry 8}) whereas the \(\gamma\)-adduct was protonated to the imine. The extent to which the reaction can tolerate steric hindrance was tested using \(\beta\)-phenyl substituted cinnamaldimine upon which the desired rearranged product was not observed. We identified a direct relationship between high yield and steric effects in both the nucleophile source and the imine substrate. Sterically endowed substrates with non-enolizable protons provided excellent yields. Disubstitution at the \(\beta\)-position blocks this position, shutting down the reaction.
Upon establishing the optimal reaction conditions for the high yielding three-step ‘one-pot’ reaction, we turned our attention to exploration of the substrate scope. We subjected alkyl- and aryl-conjugated sulfinimines to our reaction conditions and we were rewarded with a variety of di-substituted vinylogous amides with excellent diastereoselectivity observed in all cases. Absolute stereochemistry of the C3 center was determined by single crystal X-ray analysis (Figure 4.2).

![Figure 4.2. X-ray Structure chiral for 4.7b₁](image)

Although the mechanism of the anionic rearrangement is postulated to proceed by fragmentation and recombination of the vinyl moiety of the 1,5-hexadienyl system, we have observed that the presence of the chiral sulfoxide perfectly directs and restricts the reactive groups creating maximum overlap between the two π-systems in such a way that the dissociation and re-association occurs in a rapid and controlled manner without loss of chiral memory. Additionally, the carbonyl of the ester is engaged in ionic association which ensures contact ion pairing at the dissociation state. In our case, the ester functionality is also very important from a reactivity standpoint. Professor Allin reported anionic [3,3]-rearrangement of 4.6a to 4.6b using nBuLi (Scheme 4.6, a) but the same compound (4.6a) did not rearrange to 4.6b when treated with KH, LDA, LiHMDS or NaHMDS. Interestingly, NaH, LiHMDS and nBuLi successfully rearranged the β-amino ester (4.5b) to the vinylogous amide (Scheme 4.5). When the amino alcohol (4.6c) is
treated with all of the above conditions, including those that worked in Allin’s report, we did not observe any reaction (Scheme 4.6, b). From our experimental data, we propose that the ester functionality plays a critical role in our facile rearrangement conditions.

Scheme 4.6. Importance of ester functionality in the anion accelerated [3,3]-rearrangement
Scheme 4.7. General aza-Cope cascade and oxidative aromatization

Table 4.1. Substrate scope of the accelerated aza-Cope cascade

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfinimine (4.7a)</th>
<th>Vinylogous amide (4.7b)</th>
<th>Yield</th>
<th>Phenol (4.7c)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure" /></td>
<td><img src="image2" alt="Structure" /></td>
<td>91%</td>
<td><img src="image3" alt="Structure" /></td>
<td>83%</td>
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<tr>
<td>2</td>
<td><img src="image4" alt="Structure" /></td>
<td><img src="image5" alt="Structure" /></td>
<td>92%</td>
<td><img src="image6" alt="Structure" /></td>
<td>84%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Structure" /></td>
<td><img src="image8" alt="Structure" /></td>
<td>83%</td>
<td><img src="image9" alt="Structure" /></td>
<td>85%</td>
</tr>
<tr>
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<td><img src="image10" alt="Structure" /></td>
<td><img src="image11" alt="Structure" /></td>
<td>95%</td>
<td><img src="image12" alt="Structure" /></td>
<td>99%</td>
</tr>
<tr>
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<td><img src="image14" alt="Structure" /></td>
<td>86%</td>
<td><img src="image15" alt="Structure" /></td>
<td>88%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16" alt="Structure" /></td>
<td><img src="image17" alt="Structure" /></td>
<td>85%</td>
<td><img src="image18" alt="Structure" /></td>
<td>88%</td>
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135
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<tr>
<th>Entry</th>
<th>Sulfanimine (4.7a)</th>
<th>Vinlylogous amide (4.7b)</th>
<th>Yield</th>
<th>Phenol (4.7c)</th>
<th>Yield</th>
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</thead>
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<tr>
<td>7</td>
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<td><img src="image2.png" alt="Image" /></td>
<td>4.7b7, 89%</td>
<td><img src="image3.png" alt="Image" /></td>
<td>4.7c7, 84%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td>4.7b8, 28%</td>
<td><img src="image6.png" alt="Image" /></td>
<td>4.7c8, 87%</td>
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<td>9</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>4.7b9, 73%</td>
<td><img src="image9.png" alt="Image" /></td>
<td>4.7c9, 81%</td>
</tr>
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<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td>4.7b10, 67%</td>
<td><img src="image12.png" alt="Image" /></td>
<td>4.7c10, 81%</td>
</tr>
<tr>
<td>11</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td>4.7b11, 65%</td>
<td><img src="image15.png" alt="Image" /></td>
<td>4.7c11, 73%</td>
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<td><img src="image16.png" alt="Image" /></td>
<td><img src="image17.png" alt="Image" /></td>
<td>4.7b12, 58%</td>
<td><img src="image18.png" alt="Image" /></td>
<td>4.7c12, 81%</td>
</tr>
<tr>
<td>13</td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
<td>4.7b13, 63%</td>
<td><img src="image21.png" alt="Image" /></td>
<td>4.7c13, 81%</td>
</tr>
<tr>
<td>14</td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td>4.7b14, 42%</td>
<td><img src="image24.png" alt="Image" /></td>
<td>4.7c14, 81%</td>
</tr>
<tr>
<td>15</td>
<td><img src="image25.png" alt="Image" /></td>
<td><img src="image26.png" alt="Image" /></td>
<td>4.7b15, 85%</td>
<td><img src="image27.png" alt="Image" /></td>
<td>4.7c15, 81%</td>
</tr>
</tbody>
</table>
We have demonstrated that the [3,3]-rearrangement products are valuable substrates for oxidative aromatization using DDQ (Scheme 4.7). Our approach provides unrivalled access to aromatic compounds with substituents that would normally require multiple steps to install. For
example, versatile chiral phenolic imines obtained in only two steps using this approach would require a number of steps to synthesize the parent aldehydes. Phenolic sulfinimines with substituents such as alkyl-, aryl- and trifluoromethyl groups have been easily assembled using simple non-metal catalyzed synthetic transformations (Table 4.1). Since the chiral sulfinimines are versatile intermediates for asymmetric synthesis of biologically significant nitrogen-containing organic compounds,\textsuperscript{[88]} this methodology will certainly be useful to the synthetic organic community. In addition, the chiral amino group masked as an imine and the ortho hydroxyl group are strategic synthetic handles for entry into the metal catalysis upon insertion of a metal.

To further probe the scope of the cyclopropanation, ethyl and methyl (\textit{E})-4-bromo-3-methylbut-2-enolate, the \textit{aza}-Cope rearrangement provided the enamine anion which displaced the bromine resulting in cyclopropanation. A second 1,2-addition by the \textalpha{}-enolate on the regenerated imine produced the cyclopropane \textbeta{}-amino ester (Scheme 4.8). The assigned stereocenters are tentative and are based on the vinylogous amides (Figure 4.2) and expected mode of addition. Efforts are currently underway to determine absolute structural assignment by X-ray crystallographic analysis.

\textbf{Scheme 4.8. Current scope of anionic cyclopropanation cascade}

Enamines are versatile reactive intermediates whose discovery revolutionized \textalpha{}-derivatization of aldehydes and ketones.\textsuperscript{[89]} The synthetic application of enamines ranges from asymmetric induction to introduction of useful functional groups.\textsuperscript{[90]} Our entry into derivatizations
of the enamide anion was first explored using the enamine functionality of the vinylogous amide. Using N-bromosuccinimide, a source of electrophilic bromine, we successfully converted the enamine to an α-bromo imine (Scheme 4.9). The brominated product is a good candidate for accessing the aromatic sulfinimines following base mediated elimination.

![Scheme 4.9 Electrophilic bromination of the enamide](image)

Encouraged by the above result, we predicted that the enamine anion could be intercepted using an electrophile such as bromine or an electrophilic carbon, enabling us to perform the alkylation in one reaction vessel. Our main challenge was to outcompete the facile intra-molecular cyclization to allow the selective inter-molecular reaction of the enamide and the added electrophile. Our plan was executed using ethyl tiglate as the source of nucleophile with the α-methyl group designed to block the intra-molecular cyclization that would otherwise lead to the vinylogous amides.

To determine the outcome of our design, we first decided to terminate the reaction with a ‘small’ electrophile, by simply protonating the enamine anion generated after the [3,3]-rearrangement. As planned, the steric effect due to the α–methyl substituent did not allow the previously observed cyclization with the non α -methylated nucleophile source (Scheme 4.5) affording the intermediate enamine (Scheme 4.10). Upon storage in chloroform (NMR tube overnight) at room temperature, the enamine tautomeredized to the imine.
We set out to accomplish the 1,2-nucleophilic addition, the [3,3]-rearrangement and the enamine-imine tautomerization in one-pot, by allowing the reaction to warm to room temperature for one hour and without any external proton source, the imine was obtained in good yield (Scheme 4.11, a). The configuration of the β-position has been assigned in accordance with the configuration of the c3 center of the vinylogous amides. The reproducibility of this protocol has been demonstrated by synthesis of the four acyclic sulfinimines. Due to the thermodynamic nature of the enamine-imine tautomerism, a cis/trans mixture of imines (1:4) were obtained. To prove that the scrambling occurred at the imine carbon, we undertook a reduction of the E/Z mixture of 4.11b and we obtained a single diastereomer of the amino alcohol 4.11c (Scheme 4.11, b). The stereochemistry at the β-position relative to the imine has been assigned following the absolute structural assignment of the vinylogous amides (Table 4.1).
Scheme 4.11. Synthesis of chiral β-substituted imines via an *aza*-Cope rearrangement

Our current studies using hetero-atoms to trap the nucleophiles are demonstrated by the two examples of dihalogenated imines using electrophilic bromine and chlorine (Scheme 4.12). We associate our challenge in obtaining a *mono*-halogenated imine derivatives to the anionic nature of our reaction conditions, which are different from the known α-halogenation strategies of neutral enamine species.\[^{91}\] We believe that our lack of control in halogenation is due to the fact that after the initial mono-halogenation, the α-hydrogen whose acidity is enhanced, is quickly abstracted forming another reactive enamine species which readily undergoes another halogenation cycle. We have without any success attempted to mitigate the over halogenation by using one equivalent of the LiHMDS.
Our lack of success in the mono-halogenation encouraged us to use an electrophile that would not impact on the acidity of the α-proton once this entity is installed. We chose allyl bromide as the source of the electrophilic carbon but to our surprise, N-alkylation occurred over the expected C-alkylation.\cite{87c} This interesting reaction profile of the enamine anion coupled with the unusual stability of the isolated enamine 4.10a (Scheme 4.10) can be explained by the electron withdrawing effects of the sulfoxide.

**Scheme 4.12.** In situ-\(N\)-trapping of enamides

**Scheme 4.13.** Inter-molecular \(N\)-alkylation of lithium enamide

### 4.3 Conclusion

We have developed a scalable practical approach for preparation of vinylogous amides. The rearrangement accommodates bulky substituents with excellent yields obtained for sterically hindered aryl and alkyl imines and the nucleophile sources. Additionally, we are able to make a
variety of products by changing the substituent of the nucleophile as shown with methyl, phenyl and trifluromethyl substituted crotonates. A synthesis of tri-substituted aromatic sulfinimines showcased applicability of the methodology in organic synthesis, in which we have used DDQ to efficiently convert the vinylogous amides to not easily accessible phenolic chiral sulfinimines.

4.4 X-ray crystal data

X-ray data were collected at the University of Arizona X-ray Diffraction Facility. Colorless plate-like crystals were mounted onto a Cryoloop under a film of Paratone oil. Diffraction data for all crystals were collected at 100° (2) K using a Bruker Kappa APEX II DUO diffractometer. Data were integrated and structure solved using Bruker SAINT and SHELXT and/ or Olex2 respectively.
X-ray crystal data for 4.7b$_1$(CCDC 1451254)

Crystal data and structure refinement for CCDC 1451254

Formula $C_{23}H_{25}NO_2S$
Formula weight 379.50
Size 0.6 x 0.6 x 0.6 mm
Crystal morphology Colorless fragment
Temperature 100.02 K
Wavelength MoKα ($\lambda = 0.71073$)
Crystal system orthorhombic
Space group $P2_12_12_1$
Unit cell dimensions $a = 5.6544(2)$ Å, $\alpha = 90^\circ$
$b = 10.1560(5)$ Å, $\beta = 90^\circ$
$c = 34.5988(15)$ Å, $\gamma = 90^\circ$
Volume 1986.87(15) Å$^3$
$Z$ 4
Density (calculated) 1.269 Mg/m$^3$
Absorption coefficient 0.181 mm$^{-1}$
$F(000)$ 808.0
Data collection range 4.18 to 52.758 °
Index ranges $-7 \leq h \leq 6$, $-11 \leq k \leq 12$, $-43 \leq l \leq 43$
Reflections collected 19935
Independent reflections 4048 [Rint = 0.0423, Rsigma = 0.0360]
Absorption correction multi-scan
Max. and min. transmission 0.745 and 0.628
Refinement method Full
Data / restraints / parameters 4048/0/247
Goodness of fit 0.772
Final R indices [$I > 2 \sigma (I)$] $R_1 = 0.0324$, $wR_2 = 0.0927$
R indices (all data) $R_1 = 0.0375$, $wR_2 = 0.0986$
Largest diff. peak and hole 0.22/-0.24 eÅ$^{-3}$
Absolute structure parameter -0.06(3)
Crystal data and structure refinement for (CCDC 1451255)

**Formula**
C₁₉H₁₉NO₅F₇S

**Formula weight**
437.39

**Size**
0.32 × 0.2 × 0.17 mm

**Crystal morphology**
Colorless fragment

**Temperature**
100.02 K

**Wavelength**
MoKα (λ = 0.71073)

**Crystal system**
monoclinic

**Space group**
P2₁

**Unit cell dimensions**
\begin{align*}
\alpha &= 5.3925(4) \text{ Å} & \alpha &= 90^\circ \\
b &= 11.4209(8) \text{ Å} & \beta &= 97.776(2)^\circ \\
c &= 16.1531(12) \text{ Å} & \gamma &= 90^\circ 
\end{align*}

**Volume**
985.68(12) Å³

**Z**
2

**Density (calculated)**
1.474 Mg/m³

**Absorption coefficient**
0.234 mm⁻¹

**F(000)**
448.0

**Data collection range**
2.544 to 50.05 °

**Index ranges**
-6 ≤ h ≤ 6, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19

**Reflections collected**
34308

**Independent reflections**
3493 [Rint = 0.0778, Rsigma = 0.0237]

**Absorption correction**
multi-scan

**Max. and min. transmission**
0.746 and 0.0701

**Refinement method**
Full

**Data / restraints / parameters**
3493/0/266

**Goodness of fit**
1.37

**Final R indices [I > 2σ(I)]**
R1 = 0.0434, wR2 = 0.1395

**R indices (all data)**
R1 = 0.0436, wR2 = 0.1402

**Largest diff. peak and hole**
0.77/-0.40 eÅ⁻³

**Absolute structure parameter**
-0.08(4)
4.5 Experimental procedure for the anionic amino-Cope cascade

To a flame dried round bottomed flask equipped with magnetic stir bar, tetrahydrofuran (THF, overall concentration, 0.1M based on the sulfinimine) and 2.0 eq. of Lithium hexamethylsilyl amide (LiHMDS) cooled to -78 °C was added (2mL/h) a solution of sulfinimine (1.0 eq., 1.0 M). Solution of the respective ester (1.0 eq., 1.0 M in THF) was added (0.5mL/h) and stirred at -78 °C for 3 h (TLC shows 100% conversion of the imine) then warmed to 0°C (ice-bath) for 30 minutes. The reaction was then quenched with saturated ammonium chloride and allowed to warm to room temperature, extracted using ethyl acetate (3 times) and washed with brine. The combined organic extracts were dried using anhydrous sodium sulfate (Na₂SO₄) and solvent evaporated. Crude material was purified by flash column chromatography (silica gel, 20-40% EtOAc in hexanes) to afford the respective vinylogous amide.

4.6 Experimental procedure for DDQ-mediated oxidation of vinylogous amides

To a flame dried round bottomed flask equipped with magnetic stir bar, the respective vinylogous amide (0.1M) in toluene was added 1.5 eq. of 2,3-dichloro-5,6-dicyanobenzoquinone and reaction warmed to reflux (100 ºC) for 2 h. Reaction mixture was then cooled to room temperature, filtered over celite and toluene evaporated. Crude product was purified by flash column chromatography (silica gel, 5-10% EtOAc in hexanes) to afford the respective aromatic sulfinimine.
4.7 Characterization and spectral data for chapter 4

**Amino ester 4.5b**: white solid, 77% yield. \([\alpha]^{23}_{D} = +188.1^\circ (c = 2.0, \text{CHCl}_3)\). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 6.64 (d, $J = 15.8$ Hz, 1H), 6.02 (dd, $J = 15.8$, 8.4 Hz, 1H), 5.00 (dd, $J = 4.5$, 1.3 Hz, 2H), 4.42 (dd, $J = 8.6$, 4.3, 1.0 Hz, 1H), 4.19 (d, $J = 4.4$ Hz, 1H), 3.74 (s, 3H), 3.39 (d, $J = 8.8$ Hz, 1H), 1.76 (s, 3H), 1.22 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.08, 139.22, 136.27, 133.52, 128.44, 127.80, 126.88, 126.56, 116.88, 58.48, 57.17, 55.52, 52.11, 22.57, 20.97; IR (thin film) 3090, 2976, 2953, 2926, 1731, 1645, 1071 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 372.1604 [calculated mass for C$_{19}$H$_{27}$NNaO$_3$ (M+Na)$^+$ 372.1603].
4.7b: Yellow solid, 91% yield. [α]$_D$ = +61.4° (c 5.4, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.43 (d, $J = 10.9$ Hz, 1H), 7.50 (m, 2H), 7.41 (m, 3H), 7.38 (m, 2H), 7.63 (m, 3H), 6.62 (dt, $J = 10.9$, 0.8 Hz, 1H), 6.52 (s, 1H), 4.08 (td, $J = 7.4$, 1.4 Hz, 1H), 3.12 (m, 2H), 1.28 (s, 9H); $^1$H NMR (500 MHz, CDCl$_3$) δ 11.43 (d, $J = 10.9$ Hz, 1H), 7.50 (m, 2H), 7.41 (m, 3H), 7.38 (m, 2H), 7.63 (m, 3H), 6.62 (dt, $J = 10.9$, 0.8 Hz, 1H), 6.52 (s, 1H), 4.08 (td, $J = 7.4$, 1.4 Hz, 1H), 3.12 (m, 2H), 1.28 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) δ 189.55, 154.74, 144.20, 142.42, 138.45, 129.82, 128.75, 128.68, 127.98, 127.08, 126.14, 126.06, 111.18, 57.13, 43.40, 35.47, 22.30; IR (thin film) 3290, 3216, 2976, 2953, 2926, 1734, 1645, 1071 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 402.1499 [calculated mass for C$_{23}$H$_{28}$NNaO$_2$S (M+Na)$^+$ 402.1498].
**4.7C**: Colorless solid, 83%. $[\alpha]_D^{23} = +88.6^\circ$ (c 1.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.94 (s, 1H), 8.79 (s, 1H), 7.69 – 7.66 (m, 2H), 7.50 – 7.43 (m, 6H), 7.39 – 7.36 (m, 2H), 7.30 – 7.27 (m, 1H), 7.18 (d, $J$ = 1.8 Hz, 1H), 1.27 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.34, 161.39, 146.89, 146.76, 139.43, 138.46, 129.76, 128.86, 128.54, 128.50, 128.24, 127.18, 120.65, 114.84, 114.57, 57.81, 22.23; IR (thin film) 3058, 3031, 2977, 2926, 2866, 1618, 1586, 1576, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 378.1527 [calculated mass for C$_{23}$H$_{24}$NO$_2$S (M+H)$^+$ 378.1522].
4.7bent: Yellow solid, 92% yield. \([\alpha]_{D}^{23} = -108.7^\circ\) (c 2.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta 11.44\) (d, \(J = 10.9\) Hz, 1H), 7.52 – 7.49 (m, 2H), 7.38 (ddd, \(J = 4.8, 2.6, 1.4\) Hz, 3H), 7.36 – 7.32 (m, 2H), 7.29 – 7.26 (m, 3H), 6.65 – 6.60 (m, 1H), 6.51 (q, \(J = 1.2\) Hz, 1H), 4.11 – 4.05 (m, 1H), 3.11 – 3.07 (m, 2H), 1.28 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl₃) \(\delta 189.55, 154.73, 144.21, 142.42, 138.45, 129.82, 128.75, 128.68, 127.98, 127.08, 126.14, 126.06, 111.18, 57.13, 43.40, 35.47, 22.30.\) IR (thin film) 3291, 3217, 2976, 2953, 22926, 1733, 1645, 1073 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 380.1684 [calculated mass for \(\text{C}_{23}\text{H}_{26}\text{NO}_{2}\text{S} (\text{M} + \text{H})^\circ\) 380.1678].

---

**1H NMR (500 MHz, CDCl₃)**

- 12.5 ppm: 7.52 – 7.49 (m, 2H)
- 11.5 ppm: 7.38 (ddd, \(J = 4.8, 2.6, 1.4\) Hz, 3H)
- 10.5 ppm: 7.36 – 7.32 (m, 2H)
- 10.0 ppm: 7.29 – 7.26 (m, 3H)
- 9.5 ppm: 6.65 – 6.60 (m, 1H)
- 9.0 ppm: 6.51 (q, \(J = 1.2\) Hz, 1H)
- 8.5 ppm: 4.11 – 4.05 (m, 1H)
- 8.0 ppm: 3.11 – 3.07 (m, 2H)
- 7.5 ppm: 1.28 (s, 9H)

---

**13C NMR (125 MHz, CDCl₃)**

- 154.73 ppm: 189.55
- 144.21 ppm: 154.73
- 142.42 ppm: 144.21
- 138.45 ppm: 142.42
- 129.82 ppm: 138.45
- 128.75 ppm: 129.82
- 128.68 ppm: 128.75
- 127.98 ppm: 128.68
- 127.08 ppm: 127.98
- 126.14 ppm: 127.08
- 126.06 ppm: 126.14
- 111.18 ppm: 126.06
- 57.13 ppm: 111.18
- 43.40 ppm: 57.13
- 35.47 ppm: 43.40
- 22.30 ppm: 35.47

---

**IR (thin film)**

- 3291 cm\(^{-1}\)
- 3217 cm\(^{-1}\)
- 2976 cm\(^{-1}\)
- 2953 cm\(^{-1}\)
- 22926 cm\(^{-1}\)
- 1733 cm\(^{-1}\)
- 1645 cm\(^{-1}\)
- 1073 cm\(^{-1}\)

---

**HRMS (ESI\(^+\))**

- \(m/z\) 380.1684 [calculated mass for \(\text{C}_{23}\text{H}_{26}\text{NO}_{2}\text{S} (\text{M} + \text{H})^\circ\) 380.1678].
4.7c: Colorless solid, 84%. [α]$_D^{25}$ = -58.4° (c 3.7, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.94 (s, 1H), 8.79 (s, 1H), 7.68 – 7.66 (m, 2H), 7.50 – 7.44 (m, 5H), 7.43 – 7.40 (m, 1H), 7.39 – 7.36 (m, 2H), 7.28 (dd, J = 1.8, 0.5 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 1.26 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) δ 164.35, 161.41, 146.90, 146.78, 139.45, 138.48, 129.77, 128.88, 128.55, 128.51, 128.26, 127.20, 120.67, 114.86, 114.59, 57.82, 22.24; IR (thin film) 3058, 3030, 2977, 2926, 2916, 1585, 1543, 1092 cm$^{-1}$; HRMS (ESI$^+$) m/z 400.1341 [calculated mass for C$_{23}$H$_{23}$NNaO$_2$S (M+Na)$^+$ 400.1341].

[Chemical structure and NMR spectra images]

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4.7b: Yellow solid, 83% yield, [α]$_D^{23}$ = +148.2° (c 6.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.44 (d, $J$ = 10.9 Hz, 1H), 7.50 (m, 2H), 7.37 (m, 3H), 7.15 (s, 4H), 6.62 (dd, $J$ = 10.8, 1.4 Hz, 1H), 6.51 (s, 1H), 4.04 (ddd, $J$ = 8.3, 6.5, 1.4 Hz, 1H), 3.06 (m, 2H), 2.34 (s, 3H), 1.28 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.59, 154.80, 144.09, 139.25, 138.44, 136.62, 129.75, 129.38, 128.63, 127.83, 126.07, 126.02, 111.36, 57.06, 43.00, 35.52, 22.27, 20.97; IR (thin film) 3060, 3023, 2964, 1652, 1553, 1090 cm$^{-1}$; HRMS (ESI$^+$) m/z 394.1836 [calculated mass for C$_{24}$H$_{28}$NO$_2$S (M+H)$^+$ 394.1835].
4.7c: White solid, 85%. \([\alpha]_D^{23} = +67.8^\circ\) (c 3.2, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 11.93 (s, 1H), 8.82 (s, 1H), 7.67 (m, 2H), 7.46 (m, 2H), 7.41 (m, 1H), 7.27 (dd, \(J = 5.1, 2.5\) Hz, 5H), 7.18 (d, \(J = 1.8\) Hz, 1H), 2.42 (s, 3H), 1.27 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl₃) \(\delta\) 164.47, 161.36, 146.84, 139.49, 138.06, 135.49, 129.64 (2C), 129.25, 128.83, 128.43(2C), 127.16, 120.58, 114.88, 114.32, 77.77, 22.21, 21.18; IR (thin film) 3055, 3030, 2976, 2924, 2866, 1617, 1586, 1348, 1091 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 392.1679 [calculated mass for C\(_{24}\)H\(_{26}\)NO\(_2\)S (M+H)\(^+\) 392.1679].
**4.7b**: Yellow solid, 95% yield. \([\alpha]^{23}_D = +118.7^\circ \) (c 2.0, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta 11.43\) (d, \(J = 10.8\) Hz, 1H), 7.48 – 7.42 (m, 4H), 7.38 – 7.35 (m, 3H), 7.13 (d, \(J = 6.5\) Hz, 2H), 6.65 (dd, \(J = 10.8, 1.3\) Hz, 1H), 6.49 (d, \(J = 1.4\) Hz, 1H), 4.03 (ddd, \(J = 7.7, 6.1, 1.3\) Hz, 1H), 3.08 (m, 2H), 1.27 (s, 9H); \(^1^3^C\) NMR (125 MHz, CDCl₃) \(\delta 189.00, 154.18, 144.31, 141.67, 138.19, 131.73, 129.85, 129.55, 128.65, 126.01, 125.95, 120.76, 110.36, 57.12, 42.64, 35.23, 22.20\); IR (thin film) 2976, 2953, 1631 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z 458.0781\) [calculated mass for \(C_{23}H_{23}BrNO_2S\) (M+H)+ 458.0783].

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl₃)} & : \\
\text{\(\delta 11.43\) (d, \(J = 10.8\) Hz, 1H), 7.48 – 7.42 (m, 4H), 7.38 – 7.35 (m, 3H), 7.13 (d, \(J = 6.5\) Hz, 2H), 6.65 (dd, \(J = 10.8, 1.3\) Hz, 1H), 6.49 (d, \(J = 1.4\) Hz, 1H), 4.03 (ddd, \(J = 7.7, 6.1, 1.3\) Hz, 1H), 3.08 (m, 2H), 1.27 (s, 9H)}
\end{align*}
\]
4.7c: White solid, 89% yield. $[\alpha]_{23}^D = +53.6^\circ$ (c 2.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.92 (s, 1H), 8.75 (s, 1H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.46 (m, 2H), 7.42 (m, 1H), 7.29 (d, $J = 1.8$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.12 (d, $J = 1.7$ Hz, 1H), 1.26 (s, 9H); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 163.85, 161.58, 147.16, 145.42, 139.31, 137.44, 131.85, 131.38, 129.00, 128.71, 127.25, 122.85, 120.56, 115.07, 114.69, 57.99, 22.32; IR (thin film) 3062, 3033, 2961, 2927, 2866, 1593, 1175, 1092 cm$^{-1}$; HRMS (ESI$^+$) m/z 456.0629 [calculated mass for C$_{23}$H$_{23}$BrNO$_2$S (M+H)$^+$ 456.0627].
4.7b\(\alpha\): Yellow solid, 86\% yield. \([\alpha]^{23}_D = +118.4^\circ (c\ 2.1,\ \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.45 (d, \(J = 10.7\) Hz, 1H), 8.16 (d, \(J = 8.75\) Hz, 2H), 7.46 (m, 2H), 7.42 (d, \(J = 8.71\) Hz, 2H), 7.38 (m, 3H), 6.76 (d, \(J = 10.6\) Hz, 1H), 6.51 (s, 1H), 4.19 (t, \(J = 6.5\) Hz, 1H), 3.19 (ddd, \(J = 17.1,\ 6.2,\ 1.6\) Hz, 1H), 3.09 (ddd, \(J = 17.1,\ 6.7,\ 1.2\) Hz, 1H), 1.28 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 188.57, 153.67, 150.87, 146.97, 144.89, 138.12, 130.19, 128.89, 128.75, 126.21, 126.09, 124.02, 109.38, 57.44, 42.99, 35.13, 22.32; IR (thin film) 30\,61, 3027, 2961, 1654, 1553, 1092 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/\ell\) 425.1529 [calculated mass for C\(_{23}\)H\(_{25}\)N\(_2\)O\(_4\)S (M+H\(^+\)) 425.1529].
**4.7c:** White solid, 88% yield. $[\alpha]_D^{23} = +90.3^\circ$ (c 3.3, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.89 (s, 1H), 8.67 (d, $J = 0.6$ Hz, 1H), 8.32 (d, $J = 8.77$ Hz, 2H), 7.67 – 7.63 (m, 2H), 7.55 (d, $J = 8.75$ Hz, 2H), 7.47 (m, 2H), 7.42 (m, 1H), 7.34 (dd, $J = 1.7$, 0.6 Hz, 1H), 7.13 (d, $J = 1.8$ Hz, 1H), 1.25 (s, 11H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.08, 161.70, 147.79, 147.35, 145.22, 144.06, 139.01, 130.72, 129.05, 128.88, 127.21, 123.82, 120.44, 115.99, 114.49, 58.09, 22.28; IR (thin film) 3060, 3032, 2964, 2977, 2927, 2871, 1617, 1586, 1519, 1347, 1088 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 423.1373 [calculated mass for C$_{23}$H$_{23}$N$_2$O$_4$S (M+H)$^+$ 423.1373].
4.7b: yellow solid, 85%. \([\alpha]^{23}_{D} = +122^\circ\) (c 6.1, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) δ 11.41 (d, \(J = 10.8\) Hz, 1H), 7.48 (m, 2H), 7.36 (m, 3H), 7.17 (d, \(J = 8.6\) Hz, 2H), 6.87 (d, \(J = 8.6\) Hz, 2H), 6.62 (dd, \(J = 10.8, 1.4\) Hz, 1H), 6.49 (s, 1H), 4.01 (t, \(J = 7.4\) Hz, 1H), 3.78 (s, 3H), 3.04 (m, 2H), 1.27 (s, 9H); \(^1\)C NMR (125 MHz, CDCl₃) δ 189.35, 158.50, 154.71, 144.06, 138.46, 134.28, 129.67, 128.85, 128.58, 126.01, 125.96, 114.10, 111.50, 57.04, 55.14, 42.58, 35.60, 22.21; IR (thin film) 3060, 3027, 2962, 1650, 1553, 1092 cm⁻¹; HRMS (ESI⁺) \(m/z\) 410.1786 [calculated mass for C₂₄H₂₈NO₃S (M+H)⁺ 410.1784].

\[\text{\includegraphics{image1}}\]

\[\text{\includegraphics{image2}}\]

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**4.7es:** White solid, 88% yield. $[\alpha]_D^{23} = +69.2^\circ$ (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.90 (s, 1H), 8.83 (s, 1H), 7.66 (d, $J = 7.02$ Hz, 2H), 7.46 (m, 2H), 7.41 (m, 1H), 7.30 (d, $J = 8.6$ Hz, 2H), 7.25 (d, $J = 1.76$ Hz, 1H), 7.16 (d, $J = 1.8$ Hz, 1H), 7.00 (d, $J = 8.72$ Hz, 2H), 3.87 (s, 3H), 1.27 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.57, 161.46, 159.73, 146.94, 146.59, 139.59, 130.96, 130.83, 128.85, 128.45, 127.19, 120.65, 115.03, 114.24, 114.13, 57.78, 55.30, 22.25; IR (thin film) 3063, 3033, 2964, 2924, 2869, 1593, 1371, 1175, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 408.1633 [calculated mass for C$_{21}$H$_{36}$NO$_3$S (M+H)$^+$ 408.1627].
4.7ba: Yellow solid, 92% yield, [α]_D^{23} = +156.7° (c 2.6, CHCl₃). ^1H NMR (500 MHz, CDCl₃) δ 11.27 (d, J = 10.7 Hz, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.19 – 7.14 (m, 5H), 6.52 (d, J = 10.7 Hz, 1H), 6.30 (s, 1H), 3.93 (t, J = 6.8 Hz, 1H), 3.01 – 2.82 (m, 2H), 1.07 (d, J = 1.8 Hz, 9H); ^13C NMR (125 MHz, CDCl₃) δ 188.78, 153.92, 147.01, 144.43, 138.05, 129.86, 128.62, 128.10, 125.96, 125.89, 125.76 (q, J = 270 Hz), 125.52 (q, J = 3.75 Hz), 109.88, 57.10, 42.81, 35.03, 22.09; ^19F NMR (376 MHz, CDCl₃) δ −62.47; IR (thin film) 3061, 3027, 2962, 1653, 1553, 1092 cm⁻¹; HRMS (ESI⁺) m/z 448.1559 [calculated mass for C₂₄H₂₅F₃NO₂S (M+H)⁺ 448.1552].

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, CDCl₃)}
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{13}C NMR (125 MHz, CDCl₃)}
\end{align*}
\]
4.7c: White solid, 88% yield. [α]$_{D}^{20}$ = +66.5° (c 1.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.95 (s, 1H), 8.73 (s, 1H), 7.75 (d, $J = 7.2$ Hz, 2H), 7.66 (d, $J = 7.01$ Hz, 2H), 7.47 (m, 5H), 7.32 (d, $J = 1.8$ Hz, 1H), 7.14 (d, $J = 1.8$ Hz, 1H), 1.27 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 163.50, 161.57, 147.15, 145.00, 142.16, 139.12, 130.13, 128.95 (2C), 128.71, 127.17, 126.17 (q, $J = 271.25$ Hz), 125.58 (q, $J = 3.75$ Hz), 120.65, 115.40, 114.56, 57.96, 22.22; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -62.53; IR (thin film) 3062, 3034, 2961, 2927, 2866, 1593, 1175, 1092 cm$^{-1}$; HRMS (ESI$^+$) m/z 446.1400 [calculated mass for C$_{24}$H$_{23}$F$_3$NO$_2$S (M+H)$^+$446.1396].
4.7b: Yellow solid, 89% yield, [α]$_D$ = +166.8$^\circ$ (c 5.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.19 (d, $J = 10.7$ Hz, 1H), 7.52 (dd, $J = 7.7$, 2.0 Hz, 2H), 7.41 – 7.37 (m, 3H), 6.86 (d, $J = 10.7$ Hz, 1H), 6.36 (d, $J = 2.3$ Hz, 1H), 2.94 – 2.82 (m, 2H), 2.34 (ddd, $J = 8.0$, 5.9, 2.5 Hz, 1H), 1.71 – 1.65 (m, 3H), 1.61 – 1.55 (m, 2H), 1.43 – 1.35 (m, 1H), 1.31 (s, 9H), 1.07 (m, 3H), 0.90 – 0.79 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.49, 155.07, 142.96, 138.94, 129.67, 128.69, 126.07, 125.87, 116.05, 57.14, 43.31, 41.31, 31.39, 31.00, 30.57, 26.40, 26.37, 26.21, 22.37; IR (thin film) 2957, 2925, 1633, 1552, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 386.2151 [calculated mass for C$_{23}$H$_{32}$NO$_2$S (M+H)$^+$ 386.2148].
**4.7c:** White solid, 84%. [α]$_D^{23}$ = +31.1$^\circ$ (c 0.7, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 12.01 (s, 1H), 9.19 (s, 1H), 7.63 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 7.13 (d, $J$ = 1.7 Hz, 1H), 7.09 (d, $J$ = 1.7 Hz, 1H), 3.16 (tt, $J$ = 11.5, 3.1 Hz, 1H), 1.89 (m, 4H), 1.81 (ddt, $J$ = 14.6, 3.0, 1.6 Hz, 1H), 1.55 (m, 5H), 1.29 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.88, 161.67, 151.08, 147.49, 140.10, 128.77, 128.28, 127.14, 116.19, 114.03, 113.38, 57.80, 39.30, 34.79, 34.69, 26.76, 26.72, 26.09, 22.21; IR (thin film) 3058, 3032, 2927, 2852, 1621, 1585, 1544, 1090 cm$^{-1}$; HRMS (ESI$^+$) m/z 384.1998 [calculated mass for C$_{23}$H$_{30}$NO$_2$S (M+H)$^+$ 384.1991].

![1H NMR spectrum](image1.png)

![$^{13}$C NMR spectrum](image2.png)
4.7bs: Yellow oil, 28% yield. $[\alpha]_{D}^{23} = +155.6^\circ$ (c 1.3, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.05 (d, $J = 10.8$ Hz, 1H), 7.55 (m, 2H), 7.42 (m, 3H), 6.96 (d, $J = 10.8$ Hz, 1H), 6.46 (s, 1H), 2.82 – 2.77 (m, 2H), 2.69 (ddd, $J = 8.2$, 4.6, 1.3 Hz, 2H), 1.34 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 190.06, 156.84, 141.22, 138.80, 129.82, 128.74, 126.59, 126.10, 107.71, 57.23, 28.10, 27.10, 22.42; IR (thin film) 3055, 3026, 2934, 2958, 1636, 1559, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 326.1185 [calculated mass for C$_{17}$H$_{21}$NaNO$_2$S (M+Na)$^+$ 326.1185].
4.7c: Colorless oil, 87%. [α]$_D^{23}$ = +33.6° (c 1.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.15 (s, 1H), 8.77 (s, 1H), 7.66 (m, 2H), 7.50 (d, $J$ = 8.0 Hz, 1H), 7.44 (m, 1H), 7.29 (d, $J$ = 1.9 Hz, 1H), 7.27 (dd, $J$ = 8.0, 1.7 Hz, 1H), 1.32 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.80, 160.42, 147.57, 139.57, 133.63, 128.89, 128.46, 127.20, 118.81, 117.23, 115.56, 57.86, 22.30; IR (thin film) 3056, 3033, 2977, 2921, 2866, 1623, 1586, 1576, 1089 cm$^{-1}$; HRMS (ESI$^+$) m/z 324.1031 [calculated mass for C$_{17}$H$_{19}$NaNO$_2$S (M+Na)$^+$ 324.1028].
4.7b: Yellow oil, 73% yield. [α]$_{23}^{D}$ = +166.4° (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.18 (d, $J$ = 10.7 Hz, 1H), 7.52 (m, 2H), 7.39 (m, 3H), 6.89 (d, $J$ = 10.7 Hz, 1H), 6.38 (d, $J$ = 2.1 Hz, 1H), 2.94 (ddd, $J$ = 16.9, 5.8, 2.3 Hz, 1H), 2.66 (m, 2H), 1.53 (m, 1H), 1.45 (m, 1H), 1.31 (s, 9H), 1.25 (m, 4H), 0.85 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.59, 155.10, 142.17, 139.75, 129.75, 128.74, 126.13, 125.61, 111.92, 57.25, 37.57, 34.61, 33.64, 29.61, 22.67, 22.42, 14.12; IR (thin film) 3058, 3023, 2974, 2961, 1634, 1559, 1092 cm$^{-1}$; HRMS (ESI$^+$) m/z 382.1812 [calculated mass for C$_{21}$H$_{29}$NNaO$_2$S (M+Na)$^+$ 382.1812].
Yellow oil, 87% yield. [α]$_D$ = +146.7° (c 3.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.23 (d, J = 10.7 Hz, 1H), 7.50 (m, 2H), 7.37 (m, 3H), 6.87 (d, J = 10.7 Hz, 1H), 6.35 (t, J = 1.3 Hz, 1H), 2.87 (m, 2H), 2.30 (dt, J = 8.2, 4.3 Hz, 1H), 1.75 (m, 1H), 1.30 (s, 1H), 0.86 (dd, J = 6.7, 1.0 Hz, 3H), 0.81 (dd, J = 6.7, 0.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 189.63, 155.11, 143.21, 139.05, 129.76, 128.77, 126.13, 125.89, 110.72, 57.21, 44.33, 31.63, 30.82, 22.41, 21.19, 20.61; IR (thin film) 3061, 3025, 2973, 2960, 1632, 1559, 1091 cm$^{-1}$; HRMS (ESI$^+$) m/z 368.1656 [calculated mass for C$_{20}$H$_{27}$NNaO$_2$S (M+Na)$^+$ 368.1654].
**4.7c**<sub>10</sub>: White solid 81%. [α]<sup>23</sup> = +84.6° (c 3.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 11.99 (s, 1H), 9.22 (s, 1H), 7.63 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 7.15 (d, J = 1.8 Hz, 1H), 7.11 (d, J = 1.7 Hz, 1H), 3.61 (m, 1H), 1.37 (d, J = 6.88 Hz, 3H), 1.35 (d, J = 6.88 Hz, 3H), 1.29 (s, 9H); <sup>1</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 161.94, 161.75, 151.94, 147.71, 140.16, 128.89, 128.42, 127.23, 115.62, 114.13, 113.53, 57.93, 28.77, 24.33, 23.98, 22.30; IR (thin film) 3059, 3032, 2964, 2928, 2870, 1622, 1575, 1544, 1093 cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>) m/z 366.1498 [calculated mass for C<sub>20</sub>H<sub>25</sub>NNaO<sub>2</sub>S (M+Na)<sup>+</sup> 366.1498].
4.7b11: Yellow solid, 65% yield. $[\alpha]_{D}^{23} = +123.2^\circ$ (c 2.2, CHCl$_3$). $\delta$ 11.31 (d, $J = 11.0$ Hz, 1H), 7.37 – 7.33 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.21 (m, 2H), 6.52 (dd, $J = 11.0$, 1.4, Hz, 1H), 6.01 (s, 1H), 3.95 (ddd, $J = 7.9$, 6.4, 1.3 Hz, 1H), 2.67 – 2.60 (m, 2H), 1.97 (d, $J = 0.7$ Hz, 3H), 1.28 (s, 9H); $^1$H NMR (125 MHz, CDCl$_3$) $\delta$ 190.07, 157.65, 143.30, 142.71, 128.65, 127.88, 127.23, 126.93, 111.00, 57.04, 43.32, 38.22, 24.33, 22.31; IR (thin film) 3060, 3028, 2974, 2962, 1639, 1559, 1091 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 340.1341 [calculated mass for C$_{18}$H$_{23}$N$\text{Na}$O$_2$S (M+Na)$^+$ 340.1341].
4.7eH: Colorless solid, 73%. \([\alpha]^{23}_{D} = +69.6^{\circ} (c 0.8, \text{CHCl}_3)\). \(^1H\) NMR (500 MHz, CDCl\(_3\)) \(\delta 11.83\) (s, 1H), 8.71 (s, 1H), 7.46 – 7.38 (m, 3H), 7.29 (m, 2H), 6.85 (dt, \(J = 1.6, 0.7\) Hz, 1H), 6.74 (dd, \(J = 1.7, 0.7\) Hz, 1H), 2.39 (s, 3H), 1.23 (s, 9H); \(^{13}C\) NMR (125 MHz, CDCl\(_3\)) \(\delta 164.40, 161.14, 146.23, 145.57, 138.48, 129.71, 128.44, 128.06, 122.92, 116.71, 113.64, 57.63, 22.19, 21.94\); IR (thin film) 3056, 3030, 2976, 2925, 2866, 1621, 1553, 1334, 1092 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 338.1185 [calculated mass for C\(_{18}\)H\(_{21}\)NNaO\(_2\)S (M+Na)\(^+\) 338.1185].
Yellow oil, 58% yield (74.0 mg). \([\alpha]^{23}_{D} = +160.1^\circ (c 2.5, \text{CHCl}_3). {^1}H\text{ NMR (500 MHz, CDCl}_3) \delta 11.26 (d, J = 11.0\text{ Hz}, 1H), 7.11 (d, J = 8.68\text{ Hz}, 2H), 6.85 (d, J = 8.72\text{ Hz}, 2H), 6.46 (dd, J = 11.0, 1.4\text{ Hz}, 1H), 5.96 (s, 1H), 3.87 (ddd, J = 8.2, 6.3, 1.4\text{ Hz}, 1H), 3.80 (s, 3H), 2.56 (m, 2H), 1.94 (s, 3H), 1.25 (s, 9H); {^{13}}C\text{ NMR (125 MHz, CDCl}_3) \delta 190.17, 158.43, 157.83, 143.23, 134.51, 128.89, 127.21, 114.04, 111.45, 57.02, 55.24, 42.61, 38.43, 24.33, 22.33; \text{IR (thin film)} 3060, 3028, 2974, 2962, 1639, 1559, 1091\text{ cm}^{-1}; \text{HRMS (ESI})^+ m/z 348.1632 [\text{calculated mass for C}_{19}H_{26}NO_3S (M+H)^{+} 348.1627].
**4.7c12**: White solid, 81% yield. \[\alpha\] \(_D^{23}\) = +94.8° (c 1.7, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.82 (s, 1H), 8.76 (s, 1H), 7.24 (d, \(J = 8.81\) Hz, 2H), 6.99 (d, \(J = 8.77\) Hz, 2H), 6.84 (d, \(J = 1.7\) Hz, 1H), 6.74 (d, \(J = 1.7\) Hz, 1H), 3.87 (s, 3H), 2.41 (s, 3H), 1.26 (s, 9H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.62, 161.22, 159.58, 146.06, 145.63, 130.94, 130.83, 122.96, 116.37, 114.01, 113.78, 57.65, 55.30, 22.21, 21.96; IR (thin film) 3061, 3032, 2964, 2927, 2869, 1593, 1369, 1175, 1093 cm\(^{-1}\); HRMS (ESI\(^+\)) \textit{m/z} 346.1474 [calculated mass for C\(_{19}\)H\(_{24}\)NO\(_3\)S (M+H\(^+\)) 346.1471].
Yellow solid, 63 % yield. $[\alpha]_D^{23} = +133.4^\circ$ (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.33 (d, $J = 10.9$ Hz, 1H), 8.20 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.91$ Hz, 2H), 6.65 (d, $J = 10.9$ Hz, 1H), 6.03 (q, $J = 1.4$ Hz, 1H), 4.07 (m, 1H), 2.77 (dd, $J = 17.2$, 6.7 Hz, 1H), 2.60 (dd, $J = 17.15$, 6.58 Hz, 1H), 1.97 (s, 3H), 1.30 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) 189.25, 156.52, 151.20, 146.89, 143.89, 128.66, 127.43, 123.93, 109.21, 57.31, 43.00, 37.85, 24.38, 22.31, 22.27, 22.18; IR (thin film) 3060, 3027, 2962, 1650, 1553, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 385.1193 [calculated mass for C$_{18}$H$_{22}$NaO$_2$S (M$+$Na)$^+$ 385.1192].
4.7b14: Yellow oil, 42% yield. \([\alpha]_D^{23} = +140.0^\circ \text{ (c 2.0, CHCl}_3)\). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.12 (d, $J = 10.9$ Hz, 1H), 6.84 (d, $J = 10.9$ Hz, 1H), 5.91 (qd, $J = 1.4, 0.6$ Hz, 1H), 2.82 – 2.75 (m, 1H), 2.47 – 2.39 (m, 1H), 2.11 – 2.03 (m, 1H), 1.98 (d, $J = 0.8$ Hz, 3H), 1.32 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125MHz, CDCl$_3$) $\delta$ 190.48, 158.43, 140.36, 126.83, 126.79, 113.07, 57.12, 38.77, 32.04, 24.54, 22.44, 20.48; IR (thin film) 3058, 3023, 2974, 2961, 1634, 1559, 1092 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 278.1184 [calculated mass for C$_{13}$H$_{21}$NNaO$_2$S (M+Na)$^+$ 278.1185].
4.7b15: Yellow oil, 86% yield. $[\alpha]_{D}^{23} = +113.6^\circ$ (c 12.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.36 (d, $J = 10.5$ Hz, 1H), 7.38 – 7.34 (m, 2H), 7.32 – 7.27 (m, 1H), 7.23 – 7.20 (m, 2H), 6.75 (d, $J = 10.0$ Hz, 1H), 6.51 (q, $J = 1.5$ Hz, 1H), 4.05 (td, $J = 7.5$, 1.2 Hz, 1H), 2.78 (dt, $J = 7.5$, 1.4 Hz, 2H), 1.27 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 186.19, 146.96, 141.43 (q, $J = 31.94$ Hz), 129.23 (q, $J = 5.6$ Hz), 128.83, 127.69, 127.40, 122.47 (q, $J = 270.14$ Hz), 110.03, 57.32, 42.28, 29.95, 22.03; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -70.60; IR (thin film) 3063, 3030, 2965, 2930, 1635, 1559, 1314, 1091 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 394.1060 [calculated mass for C$_{18}$H$_{20}$F$_3$NNaO$_2$S (M+Na)$^+$ 394.1059].
4.7cis: White solid, 81% yield. \([\alpha]^2_d = +56.2^\circ\) (c 1.2, CHCl₃). \(^1\)H NMR (400 MHz, CDCl₃) δ 12.02 (s, 1H), 8.79 (s, 1H), 7.51–7.47 (m, 3H), 7.36–7.32 (m, 2H), 7.31 (d, \(J = 1.8\), 0.6 Hz, 1H), 7.18 (d, \(J = 1.8\), 0.6 Hz, 1H), 1.29 (s, 9H); \(^1\)C NMR (100 MHz, CDCl₃) δ 164.19, 161.14, 147.29, 137.31, 135.21 (q, \(J = 33.0\) Hz), 129.73, 128.86, 128.82, (q, \(J = 272.0\) Hz), 117.92 (q, \(J = 4.0\) Hz), 113.68 (q, \(J = 4.0\) Hz), 58.19, 22.26; \(^19\)F NMR (376 MHz, CDCl₃) δ -63.63; IR (thin film) 3061, 3033, 2964, 2927, 2869, 1593, 1371, 1175, 1097 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 370.1086 [calculated mass for C\(_{18}\)H\(_{19}\)F\(_3\)NO\(_2\)S (M+H)\(^+\) 370.1083].
4.7 b16: Yellow oil, 86% yield. [α]$_{D}^{23}$ = +143.1° ($c$ 2.3, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.32 (d, $J$ = 10.8 Hz, 1H), 7.15 (m, 2H), 7.08 (m, 2H), 6.71 (d, $J$ = 10.8 Hz, 1H), 6.49 (s, 1H), 3.98 (m, 1H), 2.73 (dt, $J$ = 8.3, 1.4 Hz, 2H), 2.33 (s, 3H), 1.25 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 186.53, 147.03, 141.78 (q, $J$ = 32.5 Hz), 137.99, 137.23, 129.68, 129.37 (q, $J$ = 5.0 Hz), 127.75, 122.64 (q, $J$ = 271.25 Hz), 110.45, 57.45, 42.14, 30.18, 22.22, 21.07; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -70.59; IR (thin film) 3060, 3030, 2963, 2930, 1635, 1559, 1314, 1090 cm$^{-1}$; HRMS (ESI$^+$) m/z 408.1213 [calculated mass for C$_{19}$H$_{22}$F$_3$NaO$_2$S (M+Na)$^+$ 408.1215].
4.7c16: White solid, 85% yield. [$\alpha$]$^\text{23}$$^\text{D} = +53.2^\circ$ (c 4.1, CHCl$_3$). 'H NMR (500 MHz, CDCl$_3$) $\delta$ 11.97 (s, 1H), 8.80 (s, 1H), 7.29 – 7.25 (m, 3H), 7.22 – 7.18 (m, 2H), 7.15 (dd, $J = 1.8$, 0.7 Hz, 1H), 2.41 (s, 3H), 1.26 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 164.30, 161.04, 147.34, 138.77, 135.11 (q, $J = 32.5$ Hz), 134.29, 129.58, 129.47, 123.16 (q, $J = 271.25$ Hz), 117.88, 117.81 (q, $J = 3.75$ Hz), 113.32 (q, $J = 3.75$ Hz), 58.13, 22.22, 21.18; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -63.64; IR (thin film) 3063, 3027, 2977, 2926, 2869, 1661,1593, 1371, 1175, 1097 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 384.1242 [calculated mass for C$_{19}$H$_{21}$F$_3$NO$_2$S (M+H)$^+$ 384.1239].
4.7b: Yellow oil, 83% yield. [α]$_D$ = +115° (c 1.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.42 (d, $J$ = 10.4 Hz, 1H), 8.22 (d, $J$ = 8.6 Hz, 2H), 7.39 (d, $J$ = 8.6 Hz, 2H), 6.87 (dt, $J$ = 10.4, 0.7 Hz, 1H), 6.54 (s, 1H), 4.16 (t, $J$ = 6.7 Hz, 1H), 2.88 (dd, $J$ = 17.7, 7.1 Hz, 1H), 2.76 (dd, $J$ = 17.7, 7.1 Hz, 1H), 1.27 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 184.99, 149.17, 147.71, 147.25, 140.34 (q, 32.5 Hz), 129.42 (q, 6.3 Hz), 128.60, 122.34 (q, 271.3 Hz), 108.28, 57.73, 41.90, 29.82, 22.13; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -70.67; IR (thin film) 3076, 2964, 2928, 1634, 1603, 1565, 1348, 1174, 1091 cm$^{-1}$; HRMS (ESI$^+$) m/z 439.0908 [calculated mass for C$_{18}$H$_{19}$F$_3$N$_2$NaO$_4$S (M+Na)$^+$ 439.0909].
4.7c17: White solid, 88% yield. [α]$_D$ = +98.6$^\circ$ (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 12.01 (s, 1H), 8.66 (s, 1H), 8.35 (d, J = 8.85 Hz, 2H), 7.52 (d, J = 8.68 Hz, 2H), 7.36 (m, 1H), 7.13 (dd, J = 1.7, 0.7 Hz, 1H), 1.25 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.81, 161.37, 148.05, 144.46, 143.77, 135.56 (q, J = 32.5 Hz), 130.72, 124.06, 122.93 (q, J = 271.25 Hz), 117.62 (q, J = 3.75 Hz), 117.55, 115.21 (q, J = 3.75 Hz), 58.49, 22.29; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -63.69; IR (thin film) 3062, 3031, 2964, 2927, 2869, 1577, 1371, 1175, 1097 cm$^{-1}$; HRMS (ESI$^+$) m/z 415.0931 [calculated mass for C$_{18}$H$_{18}$F$_3$N$_2$_O$_4$S (M+H)$^+$ 415.0933].
**4.7bR**: Yellow oil, 81% yield. \([\alpha]^{23}_{D} = +103.6^\circ (c 5.0, \text{CHCl}_3)\).\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.31 (d, \(J = 10.8\) Hz, 1H), 7.11 (d, \(J = 8.59\) Hz, 2H), 6.87 (d, \(J = 8.73\) Hz, 2H), 6.69 (dd, \(J = 10.8, 1.3\) Hz, 1H), 6.48 (s, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 2.72 (dt, \(J = 7.8, 1.4\) Hz, 2H), 1.25 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 186.55, 158.88, 147.03, 142.20, 141.95, 141.69, 141.44, 132.88, 129.42, 129.38, 129.34, 129.29, 128.92, 125.90, 123.72, 121.55, 119.37, 114.37, 110.67, 57.46, 55.31, 41.79, 30.27, 22.22; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -70.60; IR (thin film) 3072, 2964, 2926, 1632, 1603, 1565, 1344, 1174, 1092 cm\(^{-1}\); HRMS (ESI\(^{+}\)) \(m/z\) 402.1346 [calculated mass for C\(_{19}\)H\(_{23}\)F\(_3\)NO\(_3\)S (M+H)\(^+\) 402.1345].
4.7c18: White solid, 86% yield. $[\alpha]^2_D = +57.6^\circ$ (c 1.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 11.95 (s, 1H), 8.81 (s, 1H), 7.23 (m, 3H), 7.14 (m, 1H), 7.00 (d, $J = 1.7$ Hz, 2H), 3.86 (s, 3H), 1.26 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.39, 161.16, 160.18, 147.11, 135.21 (q, $J = 32.5$ Hz), 130.98, 129.59, 123.25 (q, $J = 271.25$ Hz), 117.86 (q, $J = 3.75$ Hz), 114.36, 113.18 (q, $J = 3.75$ Hz), 58.15, 55.34, 22.28; IR (thin film) 3061, 3033, 2964, 2927, 2869, 1593, 1371, 1175, 1097 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 422.1013 [calculated mass for C$_{19}$H$_{20}$F$_3$NNaO$_3$S (M+Na)$^+$ 422.1008].
4.7b: yellow oil, 88% yield. [α]$_{23}^{23}$ = +108.2$^\circ$ (c 1.6, CHCl$_3$)$_1$. H NMR (500 MHz, CDCl$_3$) $\delta$ 11.39 (d, $J$ = 10.6 Hz, 1H), 7.65 – 7.58 (d, $J$ = 8.6 Hz, 2H), 7.36 – 7.31 (d, $J$ = 8.4 Hz, 2H), 6.80 (dd, $J$ = 10.6, 1.1 Hz, 1H), 6.53 (s, 1H), 4.11 (t, $J$ = 7.0 Hz, 1H). 2.89 – 2.80 (m, 1H), 2.80 – 2.71 (m, 1H), 1.27 (s, 9H); C NMR (125 MHz, CDCl$_3$) $\delta$ 185.64, 147.50, 145.62, 141.04 (q, $J$ = 32.5 Hz), 129.92 (q, $J$ = 30.0 Hz), 129.44 (q, $J$ = 5.0 Hz), 125.99 (q, $J$ = 37.5 Hz), 126.59 (q, $J$ = 271.25 Hz), 125.37 (q, $J$ = 271.25 Hz), 109.05, 57.65, 42.10, 29.97, 22.21; F NMR (376 MHz, CDCl$_3$) $\delta$ -62.60, -70.65; IR (thin film) 3076, 2964, 2928, 1634, 1603, 1565, 1348, 1174, 1091 cm$^{-1}$; HRMS (ESI$^+$) m/z 440.1115 [calculated mass for C$_{19}$H$_{20}$F$_6$NO$_2$S (M+H)$^+$ 440.1113].
**4.7c**: White solid, 91% yield. \([\alpha]^{23}_D = +64.8^\circ \) (c 4.8, CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 12.04 (s, 1H), 8.72 (s, 1H), 7.75 (d, \(J = 1.8\) Hz, 2H), 7.46 (d, \(J = 1.8\) Hz, 2H), 7.33 (d, \(J = 1.8\) Hz, 1H), 7.13 (d, \(J = 1.8\) Hz, 1H), 1.26 (s, 9H); \(^13\)C NMR (125 MHz, CDCl₃) \(\delta\) 163.29, 161.29, 145.44, 140.88, 135.42 (q, \(J = 32.5\) Hz), 130.00 (q, \(J = 30.0\) Hz), 130.08, 125.83 (q, \(J = 2.5\) Hz), 123.80 (q, \(J = 271.25\) Hz), 126.25 (q, \(J = 271.25\) Hz), 117.82 (q, \(J = 3.75\) Hz), 117.63, 114.60 (q, \(J = 3.75\) Hz), 58.34, 22.24; \(^19\)F NMR (376 MHz, CDCl₃) \(\delta\) -62.70, -63.71; IR (thin film) 3062, 3034, 2961, 2927, 2866, 1593, 1175, 1092 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 460.0776 [calculated mass for C\(_{19}\)H\(_{17}\)F\(_{5}\)NNaO\(_2\)S (M+Na\(^+\) 460.0776].
**4.7b:** Yellow oil, 93% yield. \([\alpha]_D^{23} = +138.2^\circ \text{ (c 1.6, CHCl}_3)\). \[^1^H\text{NMR (500 MHz, CDCl}_3\) \(\delta 11.34 (d, J = 10.6 \text{ Hz, 1H}), 7.45 (d, J = 8.36 \text{ Hz, 2H}), 7.09 (d, J = 8.43 \text{ Hz, 2H}), 6.76 (d, J = 10.6 \text{ Hz, 1H}), 6.48 (q, J = 1.6 \text{ Hz, 1H}), 3.99 (m, 1H), 2.79 - 2.73 (m, 1H), 2.72 - 2.65 (m, 1H), 1.24 (s, 9H); \[^1^C\text{NMR (125 MHz, CDCl}_3\) \(\delta 185.73, 147.21, 141.00 (q, J = 31.25 \text{ Hz}), 140.29, 131.99, 129.40, 129.27 (q, J = 5 \text{ Hz}), 122.39 (q, J = 272.5 \text{ Hz}), 121.30, 109.35, 57.45, 41.68, 29.88, 22.06; \[^1^F\text{NMR (376 MHz, CDCl}_3\) \(\delta -70.61; \text{IR (thin film) 3152, 3064, 2963, 2969, 1635, 1559, 1365, 1128, 1096 cm}^{-1}; \text{HRMS (ESI)} m/z 448.0186 \text{ [calculated mass for C}_{18}H_{19}BrF_3NO_2S (M+H)}^+ 448.0188].

\(^1^H\text{NMR (500 MHz, CDCl}_3\)

\[^1^C\text{NMR (125 MHz, CDCl}_3\)

\[^1^F\text{NMR (376 MHz, CDCl}_3\)

\[30 150 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0\]
White solid, 87% yield. $[^{1}]_{D}^{23} = +64.8^\circ$ (c 4.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.98 (s, 1H), 8.73 (s, 1H), 7.60 (d, $J$ = 8.48 Hz, 2H), 7.28 (d, $J$ = 1.7 Hz, 1H), 7.19 (d, $J$ = 8.40 Hz, 2H), 7.10 (d, $J$ = 1.9 Hz, 1H), 1.25 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.49, 161.14, 145.75, 136.06, 135.23 (q, $J$ = 32.5 Hz), 131.96, 131.14, 123.37, 122.98 (q, $J$ = 271.25 Hz), 117.59 (q, $J$ = 3.75 Hz), 114.03 (q, $J$ = 3.75 Hz), 58.20, 22.17; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -63.63; IR (thin film) 3058, 3032, 2962, 2926, 2866, 1615, 1175, 1091 cm$^{-1}$ HRMS (ESI) $m/z$ 446.0034 [calculated mass for C$_{18}$H$_{16}$BrF$_3$NO$_2$S (M+H)$^+$ 446.0031].
**4.7b2**: Yellow oil, 82 % yield. $[\alpha]_{25}^{21} = +142.8^\circ$ (c 3.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.13 (d, $J = 10.3$ Hz, 1H), 6.97 (d, $J = 10.3$ Hz, 1H), 6.32 (s, 1H), 2.58 – 2.46 (m, 2H), 2.27 (ddd, $J = 8.4, 6.2, 2.6$ Hz, 1H), 1.70 – 1.63 (m, 3H), 1.52 – 1.46 (m, 1H), 1.24 (s, 9H), 1.15 – 0.98 (m, 4H), 0.84 – 0.73 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 185.57, 146.30, 141.47 (q, $J = 32.5$ Hz), 128.71 (q, $J = 5.0$ Hz), 122.72 (q, $J = 271.25$ Hz), 109.33, 57.33, 42.23, 40.93, 30.94, 30.32, 26.17, 26.14, 26.03, 24.84, 22.05; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -70.62; IR (thin film) 2927, 2854, 1634, 1559, 1314, 1173, 1096 cm$^{-1}$; HRMS (ESI$^+$) m/z 400.1535 [calculated mass for C$_{18}$H$_{26}$F$_3$NaO$_2$S (M+Na)$^+$ 400.1528].
4.7c21: White solid, 85% yield. [α]$_D^23$ = +44.8° (c 3.2, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 12.00 (s, 1H), 9.15 (s, 1H), 7.08 (s, 2H), 3.12 (tt, $J$ = 11.4, 3.1 Hz, 1H), 1.90 – 1.74 (m, 6H), 1.53 – 1.45 (m, 4H), 1.26 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 161.90, 161.32, 151.87, 135.70 (q, $J$ = 32.5 Hz), 123.37 (q, $J$ = 271.25 Hz), 117.13, 113.36 (q, $J$ = 3.75 Hz), 112.47 (q, $J$ = 3.75 Hz), 58.20, 39.38, 34.70, 34.41, 26.65, 26.60, 25.93, 22.24; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -63.78; IR (thin film) 3062, 3034, 2930, 2855, 1594, 1557, 1372, 1095 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 376.1557 [calculated mass for C$_{18}$H$_{25}$F$_3$NO$_2$S (M+H)$^+$ 376.1552].
**4.7b2**: Yellow oil, 68 % yield. [α]$_{D}^{23}$ = +149.1$^\circ$ (c 5.0, CHCl$_3$).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.10 (d, $J$ = 10.5 Hz, 1H), 7.00 (d, $J$ = 10.5 Hz, 1H), 6.35 (dd, $J$ = 2.7, 1.4 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.35 – 2.28 (m, 1H), 1.42 – 1.35 (m, 2H), 1.19 – 1.13 (m, 4H), 1.25 (s, 9H) 0.82 (t, $J$ = 7.2 Hz, 4H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 185.94, 145.41, 141.50 (q, $J$ = 32.5 Hz), 128.58 (q, $J$ = 5.0 Hz), 122.82 (q, $J$ = 271.25 Hz), 110.90, 57.49, 36.51, 34.26, 29.20, 27.78, 22.49, 22.17, 13.97; $^1$F NMR (376 MHz, CDCl$_3$) $\delta$ -70.80; IR (thin film) 2927, 2854, 1634, 1559, 1314, 1173, 1096 cm$^{-1}$; HRMS (ESI$^+$) m/z 374.1374 [calculated mass for C$_{16}$H$_{24}$F$_3$NNaO$_2$S (M+Na)$^+$ 374.1372].
4.7b: Yellow oil, 81% yield. $[\alpha]^{23}_{D} = +159.6^\circ$ (c 2.1, CHCl$_3$).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.11 (d, $J = 10.5$ Hz, 1H), 6.95 (d, $J = 10.5$ Hz, 1H), 6.27 (q, $J = 1.6$ Hz, 1H), 2.48 (s, 2H), 2.20 (ddd, $J = 8.4, 5.2, 3.5$ Hz, 1H), 1.58 (m, $J = 7.1$ Hz, 1H), 1.20 (s, 9H), 0.78 (d, $J = 6.7$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 185.73, 146.30, 141.27 (q, $J = 31.25$ Hz), 128.59 (q, $J = 5.0$ Hz), 122.64 (q, $J = 271.25$ Hz), 109.26, 57.18, 42.92, 31.22, 24.92, 21.90, 20.48, 19.72; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -70.77; IR (thin film) 2962, 2926, 1633, 1613, 1558, 1343, 1170, 1092 cm$^{-1}$; HRMS (ESI$^+$) m/z 360.1216 [calculated mass for C$_{15}$H$_{22}$F$_3$NNaO$_2$S (M+Na)$^+$ 360.1215].
Yellow oil, 82%. $[\alpha]_{D}^{23}=+67.5^\circ$ (c 2.5, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.78 (s, 1H), 9.07 (s, 1H), 7.63 – 7.59 (m, 2H), 7.46 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 7.10 (d, $J = 1.7$ Hz, 1H), 7.01 (dd, $J = 1.8$, 0.9 Hz, 1H), 2.61 (s, 3H), 1.28 (s, 9H); $^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.20, 161.51, 147.43, 141.17, 139.52, 128.74, 128.32, 127.01, 120.65, 115.49, 113.69, 57.70, 22.19, 19.41; IR (thin film) 3059, 3033, 2962, 2926, 1623, 1557, 1346, 1090 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 338.1187 [calculated mass for C$_{18}$H$_{21}$NNaO$_2$S (M+Na)$^+$ 338.1185].

[Chemical structures and NMR spectra images are present in the document.]

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Cyclopropane 4.3c
colorless oil, 45% yield. [α]₂⁰⁺ = +32.6° (c 1.2, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 7.27 – 7.09 (m, 5H), 6.21 (q, J = 1.5 Hz, 1H), 5.61 (q, J = 1.2 Hz, 1H), 4.59 (d, J = 7.3 Hz, 1H), 4.24 (d, J = 6.4 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.44 – 3.34 (m, 1H), 2.57 – 2.51 (m, 1H), 2.03 (d, J = 6.2 Hz, 2H), 1.90 (d, J = 1.5 Hz, 3H), 1.75 (d, J = 1.3 Hz, 3H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.04, 166.59, 155.49, 136.28, 135.97, 128.40, 128.11, 126.48, 116.84, 106.61, 60.82, 56.21, 54.30, 52.38, 50.86, 35.41, 30.84, 28.15, 22.68, 21.00, 18.83; IR (thin film) 3160, 3027, 2907, 1699, 1626, 1476, 1091 cm⁻¹; HRMS (ESI⁺) m/z 540.1415 [calculated mass for C₂₅H₃₅BrNO₅S (M+H)⁺ 540.1413].
Cyclopropane 4.8a
colorless oil, 68% yield. \([\alpha]_{D}^{23} = +58.6^\circ (c 4.2, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.02 (d, J = 8.7 \text{ Hz}, 2\text{H}), 6.74 (d, J = 8.7 \text{ Hz}, 2\text{H}), 6.18 (q, J = 1.6 \text{ Hz}, 1\text{H}), 5.57 (q, J = 1.3 \text{ Hz}, 1\text{H}), 4.70 (d, J = 7.3 \text{ Hz}, 1\text{H}), 4.23 (m, 2\text{H}), 4.15 (dd, J = 5.8, 1.5 \text{ Hz}, 1\text{H}), 4.07 (m, 2\text{H}), 3.76 (s, 3\text{H}), 3.31 (m, 1\text{H}), 2.45 (dd, J = 8.9, 6.7 \text{ Hz}, 1\text{H}), 1.95 (m, 2\text{H}), 1.88 (t, J = 1.5 \text{ Hz}, 3\text{H}), 1.74 (d, J = 1.3 \text{ Hz}, 3\text{H}), 1.30 (t, J = 7.1 \text{ Hz}, 3\text{H}), 1.23 (t, J = 7.1 \text{ Hz}, 3\text{H}), 1.15 (s, 9\text{H}); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 171.74, 166.13, 158.10, 155.44, 136.50, 129.32, 128.03, 117.18, 113.49, 106.25, 61.47, 61.05, 59.43, 56.11, 55.11, 54.08, 35.16, 30.34, 28.44, 22.70, 21.18, 18.82, 14.27, 14.14; IR (thin film) 2980, 2959, 1715, 1612, 1443, 1071, 1031 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z 620.1647\) [calculated mass for C\(_{28}\)H\(_{40}\)BrN\(_{2}\)O\(_{6}\)S (M+Na\(^+\)] 620.1651].
Cyclopropane 4.8b
Colorless oil, 65% yield. [α] <sup>23</sup>D = +63.4° (c 1.1, CHCl₃). <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 7.23 – 7.17 (m, 2H), 7.16 – 7.11 (m, 1H), 7.10 – 7.06 (m, 2H), 6.20 – 6.16 (m, 1H), 5.59 (q, J = 1.2 Hz, 1H), 4.73 (d, J = 7.6 Hz, 1H), 4.27 – 4.20 (m, 2H), 4.18 – 4.13 (m, 1H), 4.09 – 4.03 (m, 2H), 2.49 (dd, J = 9.2, 6.6 Hz, 1H), 2.03 – 1.99 (m, 2H), 1.89 (d, J = 1.6 Hz, 3H), 1.73 (d, J = 1.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 – 1.21 (m, 3H), 1.14 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl₃) δ 171.82, 166.15, 155.09, 136.55, 136.14, 128.27, 128.06, 126.39, 117.47, 106.33, 61.55, 61.08, 59.50, 56.19, 35.43, 30.95, 28.56, 22.73, 21.27, 18.88, 14.29, 14.17; IR (thin film) 3167, 3061, 2982, 2907, 1705, 1645, 1095 cm⁻¹; HRMS (ESI⁺) m/z 590.1543 [calculated mass for C<sub>27</sub>H<sub>38</sub>BrN<sub>3</sub>O<sub>5</sub>S (M+Na)<sup>+</sup> 590.1546].

![NMR spectrum of Cyclopropane 4.8b](image)
Bromo-imine 4.9a
yellow oil, 78% yield. $[\alpha]^2_{23} = +123.2^\circ$ (c 2.2, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.50 (s, 1H), 7.25 (m, 3H), 7.09 (m, 2H), 6.19 (q, $J = 1.4$ Hz, 1H), 4.12 (t, $J = 5.2$ Hz, 1H), 3.17 (m, 1H), 2.67 (dd, $J = 18.8, 5.0$ Hz, 1H), 2.01 (m, 3H), 0.87 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 188.86, 163.05, 160.33, 139.66, 128.80, 128.36, 127.49, 124.44, 57.92, 50.03, 38.19, 24.56, 22.20; IR (thin film) 3060, 3028, 2974, 2962, 1639, 1559, 1091 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 418.0448 [calculated mass for C$_{18}$H$_{22}$BrN$_2$O$_2$S (M+Na)$^+$ 418.0446].

![1H NMR](image1)

![13C NMR](image2)
Enamine 4.10a

colorless oil, yield not determined. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (m, 2H), 7.19 (m, 3H), 6.69 (tq, J = 7.3, 1.5 Hz, 1H), 6.09 (ddd, J = 13.7, 10.1, 1.1 Hz, 1H), 5.38 (d, J = 10.1 Hz, 1H), 5.21 (dd, J = 13.8, 7.8 Hz, 1H), 4.14 (m, 3H), 3.38 (m, 1H), 2.56 (td, J = 7.3, 1.1 Hz, 2H), 1.77 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 167.96, 143.85, 139.51, 128.90, 128.88, 128.52, 127.40, 126.47, 113.61, 60.41, 56.46, 45.45, 35.71, 22.44, 14.24, 12.58; IR (thin film) 2982, 2958, 2926, 1708, 1623, 1081 cm⁻¹; HRMS (ESI⁺) m/z 364.1942 [calculated mass for C₂₀H₃₀NO₅S (M+H)⁺ 364.1941].
Imine 4.10b

E:Z 4:1. Colorless oil, 82% yield. \([\alpha]^{23}_{D} = +228.1^\circ\ (c\ 2.8,\ CHCl_3)\). \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\ 7.98\ (t,\ J = 4.1\ Hz,\ 1H),\ 7.27\ (m,\ 2H),\ 7.18\ (ddd,\ J = 6.5, 3.4, 2.1\ Hz,\ 3H),\ 6.68\ (m,\ 1H),\ 4.15\ (q,\ J = 7.1\ Hz,\ 2H),\ 3.29\ (m,\ 1H),\ 2.95\ (ddd,\ J = 16.8, 9.0, 4.2\ Hz,\ 1H),\ 2.87\ (ddd,\ J = 16.8, 5.7, 4.0\ Hz,\ 1H),\ 2.55\ (ddt,\ J = 14.9, 7.0, 0.9\ Hz,\ 1H),\ 2.49\ (ddd,\ J = 14.9, 7.5, 1.1\ Hz,\ 1H),\ 1.73\ (d,\ J = 1.4\ Hz,\ 3H),\ 1.25\ (t,\ J = 7.1\ Hz,\ 3H),\ 1.01\ (s,\ 9H); \(^1^3^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\ 167.81,\ 167.48,\ 142.96,\ 138.68,\ 129.59,\ 128.65,\ 127.37,\ 126.78,\ 60.50,\ 56.56,\ 41.74,\ 41.45,\ 36.10,\ 22.17,\ 14.27,\ 12.52;\) IR (thin film) 2980, 2958, 2927, 1708, 1623, 1083 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\ 364.1942\) [calculated mass for \(C_{20}H_{30}NNO_3S\ (M+H)^{+}\) 364.1941].

[Chemical structure images]
**Imine 4.11a**

*E:*Z 2.5:1. Colorless oil, 78% yield. $[\alpha]_D^{23} = +138.7^\circ$ (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.98 (t, $J = 4.0$ Hz, 1H), 7.42 (m, 2H), 7.08 (m, 2H), 6.64 (m, 1H), 4.17 (m, 2H), 3.29 (m, 1H), 2.90 (m, 2H), 2.52 (m, 2H), 1.75 (d, $J = 1.3$ Hz, 3H), 1.28 (m, 3H), 1.03 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.59, 166.91, 141.94, 138.00, 131.63, 129.77, 129.05, 120.38, 60.50, 56.51, 41.23, 41.10, 35.79, 22.05, 14.19, 12.49; IR (thin film) 2980, 2958, 2927, 1708, 1623, 1083 cm$^{-1}$; HRMS (ESI$^+$) m/z 464.0871 [calculated mass for C$_{20}$H$_{28}$BrNO$_3$S (M+H)$^+$ 464.0865].
Imine 4.11b

_E:Z_ 4:1, Colorless oil, 75% yield. [α]$_{D}$+248.2° (c 1.4, CHCl$_3$). E isomer shown

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.97 (t, $J$ = 4.2 Hz, 1H), 7.10 (d, $J$ = 8.75 Hz, 2H), 6.82 (d, $J$ = 8.72 Hz, 2H), 6.68 (m, 1H), 4.16 (q, $J$ = 7.1 Hz, 2H), 3.77 (s, 3H), 3.24 (tt, $J$ = 8.5, 6.4 Hz, 1H), 2.92 – 2.83 (m, 2H), 2.56 – 2.44 (m, 2H), 1.75 (s, 3H), 1.27 (t, $J$ = 7.3 Hz 3H), 1.05 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 167.81, 167.70, 158.34, 138.86, 134.92, 129.43, 128.28, 114.05, 60.48, 56.55, 55.27, 41.74, 41.05, 36.19, 22.20, 14.28, 12.55; IR (thin film) 2978, 2956, 2926, 1708, 1643, 1093 cm$^{-1}$; HRMS (ESI$^+$) m/z 416.1872 [calculated mass for C$_{21}$H$_{31}$NaNO$_4$S (M+Na)$^+$ 416.1866].
Amino alcohol 4.11c
To a flame dried round bottomed flask equipped with magnetic stir bar and solution of the imine-ester (1.0 eq., 1.0 M), in THF cooled to -78 °C was added diisobutyl aluminum hydride (Dibal-H). The reaction was stirred for 2h then quenched with saturated solution of Rochelle’s salt, extracted using ethyl acetate (3 times) and washed with brine. The combined organic extracts were dried using anhydrous sodium sulfate (Na₂SO₄) and solvent evaporated. Crude material was purified by flash column chromatography (silica gel, 90% EtOAc in hexanes) to afford amino alcohol as colorless oil, 88% yield. [α]²³D = +89.6° (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.05 (d, J = 8.59 Hz 2H), 6.82 (J = 8.67 Hz, 2H), 5.29 (ddq, J = 7.9, 6.6, 1.4 Hz, 1H), 3.90 (s, 2H), 3.77 (s, 3H), 3.09 – 2.89 (m, 3H), 2.63 (ddt, J = 9.9, 7.2, 4.8 Hz, 1H), 2.38 – 2.21 (m, 2H), 1.95 (dddd, J = 13.2, 8.2, 6.6, 4.8 Hz, 1H), 1.78 (ddddd, J = 13.6, 10.0, 8.0, 5.6 Hz, 1H), 1.57 (s, 3H), 1.14 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 157.98, 136.26, 136.13, 128.32, 123.60, 113.84, 68.59, 55.43, 55.17, 44.09, 42.69, 37.10, 35.04, 22.53, 13.80; IR (thin film) 3090, 2976, 2953, 2926, 1615, 1071 cm⁻¹; HRMS (ESI⁺) m/z 376.1919 [calculated mass for C₁₉H₃₁NNaO₃S (M+Na)⁺ 376.1916].
**α,α-Dibromo-imine 4.12a**

Colorless oil, dibromo:mono-bromo 5:1, dibromo imine shown, 52% yield. \([\alpha]_{23}^{23} D = +216.9^\circ (c \, 1.0, \text{CHCl}_3)\). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 (s, 1H), 7.38 (m, 2H), 7.31 (m, 3H), 6.45 (tq, $J$ = 7.3, 1.5 Hz, 1H), 4.08 (q, $J$ = 7.1 Hz, 2H), 3.68 (dt, $J$ = 10.9, 3.8 Hz, 1H), 3.04 (m, 1H), 2.94 (dddd, $J$ = 15.0, 11.0, 7.5, 1.1 Hz, 1H), 1.78 (s, 3H), 1.20 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.59, 163.07, 137.39, 136.95, 129.84, 129.78, 128.49, 128.36, 72.08, 60.53, 59.13, 56.95, 33.10, 22.66, 14.21, 12.70; IR (thin film) 3090, 2976, 2953, 2926, 1645, 1071 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 543.9946 [calculated mass for C$_{20}$H$_{27}$Br$_2$NNaO$_3$S (M+Na)$^+$ 543.9950].
\textbf{\textit{a,a-Dichloro imine 4.12c}}

Colorless oil, \textit{dichloro:monochloro} 5:1, \textit{dichloro imine} shown, 46\% yield. $[\alpha]_{D}^{23} = +235.2^\circ$ (c 1.0, CHCl$_3$). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.37 – 7.28 (m, 5H), 6.46 (ddt, $J = 7.3, 5.9, 1.5$ Hz, 1H), 4.12 – 4.06 (m, 2H), 3.70 (dd, $J = 10.9, 3.3$ Hz, 1H), 3.06 – 2.88 (m, 2H), 1.78 (s, 3H), 1.22 – 1.19 (m, 12H); \textsuperscript{13}C NMR (125 MHz, CDCl$_3$) $\delta$ 167.58, 162.77, 137.43, 135.95, 129.92, 129.87, 128.48, 128.46, 90.88, 60.54, 58.68, 56.64, 30.97, 22.56, 14.21, 12.66; IR (thin film) 3090, 2976, 2953, 2926, 1731, 1645, 1071 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 432.1159 [calculated mass for C$_{20}$H$_{28}$Cl$_2$NO$_3$S (M+H)$^+$ 432.1161].

![NMR spectrum](image1.png)

![NMR spectrum](image2.png)

![NMR spectrum](image3.png)
N-allylated enamine 4.13a
Colorless oil, 46% yield. \([\alpha]_{D}^{23} = +38.3^\circ (c 1.3, \text{CHCl}_3)\. 1^H NMR (500 MHz, CDCl3) \(\delta\) 7.31 (m, 2H), 7.22 (m, 3H), 6.75 (m, 1H), 6.36 (dd, \(J = 14.1, 0.9\) Hz, 1H), 5.78 (ddt, \(J = 17.3, 10.4, 5.3\) Hz, 1H), 5.23 (dq, \(J = 11.36, 1.56\) Hz 1H), 5.20 (m, 2H), 4.89 (dd, \(J = 14.1, 8.3\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.98 (m, 1H), 3.92 (ddt, \(J = 16.7, 5.1, 1.8\) Hz, 1H), 3.43 (td, \(J = 8.4, 6.1\) Hz, 1H), 2.58 (m, 2H), 1.82 (d, \(J = 1.4\) Hz, 3H), 1.31 (t, \(J = 7.1\) Hz, 3H), 1.19 (s, 9H); 13C NMR (125 MHz, CDCl3) \(\delta\) 167.93, 144.64, 139.97, 133.47, 128.70, 128.46 (2C), 127.21, 126.31, 117.38, 109.42, 60.42, 59.64, 46.21, 36.21, 22.95, 14.35, 12.68; IR (thin film) 3058, 3026, 2977, 2958, 2927, 2927, 1707, 1649, 1087 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 426.2079 [calculated mass for \(\text{C}_{23}\text{H}_{33}\text{NNaO}_3\text{S}\) (M+Na)+ 426.2073].

![NMR spectrum](image1)

![NMR spectrum](image2)

![NMR spectrum](image3)
Amino alcohol 4.6c
White solid, 63% yield. [α]²³D = +89.6° (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 7.36 (m, 4H), 7.27 (m, 1H), 6.58 (d, J = 15.8 Hz, 1H), 6.05 (dd, J = 15.8, 7.8, 1.0 Hz, 1H), 4.90 (m, 3H), 4.21 (ddd, J = 9.0, 7.7, 3.4, 1.0 Hz, 1H), 3.98 (m, 2H), 3.87 (dt, J = 10.3, 3.0 Hz, 1H), 2.51 (td, J = 8.5, 4.0 Hz, 1H), 1.74 (m, 3H), 1.27 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 143.26, 136.79, 131.77, 129.44, 128.55, 127.62, 126.51, 114.26, 65.21, 59.98, 55.79, 54.15, 22.84, 21.74; IR (thin film) 3090, 2976, 2953, 2926, 1731, 1645, 1071 cm⁻¹; HRMS (ESI⁺) m/z 344.1657 [calculated mass for C₁₈H₂₇NNaO₂S (M+Na)⁺ 344.1654].
CHAPTER 5
SYNTHESIS OF CHIRAL VINYL AZIRIDINES
VIA A VINYLOGOUS
AZA-DARZENS REACTION
5.1 Introduction

The aziridine is the smallest nitrogen-containing heterocycle whose biological and synthetic value continues to demand investigations and development of new and scalable methods for their preparation. Extensive research in this area has given rise to a number of aziridination strategies towards biologically important aziridine-containing compounds.\(^{[5b, 18a]}\) Comprehensive accounts compiled by Tanner,\(^{[7]}\) Sweeney,\(^{[92]}\) and most recently by Kimpe\(^{[18]}\) and Degennaro\(^{[4]}\) summarizes the challenges and success stories towards the aziridine and its applications in synthesis. These literature reports clearly position this reactive aza-cycle as an important synthetic intermediate due to its immense synthetic fortunes availed upon ring opening.

Njardarson’s contribution to the synthesis of vinyl aziridines\(^{[12]}\) was driven by the anticipated facile and stereospecific rearrangements triggered by opening of the aziridine to form substituted pyrrolines.\(^{[12, 93]}\) The scope of Njardarson’s approach limits the vinyl aziridines to those that can be derived from conjugated imines. Because of the variety of reactive sites in the aziridine, researchers in this field have exploited inter- or intra-molecular trapping of the aza-anion upon ring opening, to access more complex nitrogen-containing hetero-cycles (azepines, azetidine, pyrrolidine and piperidines)\(^{[29, 94]}\) including natural products.\(^{[95]}\) Such rearrangements are commonly effected when the aziridinyl motif is adjacent to a vinyl group\(^{[12, 96]}\) among other reactive functional groups.\(^{[29]}\) Despite the numerous synthetic applications of vinyl aziridines, there is scarcity of asymmetric approaches, specifically for syntheses of cis-vinyl aziridines, and especially employing non-conjugated imines.\(^{[13b, 97]}\)

The discovery of the asymmetric vinylogous aza-Darzens reaction is the result of our desire to extend the asymmetric [3+2] annulation strategy to synthesis of 2,3,4-trisubstituted-3-pyrrolines
To accomplish this, we required a nucleophile substituted at the β-position of the γ-halo crotonate reagent (5.1d). From a reactivity standpoint, the substituent at the β-position should offer low to moderate steric effects in order to allow reaction of the enolate via the desired α-position. Our other concern was the potentially labile hydrogens in the case of hydrogen-containing substituents. We also imagined that more valuable fused bicyclic pyrrole compounds would be generated when cyclic nucleophile sources were successfully reacted with the sulfinimines.

**Scheme 5.1.** Proposed synthesis of 2,3,4-trisubstituted 3-pyrrolines

### 5.2 Results and Discussion

Our initial plan to expand the scope of the asymmetric [3+2] annulation reaction to introduce substituents at the C3 position of the 3-pyrrole commenced by reaction of the cyclic vinylogous aza-Darzens nucleophile (methyl (E)-4-bromo-3-methylbut-2-enolate) and (R,E)-2-methyl-N-(3-methylbutylidene) propane-2-sulfinamide (Scheme 5.2). Using our established reaction conditions,[16] the reaction of the 4-bromobutenolide (5.2b) and the alkyl imine (5.2a) did not afford the expected the pyrrole compound (5.2c) with the fused lactone moiety. Instead, the cis-vinyl aziridine 5.2d was obtained.
Scheme 5.2. Discovery of the vinylogous aza-Darzens reaction

The divergence in regioselectivity from that observed when non-β-substituted ethyl γ-
bromocrotonate (Scheme 5.1) was employed did not surprise us since we were aware of reports of
synthesis of vinyl oxiranes and aziridines using allyl halogenated anions\cite{17,98} as the nucleophiles
for the respective transformations. Another example of anionic strategy toward vinyl aziridines is
the addition of allyl sulfonium ylide to imines.\cite{99} These examples suggest sufficient anion
stabilization by the vinyl motif and the bromine atom. In our case, steric hindrance also serves to
promote reactivity of the γ-enolate because of disrupted stabilization of the anion by the carbonyl,
which would have allowed α-attack.

Before turning our attention toward the substrate scope of the vinylogous aza-Darzens, we
wanted to compare our [3+2]-annulation reaction conditions (Table 5.1, entry 1) to the common
aza-Darzens aziridination reaction conditions (low temperatures in THF, bases such as LiHMDS
and NaHMDS). We chose LiHMDS over NaHMDS because it is known to afford better yields and
higher stereoselectivity.\cite{100} Another lesson from literature reports is the tendency of the halo-ester
to undergo self-condensation, which is commonly suppressed by addition of the base to the pre-
cooled solutions of the imine and the nucleophile precursor established by Davis and co-
workers.\cite{13b,101} The only price paid by employing this protocol is poor diastereoselectivity of the
aziridines.\cite{100} Fortunately, the addition step of the vinylogous aza-Darzens is syn selective

\[ \begin{align*}
&\text{Scheme 5.2: Discovery of the vinylogous aza-Darzens reaction} \\
&\text{The divergence in regioselectivity from that observed when non-β-substituted ethyl γ-
bromocrotonate (Scheme 5.1) was employed did not surprise us since we were aware of reports of}
\text{synthesis of vinyl oxiranes and aziridines using allyl halogenated anions\cite{17,98} as the nucleophiles}
\text{for the respective transformations. Another example of anionic strategy toward vinyl aziridines is}
\text{the addition of allyl sulfonium ylide to imines.\cite{99} These examples suggest sufficient anion}
\text{stabilization by the vinyl motif and the bromine atom. In our case, steric hindrance also serves to}
\text{promote reactivity of the γ-enolate because of disrupted stabilization of the anion by the carbonyl,}
\text{which would have allowed α-attack.}
\text{Before turning our attention toward the substrate scope of the vinylogous aza-Darzens, we}
\text{wanted to compare our [3+2]-annulation reaction conditions (Table 5.1, entry 1) to the common}
\text{aza-Darzens aziridination reaction conditions (low temperatures in THF, bases such as LiHMDS}
\text{and NaHMDS). We chose LiHMDS over NaHMDS because it is known to afford better yields and}
\text{higher stereoselectivity.\cite{100} Another lesson from literature reports is the tendency of the halo-ester}
to undergo self-condensation, which is commonly suppressed by addition of the base to the pre-
cooled solutions of the imine and the nucleophile precursor established by Davis and co-
workers.\cite{13b,101} The only price paid by employing this protocol is poor diastereoselectivity of the}
\text{aziridines.\cite{100} Fortunately, the addition step of the vinylogous aza-Darzens is syn selective}
\end{align*} \]
culminating in an overall diastereoselective formation of only two diastereomers of cis-vinyl aziridines (Scheme 5.3. Vinylogous aza-Darzens reaction results).

Scheme 5.3. Vinylogous aza-Darzens reaction results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Bromobutenolide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1.2</td>
<td>53&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>1.5</td>
<td>72&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>LiHMDS</td>
<td>1.2</td>
<td>79&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>1.5</td>
<td>82&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Table 5.1 Optimization of the asymmetric vinylogous aza-Darzens reaction

Table 5.1 summarizes optimization data of the aziridination reaction in LiHMDS compared to LDA using THF as the solvent. Our prior knowledge of possible nucleophile self-condensation, especially due to lack of stabilization of the γ-anion by the carbonyl group demanded that we determine suitable addition order of the reaction components. We explored two protocols in which, a) the nucleophile is first generated using LDA followed by addition of solution of the imine (Table 5.1, entry 1), or b) a solution of both the nucleophile and the imine are pre-cooled, then the base was added (Table 5.1, entry 2). The isolated yields are lower in case of addition
order a compared to b (Table 5.1, entries 2-3) confirming the expected self-condensation\(^{[101]}\) of the butenolide occurring instead of reacting with the imine. We therefore favored the addition order b to conduct base screens (LiHMDS and LDA). The reaction afforded higher product yields with LiHMDS compared to LDA (Table 5.1, entries 2 and 4). With respect to the amount of the nucleophile precursor, improved yields were obtained when 1.5 equivalents of the 4-bromobutenolide was used in THF and LiHMDS as the base compared to yields obtained with 1.2 equivalents of the 4-bromobutenolide. In addition to affording better yields when using LiHMDS, the reaction can be carried out at 0 °C without conversion of the aziridine products to azirines, a known transformation of the aziridines in presence of LDA.\(^{[102]}\)

![Scheme 5.4. General vinylogous aza-Darzens reaction](image)

Having determined the optimal reaction conditions and a general procedure for the aziridination, we sought to establish the substrate scope of the reaction. We prepared alkyl, aromatic and hetero-aromatic sulfinimines of medium to large steric bulk using Ellman’s protocol\(^{[31]}\). The reaction afforded cis-vinyl aziridines in good to excellent yields and with diastereoselectivity ranging from 3:1 to 1:1. Absolute structure elucidation and the configuration of the C1 and C2 stereocenters of alkyl and aryl (both diastereomers) substrates were determined by x-ray crystallographic analysis (Figure 5.1). The cis conformation in both diastereomers

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confirmed our expectation that the enolate addition on the imine occurs in \textit{syn} fashion prior to elimination of bromine.

\textbf{Figure 5.1.} X-ray crystal structures of \textit{cis}-vinyl aziridines.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfinimine (Sₜₙ)</th>
<th>Azidine (Sₜₙδ)</th>
<th>Yield (%)²</th>
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</tbody>
</table>

b. Yields reported are for both diastereomers

**Table 5.2.** Substrate scope for the asymmetric vinylogous *aza-* Darzens reaction
Although the vinylogous aza-Darzens reaction does not afford a single diastereomer, both diastereomers have cis-configuration (Figure 5.1) and the aziridines are formed in good yields (Table 5.2). Higher product yields were obtained from electron-poor aryl sulfinimines compared to the electron rich aryl, alkyl and hetero-aromatic sulfinimines (Table 5.2, entries 1, 7, 10, 12, 13, 15 - 19). In addition, we are able to access both enantiomers of the aziridines by changing the chiral auxiliary (Table 5.2, entries 15 and 15b).

The formation of exclusively cis-aziridines is in agreement with the closed chair transition state model in which the addition of α-haloenolates to imines provides predominantly cis products (Table 5.2). In our case, the vinylogous approach afforded two diastereomers arising surprisingly from failed facial stereocontrol by the auxiliary. The lack of facial selectivity is believed to be due to the high reactivity of the non-stabilized γ-anion and the remote location of the γ-bromo anionic center rendering less interaction of the nucleophile with the auxiliary (Figure 5.2).

![Figure 5.2. Chair transition state model for addition of α-haloenolates to Ellman Imines](image)

Figure 5.2. Chair transition state model for addition of α-haloenolates to Ellman Imines

In an effort to widen the scope of the reaction using acyclic nucleophiles, we subjected methyl (E)-4-bromo-3-methylbut-2-enolate (4.3b) to the conditions developed for the 4-bromobutenolide. To our surprise, this ‘small’ acyclic nucleophile did not produce the vinyl aziridine at -78 °C. Instead, the γ-adduct, the amino bromide (5.5a) was isolated alongside the self-
condensation product (5.5b) of the methyl (E)-4-bromo-3-methylbut-2-enolate (Scheme 5.5). When the amino ester was subjected to NaH at 0 °C, this intermediate was fully converted to desired vinyl aziridine (5.5c). In an effort to develop a general one step synthesis of 5.5c, which would be applicable to both nucleophiles (5.2b and 43b), we screened a new protocol using methyl (E)-4-bromo-3-methylbut-2-enolate (4.3b). The progress of the reaction was monitored using thin layer chromatography (TLC) to allow full conversion of the imine to the γ-amino adduct at -78 °C. Upon warming the reaction to 0 °C, the bromine was displaced allowing cyclization to the desired aziridine. This new protocol worked well for the bromo-butenolide affording yields similar to those obtained at -78 °C. No decomposition of the product was observed when using LiHMDS compared to LDA reaction at 0 °C. We therefore adopted these conditions for our general vinylogous aziridination procedure. The acyclic nucleophile 4.3b will be treated with other imines to further broaden the variety of vinyl aziridines products.

**Scheme 5.5.** Example of asymmetric acyclic vinylogous *aza*-Darzens reaction

We were interested in showcasing the synthetic applications of the strategy using the previously developed stereospecific vinyl aziridine ring-expansion methodology[12, 93] to access
other nitrogen-containing heterocycles. Our initial attempts employing the copper-catalyzed-
pyrroline forming conditions on the alkyl sulfone 5.6a did not afford the expected product 5.6b
(Scheme 5.6, a). We then turned our attention to the electron-rich furan-containing substrate (5.6c)
with desire to accessing azepine motifs upon thermal input. Heating in toluene, without any
additive led to ring opening of the aziridine and subsequently fragmentation to the imine (5.6d).
We then postulated an inter-molecular interruption of the fragmentation by trapping the azo-
methine ylide upon ring opening (Scheme 5.6, b). Unfortunately, the fragmentation outcompeted
the planned inter-molecular trapping using acetylene dimethyl carboxylate due to its high
reactivity as a result of the electron rich furan ring.

Scheme 5.6. Attempted ring expansions of chiral vinyl aziridines

A more attractive transformation that would leverage the value of the methodology is
access to the azepine moiety. The di-vinyl aziridines would appear to be derived from a ring
contracted azepine core and vice versa (Scheme 5.7). The merger of the reactivity of the aziridine
(5.7b), and the proximity of the cis-related C2 and C3 substituents of di-vinyl system of the
aziridine seemed to be a perfect match towards the azepine architecture (5.7c). We prepared α,β-
conjugated imines and upon exposure to the vinylogous aza-Darzens reaction conditions, none of
the \textit{di}-vinyl aziridine was formed. This type of imine did not react with our nucleophile even when the reaction was run at higher temperatures (0 °C to room temperature). Currently, we do not have an explanation for this isolated lack of reactivity of the conjugated imines with the nucleophile.

![Scheme 5.7. Vinylogous \textit{aza}-Darzens reaction of conjugated sulfinimines](image)

\textbf{5.3 Conclusion}

We have developed a rare example of regioselective vinylogous \textit{aza}-Darzens approach towards \textit{cis} vinyl aziridines. The efficient, mild and scalable access to the \textit{cis-di}-vinyl aziridines with a variety of reactive functionalities will allow selective transformations to more valuable alkaloids. We are currently investigating conditions necessary to access \textit{di}-vinyl aziridines from \textit{\alpha}, \textit{\beta}-conjugated imines which would open doors for our ring expansion adventures.

\textbf{5.4 General Procedure for the vinylogous \textit{aza}-Darzens reaction}

To a cooled (-78 °C) 0.1 M solution of imine and 3-bromomethyl-2-buten-4-olide (1.5 eq.), a solution of lithium bis(trimethylsilyl)amide (2.0 eq., 1M in ethyl benzene) was added using a syringe pump (1.0 mL/h) while the reaction temperature was maintained at -78 °C for 2 hours, then reaction is then warmed to 0 °C for \(\frac{1}{2}\) hour. The reaction was quenched with saturated ammonium chloride and allowed to warm to room temperature, extracted using ethyl acetate (3 times) and washed with brine. The combined organic extracts were dried using anhydrous sodium sulfate
(Na$_2$SO$_4$) and solvent evaporated. Crude $^1$H NMR showed diastereomer products (3:1 to 1:1) which were purified by flash column chromatography (silica gel, 20-60% EtOAc in hexanes) to afford the title compound.

5.5 X-ray crystal data for cis-vinyl aziridines

X-ray data were collected at the University of Arizona X-ray Diffraction Facility. Colorless plate-like crystals were mounted onto a Cryoloop under a film of Paratone oil. Diffraction data for all crystals were collected at 100° (2) K using a Bruker Kappa APEX II DUO diffractometer. X-ray data were integrated and structures solved using Bruker SAINT and SHELXT and/ or Olex2 respectively.
Crystal data for diastereomer ssa (CCDC 1451253)

Crystal data and structure refinement for S₆a1 (CCDC 1451253).

Formula: C₁₉H₁₈NO₅SBr
Formula weight: 384.28
Size: 0.3 x 0.15 x 0.1 mm
Crystal morphology: Colorless fragment
Temperature: 99.99 K
Wavelength: MoKα (λ = 0.71073)
Crystal system: Orthorhombic
Space group: P2₁2₁2₁
Unit cell dimensions:
- a = 8.4979(11) Å, α = 90°
- b = 6.3008(6) Å, β = 90°
- c = 31.150(4) Å, γ = 90°
Volume: 1667.9 Å³
Z: 4
Density (calculated): 1.530 Mg/m³
Absorption coefficient: 2.601 mm⁻¹
F(000): 784.0
Data collection range: 2.614 to 51.016°
Index ranges: -10 ≤ h ≤ 9, -7 ≤ k ≤ 5, -37 ≤ l ≤ 32
Reflections collected: 12889
Independent reflections: 3116 [Rint = 0.0468, Rsigma = 0.0445]
Absorption correction: Multi-scan
Max. and min. transmission: 0.745 and 0.532
Refinement method: Full
Data / restraints / parameters: 3116/0/202
Goodness of fit: 1.036
Final R indices [I > 2σ (I)]: R₁ = 0.0290, wR₂ = 0.0577
R indices (all data): R₁ = 0.0403, wR₂ = 0.0612
Largest diff. peak and hole: 0.47/ -0.45 e Å⁻³
Absolute structure parameter: 0.014(7)
Crystal data for diastereomer ssa (CCDC 1451353)

Crystal data and structure refinement for s,a (CCDC 1451353)

Formula \( \text{C}_{18}\text{H}_{32}\text{NO}_{3}\text{SBr} \)

Formula weight 384.28

Size 0.6 \times 0.04 \times 0.01 \text{ mm}

Crystal morphology Colorless fragment

Temperature 99.99 \text{ K}

Wavelength MoK\(\alpha \) (\( \lambda = 0.71073 \))

Crystal system monoclinic

Space group \( \text{P2}_1 \)

Unit cell dimensions \( a = 6.3924(13) \text{ Å} \), \( \alpha = 90^\circ \)

\( b = 14.594(3) \text{ Å} \), \( \beta = 109.540^\circ \)

\( c = 9.1182(19) \text{ Å} \), \( \gamma = 90^\circ \)

Volume 801.6(3) \text{ Å}^3

\( Z \) 2

Density (calculated) 1.592 \text{ Mg/m}^3

Absorption coefficient 2.706 \text{ mm}^{-1}

\( F(000) \) 392.0

Data collection range \( 4.74 \text{ to } 50.67^\circ \)

Index ranges \(-7 \leq h \leq 7, -17 \leq k \leq 17, -10 \leq l \leq 10 \)

Reflections collected 8579

Independent reflections 2923 [\( R_{int} = 0.0454, R_{merge} = 0.0529 \)]

Absorption correction multi-scan

Max. and min. transmission 0.7453 and 0.6092

Refinement method Full

Data / restraints / parameters 2923/187/202

Goodness of fit 1.023

Final R indices \([I \geq 2 \sigma (I)] \) \( R_I = 0.0321, wR_I = 0.0666 \)

R Indices (all data) \( R_I = 0.0380, wR_I = 0.0688 \)

Largest diff. peak and hole 0.53 and -0.43 e Å\(^{-3} \)

Absolute structure parameter -0.016(7)
Crystal data for diastereomer 5.2d (CCDC 1062145)

Crystal data and structure refinement for 5.2d (CCDC 1062145)

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5.6 Characterization and spectral data for Chapter 5

5.2d; White solid, 63% yield. \([\alpha]_{D}^{23} = -259.8^\circ (c 1.0, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 5.99 (dd, J = 1.6 \text{ Hz}, 1\text{H}), 4.85 (dd, J = 17.8, 1.8 \text{ Hz}, 1\text{H}), 4.77 (dd, J = 17.6, 1.9 \text{ Hz}, 1\text{H}), 3.43 (d, J = 7.0 \text{ Hz}, 1\text{H}), 2.56 (td, J = 7.3, 5.4 \text{ Hz}, 1\text{H}), 1.81 – 1.70 (m, J = 6.8 \text{ Hz}, 1\text{H}), 1.41 – 1.27 (m, 2\text{H}), 1.21 (s, 9\text{H}), 0.97 (d, J = 6.7 \text{ Hz}, 3\text{H}), 0.93 (d, J = 6.7 \text{ Hz}, 3\text{H}); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 172.83, 164.02, 118.85, 72.31, 57.01, 40.15, 35.58, 30.24, 27.01, 22.50, 22.48, 22.46; IR (thin film) 2956, 2927, 2868, 1739, 1639, 1076 \text{ cm}^{-1}; \) HRMS (ESI\(^+\)) \(m/\zeta 286.1473\) [calculated mass for C\(_{14}\)H\(_{24}\)NO\(_3\)S (M+H\(^+\)) 286.1471].
S1a: White solid, 82% yield (112.0 mg). $[\alpha]_{D}^{23} = -22.1^\circ$ (c 1.8, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (d, J = 10 Hz, 2H), 7.49 (d, J = 10 Hz, 2H), 5.99 (td, J = 1.9, 0.9 Hz, 1H), 4.43 (dd, J = 17.7, 2.0 Hz, 1H), 4.32 (ddd, J = 17.7, 1.9, 0.7 Hz, 1H), 3.89 (d, J = 7.1 Hz, 1H), 3.82 (d, J = 7.1 Hz, 1H), 1.33 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$), $\delta$ 171.85, 161.14, 148.06, 139.62, 128.47, 124.00, 120.25, 71.52, 57.72, 41.50, 33.42, 22.58; IR (thin film) 3094, 2961, 2868, 1734, 1522, 1078 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 373.0831 [calculated mass for C$_{16}$H$_{18}$N$_2$NaO$_5$S (M+Na)$^+$ 373.0828].
S\textsubscript{3a}: White solid, 51\% yield. \([\alpha]\)^D\textsubscript{23} = -15.2\textdegree (c 0.82, CHCl\textsubscript{3}) \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 6.00 (td, \(J = 1.9, 1.0\) Hz, 1H), 4.86 (ddd, \(J = 17.7, 1.9, 0.7\) Hz, 1H), 4.79 (dd, \(J = 17.7, 1.9\) Hz, 1H), 3.47 (d, \(J = 7.0\) Hz, 1H), 2.25 (dd, \(J = 9.8, 7.0\) Hz, 1H), 1.37 (m, 1H), 1.21 (s, 9H), 1.11 (d, \(J = 6.6\) Hz, 3H), 0.89 (d, \(J = 6.8\) Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 172.72, 163.88, 118.70, 72.41, 57.02, 47.75, 31.15, 26.98, 22.50, 20.04, 19.47; IR (thin film) 309, 2961, 2868, 1734, 1522, 1078 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) \textit{m/z} 294.1134 [calculated mass for C\textsubscript{13}H\textsubscript{21}NNaO\textsubscript{3}S (M+Na)+ 294.1134].
**Saa**: White solid, 61% yield (112.0 mg). \([\alpha]_D^{23} = -28.4^\circ (c 0.86, \text{CHCl}_3)\) \(^1\text{H} \text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.37 - 7.28 (m, 5H), 6.02 (td, \(J = 1.9, 0.8 \text{ Hz}, 1\text{H})\), 4.39 (dd, \(J = 17.8, 1.9 \text{ Hz}, 1\text{H})\), 4.13 (ddd, \(J = 17.8, 1.9, 0.7 \text{ Hz}, 1\text{H})\), 3.85 (d, \(J = 7.1 \text{ Hz}, 1\text{H})\), 3.78 (d, \(J = 7.0 \text{ Hz}, 1\text{H})\), 1.31 (s, 9H); \(^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 172.48, 162.66, 132.54, 128.80, 128.75, 127.39, 119.99, 71.71, 57.46, 42.19, 33.34, 22.65; \text{IR (thin film)} 2958, 2927, 1741, 1219, 1071 \text{ cm}^{-1}; \text{HRMS (ESI)} m/z 328.0978 [calculated mass for C\text{_{16}}H\text{_{19}}NNaO\text{_3} S (M+Na)^+ 328.0977].
**Sa**: White solid, 77% yield (d.r 2:1). Major diastereomer shown. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.61 – 8.57 (m, 2H), 7.57 (ddt, $J = 13.3$, 8.0, 2.0 Hz, 1H), 7.29 (ddddd, $J = 7.6$, 4.8, 2.5 Hz, 1H), 5.99 (td, $J = 2.0$, 0.9 Hz, 1H), 4.41 (dd, $J = 17.1$, 2.0 Hz, 1H), 4.30 (ddd, $J = 17.7$, 1.8, 0.7 Hz, 1H), 3.85 (d, $J = 7.0$ Hz, 1H), 3.76 (d, $J = 6.9$ Hz, 1H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.01, 161.53, 150.04, 149.27, 149.06, 134.97, 123.39, 120.11, 71.59, 57.61, 40.07, 33.05, 22.55; IR (thin film) 2959, 2927, 1741, 1518, 1071 cm$^{-1}$; HRMS (ESI$^+$) m/z 307.1111 [calculated mass for C$_{15}$H$_{19}$N$_2$O$_3$S (M+H)$^+$ 307.1110].
**Ssa**: White solid, 78% yield (d.r 3:1). Major diastereomer [α]$_{23}^{23}$D = -24.8° (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (d, $J$ = 10 Hz, 2H), 7.17 (d, $J$ = 10 Hz, 2H), 5.99 (td, $J$ = 1.9, 0.8 Hz, 1H), 4.40 (dd, $J$ = 17.7, 1.9 Hz, 1H), 4.22 (ddd, $J$ = 17.7, 1.9, 0.8 Hz, 1H), 3.82 (d, $J$ = 7.0 Hz, 1H), 3.70 (d, $J$ = 7.0 Hz, 1H), 1.30 (s, 9H); $^{13}$C NMR (125MHz, CDCl$_3$) δ 172.21, 162.05, 131.98, 131.52, 129.02, 122.87, 120.05, 71.62, 57.51, 41.61, 33.23, 22.59; IR (thin film) 3094, 2959, 2926, 1740, 1165, 1078 cm$^{-1}$; HRMS (ESI$^+$) m/z 406.0083 [calculated mass for C$_{16}$H$_{18}$BrN$_2$NaO$_3$S (M+Na)$^+$ 406.0083].
**Ssa diast.**; Minor diastereomer. [α]$_{23}^D$ = -20.5° (c 0.86, CHCl$_3$).$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.48 (d, $J = 10$ Hz, 2H), 7.16 (d, $J = 10$ Hz, 2H), 6.02 (q, $J = 1.7$ Hz, 1H), 4.50 (ddd, $J = 17.6, 1.9, 0.9$ Hz, 1H), 4.40 (dd, $J = 17.6, 2.0$ Hz, 1H), 4.13 (d, $J = 7.1$ Hz, 1H), 3.32 (d, $J = 7.0$ Hz, 1H), 1.27 (s, 9H);$^1$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.33, 161.78, 132.04, 131.00, 129.24, 122.90, 119.83, 71.55, 57.55, 38.17, 36.79, 22.59; IR (thin film) 3094, 2959, 2926, 1740, 1078 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 406.0087 [calculated mass for C$_{16}$H$_{18}$BrNaO$_3$S (M+Na)$^+$ 406.0083].
**S6a**: Major diastereomer. White solid, 75% yield (d.r 2:1). $[\alpha]_{23}^{\text{D}} = -30.7^\circ$ (c 2.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.62 (d, $J = 8.1$ Hz, 2H), 7.42 (d, $J = 8.2$ Hz, 2H), 6.01 (td, $J = 1.9, 0.9$ Hz, 1H), 4.41 (dd, $J = 17.7, 2.0$ Hz, 1H), 4.24 (ddd, $J = 17.8, 1.9, 0.8$ Hz, 1H), 3.87 (d, $J = 7.1$ Hz, 1H), 3.79 (d, $J = 7.0$ Hz, 1H), 1.31 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.09, 161.69, 136.51, 130.98 (q, 33 Hz), 127.88, 125.78 (q, 3.7 Hz), 123.66 (q, 274 Hz), 120.15, 71.57, 57.58, 41.66, 33.32, 22.58; IR (thin film) 2964, 2930, 1749, 1324, 1066 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 396.0852 [calculated mass for C$_{17}$H$_{18}$F$_3$NNaO$_3$S (M+Na)$^+$ 396.0851].
S9a: White solid, 51% yield. [α]$_D$ = -17.9$^\circ$ (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, Chloroform-$d$) δ 7.42 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 3.1 Hz, 1H), 6.75 (dd, J = 8.8, 3.1 Hz, 1H), 5.86 (td, J = 1.9, 0.8 Hz, 1H), 4.60 (dd, J = 17.8, 2.0 Hz, 1H), 4.34 (dd, J = 17.7, 1.9 Hz, 1H), 3.92 (d, J = 7.0 Hz, 1H), 3.79 (s, 3H), 3.74 (dt, J = 7.0, 0.6 Hz, 1H), 1.31 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.51, 162.21, 158.88, 133.46, 133.42, 119.33, 116.47, 114.74, 113.59, 71.98, 57.59, 55.48, 43.59, 32.99, 22.60; IR (thin film) 2959, 2927, 1741, 1518, 1071 cm$^{-1}$; HRMS (ESI$^+$) m/z 436.01884 [calculated mass for C$_{17}$H$_{20}$BrNNaO$_4$S (M+Na)$^+$ 436.0188].
**Smp:** White solid, 68%. Major product; $[\alpha]_D^{23} = -39.6^\circ$ (c 1.9, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67 (d, $J = 8.3$ Hz, 2H), 7.43 (d, $J = 7.9$ Hz, 2H), 5.99 (td, $J = 2.0$, 0.9 Hz, 1H), 4.41 (dd, $J = 17.7$, 2.0 Hz, 1H), 4.29 (dd, $J = 17.8$, 2.5 Hz, 1H), 3.87 (d, $J = 7.3$ Hz, 1H), 3.78 (d, $J = 7.1$ Hz, 1H), 1.32 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.91, 161.31, 137.73, 132.48, 128.26, 120.10, 117.98, 112.72, 71.50, 57.62, 41.60, 33.38, 22.52; IR (thin film) 2927, 2861, 2228, 1750, 1080 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 353.0929 [calculated mass for C$_{17}$H$_{18}$N$_2$O$_3$S (M+Na)$^+$ 353.0930].
Sa diast.; Minor diastereomer. white solid. \( [\alpha]^{23}_{D} = -22.8^\circ \) (c 1.0, CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 7.66 (d, \( J = 8.3 \) Hz, 2H), 7.41 (d, \( J = 8.1 \) Hz, 2H), 6.02 (td, \( J = 2.0, 1.1 \) Hz, 1H), 4.54 (ddd, \( J = 17.6, 1.9, 0.9 \) Hz, 1H), 4.39 (dd, \( J = 17.6, 2.0 \) Hz, 1H), 4.20 (d, \( J = 7.1 \) Hz, 1H), 3.88 (d, \( J = 7.1 \) Hz, 1H), 1.27 (s, 9H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 172.01, 161.01, 137.37, 132.59, 128.46, 120.07, 117.93, 112.87, 71.45, 57.66, 38.13, 37.11, 22.58. IR (thin film) 2927, 2861, 2228, 1750, 1219, 1080 cm\(^{-1}\); HRMS (ESI\(^+\)) \( m/z \): 353.0929 [calculated mass for C\(_{17}\)H\(_{18}\)N\(_2\)NaO\(_3\)S (M+Na\(^+\)) 353.0930].

![NMR spectrum](image1)

![NMR spectrum](image2)
S_{Sa}: White solid, 75%, $[\alpha]_{D}^{23} = -38.1^\circ$ (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.28 (mt, 2H), 7.05 (m, 2H), 6.00 (td, $J = 1.9, 0.8$ Hz, 1H), 4.40 (dd, $J = 17.8, 1.9$ Hz, 1H), 4.19 (dd, $J = 17.7, 1.9, 0.7$ Hz, 1H), 3.82 (d, $J = 7.0$ Hz, 1H), 3.74 (d, $J = 7.0$ Hz, 1H), 3.11 (s, 9H); $^3$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.32, 162.76 (d, 247.5 Hz), 162.30, 129.15 (d, 8.8 Hz), 128.32 (d, 2.5 Hz), 120.05, 115.97 (d, 21.3 Hz), 71.68, 57.52, 41.57, 33.32, 22.65; IR (thin film) 309, 2961, 2868, 1734, 1522, 1078 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 346.0885 [calculated mass for C$_{16}$H$_{14}$FNNaO$_3$S (M+Na)$^+$ 346.0883].
White solid, 46% yield. 

$^{[\alpha]}_{\text{D}} = -34.8^\circ$ (c 1.0, CHCl$_3$).  

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.77 (d, $J = 1.1$ Hz, 2H), 6.74 (q, $J = 0.9$ Hz, 1H), 6.01 (td, $J = 1.9$, 0.8 Hz, 1H), 5.99 (q, $J = 1.5$ Hz, 2H), 4.44 (dd, $J = 17.8$, 1.9 Hz, 1H), 4.24 (ddd, $J = 17.8$, 2.0, 0.7 Hz, 1H), 3.78 (d, $J = 6.9$ Hz, 1H), 3.69 (d, $J = 6.9$ Hz, 1H), 3.02 (s, 9H).  

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.54, 162.67, 148.03, 147.94, 126.17, 120.94, 119.88, 108.58, 107.60, 101.42, 71.79, 57.44, 42.00, 33.43, 22.64;  

IR (thin film) 2959, 2925, 1748, 1504, 1079 cm$^{-1}$;  

HRMS (ESI$^+$) $m/z$ 372.0880 [calculated mass for C$_{17}$H$_{19}$NaOsS (M+Na)$^+$. 372.0876].
S_{11a} (d.r 1:1): white solid, 80% yield. $^1$H NMR (500 MHz, CDCl$_3$) cis: δ 5.78 (td, $J = 2.0$, 0.8 Hz, 1H), 4.81 (dd, $J = 17.8$, 2.0 Hz, 1H), 4.62 (dd, $J = 17.7$, 1.8 Hz, 1H), 3.79 (d, $J = 6.0$ Hz, 1H), 3.62 (d, $J = 6.2$ Hz, 1H), 1.32 (s, 9H), trans: δ 5.99 (td, $J = 2.0$, 1.0 Hz, 1H), 4.65 (m, 2H), 4.62 (dd, $J = 17.7$, 1.8 Hz, 1H), 4.19 (d, $J = 6.6$ Hz, 1H), 3.34 (d, $J = 6.8$ Hz, 1H), 1.27 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ cis and trans 172.05, 171.93, 161.99, 161.50, 146.75 (m), 146.44 (m), 144.74 (m), 144.45 (m), 142.52 (m), 142.21 (m), 138.61 (m), 136.61 (m), 119.11, 119.02, 107.03 (dt, 4.3, 15.5 Hz), 106.58 (dt, 4.2, 14.3 Hz), 71.70, 71.26, 57.88, 57.49, 34.96, 34.20, 31.94, 30.02, 22.31, 22.10; IR (thin film) 2963, 2929, 2871, 1752, 1525, 1084 cm$^{-1}$; HRMS (ESI$^+$) m/z 418.0510 [calculated mass for C$_{16}$H$_{14}$F$_5$NNaO$_3$S (M+Na)$^+$ 418.0506].

$^1$H NMR (500 MHz, CDCl$_3$)

$^{13}$C NMR (125 MHz, CDCl$_3$)
$S_{12a}$; White solid, 56% yield, $[\alpha]^{23}_D = -74.5^\circ$ (c 0.8, CHCl$_3$). NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 – 7.37 (m, 2H), 6.30 (dd, $J = 1.8, 0.9$ Hz, 1H), 6.04 (td, $J = 1.9, 0.8$ Hz, 1H), 4.55 – 4.45 (m, 2H), 3.74 (d, $J = 6.8$ Hz, 1H), 3.54 (dd, $J = 6.9, 1.0$ Hz, 1H), 1.27 (s, 9H); $^1$H NMR (125 MHz, CDCl$_3$) $\delta$ 172.48, 162.55, 143.94, 141.26, 119.80, 118.43, 109.59, 71.79, 57.36, 35.78, 22.57; IR (thin film) 2959, 2927, 1741, 1518, 1071 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 318.0770 [calculated mass for C$_{14}$H$_{17}$NNaO$_4$S (M+Na)$^+$ 318.0770].
$S_{13a}$: White solid, 58% yield. $[\alpha]^{23}_D = -47.2^\circ$ (c 2.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.33 (dd, $J = 5.0, 3.0$ Hz, 1H), 7.23 (m, 1H), 6.99 (dd, $J = 5.0, 1.3$ Hz, 1H), 6.05 (t, $J = 1.9$ Hz, 1H), 4.45 (dd, $J = 17.8, 1.9$ Hz, 1H), 4.20 (dd, $J = 17.7, 1.9$ Hz, 1H), 3.79 (d, $J = 6.8$ Hz, 1H), 3.72 (d, $J = 6.9, 1.0$ Hz, 1H), 1.29 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.47, 162.70, 134.04, 127.18, 126.48, 123.76, 119.99, 77.25, 77.00, 76.74, 71.65, 57.40, 39.02, 33.20, 22.62; IR (thin film) 2957, 2926, 1738, 1518, 1091 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 334.0544 [calculated mass for C$_{14}$H$_{17}$NaO$_2$S$_2$ (M+Na)$^+$ 334.0542].
S14a: White solid, 56% yield. $[\alpha]^{23}_D = -18.6^\circ$ (c 1.1, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.79 (d, $J = 3.2$ Hz, 1H), 7.33 (d, $J = 3.3$ Hz, 1H), 6.08 (td, $J = 2.0$, 1.0 Hz, 1H), 4.60 (d, $J = 1.9$ Hz, 2H), 4.02 (d, $J = 6.9$ Hz, 1H), 3.88 (dd, $J = 7.0$, 1.1 Hz, 1H), 1.32 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.21, 162.92, 160.95, 144.07, 120.26, 120.17, 71.75, 57.65, 40.27, 33.68, 22.47. IR (thin film) 2959, 2923, 1738, 1518, 1071 cm$^{-1}$; HRMS (ESI$^+$) m/z 313.0676 [calculated mass for C$_{13}$H$_{17}$N$_2$O$_3$S$_2$ (M+H)$^+$ 313.0675].

![1H NMR (500 MHz, CDCl$_3$)](image1)

![13C NMR (125 MHz, CDCl$_3$)](image2)
S15a: White solid, 65% yield. [α]$_D^{23}$ = -28.2° (c 0.85, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.99 (td, $J$ = 1.9, 1.0 Hz, 1H), 4.85 (dd, $J$ = 17.7, 1.9, 0.7 Hz, 1H), 4.77 (dd, $J$ = 17.7, 1.9 Hz, 1H), 3.43 (d, $J$ = 7.1 Hz, 1H), 2.52 (dq, $J$ = 7.1, 7.3 Hz, 1H), 1.44 (m, 3H), 1.20 (m, 9H), 1.27 (m, 9H), 0.87 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 172.72, 163.91, 118.78, 72.31, 57.01, 41.32, 31.65, 30.61, 29.05, 29.01, 26.90, 26.84, 22.56, 22.51, 14.04; IR (thin film) 2958, 2923, 1738, 1639, 1076 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 350.1761 [calculated mass for C$_{17}$H$_{29}$NNaO$_3$S (M+Na)$^+$ 350.1760].

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[Image of NMR spectra]
S16a: White solid, 63% yield. $[\alpha]^{23}_D = -145.4^\circ$ (c 1.6, CHCl₃). $^1$H NMR (500 MHz, CDCl₃) $\delta$ 5.99 (q, J = 1.6 Hz, 1H), 4.86 (dd, J = 17.5, 1.7 Hz, 1H), 4.77 (dd, J = 17.7, 1.9 Hz, 1H), 3.44 (d, J = 7.0 Hz, 1H), 2.53 (q, J = 6.6 Hz, 1H), 1.43 (m, 3H), 1.27 (m, 9H), 1.21 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl₃) $\delta$ 172.74, 163.91, 118.79, 72.32, 57.02, 41.33, 31.66, 30.62, 29.05, 29.02, 26.91, 26.84, 22.57, 22.51, 14.05; IR (thin film) 2954, 2923, 2854, 1738, 1076 cm⁻¹; HRMS (ESI⁺) m/z 350.1760 [calculated mass for C₁₇H₂₀NNaO₃S (M+Na)⁺ 350.1760].

$^1$H NMR (500 MHz, CDCl₃)

$^{13}$C NMR (125 MHz, CDCl₃)
S16a: Colorless oil, 26% yield. Major diastereomer shown. \([\alpha]^{23}_{D} = +228.4^\circ (c 1.6, \text{CHCl}_3)\). 1H NMR (500 MHz, CDCl3) \(\delta 6.00\) (td, \(J = 1.9, 1.0\) Hz, H), 4.86 (ddd, \(J = 17.7, 1.9, 0.7\) Hz, 1H), 4.77 (dd, \(J = 17.7, 2.0\) Hz, 1H), 3.65 – 3.57 (m, 3H), 3.46 (dt, \(J = 7.2, 0.8\) Hz, 1H), 2.57 (q, \(J = 6.6\) Hz, 1H), 1.62 – 1.50 (m, 4H), 1.20 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H); 13C NMR (125 MHz, CDCl3) \(\delta 172.68, 163.80, 118.98, 72.28, 62.04, 57.03, 41.08, 30.78, 29.95, 25.86, 23.74, 22.50, 18.24, -5.36\); IR (thin film) 2955, 2929, 2857, 1751, 1084 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 402.2136 [calculated mass for C\(_{19}\)H\(_{36}\)NO\(_4\)SiS (M+H\(^+\)) 402.2128].
**Sra;** White solid, 58% yield. \([\alpha]_D^{23} = -52.4^\circ (c 1.0, \text{CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.09 \text{ (dq, } J = 2.0, 1.0 \text{ Hz, } 1\text{H}), 4.91 \text{ (d, } J = 17.9, 1.8 \text{ Hz, } 1\text{H}), 4.81 \text{ (dd, } J = 17.7, 1.9 \text{ Hz, } 1\text{H}), 3.47 \text{ (d, } J = 6.9 \text{ Hz, } 1\text{H}), 2.19 \text{ (t, } J = 6.6 \text{ Hz, } 1\text{H}), 1.22 \text{ (s, } 9\text{H}), 0.70 \text{ (m, } 1\text{H}), 0.63 \text{ (m, } 2\text{H}), 0.55 \text{ (dt, } J = 9.6, 5.0, 3.6 \text{ Hz, } 1\text{H}), 0.34 \text{ (dt, } J = 10.2, 5.1, 3.6 \text{ Hz, } 1\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 172.85, 164.11, 119.12, 72.25, 57.18, 44.00, 31.12, 22.54, 8.01, 4.07, 3.19\); IR (thin film) 2964, 2928, 2868, 1750, 1219, 1078 cm\(^{-1}\); HRMS (ESI\(^+\)) \(m/z\) 292.0980 [calculated mass for C\(_{13}\)H\(_{19}\)NNaO\(_3\)S (M+Na)]\(^+\) 292.0977.

\[\text{H NMR (500 MHz, CDCl}_3)\]

\[\text{\(^{13}\)C NMR (125 MHz, CDCl}_3)\]
S₁₈₆; White solid, 52% yield. [α] D = -48.3° (c 2.2, CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 6.01 (td, J = 1.8, 0.9 Hz, 1H), 4.86 (ddd, J = 17.7, 1.9, 0.7 Hz, 1H), 4.77 (dd, J = 17.7, 1.9 Hz, 1H), 3.45 (d, J = 7.1, Hz, 1H), 2.37 (dd, J = 9.2, 7.0 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.70 – 1.54 (m, 8H), 1.21 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 172.82, 164.21, 118.55, 72.31, 57.01, 46.12, 37.67, 31.01, 30.97, 29.66, 25.30, 25.07, 22.50; IR (thin film) 2955, 2868, 1748, 1643, 1078 cm⁻¹; HRMS (ESI⁺) m/z 320.1292 [calculated mass for C₁₅H₂₃NNaO₃S (M+Na)⁺ 320.1290].

[Image of the NMR spectrum with chemical shift details]

[Image of the ¹³C NMR spectrum with chemical shift details]
S_{19a}; major diastereomer. White solid, 44% yield. $\alpha$]$_{23}^{D}$ = -29.6 (c 2.2, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.00 (td, $J$ = 1.9, 1.0 Hz, 1H), 4.86 (dd, $J$ = 17.6, 1.9 Hz, 1H), 4.79 (dd, $J$ = 17.7, 1.9 Hz, 1H), 3.44 (d, $J$ = 7.0 Hz, 1H), 2.28 (dd, $J$ = 9.1, 7.0 Hz, 1H), 1.88 (d, $J$=11.7 Hz, 1H), 1.82 – 1.73 (m, 2H), 1.72 (m, 4H), 1.43 – 1.35 (m, 1H), 1.30 – 1.27 (m, 3H), 1.21 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 172.83, 164.09, 118.58, 72.43, 57.05, 46.34, 35.91, 30.70, 30.46, 30.02, 25.93, 25.28, 22.53; IR (thin film) 2925, 2853, 1751, 1074 cm$^{-1}$; HRMS (ESI$^+$) $m/z$ 312.1630 [calculated mass for C$_{16}$H$_{26}$NO$_3$S (M+H)$^+$ 312.1627].

![1H NMR (500 MHz, CDCl$_3$)](image1)

![13C NMR (125 MHz, CDCl$_3$)](image2)
5.5c: Major diastereomer. Colorless oil, 51% yield. $[\alpha]_D^{23} = -14.6^\circ$ (c 5.6, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.23 (d, $J = 8.6$ Hz, 2H), 7.60 (d, $J = 8.5$ Hz, 2H), 6.10 (s, 1H), 3.75 (d, $J = 5$ Hz, 1H), 3.74 (s, 3H), 3.38 (dd, $J = 5$, 0.7 Hz, 1H), 2.30 (d, $J = 1.3$ Hz, 3H), 1.22 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.81, 150.67, 147.92, 140.24, 129.60, 123.63, 119.78, 57.38, 51.30, 50.00, 45.60, 22.13, 16.19; IR (thin film) 2955, 2929, 2857, 1751, 1084 cm$^{-1}$; HRMS (ESI$^+$) m/z 389.1141 [calculated mass for C$_{17}$H$_{22}$N$_2$O$_5$S (M+Na)$^+$ 389.1141].
5.5b; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.09 (q, $J = 1.5$ Hz, 1H), 5.69 (h, $J = 1.3$ Hz, 1H), 4.14 (dd, $J = 8.1$, 7.1 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.74 (ddd, $J = 14.4$, 7.2, 1.3 Hz, 1H), 2.37 (ddd, $J = 14.4$, 8.1, 1.1 Hz, 1H), 2.20 (d, $J = 1.3$ Hz, 3H), 1.74 (d, $J = 1.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.86, 166.75, 155.80, 137.24, 117.22, 105.21, 52.26, 50.92, 46.61, 39.84, 18.87, 18.73.
REFERENCES

[29] Y. Heo, S.-M. Paek, Molecules 2013, 18, 9650.


