I. INCORPORATION OF FUNCTIONALITY AT THE $\beta$-POSITION FOR THE ZINC-MEDIATED CHAIN EXTENSION REACTION II. FORMAL SYNTHESIS OF HELIOTRIDANE AND PSEUDOHELIOTRIDANE THROUGH A ZINC-MEDIATED CHAIN EXTENSION APPROACH

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University of New Hampshire, Durham

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I. INCORPORATION OF FUNCTIONALITY AT THE β-POSITION FOR THE ZINC-MEDIATED CHAIN EXTENSION REACTION

II. FORMAL SYNTHESIS OF HELIOTRIDANE AND PSEUDOHELIOTRIDANE THROUGH A ZINC-MEDIATED CHAIN EXTENSION APPROACH

By

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B. S., Central Connecticut State University, 2016

DISSERTATION

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Doctor of Philosophy in Chemistry

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On November 23rd, 2021

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DEDICATION

I would like to dedicate this dissertation to my parents, grandparents, and my sister. I couldn’t have done this without you all!
ACKNOWLEDGEMENTS

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<td>AcOH</td>
<td>Acetic Acid</td>
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<tr>
<td>Boc</td>
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</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Et$_2$Zn</td>
<td>Diethylzinc</td>
</tr>
<tr>
<td>HRMS</td>
<td>High-resolution Mass Spectrometry</td>
</tr>
<tr>
<td>I$_2$</td>
<td>Iodine</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium Hexamethyldisilazide</td>
</tr>
<tr>
<td>LAH</td>
<td>Lithium Aluminum Hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium Diisopropylamide</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MeNH$_2$</td>
<td>Methylamine</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>NaH</td>
<td>Sodium Hydride</td>
</tr>
</tbody>
</table>
NaHMDS  Sodium Hexamethyldisilazide
NOESY  Nuclear Overhauser Effect Spectroscopy
NMR  Nuclear Magnetic Resonance
PAF  Platelet-activating Factor
PCC  Pyridinium Chlorochromate
Phth  Phthalimide
PPh$_3$  Triphenylphosphine
$i$-Pr  Isopropyl
PG  Protecting Group
RCM  Ring-closing Metathesis
SES  2-Trimethylsilylethanesulfonyl
TBAF  Tetra-$n$-butylammonium Fluoride
TBDPS  $t$-Butyldiphenylsilyl
TBS  $t$-Butyldimethylsilyl
TFA  Trifluoroacetic Acid
THF  Tetrahydrofuran
TIPS  Triisopropylsilyl
TMS  Trimethylsilyl
Ts  Tosyl
ABSTRACT

I. INCORPORATION OF FUNCTIONALITY AT THE β-POSITION FOR THE ZINC-MEDIATED CHAIN EXTENSION REACTION

II. FORMAL SYNTHESIS OF HELIOTRIDANE AND PSEUDOHELIOTRIDANE THROUGH A ZINC-MEDIATED CHAIN EXTENSION APPROACH

BY

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University of New Hampshire, December 2021

The zinc-mediated chain extension reaction has been previously developed to incorporate alkyl or aryl substituents at the β position of the chain-extended product. The incorporation of heteroatom functionality at the β position of the chain-extended product was demonstrated through the use of a functionalized zinc carbenoid species. Silyl ether-functionalized geminal diiodides were used in the chain extension reaction with low to modest yields. Optimization of the chain extension reaction was performed by modification of solvent, reaction temperature, reaction time, and addition of diiodide. The chain extension reaction was performed on several different
substrates, such as β-keto esters, β-keto amides, and β-keto phosphonates. Removal of the silyl group from γ-keto esters led to products which contained a cis-fused tetrahydrofuran-γ-lactone ring system. This new methodology is useful for the synthesis of β-functionalized γ-keto carbonyls. The methodology allows for the formation of the cis-fused tetrahydrofuran-γ-lactone ring system in two steps from commercially available β-keto esters.

Heliotridane is a natural product and a member of the pyrrolizidine alkaloid family. Heliotridane is a common target molecule for synthetic approaches, due to its simple structure. The formal synthesis of heliotridane and pseudoheliotridane was completed through the use of a zinc-mediated chain extension approach. Several different synthetic approaches were attempted, most of which encountered challenges during chain extension. A phthalimide protecting group was used to circumvent these challenges. The formal synthesis of heliotridane and pseudoheliotridane was accomplished in four steps, in 12% overall yield. This synthesis broadens the array of applications of the zinc-mediated chain extension reaction in natural product synthesis.
CHAPTER I

INTRODUCTION

Carbenoids

Carbenes are divalent carbon species that possess a lone pair of electrons.¹ This lone pair can have anti-parallel spins in a single orbital, which is referred to as singlet carbene. The lone pair can also have parallel spins in two different orbitals, which is referred to as triplet carbene. Carbene species are both electrophilic and nucleophilic in reactivity.² This duality is commonly referred to as ambiphilicity.² The lone pair of electrons allows for nucleophilicity, whereas an empty p-orbital allows for electrophilicity. The electronic state of carbenes can be tuned through modification of substituents on the carbene carbon. For example, substitution of electron-withdrawing groups enhances the stability of the singlet electronic state of carbenes.³ The term carbenoid has been suggested for intermediates which display similar reactivity as carbenes without being free divalent species.⁴ Carbenoid character has been found to be present in species that possess a metallated carbon atom which also possesses a leaving group bonded to the same carbon. The metal is usually an s-block metal or zinc.⁵ The leaving group is usually a halogen, but can also be an amine, or an ether.⁶ The similarities in reactivity between carbenes and carbenoids can be seen in Figure 1. One of the major differences between carbenes and carbenoids is in terms of stereocontrol. For example, the cyclopropanation of (Z)-2-butene using diphenylcarbene produces a mixture of diastereomers.⁷ However, the cyclopropanation of (Z)-2-butene using a lithium carbenoid produces only the cis diastereomer.⁷ Therefore, carbenoids and carbenes can differ in reactivity in some cases.
Zinc carbenoids use zinc as the metal source. The first zinc carbenoid was prepared by Emschwiller in 1929. One of the most well-known uses of zinc carbenoids is the Simmons-Smith reaction. The Simmons-Smith reaction uses diiodomethane and a zinc-copper couple to generate a zinc carbenoid which can be used to cyclopropanate alkenes stereoselectively. The zinc carbenoid that is generated is iodomethyl zinc iodide (IZnCH₂I). The Furukawa reagent (EtZnCH₂I) has also been developed for use in cyclopropanations. This zinc carbenoid is generated using diiodomethane and Et₂Zn as the zinc source. The Furukawa reagent was developed for cyclopropanation of vinyl ethers because Simmons-Smith conditions led to cationic polymerization. Denmark developed a bis(iodomethyl) zinc carbenoid using two equiv of diiodomethane relative to Et₂Zn. Several other zinc carbenoids have also been developed for use in cyclopropanation of alkenes. Charette has developed a zinc carbenoid which contains a phosphate group bonded to zinc. This carbenoid has been shown to be stable in solution for several days when stored at -20 °C. Shi has developed a zinc carbenoid which contains a trifluoroacetate group bonded to zinc. The trifluoroacetate acts as an electron-withdrawing group and greatly enhances the reactivity of the carbenoid. These examples of previously developed zinc carbenoids can be seen in Figure 2.
A zinc-mediated chain extension reaction was discovered in the Zercher research group in 1997. The original reaction that illustrated chain extension can be seen in Scheme 1. Initially, 1 was subjected to Furukawa conditions in an attempt to cyclopropanate the terminal alkenes of the ketal ring. Upon inspection of the spectroscopic data, an additional carbon was inserted in between the ketone and the ester, which led to the identification of 2 as the product. The chain extension involves the use of a zinc carbenoid that can be generated using Et₂Zn and diiodomethane. This reaction is used to convert β-dicarbonyls to γ-dicarbonyls. It can be used on several different substrates, such as β-keto esters 3, β-keto amides 5, β-keto phosphonates 7, β-keto imides 9, diimides 11, etc. The various substrates that have been used in the chain extension reaction can be seen in Scheme 2.
The yields of these reactions are generally good (>70%) and some examples can be seen in Table 1. The chemoselectivity of this reaction for each of these substrates is very good. Although zinc carbenoids are cyclopropanating reagents, the chain extension reaction can occur preferentially in the presence of some terminal and conjugated $E$-alkenes.\textsuperscript{15,16} This has been shown in both $\beta$-keto esters and $\beta$-keto amides. As for $\beta$-keto phosphonates, which appear to react more slowly than $\beta$-keto esters and $\beta$-keto amides, the chain extension reaction competes with cyclopropanation and leads to a mixture of products.\textsuperscript{17} The regioselectivity of this reaction is excellent. The carbenoid carbon is always inserted adjacent to the ketone of the substrate. The presence of substituents on the $\alpha$ position of $\beta$-keto esters leads to much lower yields of the corresponding $\gamma$-keto ester (around 20%).\textsuperscript{15} However, the products of these substrates have proven the incorporated methylene unit is adjacent to the ketone functionality. The reaction has also been done on cyclic $\beta$-keto esters.\textsuperscript{15} Cyclohexanone 13 was converted into 14 using chain extension conditions, as illustrated in Scheme 3.\textsuperscript{15} This reaction allowed for the conversion of a 6-membered ring into a 7-membered ring. Although the yield for the reaction was low (20%), methodology that allows for the formation of 7-membered rings is very useful.

**Scheme 2.** Substrates for the zinc-mediated chain extension reaction.
Table 1. Zinc-mediated chain extension reaction using diiodomethane.

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>OMe</td>
<td>81</td>
</tr>
<tr>
<td>Me</td>
<td>Or-Bu</td>
<td>74</td>
</tr>
<tr>
<td>CH₂=CH(CH₂)₂-</td>
<td>OMe</td>
<td>74</td>
</tr>
<tr>
<td>PhCH=CH-</td>
<td>OMe</td>
<td>68</td>
</tr>
<tr>
<td>Me</td>
<td>N(n-Bu)₂</td>
<td>70</td>
</tr>
<tr>
<td>Allyl</td>
<td>N(Bn)₂</td>
<td>70</td>
</tr>
</tbody>
</table>

Scheme 3. Ring expansion of α-carboethyloxy cyclohexanone.

The mechanism for this reaction is thought to occur in a stepwise fashion and can be seen in Scheme 4. The first step in the proposed mechanism is the formation of zinc enolate 15 by deprotonation of an α proton of β-keto esters 3 with Et₂Zn or EtZnCH₂I. Deprotonation of the starting β-keto ester is supported by the observation of ethane gas evolution. The second step in the mechanism is reaction of the zinc enolate with the carbenoid species to form an organometallic intermediate 16. The organometallic intermediate then undergoes ring closure to form cyclopropoxide zinc intermediate 17. This intermediate then undergoes ring opening to form a Reformatsky-type intermediate 18. The Reformatsky intermediate is dimeric in nature and is less
nucleophilic than a typical enolate. The dimeric structure of Reformatsky intermediate 18 can be seen in Scheme 4. Although the Reformatsky intermediate is dimeric in nature, the possibility of higher oligomeric states cannot be ruled out. The Reformatsky intermediate can be protonated to yield the chain-extended product 19.

![Scheme 4. Mechanism for the zinc-mediated chain extension reaction.](image)

This mechanism has been supported by NMR studies and computational evidence.\textsuperscript{18,19} Cyclopropoxide zinc intermediate 17 has never been observed by NMR, whereas zinc enolate 15 and Reformatsky-type intermediate 18 have been.\textsuperscript{17} The absence of the cyclopropane intermediate has been explained computationally.\textsuperscript{18} The energy barrier for the subsequent transition state is so low (4 kJ/mol) that the lifetime for any cyclopropane intermediate that is formed is very short.\textsuperscript{18} Another pathway has been proposed in which a cyclopropoxide zinc intermediate 17 never forms. In this pathway it is proposed that organometallic intermediate 16 is converted directly to the Reformatsky intermediate via a 1,2-shift.\textsuperscript{18} However, when solvation is taken into consideration the energy of the cyclopropane intermediate pathway is lower than the path without it.\textsuperscript{18} In solution, the reaction more than likely proceeds through a cyclopropane intermediate.
β-substituted zinc-mediated chain extension reaction

The chain extension has been performed with three different geminal diiodides. The diiodides that have been implemented are diiodomethane, 1,1-diiodoethane, and α,α-diiodotoluene. The carbon unit that is inserted between the carbonyls is dependent upon the geminal diiodide that is used. If diiodomethane is used, then a methylene is inserted. If 1,1-diiodoethane is used, then a methyl-substituted methine is inserted to form γ-keto esters 20. If α,α-diiodotoluene is used, then a phenyl-substituted methine is inserted to form γ-keto esters 21. The carbon unit is always inserted adjacent to the ketone of the β-dicarbonyl substrate. Some generic examples of these chain extension reactions can be seen in Scheme 5.

![Scheme 5](image)

Scheme 5. Zinc-mediated chain extension examples using β-keto esters as substrates.

There are several experimental differences between the β-substituted chain extensions and the chain extension reactions using diiodomethane. The order of reagent addition is dependent on the geminal diiodide that is used. When diiodomethane is used, β-keto substrates are added to a 0 °C solution of EtZnCH2I. When 1,1-diiodoethane or α,α-diiodotoluene is used, β-keto substrates are added to a 0 °C solution of Et2Zn in DCM, followed by the addition of the geminal diiodide. The reaction is then warmed to room temperature. It was found that the generation of the substituted zinc carbenoids first led to incomplete conversion of the starting material. Another
difference is that some β-keto substrates require the use of a second dose of carbenoid. This because the more substituted carbenoids are slower to react than the Furukawa carbenoid.\textsuperscript{20} This difference in reaction rate likely leads to decomposition of the carbenoid prior to chain extension. While the full extent of decomposition has not been explored, the zinc carbenoid can undergo reductive elimination, which leads to the formation of 2-iodobutane.\textsuperscript{20} The yields of the β-substituted chain extensions are generally good (>70%). Some specific examples of chain extensions using 1,1-diiodoethane that have been reported can be seen in Table 2.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{reaction_diagram}
\caption{Zinc-mediated chain extension reaction using 1,1-diiodoethane.}
\end{figure}

\begin{table}
\centering
\caption{Zinc-mediated chain extension reaction using 1,1-diiodoethane.}
\begin{tabular}{lll}
\hline
R & R' & Yield (%) \\
\hline
Me & OMe & 76 \\
Me & Or-Bu & 88 \\
Me & OAllyl & 74 \\
Ph & OEt & 84 \\
Me & N(Me)\textsubscript{2} & 67 \\
\hline
\end{tabular}
\end{table}

The use of substituted carbenoids leads to the creation of a stereogenic center in the chain-extended product. Previous attempts to perform this reaction enantioselectively have been met with limited success. Lin used \textit{N},\textit{N}-bis(methanesulfonyl) derivative \textsuperscript{24} catalytically in an attempt to influence the stereoselectivity of the chain extension reaction of methyl acetoacetate and 1,1-diiodoethane.\textsuperscript{21} The structure of \textit{N},\textit{N}-bis(methanesulfonyl) derivative \textsuperscript{24} can be seen in Figure 3. This reaction led to a racemic mixture of the corresponding methyl-γ-keto ester.\textsuperscript{21} Lin also synthesized a β-keto imide substrate \textsuperscript{25} that included an Evan’s auxiliary in an attempt to influence
the stereoselectivity of the chain extension reaction. No stereocontrol was observed in this chain extension reaction, which formed a 1:1 mixture of diastereomers of 26 (Scheme 6).

![Figure 3. N,N-bis(methanesulfonyl) derivative.](image)

**Figure 3.** N,N-bis(methanesulfonyl) derivative.

![Scheme 6. Evan’s auxiliary attempt at stereocontrol.](image)

**Scheme 6.** Evan’s auxiliary attempt at stereocontrol.

Mazzone was able to induce stereocontrol in the chain extension using L-serine derived β-keto esters 27. Diastereomeric ratios for γ-keto esters 28 of up to 20:1 were obtained. The reaction that Mazzone developed can be seen in Scheme 7. The primary amine was protected via a Boc group and the protecting group that was used on the hydroxyl was either a Bn group or a TBS group. The diastereomeric ratio was determined using 1H-NMR analysis of the diastereomeric mixture. However, the stereochemistry of the major diastereomer was never elucidated.

![Scheme 7. L-Serine auxiliary stereocontrol.](image)

**Scheme 7.** L-Serine auxiliary stereocontrol.
Tandem chain extension reaction

Reformatsky intermediate 18, which is formed during the course of the chain extension, can be reacted with several different electrophiles. As mentioned previously, protonation of this intermediate leads to the chain-extended product. However, reaction with different electrophiles leads to functionalization at the α position of the chain-extended product. A tandem chain extension-aldol reaction was developed which takes advantage of this reactivity. The tandem chain extension-aldol reaction process is performed in one-pot through the addition of an aldehyde to the Reformatsky intermediate. This methodology has been used in the formation of β-hydroxy esters 28, β-hydroxy amides 29, and β-hydroxy imides 30. The tandem chain extension-aldol reaction is illustrated in Scheme 8.

Scheme 8. Tandem chain extension-aldol reaction.

For the β-hydroxy esters 28, the yields ranged from 60% to 95%. The diastereomeric ratio ranged from 7:1 to >20:1. This reaction showed a preference for syn selectivity. Relative stereochemistry was determined by comparison of 1H-NMR coupling constants to literature values and by X-ray crystallography. For the formation of a β-hydroxy amide 29, only one example was reported with a yield of 46% and a diastereomeric ratio of 3:1. This reaction also showed a preference for syn selectivity, like the β-keto esters. Formation of the syn products may be due to a bias in formation of (Z)-zinc enolate 31 (Figure 4) through complexation with the nearby carbonyl of the ketone. The reaction has been used to form β-hydroxy imide 30 with a reported
yield of 60%. The \textit{anti} isomer was the only diastereomer isolated from the reaction mixture, which is in direct contrast to the β-keto esters and amides. This result is consistent with the Heathcock model which predicts that excess zinc counterions can affect stereochemical outcomes via an open transition state.  

![Figure 4](image-url) Proposed (Z)-zinc enolate.

The Reformatsky intermediate has also been used in a tandem chain extension-Mannich reaction. This tandem reaction has been developed for use with activated imines as electrophiles. Deprotection of the β-amino ester, followed by imine reduction leads to the formation of β-proline derivatives. The reaction was performed using a diphenylphosphinoyl group and a Boc group as activating groups. The reactions that were performed, which used methyl pivaloyl acetate (32) as the starting β-keto ester, that were performed can be seen in Scheme 9.

![Scheme 9](image-url) Examples of tandem chain extension-Mannich reactions.
The reaction using diphenylphosphinoyl imine 33 proved to be problematic. Reaction times for nucleophilic addition of the imine were long (48 h) and 34 was obtained in only 27% yield.\textsuperscript{24} However, a diastereomeric ratio 10:1 was achieved with a preference for syn selectivity.\textsuperscript{24} An activated imine containing a Boc group (35) was also used as an electrophile. This reaction proceeded much quicker than the diphenylphosphinoyl group, however it was still relatively slow (15 h).\textsuperscript{24} The reaction was performed using several different aryl substituents on the imine. When the reaction was performed with a phenyl group on the imine the yield of 36 was 52%.\textsuperscript{24} The diastereomeric ratio for this reaction was only 4:1, but it favored the formation of the anti diastereomer.\textsuperscript{24} Both the diphenylphosphinoyl and the Boc groups were removed in the subsequent step. The diphenylphosphinoyl group was removed using SOCl\textsubscript{2} in MeOH. The Boc group was removed using TFA.\textsuperscript{24} These deprotections led to the formation of cyclic imines which were reduced with NaBH\textsubscript{3}CN to form β-proline derivatives.\textsuperscript{24} The relative stereochemistry of the final β-proline product can be tuned based upon the activating group that is used on the imine.

A tandem chain extension-oxidation/elimination method has also been developed for the synthesis of α,β-unsaturated γ-keto esters 37 and amides 38.\textsuperscript{25} The method first uses the chain extension conditions followed by addition of I\textsubscript{2} as an electrophile. This leads to the formation an α-iodo ester 39. The reaction was also attempted with several different bromine sources for the halogenation step. Both N-bromosuccinimide and 1,2-dibromoethane were unsuccessful and led to the formation of the saturated γ-keto ester 4, which is the typical chain-extended product of the EtZnCH\textsubscript{2}I carbenoid.\textsuperscript{25} Therefore, treatment with I\textsubscript{2} was utilized. Excess I\textsubscript{2} is quenched by addition of saturated Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution. DBU is added as a base to deprotonate α-iodo ester 39, which eliminates the iodide and forms the α,β-unsaturated product. An additional base, Et\textsubscript{3}N, was also
implemented. However, this led to isolation of $\alpha$-iodo ester 39 and saturated $\gamma$-keto ester 4.\textsuperscript{25} The scheme for the optimized reaction and proposed intermediates can be seen in Scheme 10.

![Scheme 10](image)

**Scheme 10.** Tandem chain extension-oxidation/elimination reaction and proposed intermediates.

The tandem chain extension-oxidation/elimination was performed with a number of different $\beta$-keto esters with yields ranging from 59% to 86%.\textsuperscript{25} The reaction was also performed in the presence of a terminal alkene, and the $\alpha,\beta$-unsaturated $\gamma$-keto ester product was obtained in 71% yield without observation of cyclopropanation or iodination of the alkene.\textsuperscript{25} The reaction was also performed on a $\beta$-keto amide, and the $\alpha,\beta$-unsaturated $\gamma$-keto amide was obtained in 63% yield.\textsuperscript{25} In all cases, the reaction exhibited $E$-selectivity. There was no evidence of $Z$-alkene formation in any of the reactions.\textsuperscript{25} The reaction was also attempted on several amino-acid derived $\beta$-keto esters and amides. When monoprotected amino acid derivatives were used, the reaction resulted in a complex reaction mixture and a very low yield of product. Benzyl protection of the nitrogen increased the purity of the reaction mixture and lead to modest yields ($> 60\%$).\textsuperscript{25} Chiral HPLC analysis showed that the products of the reaction that contained stereogenic centers were racemic mixtures.\textsuperscript{25} This means that during the elimination step of the reaction sequence the stereogenic centers undergo epimerization.
A tandem chain extension-homoenolate formation reaction has also been developed for the synthesis of α-methyl γ-keto esters 41 and amides 42. These products were previously inaccessible through the chain extension of α-methyl β-keto esters. The tandem reaction first exposes the β-keto substrate to chain extension reaction conditions, which contains excess carbenoid. A catalytic amount of TMSCl is added to the reaction mixture shortly after exposure of the β-keto substrate to the carbenoid. The amount of TMSCl that was added was varied from 10-80 mol %, with no change observed in the product mixture. The reaction takes advantage of Reformatsky intermediate 18 of the chain extension, much like previous tandem reactions. The reaction is proposed to proceed through the TMS-ether cyclopropane 42. However, 42 could also exist as the TMS-ketene acetal. Intermediate 42 could then ring open via reaction with an equivalent of carbenoid to form zinc homoenolate 43. The reaction can be quenched with a proton source to provide the product. The reaction can also be quenched with a source of deuterium to incorporate a –CH₂D group. The scheme for this reaction and proposed intermediates can be seen in Scheme 11.

**Scheme 11.** Tandem chain extension-homoenolate formation and proposed intermediates.
The reaction was done using several $\beta$-keto esters, with yields ranging from 57% to 73%. The yields for the reactions were not affected by steric bulk or by the presence of aromatic substituents. The reaction was also performed on a tertiary $\beta$-keto amide. Although only one example was reported, the reaction proceeded efficiently, and the yield was 53%. When a secondary amide was subjected to these reaction conditions, the major product was the unmethylated $\gamma$-keto amide. $\alpha$-Methyl $\gamma$-keto amide 41 was also formed but in a small amount (1:3 relative to the unmethylated $\gamma$-keto amide). The reasoning behind this result is that the secondary $\beta$-keto amide’s hydrogen is able to quench the Reformatsky intermediate prior to reaction with TMSCl. In all cases, a minor amount of the unmethylated $\gamma$-keto ester was observed in the crude reaction mixture. This is presumably due to quenching of Reformatsky intermediate 18, possibly due to a trace amount of water in the reaction mixture.

**Natural product synthesis**

The $\gamma$-keto ester structural moiety can be found within several different natural products. This structural moiety can also be converted to other functionality found in natural products. Therefore, the zinc-mediated chain extension methodology has been used in the syntheses of several different natural products. The zinc-mediated ring expansion reaction has been applied to a formal synthesis of (+)-brefeldin A. (+)-Brefeldin A is a natural product that was originally isolated from several fungi in 1958 by Singleton, and its structure was elucidated in 1971 by Higgs. (+)-Brefeldin A has been shown to have antiviral properties and has also been shown to inhibit protein transport within cells. The structure of (+)-brefeldin A (Figure 5) contains a 13-membered macrocyclic lactone and 5 stereogenic centers. The structure also contains two $E$-alkenes within the macrocycle.
The structural moiety that is relevant to ring expansion methodology is the γ-oxygenated α,β-unsaturated lactone. A ring expansion of lactone 44 using EtZnCH₂I, followed by oxidation/elimination using I₂ and DBU can be used to form lactone 45 (Scheme 12). The 12-membered lactone 44 was formed using a RCM with Grubbs first generation catalyst. This led to the formation of E and Z alkene stereochemistry in a ratio of 7:2, respectively. The Z-alkene could be converted to the E-alkene through reaction with thiophenol in the presence of azobisisobutyronitrile at 80 °C. The zinc-mediated ring expansion of lactone 44 was performed using 7.5 equiv of EtZnCH₂I in two separate doses. Lactone 44 was initially reacted with 5 equiv of the carbenoid, and after 30 minutes a second dose of 2.5 equiv of carbenoid was added. This was to ensure complete conversion of the lactone starting material. Once ring expansion was complete, an excess of I₂ (14 equiv) was added to trap the Reformatsky intermediate. Elimination of iodide and formation of the α,β-unsaturated system was performed using DBU. This led to the formation of lactone 45 in 46% yield. The newly formed double bond showed E stereochemistry exclusively. Conversion of lactone 45 to (+)-brefeldin A has been previously reported in the literature, so its formation constituted a formal synthesis of (+)-brefeldin A.

Figure 5. Structure of (+)-brefeldin A.
The zinc-mediated ring expansion reaction has also been applied to the total synthesis of both (+)-patulolide A and patulolide B.\textsuperscript{32} Patulolides A and B are natural products and were initially isolated in 1986 by Yamada and co-workers.\textsuperscript{33} Both patulolide A and patulolide B have been shown to possess antifungal, antibacterial, and anti-inflammatory properties.\textsuperscript{33} The structures for (+)-patulolide A and (-)-patulolide B can be seen in Figure 6. Both (+)-patulolide A and patulolide B are 12-membered macrocyclic lactones. Both contain one stereogenic center and one alkene. Patulolides A and B differ at the stereochemistry of the alkene. Patulolide A has $E$ stereochemistry, whereas patulolide B has $Z$ stereochemistry. (+)-Patulolide A and (-)-patulolide B also have the same configuration at their respective stereogenic centers.

The structural moiety that is relevant to ring expansion methodology is the $\alpha,\beta$-unsaturated $\gamma$-keto ester in the macrocycle. A ring expansion of lactone 46 using EtZnCH$_2$I, followed by oxidation/elimination using I$_2$ and DBU can also be used to form both natural products. The reactions that were done in the reported total syntheses of (+)-patulolide A and patulolide B can
be seen in Scheme 13. The 11-membered lactone ring system was synthesized with a RCM reaction using Grubbs first generation catalyst. This led to the formation of an unsaturated lactone with Z-alkene stereochemistry exclusively. The alkene was then reduced using catalytic hydrogenation (H\textsubscript{2}, Pd/C) to form lactone 46. Lactone 46 was then exposed to typical chain extension conditions (DCM, 0 °C) and was also heated to reflux in DCM. However, both sets of conditions led to recovery of lactone 46. The reaction was attempted in benzene, as well, and the ring expansion proceeded at room temperature. Benzene has been shown to increase the rate of the chain extension reaction. Patulolide B has been shown to be the more stable of the two isomers. The ring expansion-oxidation/elimination of 46 led to the formation of racemic patulolide B in 66% yield. The isolation of the more stable isomer (patulolide B) indicates that this reaction operated under thermodynamic control. The elimination step was also done under kinetic control, where enantiomerically pure lactone 47 led to the formation of (+)-patulolide A as a single isomer in 48% yield.

Scheme 13. Syntheses of (+)-patulolide A and patulolide B.
Another set of syntheses which used chain extension methodology as a key step are the formal syntheses of CJ-12,954 and CJ-13,014. These syntheses specifically use the tandem chain extension-aldol methodology.\textsuperscript{34} CJ-12,954 and CJ-13,014 were two of seven 5,7-dimethoxyphthalide antibiotics isolated from fungi by Dekker, which demonstrated potent antibacterial activity.\textsuperscript{35} The enantiomers of CJ-12,954 and CJ-13,014 have been synthesized by Brimble and Bryant (Figure 7).\textsuperscript{36} CJ-12,954 and CJ-13,014 contain a 5,5-spiroacetal ring system which is connected to a 5,7-dimethoxyphthalide ring through a polymethylene chain. Both CJ-12,954 and CJ-13,014 contain four stereogenic centers and are diastereomers relative to one another with opposite stereochemistry at the spirocyclic carbon.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{Previously synthesized enantiomers of CJ-12,954 and CJ-13,014.}
\end{figure}
The structural moiety of interest is the spiroacetal ring system. The formal synthesis of the natural products CJ-12,954 and CJ-13,014 with natural stereochemistry was the goal of this synthesis. The spiroacetal targets (48a, 48b) of this synthesis can be seen in Figure 8. Spiroacetals 48a and 48b have opposite stereochemistry as previously synthesized spiroacetals. A tandem chain extension-aldol reaction was used as a key step in the synthesis of these spiroacetals.34 The reaction that was done can be seen in Scheme 14. The starting material for this chain extension was β-keto imide 49. β-Keto imide 49 contained a chiral auxiliary which allows for the aldol reaction to be done asymmetrically with aldehyde 50 as the electrophile. This reaction led to the formation of β-hydroxy imide 51, which was in equilibrium with its hemiacetal isomer 52, in 44% yield.34 The major isomer of β-hydroxy imide 51 that was formed had anti stereochemistry.34 The next step in the synthesis was spirocyclization of the hemiacetal. Camphorsulfonic acid was used to form the spiroacetal ring system.34 The chiral auxiliary was removed using LiOH/H₂O₂ to afford the carboxylic acid.34 The carboxylic acid groups were removed using Barton decarboxylation conditions to form spiroketals 48a and 48b.34 This resulted in a successful formal synthesis of CJ-12,954 and CJ-13,014 with natural stereochemistry.

Figure 8. Spiroacetal targets for the formal synthesis CJ-12,954 and CJ-13,014.
Summary

The zinc-mediated chain extension reaction is a highly-efficient method for the conversion of β-dicarbonyls to γ-dicarbonyls. The reaction can also be done using several geminal diiodides to yield β-substituted γ-dicarbonyls. The geminal diiodides that have been implemented thus far are: diiodomethane, 1,1-diiodoethane, and α,α-diiodotoluene. The reaction presumably occurs via a donor-acceptor cyclopropane intermediate which undergoes ring-opening to form a Reformatsky-type intermediate. The Reformatsky intermediate has been utilized for several post-chain extension modifications, including aldol reactions, Mannich reactions, oxidation/eliminations, and homoenolate formation. The zinc-mediated chain extension reaction has also been used in the synthesis of natural products, such as (+)-brefeldin A, (+)-patulolid A, patulolid B, CJ-12,954, and CJ-13,014. The development of zinc-mediated chain extension reactions using functionalized geminal diiodides will be introduced in the next chapter. The formal
synthesis of heliotridane and pseudoheliotridane using a zinc-mediated chain extension approach will be discussed in the third chapter.
CHAPTER II

INCORPORATION OF FUNCTIONALITY AT THE β-POSITION FOR THE ZINC-MEDIATED CHAIN EXTENSION REACTION

Functionalized geminal diiodide syntheses

Several different variations of the zinc-mediated chain extension reaction have been developed.¹⁵, ²⁰ Methods have been developed to add substituents to both the α and β positions of the chain-extended product 4. The α and β positions of the chain-extended product 4 can be seen in Figure 9. Tandem chain extensions have been used to incorporate several different substituents at the α position, such as hydroxymethyl groups, aminomethyl groups, methyl groups, halogens, etc.²³-²⁶ The addition of functionality at the α position has been studied extensively. Substituted zinc carbenoids have also been used to incorporate a methyl or a phenyl substituent at the β position using 1,1-diiodoethane and α,α-diiodotoluene.²⁰

![Figure 9](image)

**Figure 9.** α and β positions of the chain-extended product.

However, functionalized zinc carbenoids have not been developed to incorporate heteroatom functionality at the β position previously. Therefore, there is a need for the development of a functionalized zinc carbenoid for use in the zinc-mediated chain extension reaction. The formation of a functionalized zinc carbenoid requires the synthesis of functionalized geminal diiodides, followed by reaction with \( \text{Et}_2\text{Zn} \).
There are several different methods that have been developed to synthesize functionalized geminal diiodides. Barton developed hydrazone iodination, which is a method that converts hyrazones 53 to the corresponding geminal diiodides 54.\textsuperscript{37} The reaction has also been used to generate vinyl iodides. This method can be seen in Scheme 15. This method reacts a hydrazone with I\textsubscript{2} in the presence of a non-nucleophilic base, such as Et\textsubscript{3}N, DBU, or a strong guanidine base.\textsuperscript{37,38} Hyrazones can be easily made from the corresponding aldehyde and N\textsubscript{2}H\textsubscript{4}-H\textsubscript{2}O. Hyrazones derived from ketones can also be used with this method, however they mainly lead to the formation of vinyl iodides rather than geminal diiodides.\textsuperscript{37,38}

\begin{align*}
\text{H}_2\text{N} & \quad \text{I}_2, \text{Base} \\
\text{R} & \quad \rightarrow \\
\text{N} & \quad \text{I} \\
\text{H} & \quad \text{I} \\
\text{R} & \quad 53 \\
\end{align*}

Scheme 15. Hydrazone iodination.

The conversion of triflylacetals and geminal dichlorides to the corresponding geminal diiodides has also been reported using various metal iodides. The conversion of triflylacetals to geminal diiodides was initially reported by Martinez and co-workers.\textsuperscript{39} The reactions of several different triflylacetals 55 with MgI\textsubscript{2} in the presence of CS\textsubscript{2} and TiCl\textsubscript{4} led to geminal diiodides 54 in yields ranging from 68 to 80%.\textsuperscript{39} This reaction can be seen in Scheme 16. The conversion of geminal dichlorides to the corresponding geminal diiodides has been reported using several different reagents, such as AlCl\textsubscript{3}/EtI, FeCl\textsubscript{3}/NaI, and AlI\textsubscript{3}.\textsuperscript{40-42}

\begin{align*}
\text{OSO}_2\text{CF}_3 & \quad \text{MgI}_2, \text{CS}_2, \text{TiCl}_4 \\
\text{R} & \quad \rightarrow \\
\text{OSO}_2\text{CF}_3 & \quad \text{DCM, 0 °C} \\
\text{R} & \quad \text{I} \\
\text{I} & \quad 54 \\
\end{align*}

Charette has developed several different methods for the synthesis of functionalized geminal diiodides. One method utilizes a trisubstituted geminal diiodoalkene \textit{56} which is reduced with the diazene derived from \textit{57}.\textsuperscript{43} This method can be seen in Scheme 17. This method was shown to be tolerant of several different functional groups, such as benzyl ethers, carbamates, esters, hydroxyl groups, silyl ethers, nitro groups, etc.\textsuperscript{43} The yields of these reactions ranged from 55\% to 91\% with >95\% conversion of starting material.\textsuperscript{43}

\begin{center}
\begin{tikzpicture}
  \node [circular, rotate=90, draw] (56) at (0, 0) \textit{56};
  \draw [->] (56) -- node [midway, above] {\textit{57}} (0, 1);
  \draw [->] (0, 1) -- node [midway, above] {\textit{54}} (0, 2);
  \node [right, rotate=90] at (0, 1) {\textit{o-xylene, reflux}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 17.} Geminal diodoalkene diazene reduction.

Another method that has been developed by Charette uses NaHMDS and diiodomethane to generate NaCHI$_2$, followed by reaction with alkyl iodides \textit{58}.\textsuperscript{44} This method can be seen in Scheme 18. This method was demonstrated to be compatible with alkenes, silyl ethers, benzyl ethers, esters, and carbamates.\textsuperscript{44} The yields for this reaction ranged from 55 to 91\% with complete conversion of starting material.\textsuperscript{44} One drawback of this reaction is that it requires five equiv of NaHMDS and diiodomethane, which would make it difficult to synthesize geminal diiodides on a large scale. The reaction can also be performed using benzylic or allylic bromides and LiHMDS and diiodomethane.\textsuperscript{44}

\begin{center}
\begin{tikzpicture}
  \node [circular, rotate=90, draw] (58) at (0, 0) \textit{58};
  \draw [->] (58) -- node [midway, above] {\textit{NaHMDS, CH$_2$I$_2$}} (0, 1);
  \draw [->] (0, 1) -- node [midway, above] {\textit{THF/Et$_2$O (1:1)}} (0, 2);
  \draw [->] (0, 2) -- node [midway, above] {-78 $^\circ$C to rt} (0, 3);
\end{tikzpicture}
\end{center}

\textbf{Scheme 18.} Diiodomethane alkylation of alkyl iodides.
**Functionalized zinc carbenoids and their use in cyclopropanations**

Functionalized geminal diiodides have been used to generate functionalized zinc carbenoids. These carbenoids have been used in cyclopropanations of alkenes. Charette reported the use of zinc carbenoids which also contain allylic hydroxyl groups in intramolecular Simmons-Smith cyclopropanations.\(^{45}\) This reaction led to the formation of bicyclic [n.1.0] ring systems \(^{59}\). The reaction that was done can be seen in Scheme 19. The reaction uses Et\(_2\)Zn to generate the zinc carbenoid, and the reaction was optimized in DCM at 0 °C.\(^ {45}\) Charette was able to demonstrate that the presence of allylic directing groups led to facial selectivity of the intramolecular cyclopropanations. These reactions were done using geminal diiodides \(^{60}\) with several different functional groups (-OR), such hydroxyl groups, benzyl ethers, cyclic acetals, silyl ethers, and carbamates.\(^ {45}\) The yields of the bicyclic [n.1.0] ring systems varied drastically based on the directing group that was used. Yields ranged from 19 to 89% with the only difference being the directing group.\(^ {45}\)

![Scheme 19. Diastereoselective intramolecular cyclopropanation.](image)

There are a limited number of functionalized zinc carbenoids being used in intermolecular cyclopropanations of alkenes. Charette reported cyclopropanations using silyl ether-functionalized geminal diiodides.\(^ {46}\) This method led to the formation of functionalized cyclopropanes \(^{61}\) and \(^{62}\). Charette formed a functionalized zinc carbenoid using diiodide \(^{63}\) and Et\(_2\)Zn. The cyclopropanation reactions were done on cinnamyl alcohol \(^{64}\) and allyl alcohol \(^{65}\). These reactions can be seen in Scheme 20. The substituted cyclopropanes were obtained in good yields (>70%).\(^ {46}\) The addition of chiral dioxaborolane ligand \(^{66}\) allowed for stereocontrol of the cyclopropanation
which led to an enantiomeric excess greater than 95% for both cyclopropanations. These reactions were the first examples of a functionalized zinc carbenoid being used in cyclopropanations of alkenes.

Scheme 20. OTIPS-functionalized zinc carbenoid cyclopropanations.

Functionalized zinc carbenoids have also been formed from orthoformate 67. The deoxygenation of orthoformate 67 to zinc carbenoid 68 was reported using zinc and TMSCl. In the presence of alkene 69, this led to the generation of cyclopropane products 70a and 70b. This method allows for the formation of alkoxy-substituted cyclopropanes. An example of this type of cyclopropanation can be seen in Scheme 21. The reaction proceeded in 55% yield with a 3:1 ratio of cis and trans isomers.

Scheme 21. Functionalized zinc carbenoid derived from orthoformates.
Synthesis of functionalized geminal diiodides

The synthesis of a variety of novel geminal diiodides was accomplished using Barton’s method of hydrazone iodination. Several different functionalized aldehydes were required to be made as starting material for hydrazone iodination. The first set of functionalized aldehydes that were made all contained a protected hydroxyl group. The initial step in the synthesis of these aldehydes was monoprotection of either 1,3-propanediol (71) or 1,4-butanediol (72). The protecting groups that were introduced and the reaction yields can be seen in Table 3.

![Diagram](image)

Table 3. Monoprotection of 1,3-propanediol and 1,4-butanediol.

<table>
<thead>
<tr>
<th>Diol</th>
<th>Product</th>
<th>R</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>71</td>
<td>73</td>
<td>OTBS</td>
<td>TBSCI, Et$_3$N, DCM, 0 °C to rt</td>
<td>87</td>
</tr>
<tr>
<td>72</td>
<td>74</td>
<td>CH$_2$OTBS</td>
<td>TBSCI, Et$_3$N, DCM, 0 °C to rt</td>
<td>94</td>
</tr>
<tr>
<td>71</td>
<td>75</td>
<td>OTBDPS</td>
<td>TBDPSCI, Et$_3$N, DCM, rt</td>
<td>79</td>
</tr>
<tr>
<td>71</td>
<td>76</td>
<td>OTIPS</td>
<td>TIPSCI, NaH, THF, 0 °C to rt</td>
<td>42</td>
</tr>
<tr>
<td>71</td>
<td>77</td>
<td>OBn</td>
<td>BnBr, NaH, THF, reflux</td>
<td>50</td>
</tr>
</tbody>
</table>

The protecting groups mainly consisted of silyl ethers: OTBS, OTBDPS, and OTIPS (73, 74, 75, and 76). These protecting groups were chosen in accordance with the OTIPS-functionalized cyclopropanations previously reported by Charette.$^{46}$ A Bn protecting group (77) was also
introduced as it would allow for deprotection by catalytic hydrogenation in a future step. The protection reactions were all based on previously reported literature procedures. The reaction yields ranged from 42 to 94%. The protection reactions that used NaH as base led to lower yields. These yields were presumably lower due to the formation of a large amount of the diprotected by-products, which were observed in the crude $^1$H NMR of the reaction mixtures and by TLC analysis. The yields could potentially be increased by using a lower equivalence of TIPSCI or BnBr (< 1 equiv). The yields of 76 and 77 that were obtained were sufficient for carrying out the remainder of the syntheses.

![Oxidation of monoprotected diols to the corresponding aldehydes.](image)

**Table 4.** Oxidation of monoprotected diols to the corresponding aldehydes.

<table>
<thead>
<tr>
<th>Monoprotected Diol</th>
<th>Product</th>
<th>R</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>78</td>
<td>OTBS</td>
<td>DMP, NaHCO$_3$, DCM, 0 °C to rt</td>
<td>76</td>
</tr>
<tr>
<td>74</td>
<td>79</td>
<td>CH$_2$OTBS</td>
<td>DMP, DCM, rt</td>
<td>62</td>
</tr>
<tr>
<td>75</td>
<td>80</td>
<td>OTBDPS</td>
<td>DMP, DCM, 0 °C to rt</td>
<td>61</td>
</tr>
<tr>
<td>76</td>
<td>81</td>
<td>OTIPS</td>
<td>DMP, DCM, 0 °C to rt</td>
<td>56</td>
</tr>
<tr>
<td>77</td>
<td>82</td>
<td>OBn</td>
<td>DMP, DCM, 0 °C to rt</td>
<td>75</td>
</tr>
</tbody>
</table>
The monoprotected diols were oxidized to the aldehydes with DMP oxidation. The oxidation conditions as well as reaction yields can be seen in Table 4. The oxidation reactions were all based on previously reported literature procedures.\textsuperscript{49, 52-54} In all cases, fair to good yields were obtained with reaction times \( \leq 4 \) h. DMP oxidation was chosen as the oxidative methodology due to its mild and convenient reaction conditions. For the formation of aldehyde \textsuperscript{78}, \( \text{NaHCO}_3 \) was added as a buffer to neutralize any formation of acetic acid in the reaction mixture.\textsuperscript{52} This addition was done to prevent potential TBS removal under the mildly acidic conditions, although this was determined not to be necessary for the reaction to proceed efficiently. The DMP oxidation to form aldehyde \textsuperscript{79} did not require the use of \( \text{NaHCO}_3 \).\textsuperscript{53}

\[ \text{Scheme 22. Attempted synthesis of phthalimide-protected geminal diiodide 86.} \]

Several additional geminal diiodides containing protected amines were also synthesized for use in the zinc-mediated chain extension reaction. It was initially questioned whether a phthalimide-protected diiodide (86) could be synthesized using hydrazone iodination. Hydrazine is known to remove phthalimide groups, so hydrazone formation could be problematic.\textsuperscript{55} The first attempt at synthesizing geminal diiodide 86 can be seen in Scheme 22. The initial step in this synthesis was phthalimide protection of 2-aminoethanol (83) which gave 84 in 66\% yield.\textsuperscript{56} The second step was an Appel reaction, which used PPh\textsubscript{3} and I\textsubscript{2} in the presence of imidazole. This converted the primary alcohol to the primary iodide (85) in 88\% yield.\textsuperscript{57} The final step was an
attempted alkylation of diiodomethane using the conditions described by Bull and Charette.\textsuperscript{44} However, only starting material was observed in the $^1$H NMR of the crude reaction mixture. The reaction was attempted a second time, but a brown sludge was obtained and the $^1$H NMR of the crude reaction mixture indicated decomposition of starting material and no presence of product.

![Chemical structure](image)

**Table 5.** Amine protection of 3-aminopropanol (87).

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R’</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>Ts</td>
<td>H</td>
<td>TsCl, Et\textsubscript{3}N,</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DCM, 0 °C to rt</td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>Phth</td>
<td></td>
<td>Phthalic anhydride, Et\textsubscript{3}N, Toluene, reflux</td>
<td>62</td>
</tr>
</tbody>
</table>

A hydrazone iodination synthetic approach was envisioned for use in synthesis of diiodides containing protected amines. The protecting groups that were introduced along with reaction yields can be seen in Table 5. 3-Aminopropanol (87) was monoprotected with a Ts group using TsCl in the presence of Et\textsubscript{3}N and 88 was obtained in 83\% yield.\textsuperscript{58} Only amine protection was observed; there was no evidence of $O$-tosylation. The amine of 3-aminopropanol (87) was also diprotected using a phthalimide protecting group. The phthalimide was introduced using the same conditions as the synthesis of 84, which gave 89 with a yield of 62\%.\textsuperscript{59}
The primary alcohols (88 and 89) were then oxidized to the aldehyde using DMP or the Swern oxidation.\textsuperscript{60,61} The yields and reaction conditions can be seen in Table 6. Oxidation of 88 using DMP led to a product mixture that required a difficult separation of the aldehyde and an unidentified by-product of the oxidative method (which was presumably iodosobenzoic acid (IBA)). A residual amount of impurity (<1%) remained with 88 even after column chromatography; therefore, the Swern oxidation was employed in an attempt to obtain pure aldehyde 90.\textsuperscript{61} The Swern oxidation did make the purification of aldehyde 90 easier, but led to a substantially lower yield. It was also observed that aldehyde 88 was unstable and would decompose over the course of several days, even when stored at 4 °C. The DMP oxidation of 89 worked well and gave aldehyde 91 in 91% yield.\textsuperscript{62}
The aldehydes that were synthesized were then subjected to hydrazone formation reaction conditions. The yields for each of these reactions can be seen in Table 7. Each of the aldehydes were reacted with 2 equiv of N$_2$H$_4$∙H$_2$O for 30 min to ensure complete conversion of aldehyde.$^{63}$ However, only 1 equiv of N$_2$H$_4$∙H$_2$O was used for the reaction with aldehyde 91 and the reaction was only run for 15 min. This was done to prevent potential phthalimide removal.$^{55}$ No removal of the phthalimide group was observed in the crude $^1$H NMR after work-up. In all cases, the reaction produced a mixture of hydrazone stereoisomers. Both the $E$ and $Z$ isomers of the hydrazones were observed, with the $E$ isomer being the predominant isomer in the mixture.$^{64}$ The hydrazones were also observed to be unstable, with dimerization to form the azine taking place within minutes of reaction completion. Therefore, the hydrazones were all used in the subsequent iodination step without purification due to their instability.
Hydrazone iodination was performed on hydrazone $92a$, $92b$ using I$_2$ in the presence of Et$_3$N. This led to a 5:2 mixture of geminal diiodide $99$ and mono-iodide, respectively. This mixture of products was inseparable by chromatography. The iodination was then attempted using I$_2$ in the presence of DBU. Upon addition of I$_2$, a large amount of gas evolution was observed, presumably the formation of N$_2$. These conditions led to the formation of the geminal diiodide with the presence of a minor amount of vinyl iodide impurity. The amount of vinyl iodide could be minimized by changing the equivalents of base used. The results of this optimization can be seen in Table 8. The optimized reaction conditions were then applied in the iodination of the other functionalized hydrazones. The yields of these reactions can be seen in Table 9. The iodinations of the hydrazones containing protected alcohols all proceeded in yields consistent with literature values. The yields for the protected amines were substantially lower. However, these diiodides were isolated in suitable quantity for use in the zinc-mediated chain extension reaction.
Table 9. Hydrazone iodination to form functionalized geminal diiodides.

<table>
<thead>
<tr>
<th>Hydrazone</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>92a, 92b</td>
<td>99</td>
<td>OTBS</td>
<td>47</td>
</tr>
<tr>
<td>93a, 93b</td>
<td>100</td>
<td>CH$_2$OTBS</td>
<td>41</td>
</tr>
<tr>
<td>94a, 94b</td>
<td>101</td>
<td>OTBDPS</td>
<td>47</td>
</tr>
<tr>
<td>95a, 95b</td>
<td>63</td>
<td>OTIPS</td>
<td>47</td>
</tr>
<tr>
<td>96a, 96b</td>
<td>102</td>
<td>OBn</td>
<td>46</td>
</tr>
<tr>
<td>97a, 97b</td>
<td>103</td>
<td>NHTs</td>
<td>30</td>
</tr>
<tr>
<td>98a, 98b</td>
<td>86</td>
<td>NPhth</td>
<td>18</td>
</tr>
</tbody>
</table>
Zinc-mediated chain extensions using functionalized geminal diiodides

![Reaction Scheme]

Table 10. Optimization of chain extension reaction using diiodide 99.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCM</td>
<td>0 °C</td>
<td>26</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCM</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCE</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>37</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Toluene</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hexanes</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>27</td>
</tr>
<tr>
<td>7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DCE</td>
<td>0 °C to 50 °C&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>8&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>DCM</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33</td>
</tr>
<tr>
<td>9&lt;sup&gt;e&lt;/sup&gt;</td>
<td>DCM</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16</td>
</tr>
<tr>
<td>10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>DCM</td>
<td>0 °C to rt&lt;sup&gt;b&lt;/sup&gt;</td>
<td>43</td>
</tr>
</tbody>
</table>

<sup>a</sup>) Reaction was performed on a 0.15-mmol scale for 1 h, reaction used 5 equiv of Et<sub>2</sub>Zn and diiodide 99 relative to 104a.  
<sup>b</sup>) Diiodide 99 was added at 0 °C, then the mixture was warmed to rt.  
<sup>c</sup>) Diiodide 99 was added at 0 °C, then the reaction was cautiously heated to 50 °C.  
<sup>d</sup>) Diiodide 99 was added via syringe pump.  
<sup>e</sup>) Reaction was run for 30 min.  
<sup>f</sup>) Reaction was run for 2 h.

The chain extension reaction using diiodide 99 was attempted on methyl acetoacetate (104a) and optimized by modification of solvent, reaction temperature, and reagent addition. The optimization conditions can be seen in Table 10. The reaction was initially run in DCM at 0 °C, however this led to a much lower yield than subsequent reactions in which the mixture was warmed.
to rt after addition of diiodide 99 (Entry 1). The solvent used for the chain extension reaction was then modified. The reaction worked well in chlorinated solvents, DCM and DCE (Entries 2 and 3). The reaction was also attempted in other common solvents, such as toluene, Et$_2$O, and hexanes. However, the yields for these chain extensions were lower than those obtained when using DCM and DCE (Entries 4, 5, and 6). The chain extension reaction has been reported to proceed efficiently in benzene, however this solvent choice was omitted due to benzene’s carcinogenic properties.$^{32,66}$ Higher reaction temperatures were also investigated. DCE was chosen as a reaction solvent, due to it having a higher boiling point than DCM (83 ºC). The reaction mixture was cautiously heated to 50 ºC in DCE, however this did not lead to increase in yield (Entry 7). Diiodide 99 was also added dropwise to the zinc enolate over the course of 30 min via a syringe pump. Diiodide 99 was dissolved in 3 mL of DCM and added at a rate of 0.1 mL/min. This approach also did not lead to an increase in yield (Entry 8). The conditions from Entry 2 were further investigated by changing reaction times. The reaction was allowed to proceed for 30 min and 2 h, but these changes did not significantly increase conversion of 104a to 105a (Entries 9 and 10).
The optimized conditions that had been identified were then applied to a number of different β-keto ester substrates. The β-keto esters that were used along with reaction yields can be seen in Table 11. The substituents on the ester and the substituent adjacent to the ketone were altered. The reaction proceeded in modest to low yields in all examples. This is due to incomplete conversion of starting material. A large amount of starting material was observed via $^1$H NMR and TLC analysis of the crude reaction mixtures. The chain extension reaction involving diiodide 99 is slower than chain extension reactions which use diiodomethane.$^{15}$ This allows for significant

### Table 11. Chain extension reaction of diiodide 99 on β-keto esters.

<table>
<thead>
<tr>
<th>β-Keto Ester</th>
<th>Product</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>104a</td>
<td>105a$^a$</td>
<td>Me</td>
<td>Me</td>
<td>47</td>
</tr>
<tr>
<td>104b</td>
<td>105b$^b$</td>
<td>Me</td>
<td>Et</td>
<td>47</td>
</tr>
<tr>
<td>104c</td>
<td>105c$^b$</td>
<td>Me</td>
<td>Bn</td>
<td>46</td>
</tr>
<tr>
<td>104d</td>
<td>105d$^b$</td>
<td>Me</td>
<td>Allyl</td>
<td>35</td>
</tr>
<tr>
<td>104e</td>
<td>105e$^a$</td>
<td>Et</td>
<td>Me</td>
<td>57</td>
</tr>
<tr>
<td>104f</td>
<td>105f$^a$</td>
<td>i-Pr</td>
<td>Me</td>
<td>21</td>
</tr>
<tr>
<td>104g</td>
<td>105g$^a$</td>
<td>4-MeOPh</td>
<td>Me</td>
<td>44</td>
</tr>
<tr>
<td>104h</td>
<td>105h$^c$</td>
<td>Me</td>
<td>t-Bu</td>
<td>45</td>
</tr>
<tr>
<td>104i</td>
<td>105i$^c$</td>
<td>t-Bu</td>
<td>Me</td>
<td>6</td>
</tr>
</tbody>
</table>

a.) β-keto ester (1 equiv), Et$_2$Zn (5 equiv), diiodide 99 (5 equiv). b.) β-keto ester (1 equiv), Et$_2$Zn (2 x 3 equiv doses), diiodide 99 (2 x 3 equiv doses). c.) Reaction used DCE as solvent.
decomposition of the carbenoid to occur prior to chain extension.\textsuperscript{20} It was found that the chain extension reaction proceeded in the presence of an allyl group. No cyclopropanation of the allyl group was observed. This observation demonstrates the chemoselectivity of the zinc carbenoid derived from diiodide 99 is unchanged from diiodomethane. When the steric bulk of the substituent adjacent to the ketone increased, the yield of the chain extension reaction decreased. This decrease in yield along with the aforementioned appearance of starting material suggests that steric effects may inhibit the nucleophilic attack of the zinc enolate species on the carbenoid derived from diiodide 99.

![Chemical structure](image)

Table 12. Chain extension reaction of diiodide 99 on β-keto amides.

<table>
<thead>
<tr>
<th>β-Keto Amide</th>
<th>Product</th>
<th>R</th>
<th>R’</th>
<th>R''</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>106a</td>
<td>107a</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>50</td>
</tr>
<tr>
<td>106b</td>
<td>107b</td>
<td>Me</td>
<td>-(CH₂)₂O(CH₂)₂⁻</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>
Table 13. Chain extension reaction of diiodide 99 on β-keto phosphonates.

<table>
<thead>
<tr>
<th>β-Keto Phosphonate</th>
<th>Product</th>
<th>R</th>
<th>R’</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>108a</td>
<td>109a</td>
<td>Me</td>
<td>Me</td>
<td>33</td>
</tr>
<tr>
<td>108b</td>
<td>109b</td>
<td>Me</td>
<td>Et</td>
<td>34</td>
</tr>
<tr>
<td>108c</td>
<td>109c</td>
<td>Ph(CH₂)₂-</td>
<td>Me</td>
<td>21</td>
</tr>
</tbody>
</table>

The chain extension reaction using diiodide 99 was also performed on several β-keto amides and β-keto phosphonates. The β-keto amides that were used can be seen in Table 12 and the β-keto phosphonates that were used can be seen in Table 13. The reaction proceeded in modest yields for the β-keto amides. Incomplete conversion of starting material was also observed for these substrates. The reaction proceeded in lower yields for β-keto phosphonates than for other β-keto substrates. Chain extensions of β-keto phosphonates are known to be slower than those of β-keto esters and β-keto amides, therefore this slower reaction rate allows for greater carbenoid decomposition prior to initiation of the chain extension reaction.

Scheme 23. Attempted chain extension reaction using diiodide 100 and alkene side-product 111.
Several other chain extension reactions were attempted on methyl acetoacetate (104a) using silyl ether-functionalized diiodides 100, 101, and 63. The chain extension reaction using diiodide 100 can be seen in Scheme 23. This chain extension reaction resulted in no formation of the chain-extended product (110). However, a large amount of terminal alkene 111 (Scheme 23) was observed in the $^1$H NMR of the crude reaction mixture. A mechanistic explanation of alkene formation will be discussed later in this chapter. The chain extension reaction was also successfully performed using several alternate silyl ether protecting groups. These chain extension reactions are illustrated in Scheme 24. Diiodides 101 and 63 were used in the chain extension reaction successfully. However, the product yields for these chain extension reactions were considerably lower than the yields obtained from the chain extension reaction involving diiodide 99. It has been shown that the chain extension reaction using diiodide 99 is sensitive to steric bulk on the ketone terminus of the β-keto ester. The lower yields for the chain extension reactions using diiodides 101 and 63 could potentially be due to an increase of steric bulk on the carbenoids, which could hinder nucleophilic attack by the zinc enolate. The existence of a large amount of starting material as determined by $^1$H NMR and TLC analysis supports this explanation. However, the lower yields for the chain extension reactions could also be due to increased decomposition of the carbenoids through alternate mechanisms. The reason for this decrease in yield currently remains unclear.

![Scheme 24](image-url)

**Scheme 24.** Chain extension reactions using diiodides 101 and 63.
The chain extension reactions using diiodides $102$, $103$, and $86$ were also attempted and were all unsuccessful. These attempted chain extensions can be seen in Scheme 25. In all these reactions, no $\gamma$-keto ester formation was observed. In the reactions with diiodides $102$ and $86$, residual diiodide remained along with unreacted $\beta$-keto ester. In the reaction using diiodide $103$, a large amount of tosyl allylamine (117) (Scheme 25) was observed in the $^1$H NMR of the crude reaction mixture. A plausible explanation for the formation of alkenes 111 and 117 can be seen in Scheme 26.\textsuperscript{45} It is possible for the zinc carbenoids derived from diiodides $100$ and $103$ to undergo a 1,2-hydride shift which would lead to the formation of the terminal alkene and ethyl zinc iodide.\textsuperscript{45} This type of 1,2-shift has been proposed by Bull and Charette.\textsuperscript{45,46} The operative mechanism for the formation of 111 and 117 has not been confirmed. Additional studies, such as deuterium labeling, would need to be conducted to confirm that a 1,2-shift is occurring.

**Scheme 25.** Chain extensions using diiodides $102$, $103$ and $86$. Terminal alkene side-product 117.

**Scheme 26.** Mechanistic explanation for the formation of terminal alkene side-product 117.
Removal of the TBS group

The TBS removal of the γ-keto esters obtained from the chain extension reaction involving diiodide 99 could lead to the formation of several different products. Pathways to these different products can be seen in Scheme 27. If γ-keto ester 105a were subjected to a fluoride source, such as TBAF, it would initially generate alkoxide intermediate 119. Nucleophilic attack of the nearby ketone would lead to hemiketal 120 (Path A). While the formation of the hemiketal would be reversible, a sequential cyclization step involving nucleophilic attack on the nearby ester would lead to the formation of bicyclic lactone 121. In a separate pathway (Path B), the alkoxide intermediate 119 could undergo cyclization via direct attack on the nearby ester. This would lead to the formation of δ-lactone 122.

Scheme 27. Potential product formation pathways after TBS removal of γ-keto ester 105a.

Scheme 28. Previously reported TBS removal of β-keto ester 123.
The TBS removal from β-keto ester 123 using TBAF has been reported in the literature (Scheme 28).\(^6^7\) When β-keto ester 123 was exposed to TBAF in THF under reflux, the reaction led to the formation of γ-lactone 124.\(^6^7\) In this case, the resulting alkoxide from TBS removal attacked the nearby ethyl ester. This pathway is similar to Path B in Scheme 27. Path A in Scheme 27 is not operative in this specific reaction because the second cyclization step would result in the formation of a β-lactone. This β-lactone product would be higher in energy when compared to the γ-lactone due to the higher amount of ring strain.\(^6^8\)

![Diagram of TBS removal reaction](image)

**Table 14. Deprotection of γ-keto esters.**

<table>
<thead>
<tr>
<th>γ-keto Ester</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>105a</td>
<td>125a</td>
<td>Me</td>
<td>53</td>
</tr>
<tr>
<td>105e</td>
<td>125e</td>
<td>Et</td>
<td>73</td>
</tr>
<tr>
<td>105f</td>
<td>125f</td>
<td>i-Pr</td>
<td>65</td>
</tr>
</tbody>
</table>

When γ-keto esters were subjected to TBAF, the bicyclic lactone products were indeed the products that were isolated. The γ-keto esters that were deprotected and the yields that were obtained are listed in Table 14. The reactions were very clean as only one spot was observed by TLC analysis of the crude reaction mixtures. The reaction was determined to be diastereoselective, with a single diastereomer being formed. The relative stereochemistry was determined using \(^1\)H-\(^1\)H NOESY experiments, which revealed that the isolated products all contained a *cis*-fused ring.
system. The formation of these products is the result of the first pathway (Path A) proposed in Scheme 27.

**Attempted synthesis of paeonilide**

Paeonilide is a highly-oxygenated monoterpenoid which was originally isolated from the roots of *Paeonia delavayi*. This natural product has been demonstrated to be an anti-PAF monoterpenoid. Paeonilide’s bioassay showed that it selectively inhibits platelet aggregation induced by PAFs with an IC\(_{50}\) value of 8 μg/mL. Paeonilide is a scarce monoterpenoid. Only 8 mg of the compound was isolated from 1.13 kg of *Paeonia delavayi*. The synthesis of this natural product has been reported previously in 5 steps with 59% overall yield. An alternative synthesis of paeonilide was envisioned utilizing a functionalized zinc-mediated chain extension approach. The alternate disconnection might allow access to various analogues of paeonilide, if desired.

![Scheme 29](image)

Scheme 29. Synthetic approach for the formal synthesis of paeonilide.

A proposed synthesis of paeonilide can be seen in Scheme 29. β-Keto ester 126 could be converted into γ-keto ester 128 using Et\(_2\)Zn and diiodide 127. This would complete the formal synthesis of paeonilide in one step. Conversion of γ-keto ester 128 into paeonilide has been reported to occur through a two-step process. The first of these two steps was removal of both ketal groups using 1 M HCl, which was reported to form the bicyclic lactone ring system in 91%
yield. The second and final step was benzylation of a primary alcohol using BzCl, which was reported with 98% yield.

![Chemical diagram]

**Scheme 30.** Attempted synthesis of diiodide 127.

The synthesis of diiodide 127 was attempted using hydrazone iodination. The attempted synthesis can be seen in Scheme 30. Alcohol 129 is commercially available and was oxidized to the corresponding aldehyde using DMP oxidation. This led to aldehyde 130 in 46% yield. PCC oxidation of alcohol 129 was also attempted according to a literature procedure; however, the pure aldehyde was not isolated and numerous impurities were observed in the chromatographed material via $^1$H NMR and TLC analyses. Aldehyde 130 was then converted to the mixture of hydrazones 131a, 131b using N$_2$H$_4$H$_2$O. A mixture of E and Z stereoisomers was obtained in a similar fashion as hydrazones 92a-98a, 92b-98b. The iodination of mixture of hydrazones 131a, 131b was unsuccessful. Upon addition of I$_2$, little to no gas evolution was observed. This suggests that the reaction was not proceeding in the same manner as previous iodination reactions. The $^1$H NMR of the crude reaction mixture indicated a small amount of product being formed, but the mixture was quite complex and diiodide 127 was not isolated from the reaction mixture. One potential reason why the iodination step failed is due to potential instability of the hydrazone mixture. Dimerization of hydrazones (131a, b) would result in formation of azine dimer 132 (Figure 10). Evidence of dimerization of the hydrazones was indicated by a doublet at 7.84 ppm.
in the $^1$H NMR of the crude reaction mixture for the hydrazone formation step. The starting hydrazone was completely consumed in the iodination step. However, the dimer did not react under iodination conditions, thereby preventing formation of diiodide 127. The dimer was also observed in $^1$H NMR of the crude reaction mixture of the iodination step, indicating that no reaction of the dimer occurred.

![Dimer](image.png)

**Figure 10.** Azine dimer resulting from hydrazones 131a, 131b.

**Future work**

The incorporation of functionality at the β position of the chain-extended product was investigated using several functionalized zinc carbenoids. The synthesis of functionalized geminal diiodides was achieved using hydrazone iodination. Silyl ether-functionalized geminal diiodides were used in the chain extension efficiently and with yields ranging from 6% to 57%. The chain extension reaction was performed on nine β-keto esters, two β-keto amides, and three β-keto phosphonates. Chain extension reactions using a benzyl protecting group and protected amines were unsuccessful. Removal of the TBS group from several γ-keto ester products led to the formation of the cis-fused tetrahydrofuran-γ-lactone ring system. The formal synthesis of
Paeonilide was attempted using a zinc-mediated chain extension approach, however synthesis of
the required diiodide was unsuccessful.

The next step for this project would be incorporation of more diverse functionality into the
chain extension reaction rather than just a silyl ether group. A tandem chain extension reaction
using 1,1-diiodoethane as the geminal diiodide and hexanal as the electrophile has been previously
reported. However, this method only provides methyl substitution at the β position. The chain
extension reaction using diiodide 99 could also be accompanied with a tandem reaction. This
would lead to heteroatom functionality at both the α and β positions of the chain-extended product
in one step. The deprotection of the γ-keto amide and γ-keto phosphonate products could also be
investigated. For the formal synthesis of paeonilide, the diiodide could potentially be synthesized
using different methodology. Perhaps conversion of the triflylacetal derived from aldehyde 130
using conditions described by Martinez et al. could lead to formation of diiodide 127.39
CHAPTER III

FORMAL SYNTHESIS OF HELIOTRIDANE AND PSEUDOHELIOTRIDANE THROUGH A ZINC-MEDIATED CHAIN EXTENSION APPROACH

Heliotridane

Heliotridane is a natural product that is part of the pyrrolizidine alkaloid family. Pyrrolizidine alkaloids are found worldwide in various species of plants. Approximately 3% of the world’s flowering plants, which amounts to 6000 species, produce pyrrolizidine alkaloids. Some examples of plant genera that contain pyrrolizidine alkaloids can be seen in Table 15.

Table 15. Various plant genera which produce pyrrolizidine alkaloids.

<table>
<thead>
<tr>
<th>Genus</th>
<th>Pyrrolizidine Alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crotalaria</td>
<td>Crotaline, Crotaburnine, Crotastractine</td>
</tr>
<tr>
<td>Cynoglossum</td>
<td>Amabiline, Latifoline, Cynaustine</td>
</tr>
<tr>
<td>Eupatorium</td>
<td>Echinatine, Supinine, Trachelantimididine</td>
</tr>
<tr>
<td>Heliotropium</td>
<td>Heliotrine, Heliofoline, Heliosupine</td>
</tr>
<tr>
<td>Senecio</td>
<td>Retrorsine, Senecionine, Seneciphylline</td>
</tr>
<tr>
<td>Symphytum</td>
<td>Symphytine, Asperumine, Lasiocarpine</td>
</tr>
</tbody>
</table>

Members of this family of compounds have potent biological activity, and some members have been shown to be toxic to several species of mammals, including humans. These compounds have exhibited hepatotoxicity, pneumotoxicity, and nucleotoxicity. Animal tests have shown that a single exposure to a pyrrolizidine alkaloid toxin could result in the progression of liver disease. Studies have also shown that administering a diet of 1-4 mg/kg of pyrrolizidine alkaloid toxins resulted in various types of liver ailments. Several human diseases have been
shown to be caused by exposure to pyrrolizidine alkaloids, such as chronic liver disease and veno-occlusive disease.\textsuperscript{77,78} This toxicity is due to pyrrolic metabolites that are formed in the liver. These metabolites can form adducts with DNA and act as alkylating agents. There are more than 600 naturally occurring pyrrolizidine alkaloid compounds. The structures of several pyrrolizidine alkaloids can be seen in Figure 11.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{pyrrole_alkaloids.png}
\caption{Examples of pyrrolizidine alkaloids found in nature.}
\end{figure}

Heliotridane possesses the simplest structure of pyrrolizidine alkaloid compounds. This natural product has been isolated as a degradation product from various plants, such as \textit{Heliotrofiuna}, \textit{Erechtites}, and \textit{Trichodesma} genera.\textsuperscript{79} The pyrrolizidine alkaloid is chiral (\(-\)-heliotridane and \(\text{+}\)-heliotridane) and both enantiomers have been found in nature.\textsuperscript{79} The structures for this enantiomeric pair can be seen in Figure 12. Heliotridane possesses a bicyclic core structure with a methyl substituent at position one of the ring system. The 3-dimensional structure of heliotridane is interesting because an \(\text{sp}^3\)-hybridized nitrogen is located at one of the fused points of the ring system. \(\text{sp}^3\)-Hybridized nitrogens are pyramidal in geometry, so this causes heliotridane to have a bowl-shaped structure. The 3-dimensional structure for \((-\)-heliotridane can be seen in Figure 13. The simple structure of heliotridane allows it to act as a test bed for developing synthetic strategies for the synthesis of other pyrrolizidine alkaloids.
Due to its simple structure, heliotridane has been the target of several different synthetic approaches in the past. One example of a synthetic approach to (-)-heliotridane was developed by Knight and Ley. Their approach utilized a π-allyltricarbonyl lactam complex (133) (Figure 14) to form a new carbon-carbon bond between C2 and C3 of the ring system. Although their approach led to the formal synthesis of (-)-heliotridane, Knight and Ley’s synthetic approach to (-)-heliotridane required thirteen steps to obtain the target molecule. This is a long synthetic sequence for such a simple compound. Their synthesis also requires harsh conditions to convert the π-allyltricarbonyl lactam complex to the corresponding lactam. This step requires exhaustive carbonylation using carbon monoxide gas at high pressures and temperatures.
Another synthetic approach used to synthesize heliotridane was developed by Robertson, Peplow, and Pillai (Scheme 31). Their approach utilized a radical cyclization to convert vinyl bromide-substituted pyrrolidine 136 into heliotridane. Their method only required three steps to synthesize heliotridane, diastereoselectively. Their approach led to the formation of heliotridane and pseudoheliotridane as their hydrobromide salts. A diastereomeric ratio of 13:1 was achieved and the diastereomers were obtained in an overall yield of 29%.

Scheme 31. Robertson, Peplow, and Pillai’s synthesis of heliotridane.

A more recent synthesis of heliotridane was accomplished by Koc and Kwon. They were able to synthesize heliotridane in 24% overall yield. Their synthesis utilized a tandem isomerization/6π-electrocyclization/[3+2] cycloaddition of 1-nitro-2-methyl-1,3-butadiene (137) with methyl acrylate. This resulted in the formation of nitroso acetals 138a and 138b (Scheme 32). Subsequent reduction of 138a, 138b using H2 and Raney nickel resulted in the formation of a bicyclic lactam. The bicyclic lactam was then deoxygenated and reduced to form heliotridane. The overall synthesis required a four-step synthesis of 137 of from isoprene in addition to the six steps...
required for its conversion to heliotridane. Therefore, heliotridane has been synthesized previously, but the synthetic approaches that have been used are far from ideal.

Scheme 32. 6π-electrocyclization/[3+2] cycloaddition step in the synthesis of heliotridane.

Zinc-mediated chain extension approach for the synthesis of heliotridane

It was imagined that a zinc-mediated chain extension reaction could be applied to the synthesis of heliotridane. The synthetic approach could be envisioned as requiring only five steps. The proposed synthesis of racemic heliotridane can be seen in Scheme 33. The first step in this synthetic approach would involve protection of 2-pyrrolidinone using an amine protecting group. Several different protecting groups could potentially be used, such as a Boc group (139), Cbz group (140), or a sulfonamide protecting group variant (Ts (141) or SES (142)). The second step would involve enolate-mediated ring opening of protected pyrrolidinones 139-43 using the enolate derived from EtOAc to form β-keto esters 144-148. All the protecting groups that were previously mentioned have to the ability to make this ring-opening reaction more favorable by activating the carbonyl for nucleophilic attack. The zinc-mediated chain extension reaction using Et₂Zn and 1,1-diiodoethane would then lead to the formation of the β-methylated γ-keto esters 149-151. The next transformation requires multiple steps, in which the amine is first deprotected. The deprotection method would depend on the protecting group. For example, Boc groups can be removed through the addition of TFA and Cbz groups are typically removed by catalytic hydrogenation (H₂, Pd/C). Deprotection of the amine should result in cyclization through attack
of the amine on the nearby ketone to form a cyclic imine. The next step in the tandem reaction sequence involves reduction of the imine, the conditions of which depend on the protecting group that is used. For example, if a Boc group is used the imine must be reduced in a second step using a hydride reducing agent, but if a Cbz group is used the imine might be reducible under catalytic hydrogenation conditions as well. In either case, a cyclic amine is generated and is available to react with the nearby ester to form bicyclic lactam **152a**. The relative stereochemistry obtained is uncertain. The existing methyl group may influence the reduction of the cyclic imine. The issue of stereocontrol will be explained in more detail later in this chapter. The final step in the proposed synthesis would involve the reduction of the lactam to the amine using LAH to form heliotridane. This reduction step has been previously reported in the literature. The target for the formal synthesis of heliotridane would be bicyclic lactam **152a**. This lactam was the target of Knight and Ley’s synthesis and was also isolated by Mori prior to LAH reduction.

![Scheme 33](image)

**Scheme 33.** Zinc-mediated chain extension approach for the synthesis of heliotridane.
1,1-Diiodoethane (154) was synthesized using hydrazone iodination according to the literature procedure by Friedrich and coworkers (Scheme 34). In the first step acetaldehyde is converted to the corresponding hydrazone (153a, 153b) through reaction with N₂H₄·H₂O, which leads to the formation of a mixture of stereoisomers. Both the E and Z stereoisomers are formed and can be observed in the ¹H NMR of the crude reaction mixture. The hydrazone does not require purification prior to the next step in the synthesis. The second step utilizes I₂ in the presence of Et₃N to form 1,1-diiodoethane. The presence of Et₃N prevents the formation of an azine dimer which is produced through a radical mechanism. The procedure for this reaction was modified slightly from the literature procedure to increase the purity of the product. Excess I₂ was believed to be contaminating the product, so additional washes with saturated Na₂S₂O₃ were incorporated to remove the excess I₂ by reducing it to iodide. The iodide was then removed through subsequent water washes. The overall yield for this reaction was around 20% and the literature overall yield is around 38%. This difference in yield is probably due to the extra washes in which some of the product could have been lost.

**Scheme 34.** Synthesis of 1,1-diiodoethane using hydrazone iodination.

The starting lactam, 2-pyrrolidinone, was N-protected using a variety of protecting groups. The protecting groups that were introduced along with reaction conditions and yields can be seen in Table 16. A Boc group was introduced using Boc₂O and n-BuLi, following a literature procedure. The reaction worked well and produced 139 in 98% yield without the need for further
purification. A Cbz group was also introduced, using CbzCl in the presence of \( n-\text{BuLi} \). These conditions led to the formation of 140 as one spot in 87\% yield. Reactions that led to formation of sulfonamide-protected lactams 141 and 142 were accomplished using literature procedures. The literature yield for the synthesis of 142 was reported to be only 25\%. However, the yield that was obtained was 73\%, which is a substantial improvement over what has been previously reported. 2-Pyrrolidinone was also protected with a Bn group using a literature procedure. This reaction led to the formation of 143 in 81\% yield.

![Diagram](image)

**Table 16.** \( N \)-protection of 2-pyrrolidinone.

<table>
<thead>
<tr>
<th>Product</th>
<th>PG</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>Boc</td>
<td>Boc(_2)O, ( n-\text{BuLi} ), THF, -78 °C</td>
<td>98</td>
</tr>
<tr>
<td>140</td>
<td>Cbz</td>
<td>CbzCl, ( n-\text{BuLi} ), THF, -78 °C</td>
<td>87</td>
</tr>
<tr>
<td>141</td>
<td>Ts</td>
<td>TsCl, ( n-\text{BuLi} ), THF, -78 °C to rt</td>
<td>69</td>
</tr>
<tr>
<td>142</td>
<td>SES</td>
<td>SESCl, ( n-\text{BuLi} ), THF, -78 °C to rt</td>
<td>73</td>
</tr>
<tr>
<td>143</td>
<td>Bn</td>
<td>BnBr, NaH, THF, 0 °C to rt</td>
<td>81</td>
</tr>
</tbody>
</table>

The next step in the synthesis was the enolate ring opening of the \( N \)-protected lactams 139-143. The enolate ring openings that were studied are reported in Table 17. The enolate ring openings were all based on a literature procedure. The enolate ring opening of 139 proceeded
efficiently with one equiv of enolate. The ring opening of 140 required the use of 2 equiv of enolate to achieve sufficient product formation. For the subsequent ring openings of 141 and 142, 2 equiv of enolate were also used. The ring opening was also attempted on 143; however, a large amount of starting material was observed by 1H NMR of the crude reaction mixture and the product could not be isolated. The rationale behind this failed ring opening is that the Bn protecting group is not electron-withdrawing, which leads to a lower degree of electrophilicity of the carbonyl when compared to lactams 139-142. It should be noted that each of the isolated β-keto ester products 144-147 existed predominantly in the keto form; however, evidence of the enol form in each compound is observable by 1H and 13C NMR analysis.

![Diagram of enolate ring opening]

**Table 17. Enolate ring opening of N-protected pyrrolidinones.**

<table>
<thead>
<tr>
<th>Lactam</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>144</td>
<td>Boc</td>
<td>44</td>
</tr>
<tr>
<td>140</td>
<td>145</td>
<td>Cbz</td>
<td>48</td>
</tr>
<tr>
<td>141</td>
<td>146</td>
<td>Ts</td>
<td>71</td>
</tr>
<tr>
<td>142</td>
<td>147</td>
<td>SES</td>
<td>40</td>
</tr>
<tr>
<td>143</td>
<td>148</td>
<td>Bn</td>
<td>-</td>
</tr>
</tbody>
</table>

A zinc-mediated chain extension reaction was explored for the conversion of the β-keto esters to the β-methylated γ-keto esters using Et₂Zn and 1,1-diiodoethane. The various chain extension reactions that were attempted can be seen in Table 18. The first substrate studied was β-keto ester 144. The chain extension reaction was attempted multiple times, but a chain-extended product was never isolated. Modifications to the standard chain extension reaction procedure
included stirring for up to 6 h, introducing a second dose of carbenoid, and the generation of a dicarbenoid species (bis(iodomethyl)zinc) was utilized by using double the equivalents of 1,1-diiodoethane relative to Et₂Zn. All these attempts failed and led to the recovery of starting material. The reaction was also attempted in benzene, but no conversion to γ-keto ester 149 was observed. A large amount of 2-iodobutane was observed in the crude reaction mixtures, which indicates decomposition of the carbenoid was occurring during the course of the reaction.²⁰ The chain extension reaction was then attempted with β-keto ester 145. While this reaction resulted in some conversion to γ-keto ester 150, the ratio of starting material to product was determined to be 3:1 by ¹H NMR analysis of the crude reaction mixture. The product could not be separated from the starting material by column chromatography. The chain extension reaction was also attempted with β-keto ester 146. This reaction provided greater amounts of γ-keto ester 151; the ratio of starting material to product was determined to be 3:2 by integration of the ¹H NMR of the crude reaction mixture. Nevertheless, the chain-extended product could not be separated from the starting material by column chromatography.

![Reaction Scheme](image)

Table 18. Attempted chain extension reactions of β-keto esters 144-146 using 1,1-diiodoethane.

<table>
<thead>
<tr>
<th>β-keto ester</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>149</td>
<td>Boc</td>
<td>No conversion</td>
</tr>
<tr>
<td>145</td>
<td>150</td>
<td>Cbz</td>
<td>Incomplete conversion</td>
</tr>
<tr>
<td>146</td>
<td>151</td>
<td>Ts</td>
<td>Incomplete conversion</td>
</tr>
</tbody>
</table>
The chain extension reaction of β-keto esters 144-147 using diiodomethane was also investigated.\textsuperscript{15} The chain extension reactions that were performed along with reaction yields can be seen in Table 19. The chain extension reactions with β-keto esters 144, 157, and 158 all worked well with yields > 50%. The yield (61%) for the chain extension reaction using β-keto ester 144 was unexpected, since the chain extension reaction with 1,1-diiodoethane had resulted in no conversion. The chain extension reaction using β-keto ester 145 did not work well compared to the other β-keto esters. A mixture of products was observed by TLC analysis, and the γ-keto ester (156) product was isolated in only 12% yield. These reactions demonstrated that the chain extension reaction methodology using diiodomethane can be applied to these amine-protected β-keto esters; therefore, a modified synthetic approach using this chain extension methodology was proposed for the synthesis of heliotridane.

![Reaction Scheme](image)

**Table 19.** Chain extension reactions of β-keto esters 144-147 using diiodomethane.

<table>
<thead>
<tr>
<th>β-keto ester</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>144</td>
<td>155</td>
<td>Boc</td>
<td>61</td>
</tr>
<tr>
<td>145</td>
<td>156</td>
<td>Cbz</td>
<td>12</td>
</tr>
<tr>
<td>146</td>
<td>157</td>
<td>Ts</td>
<td>53</td>
</tr>
<tr>
<td>147</td>
<td>158</td>
<td>SES</td>
<td>82</td>
</tr>
</tbody>
</table>
The revised synthetic approach for the synthesis of heliotridane can be seen in Scheme 35. The first step in this synthesis would again involve N-protection of 2-pyrrolidinone, as has been previously discussed. α-Methylation of the protected pyrrolidinones using CH₃I in the presence of a strong, non-nucleophilic base would be used to form α-methylated lactams 159-162, which would be subjected to enolate-mediated ring opening using the enolate derived from EtOAc to form methylated β-keto esters 163-166. These β-keto esters could then be subjected to the chain extension reaction conditions using Et₂Zn and diiodomethane. This reaction would insert a methylene unit and lead to the formation of γ-keto esters 167-170. Conversion of the γ-keto esters to the pyrrolizidine skeleton would proceed in a similar fashion to that proposed above (Scheme 33). This transformation would involve a tandem reaction in which the amine is first deprotected, which forms the cyclic imine. The cyclic imine could then be reduced to the amine and would then attack the nearby ester to form bicyclic lactam 171a. The final step in the synthesis would be reduction to form heliotridane.⁸⁴

Scheme 35. Revised zinc-mediated chain extension approach for the synthesis of heliotridane.
The α-methylation of protected lactams 139-142 was performed using CH$_3$I in the presence of base. The reaction conditions and reaction yields are presented in Table 20. For lactams: 139, 141, and 142 the methylated products have been reported in the literature. The methods used to synthesize these lactams were based on literature procedures.$^{91,92}$ The methylation of lactam 140 has not been previously reported in the literature, so a new method was developed. Initially efforts to methylate lactam 140 used LiHMDS as the base at -78 ºC; however, the desired lactam product (160) was not isolated using these conditions. The reaction with LiHMDS was modified to include warming the reaction mixture to -30 ºC, but again 160 was not isolated. The base was changed to LDA, and the alkylation step was warmed to room temperature. These conditions led to formation of 160, but in only 36% yield. Attempts were made to perform the reaction under kinetic control to ensure preferential formation of monomethylated lactams 159-162. The lower yields for these products can be explained by the appearance of several side products. TLC analysis of both crude
reaction mixtures revealed numerous spots (≥ 4). The presence of the α-dimethylated lactam was observed in the crude reaction mixture along with lactams 159 and 160.

![Reaction Scheme](image)

**Table 21. Enolate ring opening of lactams 159-162.**

<table>
<thead>
<tr>
<th>Lactam</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>159</td>
<td>163</td>
<td>Boc</td>
<td>29</td>
</tr>
<tr>
<td>160</td>
<td>164</td>
<td>Cbz</td>
<td>41</td>
</tr>
<tr>
<td>161</td>
<td>165</td>
<td>Ts</td>
<td>85</td>
</tr>
<tr>
<td>162</td>
<td>166</td>
<td>SES</td>
<td>71</td>
</tr>
</tbody>
</table>

The enolate ring openings using the enolate derived from EtOAc were performed on methylated lactams 159-162 in a similar manner as lactams 139-142. The enolate ring openings that were accomplished can be seen in Table 21. The enolate ring openings were again based on a literature procedure and led to the formation of β-keto esters 163-166. Two equiv of enolate were used in each of the ring-opening reactions. The rationale for using multiple equivalents of enolate has been previously explained by Kennedy and can be seen in Scheme 36.

![Scheme 36](image)

**Scheme 36.** Rationale for using 2 equiv of enolate for enolate ring openings.
β-Keto esters 163-166 are expected to be deprotonated by an equiv of enolate once they are formed, due to the acidic nature of the α-hydrogens of the β-keto esters. This deprotonation would consume an equiv of enolate and decrease the amount in solution. In this study of ring openings, the sulfonamide-protected lactams led to much higher yields. This could be due to an enhanced electron-withdrawing effect which serves to enhance the electrophilicity of the carbonyl of the lactam, making it easier to open. Each of the β-keto ester products that were isolated existed predominantly in the keto form; however, evidence of the enol form was observed by $^1$H and $^{13}$C NMR analysis in each of the products.

![Chemical Structure](image)

Table 22. Chain extension reactions of β-keto esters 163-166 using diiodomethane.

<table>
<thead>
<tr>
<th>β-keto Ester</th>
<th>Product</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>163</td>
<td>167</td>
<td>Boc</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>164</td>
<td>168</td>
<td>Cbz</td>
<td>13</td>
</tr>
<tr>
<td>165</td>
<td>169</td>
<td>Ts</td>
<td>30</td>
</tr>
<tr>
<td>166</td>
<td>170</td>
<td>SES</td>
<td>46</td>
</tr>
</tbody>
</table>

The chain extension reaction of β-keto esters 163-166 was performed using diiodomethane. The chain extension reactions that were performed and their yields can be seen in Table 22. These chain extension reactions also proved to be problematic, but γ-keto esters 168-170 were able to be isolated. The chain extension reaction was first attempted on β-keto ester 163. This reaction led to a complex mixture of products. More than 7 spots were observed by TLC analysis, and the desired product could not be isolated. Kennedy observed the same result for this
chain extension reaction. Kennedy also attempted the chain extension in benzene; however, a complex mixture of products was also obtained when the chain extension was performed in benzene. The chain extension reaction was performed using β-keto esters 164-166 and the corresponding γ-keto esters were isolated. For β-keto ester 164 a complex mixture of products was also observed (> 6 spots by TLC analysis), but γ-keto ester 168 could be isolated in very low yield. The low yield of product due to the complex product mixture of this chain extension reaction made it problematic to carry out the synthesis of the natural product. The remainder of the synthesis was not pursued further due to low material through-put. The sulfonamide-protected β-keto esters 165 and 166 worked much better in the chain extension reaction than the previously discussed β-keto esters. γ-Keto ester 169 was isolated in 30% yield with several additional unidentified by-products being observed in crude reaction mixture. γ-Keto ester 170 was isolated in 46% yield in addition to an unidentified by-product. The difficulties associated with tosylate removal rendered the completion of the synthesis unviable. The conditions necessary to remove tosylate groups are rather harsh (metal reduction, strong acids, etc.), whereas SES removal is more facile (fluoride source). The completion of this synthesis would more than likely proceed using an SES group as a protecting group.

![Scheme 37](image)

Scheme 37. Potential mechanistic explanation of the attempted chain extension reactions.

Numerous problems were encountered in chain extension reactions of β-keto esters 144-146 when using 1,1-diiodoethane and in chain extension reactions of β-keto esters 163-166 when
using diiodomethane. The reactions of β-keto esters 144-146 led to no or incomplete conversion of starting material. If product formation did occur, the product was unable to be separated from the starting β-keto ester. The chain extension reactions of β-keto esters 164-166 did lead to formation of γ-keto ester products, however the yields of these reactions were quite low. A potential explanation for the problems associated with these chain extensions can be seen in Scheme 37. In the presence of Et₂Zn, it’s possible for the γ-protected amine to cyclize and attack the ketone (presumably via the carbamate/sulfonamide anion)⁹⁷ to form hemiaminal 171.⁹³ This cyclization is possible because zinc could act as a Lewis acid and coordinate to the ketone, making it more electrophilic. If 171 is present in the reaction mixture, then the chain extension reaction is likely prohibited from initiating. Upon quenching the reaction with aqueous acid, the starting β-keto ester could be regenerated. This cyclization/ring-opening could explain why starting material is observed in each of the chain extension reactions mentioned previously.

**Scheme 38.** Basic hydrolysis of diethyl malonate.

**Scheme 39.** Attempted Masamune-Brooks reaction to form β-keto ester 174.
It was envisioned that diprotection of the amine functionality on the β-keto ester could resolve the difficulties encountered during previous chain extension attempts. The diprotected amine would be unable to cyclize due to the absence of an acidic N-H. Two potential β-keto esters containing di-protected amine functionality were initially proposed. The first β-keto ester contained a dibenzyl-protected amine (174). According to the literature, a similar β-keto ester containing ethyl substituents on the amine has been synthesized from the corresponding carboxylic acid using the Masamune-Brooks reaction.\textsuperscript{98} The Masamune-Brooks reaction is a C-acylation reaction that can generate β-keto esters under mild conditions, which requires the use of CDI and the magnesium salt of a monoester of malonic acid.\textsuperscript{99} The mono-ethyl ester of malonic acid (172) was synthesized by basic hydrolysis of diethylmalonate.\textsuperscript{100,101} The conditions that were used are illustrated in Scheme 38. Both NaOH and KOH were used as nucleophiles to perform the hydrolysis, but the use of KOH led to a much cleaner product and did not require chromatographic purification.\textsuperscript{100,101} Carboxylic acid 173 was reacted with CDI to form the acyl imidazole, which was then added to the magnesium salt of 172 (Scheme 39). However, this method did not lead to acylation and formation of β-keto ester 174. Only starting material was recovered from the reaction mixture.

![Scheme 40](image)

**Scheme 40.** Attempted synthesis of β-keto ester 178.
The second proposed β-keto ester contained a phthalimide protecting group on the nitrogen (178). The synthesis of β-keto ester 178 has been previously reported in the literature and can be seen in Scheme 40. The first step is conversion of 4-phthalimidobutyric acid (175) into 4-phthalimidobutyryl chloride (176) through the use of SOCl₂. A literature procedure was reproduced and acid chloride 176 was obtained in 61% yield from 175. The second step in the literature procedure involves reaction of acid chloride 176 with the magnesium enolate of ethyl acetoacetate to form α-acyl β-keto ester 177. This reaction was attempted, but was unsuccessful. The crude ¹H NMR of the reaction mixture indicated that only 176 was present. No conversion to the α-acyl β-keto ester 177 was observed. If α-acyl β-keto ester 177 had been isolated, the final step of the synthesis would have been treatment with dilute NH₄OH to form the target β-keto ester 178. Alternatively, the conversion of carboxylic acid 175 to the methyl β-keto ester using the magnesium salt of the monomethyl ester of malonic acid has been previously reported. The synthesis of β-keto ester 178 was then attempted using the Masamune-Brooks reaction using the magnesium salt of 172 and acyl imidazole derived from carboxylic acid 175. This reaction can be seen in Scheme 41. This reaction worked well as only one spot was observed by TLC analysis, and β-keto ester 178 was obtained in 76% yield.

![Scheme 41. Masamune-Brooks reaction to form β-keto ester 178.](Image)
The chain extension reactions using diiodomethane and 1,1-diiodoethane were performed on β-keto ester 178.\textsuperscript{15,20} The chain extension reaction of β-keto ester 178 using diiodomethane can be seen in Scheme 42. This reaction worked well. γ-Keto ester 179 was isolated in 77% yield and complete consumption of 178 was observed. This reaction was also higher-yielding than the reactions performed on β-keto esters 144-147, which were previously used in the chain extension reaction. The chain extension reaction using 1,1-diiodoethane and β-keto ester 178 was also performed. This reaction can be seen in Scheme 43. This chain extension reaction did not work as well as the reaction using diiodomethane, but β-methylated γ-keto ester 180 was isolated in 33% yield. The reaction mixture only contained two different species as observed by TLC, and those were the product 180 and starting material 178. The reaction was initially performed using 5 equiv of carbenoid relative to the starting material, which resulted in a yield of 25%. The reaction was then performed using two 3 equiv doses of carbenoid, but this led to the previously mentioned yield of only 33%.\textsuperscript{20} The ratio of 178 to 180 was 1:1 as was determined by $^1$H NMR integration of the crude reaction mixture. Although the yield for this reaction was far from ideal, the isolation of γ-keto ester 180 allowed for the continuation of the synthetic approach to the natural product.

![Scheme 42](image1.png)

**Scheme 42.** Chain extension reaction of β-keto ester 178 using diiodomethane.

![Scheme 43](image2.png)

**Scheme 43.** Chain extension reaction of β-keto ester 178 using 1,1-diiodoethane.
Removal of phthalimide protecting groups has been reported to proceed using several different conditions. One method involves the use of $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ and leads to the formation of 1,4-phthalazinedione as well as the free amine. However, this methodology is not ideal for γ-keto esters 179 and 180 due to the presence of ketone functionality. The hydrazine reagent has the potential to attack the carbonyl and form the hydrazone, which would lead to a mixture of products. Another potential method for the removal of the phthalimide protecting group involves the use of $\text{NaBH}_4$, followed by addition of AcOH. This methodology leads to the formation of the free amine; however competitive reduction of the ketone functionality would be expected. The deprotection methodology that was viewed as having the highest potential for success involved the use of methylamine. This method would lead to the formation of a 1,2-benzenedicarboxamide species as well as the free amine. Additionally, this method has been utilized for the phthalimide removal from a β-keto ester-containing substrate resulting in the formation of a cyclic imine. γ-Keto esters 179 and 180 were exposed to methylamine, as illustrated in Scheme 44. The reactions proceeded efficiently at room temperature in good yields (≥80%). Only one spot was observed by TLC analysis (besides the 1,2-benzenedicarboxamide by-product) indicating the clean nature of this deprotection methodology.

Scheme 44. Phthalimide removal of γ-keto esters 179 and 180.
The final step in the formal synthesis of heliotridane was reduction of the cyclic imines 181 and 182, which should result in lactamization to form the core ring system of heliotridane. This tandem process has been previously reported using several different reducing agents, such as NaBH₄, NaBH₃CN, and Zn(BH₄)₂.¹⁰⁷-¹⁰⁹ Reduction of imine 181 was attempted previously by Kennedy using NaBH₄.⁹³ Kennedy observed only the appearance of starting material in the crude reaction mixture and no observation of a lactam product.⁹³ Kennedy suggested that the predicted bicyclic lactam product (183) was volatile and could have been removed during concentration of the reaction mixture.⁹³ However, the boiling point of lactam 183 has been reported to be > 90 °C at 12 mmHg;¹¹⁰ therefore, it appears unlikely that all of the product (183) would be removed by rotary evaporation. It is more likely that the starting imine was simply not reduced by NaBH₄. Therefore, a different reducing agent was implemented for the reduction of imine 181. The use of Zn(BH₄)₂ has been previously reported to reduce a 5-membered imine, which was followed by intramolecular cyclization to form a δ-lactam.¹⁰⁹ This tandem reduction and cyclization was an essential transformation in the synthesis of demissidine and solanidine.¹⁰⁹ The reduction of imine 181 was performed using Zn(BH₄)₂ as the reducing agent. This reaction can be seen in Scheme 45. The reduction of imine 181 proceeded at room temperature; however, elevated temperatures were required to induce lactamization. Bicyclic lactam 183 was isolated in 80% yield and was the only product observed by TLC analysis.

\[
\begin{align*}
181 & \xrightarrow{\text{NaBH}_4, \text{ZnCl}_2, \text{MeOH, rt to reflux}} 183 \\
& \quad \text{80%}
\end{align*}
\]

Scheme 45. Imine reduction and lactamization of cyclic imine 181.
The reduction conditions using Zn(BH₄)₂ were also applied to the reduction of imine 182 (Scheme 46). This reaction provided bicyclic lactams 152a and 152b, which were isolated in 62% yield as a mixture of diastereomers. In a similar fashion, the reduction of 182 also occurred at room temperature with lactamization requiring elevated reaction temperatures. The diastereomeric ratio of products was determined to be 1:1 by integration of the methyl groups in the ¹H NMR. The isolation of lactam diastereomers 152a, 152b completes the formal synthesis of heliotridane and pseudoheliotridane.

A diastereomeric ratio of 1:1 indicates poor selectivity. The absence of diastereoselectivity for this imine reduction is not unexpected. Imine reduction using Zn(BH₄)₂ is believed to operate via a chelate model.¹¹¹ This model would predict the formation of the trans diastereomer (152a). For the reduction of 182, this would require the formation of a 7-membered chelate (Figure 15). Although zinc has been shown to be able to form 7-membered chelates in the presence of bidentate ligands,¹¹² the chelation model is much more reliable in the cases of 5-membered and 6-membered chelates. Another potential predictive model for the reduction of imine 182, would be the Felkin-Ahn model (Figure 15).¹¹³ The Felkin-Ahn model can be used to analyze an open transition state and would predict the formation of the cis diastereomer (152b). The Felkin-Ahn model has been used previously to explain the stereochemical outcome of nucleophilic addition of allylzinc reagents to chiral imines.¹¹⁴ The chelate and Felkin-Ahn models are predictive models. It’s

![Scheme 46. Imine reduction and lactamization of cyclic imine 182.](Image)
plausible that in the case of Zn(BH$_4$)$_2$ reduction of 182, neither model can be accurately used to explain the stereochemical outcome.

![Zinc Chelate and Felkin-Ahn Model](image)

**Figure 15.** Predictive models of stereocontrol for the reduction of imine 182.

**Future work**

The future direction of this project would involve completion of the synthesis of the target natural products through an approach outlined in Scheme 35. This synthesis has the potential to be completed using an SES protecting group, which can be removed through exposure to a fluoride source such as TBAF or CsF.$^{96}$ This reaction leads to the generation of TMSF, ethylene, SO$_2$, and the formation of the free amine, which would be expected to cyclize under the reaction conditions to the imine. This imine differs in structure from 182 because the methyl group is substituted on the 1-pyrroline ring system.$^{96}$ Once deprotection of the amine is accomplished, the synthesis could be completed using Zn(BH$_4$)$_2$ to reduce the cyclic imine and induce lactamization.

![Scheme 47](image)

**Scheme 47.** Proposed enantioselective formal synthesis of heliotridane.

For the phthalimide-protected synthesis, a further development would be to implement an enantioselective version of the zinc-mediated chain extension using 1,1-diiodoethane. A potential
synthetic approach can be seen in Scheme 47. This approach would lead to the formation of the bicyclic lactam with some degree of enantioselectivity. Most enantioselective methods used in zinc carbenoid chemistry are enantioselective cyclopropanations of allylic alcohols. These methods use chiral ligands (dioxaborolanes, bis(sulfonamides), etc.), chiral auxiliaries (2-hydroxyglucopyranoside, diols, etc.), or even chiral catalysts (Ti TADDOLate). An enantioselective approach for the synthesis of heliotridane would presumably require the use of a chiral ligand. As previously mentioned, the $N,N$-bis(methanesulfonyl)-derived ligands led to no stereocontrol in the chain extension reaction using Et$_2$Zn and 1,1-diiodoethane. Therefore, a new methodology would need to be developed to achieve an enantioselective synthesis of heliotridane.
CHAPTER IV

EXPERIMENTALS

GENERAL EXPERIMENTAL SECTION

SOLVENTS:

Anhydrous solvents: tetrahydrofuran, dichloromethane, benzene, and diethyl ether were obtained from EMD Millipore Omni Solv, dispensed from the Innovative Technology Inc. solvent delivery system. All anhydrous reaction solvents (including solvent delivery solvents) were dried over 3 Å or 4 Å molecular sieves for a minimum of 24 h prior to use. All anhydrous solvents were stored under a nitrogen atmosphere. Chloroform-d was stored at 5 °C over 4 Å molecular sieves. Solvents for chromatography use were received from commercial sources and were used as received.

REAGENTS AND REACTIONS:

All reagents were received from commercial sources and were used as received unless otherwise noted. Diisopropylamine and ethyl acetate were distilled and stored over 4 Å molecular sieves and under a nitrogen atmosphere prior to use. p-Toluenesulfonyl chloride was purified from chloroform and petroleum ether prior to use. n-Butyllithium was titrated with diphenylacetic acid prior to use to determine concentration. All reactions were performed under a nitrogen atmosphere using a nitrogen inlet needle and vent needle. All reaction flasks were flushed with nitrogen for a minimum of 15 min prior to use. Sigma Aldrich® rubber septa and Teflon™-coated magnetic stir bars were used. All reaction glassware and magnetic stir bars were oven dried for at least 24 h at 150 °C. Concentration of crude reaction mixtures and pure compounds was done using
a rotary evaporator (10 mmHg, 20-30 °C). Residual solvent was removed by co-evaporation with chloroform. Liquids and oils were dried under nitrogen flow. Solids were dried under high vacuum (0.5 mmHg, 20 °C) for a minimum of 5 h. All reaction temperatures were bath temperatures unless otherwise indicated. Filtrations were performed via gravity using fluted filter paper.

**CHROMATOGRAPHY:**

Flash column chromatography was performed using Silica-P flash silica gel with 40-63 µm particle size. Mobile phases were prepared as described below. Thin layer chromatography was performed using Sigma Aldrich® glass-backed silica gel plates with 60 Å pore size and fluorescent indicator. TLC plates were visualized via UV irradiation at 254 nm, KMnO₄ stain, phosphomolybdic acid stain, or anisaldehyde stain.

**SPECTROSCOPY:**

NMR spectroscopy was conducted using a Varian Mercury Spectrometer operating at 400 MHz for ¹H and at 100 MHz for ¹³C spectroscopy. All ¹³C spectra were proton-decoupled. All NMR resonances were referenced relative to TMS at 0 ppm. All NMR experiments were conducted using CDCl₃ as solvent unless otherwise noted. Mass spectra were obtained at the University of Illinois and recorded on a Waters Synapt G2-Si ESI MS high resolution electrospray mass spectrometer or a Waters GCT Premier™ orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer. The ionization methods used are given below.
DETAILED EXPERIMENTAL SECTION

3-((tert-Butyldimethylsilyl)oxy)propan-1-ol (73)

This compound was prepared according to the procedure by Valot et al.48 An oven-dried 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 1,3-propanediol (71) (5.7 mL, 80 mmol), dichloromethane (80 mL), and triethylamine (6.7 mL, 48 mmol). The reaction mixture was cooled to 0 °C using an ice bath. tert-Butyldimethylsilyl chloride (6.02 g, 40 mmol) was dissolved in dichloromethane (10 mL) and added dropwise by syringe over the course of 10 min. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated sodium bicarbonate (20 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The organic extracts were washed with water (30 mL) and brine (30 mL). The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (8:1 → 6:1 → 4:1 hexanes:ethyl acetate, Rf of 73 = 0.48 (3:1 hexanes:ethyl acetate)) to yield 6.61 g (87%) of the known compound (73) as a clear liquid. ¹H NMR (400 MHz, CDCl₃) δ 3.85 – 3.78 (m, 4H), 2.77 (t, J = 5.1 Hz, 1H), 1.77 (p, J = 5.6 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 62.80, 62.24, 34.18, 25.84, 18.15, -5.53.

3-((tert-Butyldimethylsilyl)oxy)propanal (78)

This compound was prepared according to the procedure by Liu et al.52 An oven-dried 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 73 (2.00 g, 10.5 mmol) and dichloromethane (30 mL). The solution was cooled to 0 °C using an ice bath. Dess-Martin periodinane (5.30 g, 12.5 mmol) was added quickly in one portion. Immediately thereafter,
sodium bicarbonate (4.42 g, 52.5 mmol) was added quickly in one portion. The reaction mixture was stirred for 4 h while slowly warming to room temperature. The reaction mixture was concentrated under reduced pressure and extracted with 1:1 hexanes:ether (4 x 25 mL). The combined extracts were filtered through a pad of silica and washed with 1:1 hexanes:ether. The filtrate was concentrated under reduced pressure. The crude liquid was chromatographed on silica (6:1 hexanes:ether, Rf of 78 = 0.55 (4:1 hexanes:ether)) to yield 1.49 g (76%) of the known compound (78) as a light yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.81 (t, $J$ = 2.1 Hz, 1H), 3.99 (t, $J$ = 6.0 Hz, 2H), 2.60 (td, $J$ = 6.1, 2.1 Hz, 2H), 0.88 (s, 9H), 0.07 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 202.06, 57.39, 46.56, 25.80, 18.22, -5.45.

Mixture of (E)-3-((tert-Butyldimethylsilyl)oxy)propyldene)hydrazine (92a) and (Z)-3-((tert-Butyldimethylsilyl)oxy)propyldene)hydrazine (92b)

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 78 (1.54 g, 8.2 mmol) and dichloromethane (40 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.80 mL, 16.4 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 1.54 g (93%) of the target compounds (92a, 92b) as a yellow liquid. The hydrazones were used immediately in the next reaction without further purification.
**tert-Butyl(3,3-diiodopropoxy)dimethylsilane (99)**

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons.\(^6\) An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones **92a**, **92b** (1.54 g, 7.6 mmol) and dichloromethane (35 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.9 mL, 12.4 mmol) was added dropwise by syringe over the course of 2 min. Iodine (3.33 g, 13.1 mmol) was added in small portions (ca. 0.5 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 25 mL), water (25 mL), and brine (25 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (hexanes, \(R_f\) of 99 = 0.26). The dark red liquid was then dried under nitrogen flow to yield 1.53 g (47%) of the target compound (99) as a dark yellow liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.19 (t, \(J = 7.1\) Hz, 1H), 3.50 (t, \(J = 5.5\) Hz, 2H), 2.55 (dt, \(J = 7.1,\) 5.5 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 63.46, 50.86, 25.89, 18.25, -5.34, -29.89. HRMS (ASAP+): [M+H]+ \(m/z\) calcd for C\(_9\)H\(_{21}\)I\(_2\)OSi: 426.9451; found: 426.9454.

**4-((tert-Butyldimethylsilyl)oxy)butan-1-ol (74)**

This compound was prepared according to the procedure by Valot et al.\(^4\) An oven-dried 250-mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 1,4-butanediol (72) (3.5 mL, 40 mmol), dichloromethane (40 mL), and triethylamine (3.3 mL, 24 mmol). The reaction mixture was cooled to 0 °C using an ice bath. tert-Butyldimethylsilyl chloride (3.01 g, 20 mmol)
was dissolved in dichloromethane (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated sodium bicarbonate (25 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL). The organic extracts were washed with water (25 mL) and brine (25 mL). The combined extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (8:1 → 6:1 → 4:1 hexanes:ethyl acetate, R\textsubscript{f} of 74 = 0.26 (6:1 hexanes:ethyl acetate)) to yield 3.83 g (94%) of the known compound (74) as a clear liquid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.69 – 3.62 (m, 4H), 2.74 (t, J = 5.7 Hz, 2H), 1.68 – 1.62 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 63.36, 62.73, 30.21, 29.88, 25.91, 18.31, -5.39.

4-((tert-Butyldimethylsilyl)oxy)butanal (79)

This compound was prepared according to the procedure by Zhang \textit{et al.} An oven-dried 250 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 74 (2.12 g, 10.4 mmol) and dichloromethane (20 mL). Dess-Martin periodinane (4.61 g, 10.9 mmol) was added quickly in one portion. The reaction mixture was stirred at room temperature for 2 h. Dichloromethane (50 mL) and saturated sodium bicarbonate (35 mL) were added to the reaction mixture. The organic layer was washed with saturated sodium bicarbonate (35 mL) and water (35 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (20:1 → 15:1 → 10:1 hexanes:ethyl acetate, R\textsubscript{f} of 79 = 0.45 (15:1 hexanes:ethyl acetate)) to yield 1.30 g (62%) of the known compound (79) as a clear liquid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 9.79 (t, J = 1.7 Hz, 1H),
3.65 (t, J = 6.0 Hz, 2H), 2.51 (td, J = 7.1, 1.8 Hz, 2H), 1.86 (tt, J = 7.1, 5.9 Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 202.67, 62.07, 40.79, 25.89, 25.49, 18.28, -5.42.

**Mixture of (E)-(4-((tert-Butyldimethylsilyl)oxy)butylidene)hydrazine (93a) and (Z)-(4-((tert-Butyldimethylsilyl)oxy)butylidene)hydrazine (93b)**

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons.$^{63}$ An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 79 (0.580 g, 2.9 mmol) and dichloromethane (25 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.28 mL, 5.7 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 553 mg (89%) of the target compounds (92a, 92b) as a clear liquid. The hydrazones were used immediately in the next reaction without further purification.

**tert-Butyl(4,4-diiodobutoxy)dimethylsilane (100)**

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons.$^{63}$ An oven-dried, 100 mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 93a, 93b (1.11 g, 5.14 mmol) and dichloromethane (30 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.3 mL, 8.74 mmol) was added dropwise by syringe over the course of 2 min. Iodine (1.89 g, 7.43 mmol) was added in small portions (ca. 0.2 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added
until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 25 mL), water (25 mL), and brine (25 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (50:1 hexanes:ethyl acetate, R_f of 100 = 0.13 (hexanes)). The dark red liquid was then dried under nitrogen flow to yield 935 mg (41%) of the target compound (100) as a dark yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 5.18 (t, J = 6.5 Hz, 1H), 3.67 (t, J = 6.0 Hz, 2H), 2.50 – 2.44 (m, 2H), 1.67 – 1.60 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 61.03, 45.37, 34.68, 25.92, 18.27, -5.34, -25.47. HRMS (ASAP+): [M+H]+ m/z calcdd for C₁₀H₂₃I₂OSi: 440.9608; found: 440.9605.

3-(tert-Butyldiphenylsilyl)oxy)propan-1-ol (75)

This compound was prepared according to the procedure by Chen et al.⁴⁹ An oven-dried 250 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 1,3-propanediol (71) (1.01 g, 13.1 mmol) and dichloromethane (25 mL). Triethylamine (0.92 mL, 6.62 mmol) and tert-butyldiphenylsilyl chloride (1.22 g, 4.41 mmol) in dichloromethane (5 mL) were added dropwise by syringe successively. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with dichloromethane (50 mL). The reaction mixture was washed with water (25 mL), sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude oil was chromatographed on silica (4:1 → 1:1 hexanes:ethyl acetate, R_f of 75 = 0.12 (4:1 hexanes:ethyl acetate)) to yield 1.09 g (79%) of the known compound (75) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.69 – 7.67 (m, 4H), 7.46 – 7.37 (m, 6H), 3.87 – 3.82 (m, 4H), 2.36 (t, J =
5.5 Hz, 1H), 1.81 (p, J = 5.6 Hz, 2H), 1.05 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 135.58, 133.30, 129.81, 127.79, 63.18, 61.80, 34.34, 26.86, 19.11.

3-((tert-Butyldiphenylsilyl)oxy)propanal (80)

This compound was prepared according to the procedure by Chen et al. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 75 (1.47 g, 4.68 mmol) and dichloromethane (30 mL). The flask was cooled to 0 °C using an ice bath. Dess-Martin periodinane (2.98 g, 7.02 mmol) was added quickly in one portion. The reaction mixture was stirred for 3 h at room temperature. The reaction mixture was filtered through a pad of Celite ® and the filter cake was washed with dichloromethane (3 x 25 mL). The filtrate was washed with saturated sodium bicarbonate (25 mL) and brine (25 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (9:1 → 4:1 hexanes:ethyl acetate, R$_f$ of 80 = 0.29 (9:1 hexanes:ethyl acetate)) to yield 887 mg (61%) of the known compound (80) as a clear liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.82 (t, J = 2.2 Hz, 1H), 7.67 – 7.64 (m, 4H), 7.46 – 7.37 (m, 6H), 4.02 (t, J = 6.0 Hz, 2H), 2.61 (td, J = 6.0, 2.2 Hz, 2H), 1.04 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.93, 135.53, 133.22, 129.81, 127.76, 58.27, 46.36, 26.73, 19.13.

Mixture of (E)-3-((tert-Butyldiphenylsilyl)oxy)propyldene)hydrazine (94a) and (Z)-(3-((tert-Butyldiphenylsilyl)oxy)propyldene)hydrazine (94b)

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 80 (0.256 g, 0.82 mmol) and dichloromethane (15 mL). The solution was
cooled to 0 °C using an ice bath. Hydrazine hydrate (0.08 mL, 1.64 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (7 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 217 mg (81%) of the target compound (94a, 94b) as a clear liquid. The hydrazones were used immediately in the next reaction without further purification.

**tert-Butyl(3,3-diiodopropoxy)diphenylsilane (101)**

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 94a, 94b (0.853 g, 2.61 mmol) and dichloromethane (20 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.66 mL, 4.44 mmol) was added dropwise by syringe over the course of 1 min. Iodine (1.11 g, 4.38 mmol) was added in small portions (ca. 0.1 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 20 mL), water (20 mL), and brine (20 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (50:1 hexanes:ethyl acetate, Rf of 101 = 0.54 (25:1 hexanes:ethyl acetate)). The dark red liquid was then dried under nitrogen flow to yield 663 mg (47%) of the target compound (101) as an orange liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.69 – 7.64 (m, 4H), 7.46 – 7.37 (m, 6H), 5.32 (t, $J = 7.1$ Hz, 1H), 3.54 (t, $J = 5.5$ Hz, 2H), 2.58
(dt, $J = 7.2, 5.5$ Hz, 2H), 1.05 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.57, 133.15, 129.82, 127.78, 64.24, 50.83, 26.83, 19.22, -30.53.

3-((Triisopropylsilyl)oxy)propan-1-ol (76)

This compound was prepared according to the procedure by Park et al.$^{50}$ An oven-dried 250 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with sodium hydride (0.469 g, 11.1 mmol) and tetrahydrofuran (20 mL). The flask was cooled to 0 °C using an ice bath. 1,3-propanediol (71) (0.80 mL, 11.1 mmol) was added dropwise by syringe over the course of 3 min. The reaction mixture was stirred for 30 min at room temperature. Triisopropylsilyl chloride (1.19 mL, 11.1 mmol) was added quickly in one portion. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with diethyl ether (20 mL), followed by cautious addition of water (25 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The organic layers were combined and washed with brine (2 x 10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude oil was chromatographed on silica (9:1 hexanes:ethyl acetate, $R_f$ of 76 = 0.19) to yield 1.08 g (42%) of the known compound (76) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.94 (t, $J = 5.5$ Hz, 2H), 3.84 (q, $J = 5.4$ Hz, 2H), 2.77 (t, $J = 5.4$ Hz, 1H), 1.81 (p, $J = 5.5$ Hz, 2H), 1.14 – 1.05 (m, 21H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 63.55, 62.62, 34.16, 17.91, 11.75.

3-((Triisopropylsilyl)oxy)propanal (81)

This compound was prepared with modification to the procedure by Chen et al.$^{49}$ An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 76 (0.248 g, 1.05 mmol), and dichloromethane (10 mL). The flask was cooled to 0 °C using an ice bath. Dess-
Martin periodinane (0.680 g, 1.62 mmol) was added quickly in one portion. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with dichloromethane (3 x 10 mL). The filtrate was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (9:1 hexanes:ethyl acetate, Rf of 81 = 0.34) to yield 138 mg (56%) of the known compound (81) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 9.84 (t, J = 2.2 Hz, 1H), 4.08 (t, J = 6.1 Hz, 2H), 2.61 (td, J = 6.0, 2.2 Hz, 2H), 1.12 – 1.03 (m, 21H). ¹³C NMR (100 MHz, CDCl₃) δ 202.30, 57.90, 46.73, 17.93, 11.86.

**Mixture of (E)-(3-((Triisopropylsilyl)oxy)propyldene)hydrazine (95a) and (Z)-(3-((Triisopropylsilyl)oxy)propyldene)hydrazine (95b)**

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 81 (0.522 g, 2.26 mmol) and dichloromethane (15 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.22 mL, 4.53 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 523 mg (95%) of the target compounds (95a, 95b) as a clear liquid. The hydrazones were used immediately in the next reaction without further purification.
(3,3-Diodopropoxy)triisopropylsilane (63)

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons.63 An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 95a, 95b (0.528 g, 2.16 mmol) and dichloromethane (10 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.55 mL, 3.67 mmol) was added dropwise by syringe over the course of 1 min. Iodine (0.994 g, 3.92 mmol) was added in small portions (ca. 0.1 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 25 mL), water (25 mL), and brine (25 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (hexanes, Rf of 63 = 0.50). The dark red liquid was then dried under nitrogen flow to yield 475 mg (47%) of the target compound (63) as an orange liquid. 1H NMR (400 MHz, CDCl3) δ 5.25 (t, J = 7.1 Hz, 1H), 3.59 (t, J = 5.5 Hz, 2H), 2.57 (dt, J = 7.1, 5.5 Hz, 2H), 1.12 – 1.04 (m, 21H). 13C NMR (100 MHz, CDCl3) δ 63.77, 51.25, 18.01, 11.89, -29.87. HRMS (ES+): [M+H]+ m/z calcd for C12H27I2OSi: 468.9921; found: 468.9917.

3-(Benzyloxy)propan-1-ol (77)

This compound was prepared according to the procedure by Targel et al.51 An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with sodium hydride (60% dispersion in mineral oil, 0.548 g, 13.1 mmol) and tetrahydrofuran (5 mL). The flask was cooled to 0 °C using an ice bath. 1,3-propanediol (71) (1.02 g, 13.1 mmol) was dissolved in
tetrahydrofuran (5 mL) and was added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at room temperature for 30 min. Benzyl bromide (2.26 g, 13.1 mmol) was dissolved in tetrahydrofuran (6 mL) was added dropwise by syringe over the course of 6 min. The flask was equipped with a condenser and the reaction mixture was refluxed for 19 h using an oil bath. The reaction mixture was cooled to room temperature and quenched with cautious addition of water (25 mL). The mixture was extracted with diethyl ether (3 x 15 mL). The organic layers were washed with brine (3 x 10 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (2:1 → 1:1 hexanes:ethyl acetate, Rf of 77 = 0.36 (2:1 hexanes:ethyl acetate)) to yield 1.10 g (50%) of the known compound (77) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H), 4.53 (s, 2H), 3.79 (q, J = 5.5 Hz, 2H), 3.67 (t, J = 5.8 Hz, 2H), 2.32 – 2.28 (m, 1H), 1.87 (p, J = 5.7 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 138.11, 128.46, 127.72, 127.67, 73.23, 69.12, 61.51, 32.15.

3-(Benzyloxy)propanal (82)

This compound was prepared according to the procedure by Mukherjee et al. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 77 (0.753 g, 4.51 mmol) and dichloromethane (20 mL). The solution was cooled to 0 °C using an ice bath and Dess-Martin periodinane (2.10 g, 4.96 mmol) was added quickly in one portion. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with dichloromethane (40 mL) and quenched with an aqueous solution of sodium thiosulfate/sodium bicarbonate (1:1, 40 mL). The organic layer was washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and
concentrated under reduced pressure. The crude solid was chromatographed on silica (8:1 → 6:1 hexanes:ethyl acetate, Rf of 82 = 0.63 (2:1 hexanes:ethyl acetate)) to yield 558 mg (75%) of the known compound (82) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.80 (t, $J = 1.9$ Hz, 1H), 7.37 – 7.27 (m, 5H), 4.54 (s, 2H), 3.82 (t, $J = 6.1$ Hz, 2H), 2.70 (td, $J = 6.1, 1.9$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.22, 137.86, 128.46, 127.80, 73.25, 63.84, 43.86.

**Mixture of (E)-(3-(Benzyloxy)propylidene)hydrazine (96a) and (Z)-(3-(Benzyloxy)propylidene)hydrazine (96b)**

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons.$^{63}$ An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 82 (0.173 g, 1.05 mmol) and dichloromethane (5 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.10 mL, 2.10 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 152 mg (81%) of the target compounds (96a, 96b) as a yellow liquid. The hydrazones were used immediately in the next reaction without further purification.

**((3,3-Diiodopropoxy)methyl)benzene (102)**

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons.$^{63}$ An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 96a, 96b (0.410 g, 2.30 mmol) and dichloromethane (10 mL).
Diazabicyclo[5.4.0]undec-7-ene (0.58 mL, 3.91 mmol) was added dropwise by syringe over the course of 1 min. Iodine (0.934 g, 3.68 mmol) was added in small portions (ca. 0.1 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 20 mL), water (20 mL), and brine (20 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (30:1 hexanes:ethyl acetate, Rf of 102 = 0.58 (10:1 hexanes:ethyl acetate)). The dark red liquid was then dried under nitrogen flow to yield 425 mg (46%) of the target compound (102) as a yellow liquid. 1H NMR (400 MHz, CDCl3) δ 7.39 – 7.29 (m, 5H), 5.23 (t, J = 7.1 Hz, 1H), 4.51 (s, 2H), 3.38 (t, J = 5.5 Hz, 2H), 2.63 (dt, J = 7.2, 5.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) 137.83, 128.48, 127.84, 127.80, 73.32, 70.42, 48.28, -30.21. HRMS (EI+): [M]+ m/z calcd for C10H12I2O: 401.8978; found: 401.8979.

N-(3-Hydroxypropyl)-4-methylbenzenesulfonamide (88)

This compound was prepared according to the procedure by Beltran et al.58 An oven-dried 250 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tosyl chloride (2.30 g, 12.1 mmol) and dichloromethane (50 mL). The solution was cooled to 0 °C using an ice bath. Triethylamine (2.5 mL, 18.2 mmol) was added dropwise by syringe over the course of 3 min. 3-aminopropanol (87) (1.01 g, 13.3 mmol) was dissolved in dichloromethane (10 mL) and added dropwise by syringe over the course of 10 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with 1 M hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 x 20 mL) and diethyl ether (20 mL). The organic layers were washed separately with saturated sodium bicarbonate (30 mL) and brine.
(20 mL). The organic layers were combined and dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (1:1 → 1:2 hexanes:ethyl acetate, Rf of 88 = 0.26. (1:1 hexanes:ethyl acetate)) to yield 2.50 g (90%) of the known compound (88) as a white solid (MP: 55 – 56 °C, MP (lit.): 55 – 56 °C).\(^{120}\) \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.77 – 7.74 (m, 2H), 7.33 – 7.30 (m, 2H), 4.97 (s, 1H), 3.74 (dt, \(J = 5.7, 5.2\) Hz, 2H), 3.10 (q, \(J = 6.2\) Hz, 2H), 2.43 (s, 3H), 1.78 – 1.68 (m, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 143.42, 136.77, 129.74, 127.06, 60.56, 40.99, 31.44, 21.52.

**4-Methyl-N-(3-oxopropyl)benzenesulfonamide (90)**

**Method A:**

This compound was prepared according to the procedure by Serpier et al.\(^{60}\) An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 88 (0.251 g, 1.09 mmol) and dichloromethane (10 mL). The flask was cooled to 0 °C using an ice bath. Dess-Martin periodinane (0.693 g, 1.64 mmol) was added quickly in one portion. The reaction mixture was warmed slowly to room temperature and stirred for 19 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (30 mL). The solution was filtered through a pad of silica and the filter cake was washed with ethyl acetate (3 x 10 mL). The filtrate was concentrated under reduced pressure. The crude solid was chromatographed on silica (4:1 → 2:1 → 1:1 hexanes:ethyl acetate, Rf of 90 = 0.52 (1:1 hexanes:ethyl acetate)) to yield 191 mg (78%) of the known compound (90) as a yellow oil.

**Method B:**

This compound was prepared according to the procedure by Kokotos and Aggarwal.\(^{61}\) An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and
nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with oxalyl chloride (0.406 g, 3.17 mmol) and dichloromethane (3 mL). The solution was cooled to -78 °C using an acetone/dry ice bath. Dimethyl sulfoxide (0.75 mL, 10.6 mmol) was dissolved in dichloromethane (1 mL) and was added dropwise by syringe over the course of 1 min. Alcohol 88 (0.483 g, 2.11 mmol) was dissolved in dichloromethane (4 mL) and was added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 50 min. Diisopropylamine (2.6 mL, 14.8 mmol) was added dropwise by syringe and the reaction mixture was warmed to 0 °C over the course of 30 min. The reaction mixture was acidified with 10% citric acid solution (pH ≈ 5). The mixture was extracted with diethyl ether:ethyl acetate (1:1, 3 x 15 mL). The organic layer was washed with water (2 x 15 mL), saturated sodium bicarbonate (2 x 15 mL), and brine (15 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (2:1 → 1:1 hexanes:ethyl acetate, Rf of 90 = 0.52 (1:1 hexanes:ethyl acetate)) to yield 258 mg (54%) of the known compound (90) as a yellow oil. 1H NMR (400 MHz, CDCl₃) δ 9.74 (s, 1H), 7.76 – 7.73 (m, 2H), 7.34 – 7.31 (m, 2H), 4.96 (s, 1H), 3.20 (dt, J = 6.8, 5.8 Hz, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.44 (s, 3H). 13C NMR (100 MHz, CDCl₃) δ 200.81, 143.65, 136.78, 129.84, 127.05, 43.63, 36.83, 21.54.

Mixture of (E)-N-(3-Hydradazonopropyl)-4-methylbenzenesulfonamide (97a) and (Z)-N-(3-Hydradazonopropyl)-4-methylbenzenesulfonamide (97b)

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons.⁶³ An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 90 (0.191 g, 0.839 mmol) and dichloromethane (6 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.08 mL, 1.68 mmol) was added dropwise by
syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (8 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 180 mg (89%) of the target compounds (97a, 97b) as a gummy white solid. The hydrazones were used immediately in the next reaction without further purification.

**N-(3,3-Diodopropyl)-4-methylbenzenesulfonamide (103)**

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 97a, 97b (0.200 g, 0.83 mmol) and dichloromethane (10 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.21 mL, 1.41 mmol) was added dropwise by syringe over the course of 1 min. Iodine (0.300 g, 1.18 mmol) was added in small portions (ca. 0.1 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 10 mL), water (10 mL), and brine (10 mL). The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (5:1 → 3:1 hexanes:ethyl acetate, Rf of 103 = 0.41 (3:1 hexanes:ethyl acetate)). The dark yellow solid was then dried under nitrogen flow to yield 117 mg (30%) of the target compound (103) as a light yellow solid. 

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.78 – 7.75 (m, 2H), 7.36 – 7.32 (m, 2H), 5.09 (t, $J = 6.5$ Hz, 1H), 4.56 (s, 1H), 3.03 – 2.98 (m, 2H), 2.55 (td, $J = 6.6$, 6.0 Hz, 2H), 2.45 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.89,
136.45, 129.94, 127.15, 47.41, 44.72, 21.58, -32.88. HRMS (ES+): [M+H]^+ m/z calcd for C_{10}H_{14}I_{2}NO_{2}S: 465.8835; found: 465.8829.

2-(2-Hydroxyethyl)isoindoline-1,3-dione (84)

This compound was prepared according to the procedure by Stach et al.\textsuperscript{56} An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with phthalic anhydride (1.02 g, 6.75 mmol), 2-aminoethanol (83) (0.410 g, 6.75 mmol), and toluene (7 mL). The flask was equipped with a Dean-Stark apparatus and a condenser. The flask was charged with triethylamine (3.4 mL, 24.3 mmol). The reaction mixture was heated to 120 °C and was refluxed for 3.5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and saturated sodium bicarbonate (25 mL) was added. The organic layer was washed with brine (3 x 10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 871 mg (66\%) of the known compound (84) as an off-white solid (MP: 125 – 128 °C, MP (lit.): 126 – 127 °C).\textsuperscript{121} The crude solid was used in the next step without further purification. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.89 – 7.84 (m, 2H), 7.76 – 7.71 (m, 2H), 3.94 – 3.86 (m, 4H), 2.18 (t, J = 5.7 Hz, 1H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 168.82, 134.08, 131.92, 123.35, 60.87, 40.78.

2-(2-Iodoethyl)isoindoline-1,3-dione (85)

This compound was prepared according to the procedure by Gerpe et al.\textsuperscript{57} An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was charged with triphenylphosphine (0.162 g, 0.62 mmol), imidazole (43 mg), and dichloromethane (10 mL). Iodine (0.154 g, 0.62 mmol) was added slowly and the reaction mixture was stirred for 5 min. Alcohol 84 (0.100 g, 0.52 mmol) was then added to the reaction
mixture. The reaction mixture was stirred at room temperature for 4 h. A solution of sodium thiosulfate (5%, 15 mL) was added to the reaction mixture. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (10:1 hexanes:ethyl acetate, Rf of 85 = 0.17) to yield 138 mg (88%) of the known compound (85) as a white solid (MP: 92 – 95 °C, MP (lit.): 92 – 93 °C).122 1H NMR (400 MHz, CDCl3) δ 7.89 – 7.86 (m, 2H), 7.78 – 7.73 (m, 2H), 4.09 (t, J = 7.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 167.66, 134.24, 131.84, 123.54, 40.04, -0.04.

2-(3-Hydroxypropyl)isoindoline-1,3-dione (89)

This compound was prepared according to the procedure by Catalano et al.59 An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 3-aminopropanol (87) (0.507 g, 6.66 mmol), toluene (10 mL), triethylamine (3.3 mL, 24.0 mmol), and phthalic anhydride (0.984 g, 6.66 mmol). The flask was equipped with a Dean-Stark apparatus and a condenser. The reaction mixture was heated to 120 °C using an oil bath and was refluxed for 18 h. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (20 mL). The organic layer was washed with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was recrystallized in ethyl acetate/hexanes to yield 853 mg (62%) of the known compound (89) as a white solid (MP: 77 – 79 °C, MP (lit.): 74 – 75 °C).123 1H NMR (400 MHz, CDCl3) δ 7.88 – 7.84 (m, 2H), 7.76 – 7.72 (m, 2H), 3.87 (t, J = 6.3 Hz, 2H), 3.62 (q, J = 6.1 Hz, 2H), 2.48 (t, J = 6.6 Hz, 1H), 1.91 – 1.85 (m, 2H). 13C NMR (100 MHz, CDCl3) δ 168.95, 134.13, 131.99, 123.39, 59.02, 34.20, 31.33.
3-(1,3-Dioisoindolin-2-yl)propanal (91)

This compound was prepared according to the procedure by Klepper et al.\textsuperscript{62} An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 89 (0.249 g, 12.0 mmol) and dichloromethane (10 mL). Dess-Martin periodinane (0.749 g, 18.0 mmol) was added rapidly in one portion. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane (20 mL). The reaction mixture was washed with saturated sodium thiosulfate (10 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (2:1 hexanes:ethyl acetate, R\textsubscript{f} of 91 = 0.74) to yield 225 mg (91\%) of the known compound (91) as a white solid (MP: 115 – 120 °C, MP (lit.): 115 – 116 °C).\textsuperscript{124}\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 9.83 (t, J = 1.3 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.75 – 7.71 (m, 2H), 4.04 (t, J = 7.0 Hz, 2H), 2.88 (td, J = 7.0, 1.4 Hz, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 199.47, 168.01, 134.12, 131.92, 123.36, 42.34, 31.65.

Mixture of (E)-2-(3-Hydrazonepropyl)isoindoline-1,3-dione (98a) and (Z)-2-(3-Hydrazonepropyl)isoindoline-1,3-dione (98b)

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons.\textsuperscript{63} An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 91 (0.706 g, 3.47 mmol) and dichloromethane (20 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.17 mL, 3.47 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was quenched with water (10 mL). The aqueous layer was extracted with dichloromethane (3 x 15 mL). The
combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 582 mg (77%) of the target compounds (98a, 98b) as a white solid. The hydrazones were used immediately in the next reaction without further purification.

2-(3,3-Diiodopropyl)isoindoline-1,3-dione (86)

This compound was prepared with modification to the procedure by Friedrich, Falling, and Lyons. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with hydrazones 98a, 98b (0.582 g, 2.68 mmol) and dichloromethane (15 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.68 mL, 4.55 mmol) was added dropwise by syringe over the course of 1 min. Iodine (0.622 g, 2.45 mmol) was added in small portions (ca. 0.1 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. The reaction mixture was washed with sodium thiosulfate (2 x 15 mL), water (15 mL), and brine (15 mL). The organic layer was then dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude solid was chromatographed on silica (5:1 hexanes:ethyl acetate, Rf of 86 = 0.32). The orange solid was then dried under nitrogen flow to yield 215 mg (18%) of the target compound (86) as a yellow solid. 1H NMR (400 MHz, CDCl3) δ 7.89 – 7.84 (m, 2H), 7.76 – 7.72 (m, 2H), 5.10 (t, J = 6.6 Hz, 1H), 3.77 (t, J = 6.7 Hz, 2H), 2.82 (q, J = 6.8 Hz, 2H). 13C NMR (100 MHz, CDCl3) δ 168.10, 134.20, 131.90, 123.46, 46.26, 39.52, -34.73. HRMS (ES+): [M+H]+ m/z calcd for C11H10I2NO: 441.8801; found: 441.8795.
**Methyl 3-acetyl-5-((tert-butyldimethylsilyl)oxy)pentanoate (105a)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.91 mL, 0.91 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Methyl acetoacetate (104a) (21 mg, 0.18 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.387 g, 0.91 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (10:1 hexanes:ethyl acetate, Rf of 105a = 0.33 (3:1 hexanes:ethyl acetate)) to yield 24 mg (47%) of the target compound (105a) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 3.65 – 3.61 (m, 5H), 3.18 – 3.11 (m, 1H), 2.76 (dd, J = 16.8, 9.7 Hz, 1H), 2.40 (dd, J = 16.8, 4.6 Hz, 1H), 2.26 (s, 3H), 1.88 – 1.80 (m, 1H), 1.68 – 1.60 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) δ 210.83, 172.87, 60.30, 51.73, 44.92, 34.89, 34.08, 29.55, 25.86, 18.24, –5.48, –5.50. HRMS (ASAP+): [M+H]^+ m/z calcd for C\(_{14}\)H\(_{29}\)O\(_4\)Si: 289.1835; found: 289.1833.

**Ethyl 3-acetyl-5-((tert-butyldimethylsilyl)oxy)pentanoate (105b)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (4 mL) and diethylzinc (0.82 mL, 0.82 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Ethyl acetoacetate (104b) (22 mg, 0.16 mmol) in dichloromethane (1 mL) was added
dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min.
Geminal diiodide 99 (0.348 g, 0.82 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (15:1 hexanes:ethyl acetate, $R_f$ of 105b = 0.46 (3:1 hexanes:ethyl acetate)) to yield 24 mg (47%) of the target compound (105b) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.10 (q, $J = 7.1$ Hz, 2H), 3.63 (t, $J = 6.0$ Hz, 2H), 3.17 − 3.10 (m, 1H), 2.75 (dd, $J = 16.8$, 9.7 Hz, 1H), 2.39 (dd, $J = 16.8$, 4.6 Hz, 1H), 2.26 (s, 3H), 1.88 − 1.80 (m, 1H), 1.68 − 1.59 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.89, 172.36, 60.59, 60.33, 44.88, 35.24, 34.12, 29.59, 25.87, 18.24, 14.16, −5.47, −5.49. HRMS (ASAP+): [M+H]$^+$ m/z calcd for C$_{15}$H$_{31}$O$_4$Si: 303.1992; found: 303.1993.

**Benzyl 3-acetyl-5-((tert-butyldimethylsilyl)oxy)pentanoate (105c)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.48 mL, 0.48 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Benzyl acetoacetate (104c) (30 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.205 g, 0.48 mmol) added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 30 min. Diethylzinc (0.48 mL, 0.48 mmol, 1.0 M in hexanes) was added dropwise by syringe at room temperature and the
reaction mixture was stirred for 10 min. Geminal diiodide 99 (0.205 g, 0.48 mmol) was added dropwise by syringe over the course of 2 min and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (20:1→15:1 hexanes:ethyl acetate, Rf of 105c = 0.46 (3:1 hexanes:ethyl acetate)) to yield 26 mg (46%) of the target compound (105c) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.32 (m, 5H), 5.13 – 5.05 (m, 2H), 3.62 (t, $J$ = 6.0 Hz, 2H), 3.19 – 3.12 (m, 1H), 2.82 (dd, $J$ = 16.9, 9.7 Hz, 1H), 2.44 (dd, $J$ = 16.9, 4.5 Hz, 1H), 2.23 (s, 3H), 1.87 – 1.79 (m, 1H), 1.68 – 1.59 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.74, 172.20, 135.77, 128.57, 128.26, 128.21, 66.45, 60.29, 44.88, 35.13, 34.09, 29.55, 25.86, 18.23, –5.48, –5.49. HRMS (ASAP+): [M+H]$^+$ m/z calcd for C$_{20}$H$_{33}$O$_4$Si: 365.2148; found: 365.2144.

**Allyl 3-acetyl-5-((tert-butyldimethylsilyl)oxy)pentanoate (105d)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.48 mL, 0.48 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Allyl acetoacetate (104d) (22 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.205 g, 0.48 mmol) added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 30 min. Diethylzinc (0.48 mL, 0.48 mmol, 1.0 M in hexanes) was added dropwise by syringe at room temperature and the reaction mixture was stirred for 10 min. Geminal diiodide 99 (0.205 g, 0.48 mmol) was added
dropwise by syringe over the course of 2 min and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (20:1 hexanes:ethyl acetate, Rf of 105d = 0.50 (3:1 hexanes:ethyl acetate)) to yield 17 mg (35%) of the target compound (105d) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 5.94 – 5.84 (m, 1H), 5.33 – 5.21 (m, 2H), 4.55 (dt, J = 5.7, 1.4 Hz, 2H), 3.63 (t, J = 6.0 Hz, 2H), 3.19 – 3.12 (m, 1H), 2.79 (dd, J = 16.9, 9.7 Hz, 1H), 2.43 (dd, J = 16.9, 4.6 Hz, 1H), 2.26 (s, 3H), 1.88 – 1.80 (m, 1H), 1.69 – 1.58 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). 13C NMR (100 MHz, CDCl3) δ 210.76, 172.05, 132.01, 118.33, 65.29, 60.30, 44.88, 35.05, 34.09, 29.56, 25.87, 18.24, −5.48, −5.49. HRMS (ASAP+): [M+H]+ m/z calcd for C16H31O4Si: 315.1992; found: 315.1987.

**Methyl 3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-oxohexanoate (105e)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Methyl propionylacetate (104e) (21 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.346 g, 0.81 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and
concentrated under reduced pressure. The crude residue was chromatographed on silica (20:1 hexanes:ethyl acetate, $R_f$ of 105e = 0.64 (3:1 hexanes:ethyl acetate)) to yield 28 mg (57%) of the target compound (105e) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.64 – 3.59 (m, 5H), 3.18 – 3.11 (m, 1H), 2.78 (dd, $J = 16.8, 9.8$ Hz, 1H), 2.61 (qd, $J = 7.3, 3.5$ Hz, 2H), 2.41 (dd, $J = 16.8, 4.5$ Hz, 1H), 1.85 – 1.77 (m, 1H), 1.64 – 1.55 (m, 1H), 1.06 (t, $J = 7.3$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.53, 172.91, 60.39, 51.69, 43.89, 35.47, 35.13, 34.39, 25.87, 18.24, 7.64, -5.45, -5.46. HRMS (ES+) [M+Na]$^+$ m/z calcd for C$_{15}$H$_{30}$O$_4$NaSi: 325.1811; found: 325.1808.

Methyl 3-(2-(tert-butyldimethylsilyl)oxy)ethyl)-5-methyl-4-oxohexanoate (105f)

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (1.20 mL, 1.20 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Methyl isobutyrylacetate (104f) (34 mg, 0.24 mmol) in dichloromethane (2 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.512 g, 1.20 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (20:1 hexanes:ethyl acetate, $R_f$ of 105f = 0.71 (3:1 hexanes:ethyl acetate)) to yield 16 mg (21%) of the target compound (105f) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.64 (s, 3H), 3.62 – 3.59 (m, 2H), 3.35 – 3.30 (m, 1H), 2.89 – 2.82 (m, 1H), 2.75 (dd, $J = 16.7, 9.5$ Hz, 1H), 2.40 (dd, $J =$
16.6, 4.6 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.56 – 1.50 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 216.26, 172.78, 60.35, 51.64, 42.39, 39.66, 34.71, 34.10, 25.87, 18.77, 18.24, 17.93, -5.41, -5.43. HRMS (ES+) [M+Na]\(^+\) \(m/z\) calcd for C\(_{16}\)H\(_{32}\)O\(_4\)NaSi: 339.1968; found: 339.1968.

**Methyl 5-((tert-butyldimethylsilyl)oxy)-3-(4-methoxybenzoyl)petanoate (105g)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. 3-(4-Methoxyphenyl)-3-oxo-propionic acid methyl ester (104g) (33 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.347 g, 0.81 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (20:1 → 15:1 → 10:1 hexanes:ethyl acetate, \(R_f\) of 105g = 0.35 (5:1 hexanes:ethyl acetate)) to yield 27 mg (44%) of the target compound (105g) as a yellow oil. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.03 (d, \(J = 8.9\) Hz, 2H), 6.92 (d, \(J = 8.9\) Hz, 2H), 4.12 – 4.06 (m, 1H), 3.86 (s, 3H), 3.64 – 3.56 (m, 5H), 2.92 (dd, \(J = 16.7, 9.5\) Hz, 1H), 2.52 (dd, \(J = 16.6, 4.6\) Hz, 1H), 1.97 – 1.91 (m, 1H), 1.64 – 1.56 (m, 1H), 0.88 (s, 9H), -0.02 (s, 6H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 201.20, 172.90, 163.51, 130.96, 129.45, 113.71, 60.27, 55.47, 51.69, 38.45, 35.58, 35.43, 25.88, 18.24, -5.46, -5.48. HRMS (ES+) [M+H]\(^+\) \(m/z\) calcd for C\(_{20}\)H\(_{35}\)O\(_5\)Si: 381.2097; found: 381.2089.
**tert-Butyl 3-acetyl-5-((tert-butyldimethylsilyl)oxy)pentanoate (105h)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with 1,2-dichloroethane (3 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. *tert*-Butyl acetoacetate (104h) (25 mg, 0.16 mmol) in 1,2-dichloroethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.349 g, 0.82 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (50:1 → 40:1 → 30:1 hexanes:ethyl acetate, $R_f$ of 105h = 0.62 (5:1 hexanes:ethyl acetate)) to yield 24 mg (45%) of the target compound (105h) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.62 (t, $J = 6.1$ Hz, 2H), 3.11 – 3.04 (m, 1H), 2.66 (dd, $J = 16.6$, 9.6 Hz, 1H), 2.32 (dd, $J = 16.6$, 4.7 Hz, 1H), 2.24 (s, 3H), 1.82 (dq, $J = 13.9$, 6.3 Hz, 1H), 1.63 – 1.58 (m, 1H), 1.42 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 210.91, 171.53, 80.70, 60.41, 45.04, 36.56, 34.04, 29.52, 28.05, 25.88, 18.25, -5.46, -5.48. HRMS (ES+) [M+Na]$^+$ m/z calcd for C$_{17}$H$_{34}$O$_4$NaSi: 353.2124; found: 353.2118.

**Methyl 3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5,5-dimethyl-4-oxohexanoate (105i)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with 1,2-dichloroethane (3 mL) and diethylzinc (1.20 mL, 1.20 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using
an ice bath. Methyl pivaloylacetate (104i) (38 mg, 0.24 mmol) in 1,2-dichloroethane (2 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.485 g, 1.14 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (7 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (50:1 → 40:1 → 30:1 hexanes:ethyl acetate, Rf of 105i = 0.69 (5:1 hexanes:ethyl acetate)) to yield 5 mg (6%) of the target compound (105i) as a yellow residue. 1H NMR (400 MHz, CDCl3) δ 3.64 (s, 3H), 3.60 – 3.57 (m, 3H), 2.71 (dd, J = 16.2, 8.6 Hz, 1H), 2.41 (dd, J = 16.3, 5.3 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.50 – 1.43 (m, 1H), 1.20 (s, 9H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 217.81, 172.62, 60.28, 51.64, 44.71, 38.42, 35.91, 34.90, 26.89, 25.87, 18.22, -5.41, -5.43. HRMS (ES+) [M+Na]+ m/z calcd for C17H34O4NaSi: 353.2124; found: 353.2112.

3-Acetyl-5-((tert-butyldimethylsilyl)oxy)-N,N-dimethylpentanamide (107a)

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (2 mL) and diethylzinc (0.82 mL, 0.82 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. N,N-Dimethylacetoacetamide (106a) (19 mg, 0.16 mmol) was dissolved in dichloromethane (2 mL) and 4 Å molecular sieves were added. This solution was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.350 g, 0.82 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was
quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1 hexanes:ethyl acetate, Rf of 107a = 0.29) to yield 22 mg (50%) of the target compound (107a) as a yellow oil. \( ^1H \text{NMR (400 MHz, CDCl}_3 \) δ 3.64 (t, \( J = 6.1, 2H \)), 3.28 – 3.22 (m, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.83 (dd, \( J = 16.4, 10.3 \text{ Hz, 1H} \)), 2.38 (dd, \( J = 16.4, 3.8 \text{ Hz, 1H} \)), 2.31 (s, 3H), 1.81 – 1.75 (m, 1H), 1.66 – 1.59 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). \( ^{13}C \text{NMR (100 MHz, CDCl}_3 \) δ 212.44, 171.40, 60.83, 44.89, 37.12, 35.50, 35.38, 34.53, 30.26, 25.88, 18.23, –5.42, –5.44. HRMS (ES+): [M+H]+ m/z calcd for C\(_{15}\)H\(_{32}\)NO\(_3\)Si: 302.2151; found: 302.2153.

**3-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-1-morpholinopentane-1,4-dione (107b)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (2 mL) and diethylzinc (0.82 mL, 0.82 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. \( N \)-Acetoacetylmorpholine (106b) (27 mg, 0.16 mmol) was dissolved in dichloromethane (2 mL) and 4 Å molecular sieves were added. This solution was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.362 g, 0.85 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1 hexanes:ethyl acetate, Rf of 107b = 0.23) to yield 30 mg (55%) of the target compound (107b) as an orange oil. \( ^1H \text{NMR (400 MHz, CDCl}_3 \) δ 3.69 – 3.44 (m, 10H), 3.30 – 3.44 (m, 10H), 3.30 – 3.23 (m, 1H),
2.84 (dd, $J = 16.3, 10.3$ Hz, 1H), 2.37 (dd, $J = 16.3, 3.8$ Hz, 1H), 2.31 (s, 3H), 1.83 – 1.75 (m, 1H), 1.65 – 1.59 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 212.11, 170.14, 66.85, 66.51, 60.78, 45.84, 44.90, 41.96, 34.94, 34.46, 30.14, 25.87, 18.22, -5.43, -5.44. HRMS (ES+): $[M+H]^+$ m/z calcld for C$_{17}$H$_{34}$NO$_4$Si: 344.2257; found: 344.2256.

Dimethyl (2-acetyl-4-((tert-butyldimethylsilyl)oxy)butyl)phosphonate (109a)

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Dimethyl (2-oxopropyl)phosphonate (108a) (27 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.341 g, 0.80 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (7:1 ethyl acetate:hexanes, R$_f$ of 109a = 0.27 (ethyl acetate)) to yield 18 mg (33%) of the target compound (109a) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.71 (d, $J_{PH} = 10.8$ Hz, 3H), 3.69 (d, $J_{PH} = 10.8$ Hz, 3H), 3.63 (t, $J_{HH} = 5.9$ Hz, 2H), 3.12 – 3.02 (m, 1H), 2.33 – 2.26 (m, 1H), 2.24 (s, 3H), 1.92 – 1.70 (m, 3H), 0.89 (s, 9H), 0.04 (s, 3H) 0.03 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.96 (d, $J_{PC} = 6.1$ Hz) 60.08, 52.37 (d, $J_{PC} = 6.5$ Hz), 52.26 (d, $J_{PC} = 6.5$ Hz) 43.32 (d, $J_{PC} = 3.5$ Hz), 35.71 (d, $J_{PC} = 12.9$ Hz), 29.68, 25.85, 25.33 (d, $J_{PC} = 141.2$ Hz). 18.24, –5.53, –5.54. HRMS (ASAP+): $[M+H]^+$ m/z calcld for C$_{14}$H$_{32}$O$_5$PSi: 339.1757; found: 339.1754.
Diethyl (2-acetyl-4-((tert-butyldimethylsilyl)oxy)butyl)phosphonate (109b)

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Diethyl (2-oxopropyl)phosphonate (108b) (31 mg, 0.16 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.340 g, 0.80 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 ethyl acetate:hexanes, R_f of 109b = 0.32 (ethyl acetate)) to yield 20 mg (34%) of the target compound (109b) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 4.09 – 4.02 (m, 4H), 3.62 (t, \(J_{HH} = 5.8\) Hz, 2H), 3.12 – 3.02 (m, 1H), 2.36 – 2.19 (m, 4H), 1.90 – 1.72 (m, 3H), 1.31 (q, \(J_{HH} = 6.9\) Hz, 6H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 210.13 (d, \(J_{PC} = 6.2\) Hz), 61.74 (d, \(J_{PC} = 6.2\) Hz), 61.61 (d, \(J_{PC} = 6.5\) Hz), 60.13, 43.36 (d, \(J_{PC} = 3.5\) Hz), 35.82 (d, \(J_{PC} = 12.7\) Hz), 29.80, 26.47 (d, \(J_{PC} = 141.3\) Hz), 25.86, 18.23, 16.37 (d, \(J_{PC} = 6.1\) Hz), 16.33 (d, \(J_{PC} = 6.2\) Hz), -5.52. HRMS (ES+): [M+H]^+ m/z calcd for C\(_{16}\)H\(_{36}\)O\(_5\)PSi: 367.2070; found: 367.2068.
**Dimethyl (2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-oxo-5-phenylpentyl)phosphonate**

(109c)

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (2 mL) and diethylzinc (0.80 mL, 0.80 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Dimethyl (2-oxo-4-phenylbutyl)phosphonate (108c) (41 mg, 0.16 mmol) in dichloromethane (2 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 99 (0.348 g, 0.82 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1→1:2 hexanes:ethyl acetate, Rf of 109c = 0.50 (ethyl acetate)) to yield 14 mg (21%) of the target compound (109c) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.29 – 7.25 (m, 2H), 7.20 – 7.16 (m, 3H), 3.67 (d, $J_{PH} = 8.5$ Hz, 3H), 3.65 (d, $J_{PH} = 8.4$ Hz, 3H), 3.58 – 3.54 (m, 2H), 3.09 – 3.03 (m, 1H), 2.96 – 2.83 (m, 4H), 2.31 – 2.17 (m, 1H), 1.85 – 1.75 (m, 2H), 1.69 – 1.61 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 211.02 (d, $J_{PC} = 5.4$ Hz), 141.23, 128.44, 128.40, 126.03, 60.08, 52.37 (d, $J_{PC} = 6.2$ Hz), 52.20 (d, $J_{PC} = 6.5$ Hz), 44.20, 42.52 (d, $J_{PC} = 3.5$ Hz), 35.81 (d, $J_{PC} = 13.6$ Hz), 29.44, 25.86, 25.47 (d, $J_{PC} = 140.9$ Hz), 18.24, -5.47, -5.49. HRMS (ES+): [M+H]$^+$ m/z calcd for C$_{21}$H$_{38}$O$_5$PSi: 429.2226; found: 429.2225.
**Methyl 3-acetyl-5-((tert-butyldiphenylsilyl)oxy)pentanoate (112)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (4 mL) and diethylzinc (0.55 mL, 0.55 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using an ice bath. Methyl acetoacetate (104a) (13 mg, 0.11 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 101 (0.303 g, 0.55 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (6:1 hexanes:ethyl acetate, Rf of 112 = 0.34 (3:1 hexanes:ethyl acetate)) to yield 5 mg (11%) of the target compound (112) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.66 – 7.63 (m, 4H), 7.46 – 7.36 (m, 6H), 3.68 – 3.63 (m, 5H), 3.23 – 3.16 (m, 1H), 2.71 (dd, $J = 16.9, 9.9$ Hz, 1H), 2.31 (dd, $J = 16.9, 4.4$ Hz, 1H), 2.23 (s, 3H), 1.89 – 1.82 (m, 1H), 1.62 – 1.55 (m, 1H), 1.05 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 210.76, 172.80, 135.54, 133.37, 129.78, 127.75, 61.14, 51.72, 44.74, 34.73, 33.76, 29.50, 26.82, 19.14. HRMS (ES+): [M+Na]$^+$ m/z calcd for C$_{24}$H$_{32}$O$_4$NaSi: 435.1968; found: 435.1963.

**Methyl 3-acetyl-5-((triisopropylsilyl)oxy)pentanoate (113)**

An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with dichloromethane (4 mL) and diethylzinc (0.84 mL, 0.84 mmol, 1.0 M in hexanes). The vial was cooled to 0 °C using
Methyl acetoacetate (104a) (19 mg, 0.11 mmol) in dichloromethane (1 mL) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at 0 °C for 10 min. Geminal diiodide 63 (0.393 g, 0.84 mmol) was added dropwise by syringe over the course of 2 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (15:1 hexanes:ethyl acetate, Rf of 113 = 0.46 (3:1 hexanes:ethyl acetate)) to yield 8 mg (14%) of the target compound (113) as a yellow oil. 1H NMR (400 MHz, CDCl3) δ 3.71 (t, J = 6.0 Hz, 2H), 3.65 (s, 3H), 3.23 – 3.17 (m, 1H), 2.77 (dd, J = 16.9, 9.8 Hz, 1H), 2.43 (dd, J = 16.9, 4.5 Hz, 1H), 2.27 (s, 3H), 1.91 – 1.82 (m, 1H), 1.67 – 1.60 (m, 1H), 1.11 – 1.03 (m, 21H). 13C NMR (100 MHz, CDCl3) δ 210.99, 172.88, 60.67, 51.72, 44.81, 34.98, 34.29, 29.61, 17.99, 11.91. HRMS (ES+): [M+Na]+ m/z calcd for C17H34O4NaSi: 353.2124; found: 353.2123.

cis-6a-Methyltetrahydrofuro[2,3-b]furan-2(6aH)-one (125a)

This compound was prepared with modification to the procedure by Peña-López et al. An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with γ-keto ester 105a (23 mg, 0.08 mmol) and tetrahydrofuran (3 mL). The vial was cooled to 0 °C using an ice bath. Tetra-n-butylammonium fluoride (0.09 mL, 0.09 mmol, 1.0 M in THF) was added dropwise by syringe. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with dichloromethane (7 mL) and quenched with water (5 mL). The organic layer was washed with brine (5 mL). The organic layer was dried with anhydrous magnesium sulfate,
filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1→1:2 hexanes:ethyl acetate, R_t of 125a = 0.60 (1:1 hexanes:ethyl acetate)) to yield 6 mg (53%) of the known compound (125a) as a yellow residue. ^1H NMR (400 MHz, CDCl_3) δ 4.09 (ddd, J = 9.2, 8.1, 2.6 Hz, 1H), 3.95 (ddd, J = 10.3, 9.2, 6.2 Hz, 1H), 2.95 (dd, J = 18.3, 9.8 Hz, 1H), 2.81 (tt, J = 9.6, 2.8 Hz, 1H), 2.52 (dd, J = 18.3, 2.8 Hz, 1H), 2.30 (ddddd, J = 12.9, 10.5, 9.5, 8.1 Hz, 1H), 1.77 (ddt, J = 12.8, 5.9, 2.7 Hz, 1H), 1.67 (s, 3H). ^13C NMR (100 MHz, CDCl_3) δ 174.6, 117.5, 67.4, 42.8, 36.5, 33.1, 23.9. HRMS (ASAP+): [M+H]^+ m/z calcd for C_7H_{11}O_3: 143.0708; found: 143.0710.

**cis-6a-Ethyltetrahydrofuro[2,3-b]furan-2(6aH)-one (125e)**

This compound was prepared with modification to the procedure by Peña-López et al. An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with γ-keto ester 105e (16 mg, 0.05 mmol) and tetrahydrofuran (2 mL). The vial was cooled to 0 °C using an ice bath. Tetra-n-butylammonium fluoride (0.06 mL, 0.06 mmol, 1.0 M in THF) was added dropwise by syringe. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with dichloromethane (6 mL) and quenched with water (4 mL). The organic layer was washed with brine (5 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1→1:2 hexanes:ethyl acetate, R_t of 125e = 0.46 (1:1 hexanes:ethyl acetate)) to yield 6 mg (73%) of the target compound (125e) as a yellow residue. ^1H NMR (400 MHz, CDCl_3) δ 4.09 (ddd, J = 9.2, 8.0, 2.3 Hz, 1H), 3.95 (ddd, J = 10.7, 9.2, 5.8 Hz, 1H), 2.95 – 2.82 (m, 2H), 2.52 – 2.47 (m, 1H), 2.29 – 2.18 (m, 1H), 1.94 (q, J = 7.5 Hz, 2H), 1.77 (ddt, J = 12.8, 5.6, 2.5 Hz, 1H), 1.02
(t, J = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.88, 119.84, 67.30, 40.56, 36.62, 33.45, 30.17, 7.93. HRMS (ES+): [M+H]$^+$ m/z calcd for C$_8$H$_{13}$O$_3$: 157.0865; found: 157.0868.

**cis-6a-Isopropyltetrahydrofuro[2,3-b]furan-2(6aH)-one (125f)**

This compound was prepared with modification to the procedure by Peña-López *et al.* An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with γ-keto ester 105f (20 mg, 0.06 mmol) and tetrahydrofuran (2 mL). The vial was cooled to 0 °C using an ice bath. Tetra-n-butylammonium fluoride (0.07 mL, 0.07 mmol, 1.0 M in THF) was added dropwise by syringe. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with dichloromethane (6 mL) and quenched with water (4 mL). The organic layer was washed with brine (5 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1→1:2 hexanes:ethyl acetate, $R_f$ of 125f = 0.59 (1:1 hexanes:ethyl acetate)) to yield 7 mg (65%) of the target compound (125f) as a yellow residue. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.08 (ddd, J = 9.7, 8.0, 1.9 Hz, 1H), 3.92 (ddd, J = 11.2, 9.2, 5.6 Hz, 1H), 2.93 – 2.84 (m, 2H), 2.51 – 2.42 (m, 1H), 2.22 – 2.09 (m, 2H), 1.75 (ddt, J = 13.0, 5.7, 1.8 Hz, 1H), 1.02 (d, J = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 175.13, 121.84, 67.15, 38.80, 36.82, 34.70, 33.88, 16.77, 16.70. HRMS (ES+) [M+H]$^+$ m/z calcd for C$_9$H$_{15}$O$_3$: 171.1021; found: 171.1022.

**2,2-Dimethyl-1,3-dioxane-5-carbaldehyde (130)**

This compound was prepared with modification to the procedure by Chen *et al.* An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with alcohol 129 (0.505 g, 3.42 mmol), and dichloromethane (20 mL). The flask was cooled to 0 °C using an ice bath.
Dess-Martin periodinane (1.53 g, 3.59 mmol) was added quickly in one portion. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through a pad of Celite® and the filter cake was washed with dichloromethane (3 x 25 mL). The filtrate was concentrated under reduced pressure. The crude solid was chromatographed on silica (4:1 → 2:1 hexanes:ethyl acetate, $R_f$ of 130 = 0.29 (2:1 hexanes:ethyl acetate)) to yield 228 mg (46%) of the known compound (130) as a light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.88 (d, $J = 0.8$ Hz, 1H), 4.24 – 4.16 (m, 4H), 2.36 (td, $J = 4.2, 0.9$ Hz, 1H), 1.47 (s, 3H), 1.37 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 202.17, 98.38, 58.87, 46.41, 26.00, 21.45.

**Mixture of (E)-((2,2-Dimethyl-1,3-dioxan-5-yl)methylene)hydrazine (131a) and (Z)-((2,2-Dimethyl-1,3-dioxan-5-yl)methylene)hydrazine (131b)**

These compounds were prepared with modification to the procedure by Friedrich, Falling, and Lyons.$^{63}$ An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with aldehyde 130 (0.202 g, 1.40 mmol) and dichloromethane (10 mL). The solution was cooled to 0 °C using an ice bath. Hydrazine hydrate (0.14 mL, 2.80 mmol) was added dropwise by syringe. The reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was quenched with water (20 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 176 mg (80%) of the target compounds (131a, 131b) as a yellow liquid. The hydrazones were used immediately in the next reaction without further purification.
1,1-Diiodoethane (154)

This compound was prepared according to the procedure by Friedrich, Falling, and Lyons. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar and charged with hydrazine hydrate (10 mL, 0.2 mol). The flask was cooled to 0 °C in an ice bath. An oven-dried 25 mL, two-neck pear-shaped flask was equipped with a thermometer and was charged with acetaldehyde (6 mL, 0.1 mol). The flask was cooled to -25 °C using a 33% methanol:water/dry ice bath. Acetaldehyde was added to hydrazine hydrate dropwise by pipette over the course of 6 min. The reaction mixture was stirred at 0 °C for 15 min. The reaction mixture was extracted with dichloromethane (3 x 20 mL) at 0 °C. The extracts were combined and dried with anhydrous sodium sulfate and filtered. The extracts were dried a second time with anhydrous magnesium sulfate and filtered. No further purification was required prior to the next reaction. The extracts were diluted to 100 mL with dichloromethane and transferred to a 500 mL three-neck round-bottomed flask. The flask was equipped with a magnetic stir bar, a powder funnel, and a thermocouple. Triethylamine (24 mL, 0.17 mol) was poured over the course of 30 seconds with stirring. Iodine (24.19 g, 0.095 mol) was added in small portions (ca. 0.5 g) with stirring. The temperature was maintained between 20-30 °C using a cold-water bath. Iodine was added until nitrogen gas evolution ceased and the reaction mixture turned dark red. Saturated sodium thiosulfate (100 mL) was added and the reaction mixture was stirred for 30 min. The organic layer was washed with sodium thiosulfate (3 x 20 mL), water (3 x 20 mL), 3 M hydrochloric acid (3 x 20 mL), and brine (2 x 20 mL). The organic layer was then dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The product was purified by vacuum distillation (7.2 mmHg, bp 50-52 °C) to yield 5.25 g (20%) of the known compound (154) as a
light orange liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.21 (q, $J = 6.7$ Hz, 1H), 2.92 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 38.90, -39.06.

**tert-Butyl 2-oxopyrrolidine-1-carboxylate (139)**

This compound was prepared according to the procedure by Dunsmore *et al.* An oven-dried 250 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (30 mL) and 2-pyrrolidinone (0.88 mL, 11.6 mmol). The solution was cooled to -78 °C using an acetone/dry ice bath. $n$-Butyllithium (4.0 mL, 10 mmol, 2.5 M in hexanes) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 30 min. Di-tert-butyl dicarbonate (2.54 g, 11.6 mmol) was dissolved in tetrahydrofuran (10 mL) and added dropwise by syringe over the course of 10 min. The reaction mixture was stirred for 2 h at -78 °C. The reaction mixture was quenched with saturated ammonium chloride (15 mL). The tetrahydrofuran was removed under reduced pressure and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined extracts were washed with brine (15 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 2.11 g (98%) of the known compound (139) as a clear liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.75 (t, $J = 7.2$ Hz, 2H), 2.51 (t, $J = 8.1$ Hz, 2H), 2.00 (m, 2H), 1.53 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.34, 150.17, 82.67, 46.44, 32.91, 27.97, 17.36.

**Ethyl 6-((tert-butoxycarbonyl)amino)-3-oxohexanoate (144)**

This compound was prepared with modification to the procedure by Elliot and Wordingham. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (48 mL) and diisopropylamine (0.68 mL, 4.8 mmol). $n$-Butyllithium (1.9 mL, 4.8
mmol, 2.5 M in hexanes) was added dropwise by syringe. The solution was cooled to 0 °C using an ice bath and stirred for 15 min. Ethyl acetate (0.39 mL, 4.0 mmol) was added dropwise by syringe and the solution was cooled to -78 °C using an acetone/dry ice bath. The reaction mixture was stirred at -78 °C for 30 min. Boc-protected lactam 139 (0.74 g, 4.0 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, Rf of 144 = 0.31) to yield 238 mg (44%) of the known compound (144) as a yellow oil. 

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 4.63 (s, 1H), 4.20 (q, \( J = 6.3 \) Hz, 2H), 3.45 (s, 2H), 3.12 (q, \( J = 6.6 \) Hz, 2H), 2.60 (t, \( J = 5.2 \) Hz, 2H), 1.79 (p, \( J = 6.9 \) Hz, 2H), 1.44 (s, 9H), 1.28 (t, \( J = 6.3 \) Hz, 3H). The presence of the enol form is indicated by the singlets at \( \delta \) 12.13 and 5.00. 

\( ^{13}C \) NMR (100 MHz, CDCl₃) \( \delta \) 202.44, 167.21, 156.05, 79.16, 61.37, 49.25, 39.99, 39.61, 28.35, 23.80, 14.06. HRMS (ES+): [M+Na]⁺ m/z calcd for C₁₃H₂₃NNaO₅: 296.1474; found: 296.1471.

**Benzyl 2-oxopyrrolidine-1-carboxylate (140)**

This compound was prepared with modification to the procedure by Giovannini et al.⁸⁷ An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (30 mL) and 2-pyrrolidinone (0.76 mL, 10 mmol). The solution was cooled to -78 °C using an acetone/dry ice bath. n-Butyllithium (4.0 mL, 10 mmol, 2.5 M in hexanes) was added
dropwise by syringe. The solution was stirred at -78 °C for 30 min. Benzyl chloroformate (1.43 mL, 10 mmol) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred for 3 h at -78 °C. The reaction mixture was quenched with saturated ammonium chloride (15 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined extracts were washed with brine (3 x 10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1 hexanes:ethyl acetate, Rf of 140 = 0.22) to yield 1.90 g (87%) of the known compound (140) as a clear liquid. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.44 – 7.31 (m, 5H), 5.28 (s, 2H), 3.81 (t, \( J = 7.2 \text{ Hz} \), 2H), 2.54 (t, \( J = 8.2 \text{ Hz} \), 2H), 2.07-1.99 (m, 2H). \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 174.06, 151.47, 135.34, 128.58, 128.38, 128.20, 67.93, 46.40, 32.76, 17.53.

**Ethyl 6-(((benzyloxy)carbonyl)amino)-3-oxohexanoate (145)**

This compound was prepared with modification to the procedure by Elliot and Wordingham.\(^8^2\) An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (24 mL) and diisopropylamine (0.34 mL, 2.4 mmol). \( n \)-Butyllithium (0.95 mL, 2.4 mmol, 2.5 M in hexanes) was added dropwise by syringe. The solution was cooled to 0 °C using an ice bath and stirred for 15 min. Ethyl acetate (0.19 mL, 2.0 mmol) was added dropwise by syringe. The mixture was cooled to -78 °C using an acetone/dry ice bath. The reaction mixture was stirred for 30 min at -78 °C. Cbz-protected lactam 140 (0.220 g, 1.0 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL).
The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, R_f of 145 = 0.23) to yield 147 mg (48%) of the target compound (145) as a yellow oil. 

1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.29 (m, 5H), 5.09 (s, 2H), 4.87 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.42 (s, 2H), 3.21 (q, J = 6.6 Hz, 2H), 2.60 (t, J = 6.9 Hz, 2H), 1.81 (p, J = 6.9 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.13 and 4.99. 

13C NMR (100 MHz, CDCl_3) δ 202.42, 167.24, 156.53, 136.56, 128.50, 128.09, 128.08, 66.61, 61.42, 49.21, 40.12, 39.91, 23.63, 14.07. HRMS (ES+) [M+Na]^+ m/z calc'd for C16H21NNaO5: 330.1317; found: 330.1312.

1-((4-Methylphenyl)sulfonyl)-2-pyrrolidinone (141)

This compound was prepared according to the procedure by Kern et al. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (10 mL) and 2-pyrrolidinone (0.76 mL, 10 mmol). The solution was cooled to -78 °C using an acetone/dry ice bath. n-Butyllithium (4.2 mL, 10.5 mmol, 2.5 M in hexanes) was added dropwise by syringe. The solution was stirred at -78 °C for 45 min. p-Toluenesulfonyl chloride (2.10 g, 11 mmol) was dissolved in tetrahydrofuran (8 mL) and added dropwise by syringe over the course of 7 min. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated ammonium chloride (20 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, washed with brine (40 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by trituration with diethyl ether to yield 1.64 g (69%) of the known compound (141) as a white solid (MP: 139 – 141 °C, MP (lit.): 139 –
141 °C.\textsuperscript{125} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.93 (d, \(J = 8.4\) Hz, 2H), 7.33 (d, \(J = 8.0\) Hz, 2H), 3.90 (t, \(J = 7.2\) Hz, 2H), 2.45 − 2.41 (m, 5H), 2.11 − 2.03 (m, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 173.35, 145.18, 135.13, 129.68, 128.08, 47.26, 32.23, 21.69, 18.19.

**Ethyl 6-(4-methylphenylsulfonamido)-3-oxohexanoate (146)**

This compound was prepared with modification to the procedure by Elliot and Wordingham.\textsuperscript{82} An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (20 mL) and lithium diisopropyl amide (1.3 mL, 2.6 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.19 mL, 2.0 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. Ts-protected lactam 141 (0.240 g, 1.0 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, \(R_f\) of 146 = 0.16) to yield 232 mg (71%) of the target compound (146) as a yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.72 (d, \(J = 8.3\) Hz, 2H), 7.30 (d, \(J = 7.9\) Hz, 2H), 4.75 (br s, 1H), 4.17 (q, \(J = 7.2\) Hz, 2H), 3.42 (s, 2H), 2.94 (q, \(J = 6.6\) Hz, 2H), 2.63 (t, \(J = 6.7\) Hz, 2H), 2.42 (s, 3H), 1.76 (p, \(J = 6.6\) Hz, 2H), 1.27 (t, \(J = 7.2\) Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.08 and 4.91. \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 202.44, 167.30, 143.47, 136.87, 129.76, 127.05, 61.52, 49.23,

1-((2-(Trimethylsilyl)ethyl)sulfonyl)pyrrolidin-2-one (142)

This compound was prepared according to the procedure by Sirindil et al. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (20 mL) and 2-pyrrolidinone (0.17 mL, 2.28 mmol). The solution was cooled to -78 °C using an acetone/dry ice bath. n-Butyllithium (0.96 mL, 2.38 mmol, 2.5 M in hexanes) was added dropwise by syringe. The solution was stirred at -78 °C for 45 min. 2-(Trimethylsilyl)ethanesulfonyl chloride (0.515 g, 2.5 mmol) was dissolved in tetrahydrofuran (8 mL) and added dropwise by syringe over the course of 10 min. The reaction mixture was stirred for 30 min at -78 °C. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine (3 x 10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, Rf of 142 = 0.34) to yield 414 mg (73%) of the known compound (142) as a clear oil. 1H NMR (400 MHz, CDCl3) δ 3.89 (t, J = 6.9 Hz, 2H), 3.41 – 3.36 (m, 2H), 2.59 (t, J = 7.9 Hz, 2H), 2.16 (tt, J = 8.0, 6.9 Hz, 2H), 1.02 – 0.98 (m, 2H), 0.07 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 174.62, 49.56, 47.35, 32.30, 18.58, 9.62, -1.99.

Ethyl 3-oxo-6-(2-(trimethylsilyl)ethylsulfonamido)hexanoate (147)

This compound was prepared with modification to the procedure by Elliot and Wordingham. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum,
and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (10 mL) and lithium diisopropyl amide (0.57 mL, 1.13 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.09 mL, 0.9 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. SES-protected lactam 142 (0.113 g, 0.45 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 hexanes:ethyl acetate, Rf of 147 = 0.28 (2:1 hexanes:ethyl acetate)) to yield 62 mg (40%) of the target compound (147) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.39 (s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.47 (s, 2H), 3.14 (q, J = 6.6 Hz, 2H), 2.95 – 2.90 (m, 2H), 2.71 (t, J = 6.7 Hz, 2H), 1.87 (p, J = 6.7 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.02 – 0.98 (m, 2H), 0.06 (s, 9H). The presence of the enol form is indicated by the singlet at δ 5.02. ¹³C NMR (100 MHz, CDCl₃) δ 202.45, 167.38, 61.53, 49.23, 48.70, 42.26, 39.39, 24.01, 14.10, 10.60, -1.90. HRMS (ES+): [M+Na]⁺ m/z calcd for C₁₃H₂₇NNaO₅Si: 360.1277; found: 360.1276.

1-Benzyl-2-pyrrolidinone (143)

This compound was prepared according to the procedure by Wang et al. An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with sodium hydride (0.801 g, 20 mmol, 60% dispersion in mineral oil) and tetrahydrofuran (30 mL). The suspension was cooled
to 0 °C using an ice bath. 2-pyrrolidinone (1.5 mL, 20 mmol) was added dropwise by syringe. The reaction mixture was warmed to room temperature and stirred for 30 min. Benzyl bromide (2.4 mL, 20 mmol) was added dropwise by syringe. The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with cautious addition of water (150 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic extracts were washed with brine (3 x 15 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (1:1 hexanes:ethyl acetate → ethyl acetate, $R_f$ of 143 = 0.25 (1:1 hexanes:ethyl acetate)) to yield 2.84 g (81%) of the known compound (143) as a clear liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 – 7.22 (m, 5H), 4.45 (s, 2H), 3.25 (t, $J$ = 6.9 Hz, 2H), 2.44 (t, $J$ = 7.7 Hz, 2H), 2.02 – 1.95 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.92, 136.58, 128.65, 128.11, 127.52, 46.58, 46.57, 30.93, 17.72.

**Ethyl 7-((tert-butoxycarbonyl)amino)-4-oxoheptanoate (155)**

This compound was prepared with modification to the procedure by Brogan and Zercher.$^{15}$ An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (10 mL) and diethylzinc (1.8 mL, 1.8 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.15 mL, 1.83 mmol) was added dropwise by syringe over the course of 1 min. The resulting suspension was stirred for 10 min at 0 °C. Boc-protected β-keto ester 144 (103 mg, 0.37 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with brine (3 x 10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 → 3:1 → 1:1 hexanes:ethyl acetate, $R_f$ of 155 = 0.22
(3:1 hexanes:ethyl acetate)) to yield 64 mg (61%) of the target compound (155) as a yellow oil. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.10 (s, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 3.12 (q, $J$ = 6.6 Hz, 2H), 2.72 (t, $J$ = 6.6 Hz, 2H), 2.59 (t, $J$ = 6.6 Hz, 2H), 2.51 (t, $J$ = 7.2 Hz, 2H), 1.78 (p, $J$ = 7.0 Hz, 2H), 1.44 (s, 9H), 1.25 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.51, 172.78, 156.01, 79.15, 60.63, 39.86, 39.77, 37.08, 28.38, 28.01, 24.04, 14.15. HRMS (ES$^+$): [M+Na]$^+$ m/z calcd for C$_{14}$H$_{25}$NNaO$_5$: 310.1630; found: 310.1621.

**Ethyl 7-(((benzyloxy)carbonyl)amino)-4-oxoheptanoate (156)**

This compound was prepared with modification to the procedure by Brogan and Zercher.$^{15}$ An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (5 mL) and diethylzinc (1.6 mL, 1.6 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.13 mL, 1.63 mmol) was added dropwise by syringe over the course of 1 min. The resulting suspension was stirred for 10 min at 0 °C. Cbz-protected β-keto ester 145 (97 mg, 0.33 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 → 3:1 hexanes:ethyl acetate, $R_f$ of 156 = 0.17 (2:1 hexanes:ethyl acetate)) to yield 12 mg (12%) of the target compound (156) as a yellow residue. 

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 – 7.30 (m, 5H), 5.09 (s, 2H), 4.87 (s, 1H), 4.11 (q, $J$ = 7.1 Hz, 2H), 3.20 (q, $J$ = 6.6 Hz, 2H), 2.69 (t, $J$ = 6.4 Hz, 2H), 2.59 – 2.51 (m, 4H), 1.81 (p, $J$ = 6.9 Hz, 2H), 1.24 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.51, 172.80, 156.48, 136.58, 128.55, 128.52, 128.11, 66.64, 60.67,
40.37, 39.71, 37.07, 28.04, 23.84, 14.17. HRMS (ES+): [M+Na]$^+$ m/z calcd for C$_{17}$H$_{23}$NaO$_5$: 344.1474; found: 344.1465.

**Ethyl 7-(4-methylphenylsulfonamido)-4-oxoheptanoate (157)**

This compound was prepared with modification to the procedure by Brogan and Zercher.$^{15}$ An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (5 mL) and diethylzinc (1.2 mL, 1.2 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.10 mL, 1.21 mmol) was added dropwise by syringe over the course of 1 min. The resulting suspension was stirred for 10 min at 0 °C. Ts-protected β-keto ester 146 (79 mg, 0.24 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 → 2:1 hexanes:ethyl acetate, R$_f$ of 157 = 0.19 (2:1 hexanes:ethyl acetate)) to yield 44 mg (53%) of the target compound (157) as a clear oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 4.68 – 4.65 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.94 (q, J = 6.5 Hz, 2H), 2.70 – 2.67 (m, 2H), 2.60 – 2.54 (m, 4H), 2.42 (s, 3H), 1.77 (p, J = 6.6 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.64, 172.83, 143.40, 136.96, 129.73, 127.05, 60.71, 42.47, 39.33, 37.12, 28.08, 23.26, 21.52, 14.17. HRMS (ES+): [M+Na]$^+$ m/z calcd for C$_{16}$H$_{23}$NaO$_5$S: 364.1195; found: 364.1192.

**Ethyl 4-oxo-7-(2-trimethylsilyl)ethylsulfonamido)heptanoate (158)**

This compound was prepared with modification to the procedure by Brogan and Zercher.$^{15}$ An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen
inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (3 mL) and diethylzinc (0.31 mL, 0.31 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.03 mL, 0.31 mmol) was added dropwise by syringe over the course of 1 min. The resulting suspension was stirred for 10 min at 0 °C. SES-protected β-keto ester 147 (21 mg, 0.06 mmol) was dissolved in dichloromethane (1 mL) and added rapidly by syringe. The reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 7 mL). The organic extracts were washed with brine (5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 → 3:1 → 2:1 hexanes:ethyl acetate, Rf of 158 = 0.21 (2:1 hexanes:ethyl acetate)) to yield 18 mg (82%) of the target compound (158) as a clear oil. 1H NMR (400 MHz, CDCl3) δ 4.45 (t, J = 6.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.12 (q, J = 6.5 Hz, 2H), 2.94 – 2.90 (m, 2H), 2.72 (t, J = 7.4 Hz, 2H), 2.64 – 2.58 (m, 2H), 1.85 (p, J = 6.7 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.02 – 0.98 (m, 2H), 0.05 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 208.61, 172.86, 60.71, 48.67, 42.51, 39.22, 37.13, 28.10, 24.13, 14.17, 10.61, -1.99. HRMS (ES+): [M+Na]+ m/z calcd for C14H29NNaO5Si: 374.1433; found: 374.1427.

**tert-Butyl 3-methyl-2-oxopyrrolidin-1-carboxylate (159)**

This compound was prepared according to the procedure by Chen et al.91 An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with Boc-protected lactam 139 (0.331 g, 1.79 mmol) and tetrahydrofuran (10 mL). The solution was cooled to -78 °C using an acetone/dry ice bath. Lithium bis(trimethylsilyl)amide (1.9 mL, 1.9 mmol, 1.0 M in hexanes) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h. Methyl iodide (0.13 mL, 2.15 mmol) was added dropwise by syringe and the reaction mixture was stirred at -78 °C for
2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) at -78 °C and warmed to room temperature. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (6:1 → 4:1 hexanes:ethyl acetate, R_f of 159 = 0.38 (2:1 hexanes:ethyl acetate)) to yield 155 mg (43%) of the known compound (159) as a yellow oil. ^H NMR (400 MHz, CDCl_3) δ 3.78 – 3.72 (m, 1H), 3.60 – 3.53 (m, 1H), 2.58 – 2.52 (m, 1H), 2.23 – 2.16 (m, 1H), 1.66 – 1.55 (m, 1H), 1.52 (s, 9H), 1.22 (d, J = 7.1 Hz, 3H). ^13C NMR (100 MHz, CDCl_3) δ 176.59, 150.49, 82.72, 44.31, 38.64, 28.05, 26.43, 15.41.

**Ethyl 6-((tert-butoxycarbonyl)amino)-4-methyl-3-oxohexanoate (163)**

This compound was prepared with modification to the procedure by Elliot and Wordingham. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (10 mL) and lithium diisopropyl amide (1.2 mL, 2.4 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.18 mL, 1.8 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. Boc-protected methylated lactam 159 (0.186 g, 0.93 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (3:1 hexanes:ethyl acetate, R_f of 163 = 0.37) to yield 76 mg (29%) of the target compound (163) as a
yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.63 (s, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.55 – 3.46 (m, 2H), 3.12 (q, $J = 6.8$ Hz, 2H), 2.76 – 2.71 (m, 1H), 1.95 – 1.86 (m, 1H), 1.57 – 1.50 (m, 1H), 1.44 (s, 9H), 1.28 (t, $J = 7.2$ Hz 3H), 1.15 (d, $J = 7.0$ Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.15 and 5.00. $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.11, 167.37, 155.97, 79.28, 61.41, 47.60, 44.06, 38.35, 32.62, 28.40, 16.33, 14.12. HRMS (ES+) [M+Na]$^+$ m/z calcd for C$_{14}$H$_{25}$NNaO$_5$: 310.1630; found: 310.1630.

**Benzyl 3-methyl-2-oxopyrrolidine-1-carboxylate (160)**

An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with Cbz-protected lactam 140 (0.508 g, 2.28 mmol) and tetrahydrofuran (20 mL). The solution was cooled to -78 °C using an acetone/dry ice bath. Lithium diisopropyl amide (1.2 mL, 2.4 mmol, 2.0 M in THF) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h. Methyl iodide (0.42 mL, 4.0 mmol) was added dropwise by syringe and the reaction was slowly warmed to room temperature. The reaction mixture was quenched with saturated ammonium chloride (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The organic extracts were washed with brine (3 x 10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 hexanes:ethyl acetate, R$_f$ of 160 = 0.32 (2:1 hexanes:ethyl acetate)) to yield 192 mg (36%) of the known compound (160) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45 – 7.30 (m, 5H), 5.32 – 5.25 (m, 2H), 3.86 – 3.81 (m, 1H), 3.67 – 3.60 (m, 1H), 2.64 – 2.54 (m, 1H), 2.28 – 2.20 (m, 1H), 1.71 – 1.60 (m, 1H), 1.24 (d, $J = 7.0$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.39, 151.69, 135.37, 128.59, 128.34, 128.12, 67.96, 44.31, 38.48, 26.53, 15.34.
Ethyl 6-(((benzyloxy)carbonyl)amino)-4-methyl-3-oxohexanoate (164)

This compound was prepared with modification to the procedure by Elliot and Wordingham. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (10 mL) and lithium diisopropyl amide (1.0 mL, 2.0 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.16 mL, 1.6 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. Cbz-protected methylated lactam 160 (0.192 g, 0.82 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (3:1 hexanes:ethyl acetate, Rf of 164 = 0.31) to yield 108 mg (41%) of the target compound (164) as a yellow oil. 

$^{1}$H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.29 (m, 5H), 5.13 – 5.06 (m, 2H), 4.91 (s, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.48 (ABq, $J = 15.6$ Hz, 2H), 3.25 – 3.15 (m, 2H), 2.77 – 2.72 (m, 1H), 1.97 – 1.88 (m, 1H), 1.60 – 1.54 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.15 (d, $J = 7.0$ Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.16 and 5.00. 

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.08, 167.43, 156.45, 136.55, 128.52, 128.13, 128.12, 66.68, 61.46, 47.52, 43.93, 38.81, 32.43, 16.43, 14.10. HRMS (ES+) [M+Na]$^+$ m/z calcd for C$_{17}$H$_{23}$NNaO$_5$: 344.1474; found: 344.1466.
**Ethyl 7-(((benzyloxy)carbonyl)amino)-5-methyl-4-oxoheptanoate (168)**

This compound was prepared with modification to the procedure by Brogan and Zercher. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (5 mL) and diethylzinc (1.9 mL, 1.9 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.15 mL, 1.87 mmol) was added dropwise by syringe at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. Cbz-protected methylated β-keto ester (164) (86 mg, 0.26 mmol) was dissolved in dichloromethane (1 mL) and added rapidly by syringe. The reaction mixture was stirred for 4 h while slowly warming to room temperature. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The organic extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 hexanes:ethyl acetate → 2:1 hexanes:ethyl acetate, Rf of 168 = 0.34 (2:1 hexanes:ethyl acetate)) to yield 12 mg (13%) of the target compound (168) as a yellow residue. \(^1^H\) NMR (400 MHz, CDCl3) δ 7.42 – 7.30 (m, 5H), 5.14 – 5.07 (m, 2H), 4.86 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.18 (q, J = 6.7 Hz, 2H), 2.89 – 2.61 (m, 3H), 2.57 (t, J = 6.4 Hz, 2H), 1.94 – 1.87 (m, 1H), 1.61 – 1.54 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H). HRMS (ES+) [M+Na]⁺ m/z calcd for C₁₈H₂₅NNaO₅: 358.1630; found: 358.1623.

**3-Methyl-1-((4-methylphenyl)sulfonyl)-2-pyrrolidinone (161)**

This compound was prepared according to the procedure by Boal, Schammel, and Garg. An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with Ts-protected lactam 141 (0.600 g, 2.36 mmol) and tetrahydrofuran (15 mL). The solution was cooled to -78 °C using an acetone/dry ice bath. Sodium bis(trimethylsilyl)amide (2.5 mL, 2.5 mmol, 1.0
M in hexanes) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h. Methyl iodide (0.22 mL, 3.54 mmol) was added dropwise by syringe and the reaction mixture was stirred at -78 °C for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (3:1 hexanes:ethyl acetate, Rf of 161 = 0.28 (2:1 hexanes:ethyl acetate)) to yield 528 mg (84%) of the known compound (161) as an off-white solid (MP: 84 – 85 °C, MP (lit.): 85 – 86 °C).126 1H NMR (400 MHz, CDCl3) δ 7.94 – 7.91 (m, 2H), 7.34 – 7.31 (m, 2H), 3.97 – 3.92 (m, 1H), 3.71 – 3.65 (m, 1H), 2.52 – 2.45 (m, 1H), 2.42 (s, 3H), 2.29 – 2.22 (m, 1H), 1.75 – 1.65 (m, 1H), 1.14 (d, J = 7.1 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 175.77, 145.11, 135.15, 129.65, 128.04, 45.23, 38.22, 27.10, 21.68, 14.96.

**Ethyl 4-methyl-6-(4-methylphenylsulfonamido)-3-oxohexanoate (165)**

This compound was prepared with modification to the procedure by Elliot and Wordingham.82 An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (20 mL) and lithium diisopropyl amide (1.2 mL, 2.4 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.19 mL, 1.9 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. Ts-protected methylated lactam 161 (0.250 g, 0.99 mmol) was dissolved in tetrahydrofuran (5 mL) and added dropwise by syringe over the course of 5 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed
with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, R_f of 165 = 0.18) to yield 285 mg (85%) of the target compound (165) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 4.74 (t, J = 6.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.55 – 3.41 (ABq, J = 15.7 Hz, 2H), 3.00 – 2.80 (m, 3H), 2.42 (s, 3H), 1.93 – 1.85 (m, 1H), 1.57 – 1.49 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.10 and 4.92. ¹³C NMR (100 MHz, CDCl₃) δ 206.15, 167.62, 143.43, 136.87, 129.72, 127.04, 61.54, 47.50, 43.39, 40.84, 32.07, 21.50, 16.51, 14.08. HRMS (ES+): [M+Na]^+ m/z calcd for C₁₆H₂₃NNaO₅S: 364.1195; found: 364.1193.

**Ethyl 5-methyl-7-(4-methylphenylsulfonamido)-4-oxoheptanoate (169)**

This compound was prepared with modification to the procedure by Brogan and Zercher.¹⁵ An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (5 mL) and diethylzinc (0.87 mL, 0.87 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.07 mL, 0.87 mmol) was added dropwise by syringe at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. Ts-protected methylated β-keto ester 165 (58 mg, 0.17 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 2 h while slowly warming to room temperature. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). The organic extracts were washed with brine (3 x 5 mL), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 → 2:1 hexanes:ethyl acetate, R_f of 169 = 0.18 (2:1 hexanes:ethyl acetate)) to yield 18 mg (30%) of the target compound (169) as a yellow residue. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 4.73 (t, J = 6.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.55 – 3.41 (ABq, J = 15.7 Hz, 2H), 3.00 – 2.80 (m, 3H), 2.42 (s, 3H), 1.93 – 1.85 (m, 1H), 1.57 – 1.49 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H).
\[ J = 6.4 \text{ Hz}, 1\text{H}), 4.10 \text{(q, } J = 7.1 \text{ Hz, 2H), 2.96 – 2.86 (m, 2H), 2.80 – 2.71 (m, 3H), 2.57 (t, } J = 6.3 \text{ Hz, 2H), 2.42 (s, 3H), 1.92 – 1.84 \text{(m, 1H), 1.57 – 1.48 (m, 1H), 1.24 (t, } J = 7.1 \text{ Hz, 3H), 1.10 (d, } J = 7.2 \text{ Hz, 3H).} \]

\(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta\) 212.47, 172.96, 143.36, 136.92, 129.69, 127.02, 60.68, 43.32, 41.03, 35.68, 32.22, 28.03, 21.50, 16.83, 14.16. HRMS (ES+): [M+Na]\(^+\) \(m/z\) calcd for C\(_{17}\)H\(_{25}\)NNaO\(_3\)S: 378.1351; found: 378.1348.

### 3-Methyl-1-((2-(trimethylsilyl)ethyl)sulfonyl)pyrrolidin-2-one (162)

This compound was prepared with modification to the procedure by Boal, Schammel, and Garg.\(^92\)

An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with SES-lactam 142 (0.110 g, 0.44 mmol) and tetrahydrofuran (10 mL). The solution was cooled to -78 °C using an acetone/dry ice bath. Sodium bis(trimethylsilyl)amide (0.43 mL, 0.43 mmol, 1.0 M in hexanes) was added dropwise by syringe. The reaction mixture was stirred at -78 °C for 1 h. Methyl iodide (0.04 mL, 0.60 mmol) was added dropwise by syringe and the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and the mixture was slowly warmed to room temperature. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The organic extracts were washed with brine (10 mL), dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 hexanes:ethyl acetate, \(R_f\) of 162 = 0.52 (2:1 hexanes:ethyl acetate) to yield 68 mg (59%) of the target compound (162) as a yellow oil. \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta\) 3.91 – 3.86 (m, 1H), 3.75 – 3.69 (m, 1H), 3.41 – 3.36 (m, 2H), 2.71 – 2.64 (m, 1H), 2.39 – 2.31 (m, 1H), 1.83 – 1.73 (m, 1H), 1.26 (d, \(J = 7.1 \text{ Hz, 3H), 1.00 – 0.96 (m, 2H), 0.06 (s, 9H).\)}

\(^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta\) 176.98, 49.48, 45.31, 38.30, 27.47, 15.22, 9.65, -2.00. HRMS (ES+): [M+Na]\(^+\) \(m/z\) calcd for C\(_{10}\)H\(_{21}\)NNaO\(_3\)SSi: 286.0909; found: 286.0908.
**Ethyl 4-methyl-3-oxo-6-(2-(trimethylsilyl)ethylsulfonamido)hexanoate (166)**

This compound was prepared with modification to the procedure by Elliot and Wordingham.\(^2\) An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with tetrahydrofuran (5 mL) and lithium diisopropyl amide (0.25 mL, 0.50 mmol, 2.0 M in THF). The solution was cooled to -78 °C using an acetone/dry ice bath. Ethyl acetate (0.04 mL, 0.40 mmol) was added dropwise by syringe. The reaction mixture was stirred for 30 min at -78 °C. SES-protected methylated lactam 162 (52 mg, 0.20 mmol) was dissolved in tetrahydrofuran (3 mL) and added dropwise by syringe over the course of 3 min. The reaction mixture was stirred at -78 °C for 30 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The tetrahydrofuran was removed and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (4:1 hexanes:ethyl acetate, \(R_f\) of 166 = 0.33 (2:1 hexanes:ethyl acetate) to yield 50 mg (71%) of the target compound (166) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.47 (t, \(J = 6.5\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.61 – 3.45 (m, 2H), 3.13 – 3.07 (m, 2H), 2.94 – 2.90 (m, 3H), 2.03 – 1.95 (m, 1H), 1.65 – 1.58 (m, 1H), 1.29 (t, \(J = 7.1\) Hz, 3H), 1.17 (d, \(J = 7.2\) Hz, 3H), 1.02 – 0.98 (m, 2H), 0.05 (s, 9H). The presence of the enol form is indicated by the singlets at \(\delta\) 12.20 and 5.02. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 206.15, 167.76, 61.60, 48.68, 47.40, 43.43, 41.01, 32.99, 16.72, 14.11, 10.59, -1.99. HRMS (ES+): [M+Na]\(^+\) \(m/z\) calcd for C\(_{14}\)H\(_{29}\)NNaO\(_5\)SSi: 374.1433; found: 374.1427.

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**Ethyl 5-methyl-4-oxo-7-(2-(trimethylsilyl)ethylsulfonamido)heptanoate (170)**

This compound was prepared with modification to the procedure by Brogan and Zercher.\(^{15}\) An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The vial was charged with dichloromethane (3 mL) and diethylzinc (0.61 mL, 0.61 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.07 mL, 0.61 mmol) was added dropwise by syringe at 0 °C. The resulting suspension was stirred for 10 min at 0 °C. SES-protected methylated β-keto ester 166 (43 mg, 0.12 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 2 h while slowly warming to room temperature. The reaction mixture was quenched with saturated ammonium chloride (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with brine (7 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 → 3:1 →2:1 hexanes:ethyl acetate, R\(_f\) of = 170 0.27 (2:1 hexanes:ethyl acetate)) to yield 20 mg (46%) of the target compound (170) as a yellow residue.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.37 (t, \(J = 6.5\) Hz, 1H), 4.12 (q, \(J = 7.2\) Hz, 2H), 3.12 – 3.06 (m, 2H), 2.94 – 2.89 (m, 2H), 2.80 – 2.76 (m, 3H), 2.63 – 2.59 (m, 2H), 1.99 – 1.94 (m, 1H), 1.66 – 1.58 (m, 1H), 1.26 (t, \(J = 7.1\) Hz, 3H), 1.17 (d, \(J = 7.1\) Hz, 3H), 1.02 – 0.97 (m, 2H), 0.05 (s, 9H).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 212.44, 173.04, 60.73, 48.58, 43.40, 41.15, 35.59, 33.18, 28.05, 17.02, 14.18, 10.60, -1.99. HRMS (ES+): [M+Na]^+ \(m/z\) calcd for C\(_{15}\)H\(_{31}\)NNaO\(_5\)Si: 388.1590; found: 388.1583.

**4-(1,3-Dioxoisindolin-2-yl)butanoyl chloride (176)**

This compound was prepared according to the procedure by Chen et al.\(^{103}\) An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, condenser, rubber septum, and nitrogen inlet needle. The apparatus was flushed with nitrogen. The flask was charged with 4-
phthalimidobutanoic acid (175) (1.18 g, 5 mmol). The acid was dissolved in thionyl chloride (5 mL). The reaction mixture was refluxed under nitrogen for 2 h. The reaction mixture was cooled to room temperature. Excess thionyl chloride was removed under nitrogen flow. The crude white solid was recrystallized in dichloromethane/petroleum ether to yield 767 mg (61%) of the known compound (176) as a white solid (MP: 113 – 116 °C, MP (lit.): 112 – 113 °C).\textsuperscript{127} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.88 – 7.83 (m, 2H), 7.75 – 7.70 (m, 2H), 3.77 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 7.4 Hz, 2H), 2.03 (p, J = 7.1 Hz, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 178.47, 168.39, 134.03, 131.99, 123.33, 37.06, 31.23, 23.61.

3-Ethoxy-3-oxopropanoic acid (172)

Method A:
This compound was prepared with modification to the procedure by Kumagai \textit{et al.}\textsuperscript{100} An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar. The flask was charged with a solution of diethylmalonate (4.01 g, 25 mmol) in ethanol:water (1:1, 25 mL). The solution was stirred at room temperature while sodium hydroxide pellets (1.02 g, 24.5 mmol) were added piecewise. The reaction mixture was stirred at room temperature for 2.5 h. Ether (25 mL) and brine (25 mL) were added to the reaction mixture. The aqueous layer was separated and acidified with concentrated hydrochloric acid (pH ≈ 2). The aqueous layer was then extracted with diethyl ether (3 x 20 mL). The extracts were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude liquid was chromatographed on silica (1:1 hexanes:ethyl acetate, R\textsubscript{f} of 172 = 0.36) to yield 1.75 g (53%) of the known compound (172) as a clear liquid.

Method B:
This compound was prepared according to the procedure by Bixa \textit{et al.}\textsuperscript{101} An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar. The flask was charged with diethylmalonate (8.0 g, 50 mmol) and ethanol (10 mL). The solution was cooled to 0 °C using an
ice bath. A solution of potassium hydroxide in water (24 mL, 60 mmol, 2.5 M) was added dropwise by pipette over the course of 15 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The ethanol was removed under reduced pressure and the concentrate was diluted with water (10 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The aqueous layer was acidified with concentrated hydrochloric acid (pH ≈ 2). The aqueous layer was re-extracted with dichloromethane (3 x 30 mL). The organic layers were dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to yield 4.06 g (67%) of the known compound (172) as a clear liquid. No further purification was required prior to the next reaction.  

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\] \(\delta 4.25 (q, J = 7.2 \text{ Hz}, 2\text{H}), 3.44 (s, 2\text{H}), 1.31 (t, J = 7.2 \text{ Hz}, 3\text{H}). \]  

\[^{13}\text{C} \text{NMR (100 MHz, CDCl}_3\] \(\delta 171.53, 166.98, 62.05, 40.77, 13.98. \]  

**Ethyl 6-(1,3-dioxoisooindolin-2-yl)-3-oxohexanoate (178)**  
This compound was prepared with modification to the procedure by Coulon et al.\textsuperscript{104} An oven-dried 100 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 4-phthalimidobutanoic acid (175) (0.554 g, 2.38 mmol) and tetrahydrofuran (15 mL). Carbonyldiimidazole (0.447 g, 2.76 mmol) was added in one portion. A separate oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with 172 (0.363 g, 2.76 mmol) and tetrahydrofuran (10 mL). Magnesium ethoxide (0.163 g, 1.42 mmol) was added in one portion. Both reaction mixtures were stirred under nitrogen at room temperature for 2 h. The magnesium salt was poured into the acyl imidazole and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into a separatory funnel and diluted with ethyl acetate (75 mL). The reaction mixture was washed with 0.5 M hydrochloric acid (25 mL),
5% sodium bicarbonate (25 mL), and brine (25 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (2:1 hexanes:ethyl acetate, Rf of 178 = 0.36) to yield 549 mg (76%) of the known compound (178) as a clear oil. 1H NMR (400 MHz, CDCl3) δ 7.87 – 7.82 (m, 2H), 7.75 – 7.70 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.72 (t, J = 6.7 Hz, 2H), 3.45 (s, 2H), 2.63 (t, J = 7.1 Hz, 2H), 2.00 (p, J = 6.9 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H). The presence of the enol form is indicated by the singlets at δ 12.08 and 5.01. 13C NMR (100 MHz, CDCl3) δ 201.59, 168.44, 167.09, 134.01, 132.02, 123.28, 61.38, 49.33, 39.97, 36.99, 22.49, 14.08. HRMS (ES+): [M+H]+ m/z calcd for C16H18NO5: 304.1185; found: 304.1185.

**Ethyl 7-(1,3-dioxoisoindolin-2-yl)-4-oxoheptanoate (179)**

This compound was prepared with modification to the procedure by Brogan and Zercher.15 An oven-dried 50 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (20 mL) and diethylzinc (3.3 mL, 3.3 mmol, 1.0 M in hexanes). The solution was cooled to 0 °C using an ice bath. Diiodomethane (0.26 mL, 3.3 mmol) was added dropwise by syringe over the course of 1 min. The resulting suspension was stirred for 10 min at 0 °C. Phthalimide β-keto ester 178 (210 mg, 0.66 mmol) was dissolved in dichloromethane (2 mL) and added rapidly by syringe. The reaction mixture was stirred for 1.5 h while slowly warming to room temperature. The reaction mixture was quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with dichloromethane (3 x 20 mL). The organic extracts were washed with brine (15 mL), dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (5:1 → 3:1 → 2:1 hexanes:ethyl acetate, Rf of 179 = 0.32 (2:1 hexanes:ethyl acetate)) to yield 169 mg (77%) of the known
compound (179) as a light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 – 7.82 (m, 2H), 7.74 – 7.70 (m, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.71 (t, $J = 6.7$ Hz, 2H), 2.72 (t, $J = 7.0$ Hz, 2H), 2.59 – 2.52 (m, 4H), 1.99 (p, $J = 7.0$ Hz, 2H), 1.24 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.60, 172.73, 168.43, 133.98, 132.06, 123.23, 60.59, 39.65, 37.17, 37.06, 27.96, 22.65, 14.17. HRMS (ES+): [M+H]$^+$ m/z calcd for C$_{17}$H$_{20}$NO$_5$: 318.1341; found: 318.1348.

**Ethyl 7-(1,3-dioxoisooindolin-2-yl)-3-methyl-4-oxoheptanoate (180)**

This compound was prepared with modification to the procedure by Lin et al. An oven-dried 25 mL, round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with dichloromethane (10 mL) and phthalimide β-keto ester 178 (100 mg, 0.33 mmol). The solution was cooled to 0 °C using an ice bath. Diethylzinc (1.0 mL, 1.0 mmol, 1.0 M in hexanes) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred for 10 min at 0 °C. 1,1-diiodoethane (0.10 mL, 1.00 mmol) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred for 30 min at room temperature. Diethylzinc (1.0 mL, 1.0 mmol, 1.0 M in hexanes) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at room temperature for 10 min. 1,1-diiodoethane (0.10 mL, 1.0 mmol) was added dropwise by syringe over the course of 1 min. The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic extracts were dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was chromatographed on silica (8:1 → 6:1 → 4:1 hexanes:ethyl acetate, $R_f$ of 180 = 0.42 (2:1 hexanes:ethyl acetate)) to yield 36 mg (33%) of target compound (180) as a light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 – 7.82 (m, 2H), 7.74 – 7.69 (m, 2H), 4.08 (q, $J = 7.1$ Hz, 2H),
3.72 (t, J = 6.8 Hz, 2H), 2.98 (dq, J = 8.9, 7.2, 5.2 Hz, 1H), 2.76 (dd, J = 16.8, 8.9 Hz, 1H), 2.68 – 2.57 (m, 2H), 2.28 (dd, J = 16.8, 5.3 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H).\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 211.62, 172.28, 168.43, 133.94, 132.10, 123.24, 60.54, 41.91, 38.36, 37.33, 22.64, 16.73, 14.17. HRMS (ES+): [M+H]\(^+\) m/z calcd for C\(_{18}\)H\(_{22}\)NO\(_5\): 332.1498; found: 332.1498.

**Ethyl 3(3,4-dihydro-2H-pyrrol-5-yl)-propanoate (181)**

This compound was prepared with modification to the procedure by Quiclet-Sire et al.\(^{106}\) An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with \(\gamma\)-keto ester 179 (63 mg, 0.20 mmol) and absolute ethanol (1 mL). Methylamine (0.43 mL, 3.44 mmol, 33% in ethanol) was added dropwise by syringe. The reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure. The crude solid was chromatographed on silica (1:1 \(\rightarrow\) 1:2 hexanes:ethyl acetate, \(R_f\) of 181 = 0.10 (1:1 hexanes:ethyl acetate)) to yield 27 mg (80%) of target compound (181) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.14 (q, J = 7.1 Hz, 2H), 3.82 – 3.77 (m, 2H), 2.70 – 2.65 (m, 2H), 2.63 – 2.59 (m, 2H), 2.51 – 2.46 (m, 2H), 1.91 – 1.83 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.33, 173.16, 60.87, 60.46, 37.78, 30.65, 28.40, 22.57, 14.21. HRMS (EI+): [M]\(^+\) m/z calcd for C\(_9\)H\(_{15}\)NO\(_2\): 169.1103; found: 169.1106.

**Ethyl 3-(3,4-dihydro-2H-pyrrol-5-yl)butanoate (182)**

This compound was prepared with modification to the procedure by Quiclet-Sire et al.\(^{106}\) An oven-dried scintillation vial was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The vial was flushed with nitrogen. The vial was charged with \(\gamma\)-keto ester 180 (34 mg, 0.10 mmol) and absolute ethanol (1.3 mL). Methylamine (0.22 mL, 1.76 mmol, 33% in ethanol)
was added dropwise by syringe. The reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure. The crude solid was chromatographed on silica (1:1 → 1:3 hexanes:ethyl acetate, Rₜ of 182 = 0.10 (1:1 hexanes:ethyl acetate)) to yield 15 mg (82%) of target compound (182) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.14 (q, J = 7.1 Hz, 2H), 3.81 – 3.77 (m, 2H), 2.99 – 2.92 (m, 2H), 2.77 (dd, J = 15.7, 7.1 Hz, 1H), 2.60 – 2.43 (m, 2H), 2.39 (dd, J = 15.7, 7.2 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 180.39, 172.61, 60.72, 60.34, 39.01, 35.65, 34.24, 22.59, 18.04, 14.22. HRMS (EI+): [M]⁺ m/z calcd for C₁₀H₁₇NO₂: 183.1259; found: 183.1255.

**Tetrahydro-1H-pyrrolizin-3(2H)-one (183)**

This compound was prepared with modification to the procedure by Zhang et al.¹⁰⁹ An oven-dried 10 mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with imine 181 (64 mg, 0.38 mmol) and methanol (10 mL). Sodium borohydride (58 mg, 1.51 mmol) and zinc chloride (103 mg, 0.76 mmol) were added successively at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was heated to reflux and was refluxed under nitrogen for 4 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude solid was chromatographed on silica (Ethyl acetate, Rₜ of 183 = 0.17) to yield 38 mg (80%) of the known compound (183) as a yellow residue. ¹H NMR (400 MHz, CDCl₃) δ 3.90 (ddtd, J = 9.3, 7.5, 6.1 Hz, 1H), 3.62 – 3.47 (m, 1H), 3.13 – 3.00 (m, 1H), 2.74 (dddt, J = 16.5, 11.3, 9.0, 1.2 Hz, 1H), 2.45 (ddd, J = 16.5, 9.5, 2.0 Hz, 1H), 2.30 (dddd, J = 12.7, 8.9, 6.8, 2.0 Hz, 1H), 2.20 – 1.95 (m, 3H), 1.80 – 1.66 (m, 1H), 1.41 – 1.23 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 174.80, 62.07, 40.98, 40.98, 35.40, 32.25, 27.20, 27.02. HRMS (EI+): [M]⁺ m/z calcd for C₇H₁₁NO: 125.0841; found: 125.0843.
1-Methyltetrahydro-1H-pyrrolizin-3(2H)-one (152a, 152b)

This compound was prepared with modification to the procedure by Zhang et al. An oven-dried 10 mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, and nitrogen inlet needle. The flask was flushed with nitrogen. The flask was charged with imine 182 (13 mg, 0.07 mmol) and methanol (3 mL). Sodium borohydride (13 mg, 0.33 mmol) and zinc chloride (27 mg, 0.20 mmol) were added successively at room temperature. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was heated to reflux and was refluxed under nitrogen for 4 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude solid was chromatographed on silica (Ethyl acetate, Rf of 152a, 152b = 0.14) to yield 6 mg (62%) of the known mixture of diastereomers (dr: 1:1) (152a, 152b) as a yellow residue. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.97 (dt, $J = 9.7, 6.4$ Hz, 1H), 3.61 – 3.45 (m, 3H), 3.12 – 2.99 (m, 2H), 2.90 (dd, $J = 16.5, 8.0$ Hz, 1H), 2.61 – 2.49 (m, 2H), 2.41 (dd, $J = 16.0, 11.1$ Hz, 1H), 2.21 – 1.93 (m, 7H), 1.77 – 1.66 (m, 1H), 1.62 – 1.47 (m, 1H), 1.46 – 1.33 (m, 1H), 1.16 (d, $J = 6.6$ Hz, 3H), 0.98 (d, $J = 7.2$ Hz, 3H) $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.35, 174.29, 68.97, 65.06, 43.88, 43.11, 41.40, 41.18, 38.01, 30.77, 29.64, 27.02, 26.95, 25.11, 18.03, 15.97. HRMS (EI+): [M$^+$] m/z calcd for C$_8$H$_{15}$NO: 139.0997; found: 139.0999.
LIST OF REFERENCES


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93.) Kennedy, D.P. Senior Thesis, Studies directed toward the total synthesis of (±)-heliotridane, University of New Hampshire, 2002.


APPENDIX A

$^1$H AND $^{13}$C NMR SPECTRA
215

105g
146
152a, 152b
152a, 152b
APPENDIX B

$^1$H-$^1$H NOESY SPECTRA
APPENDIX C

HRMS SPECTRA
m/z: 142.0630
m/z: 156.0786
Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 PPM  /  DBE: min = -1.5, max = 150.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
146 formula(e) evaluated with 3 results within limits (all results up to 1000) for each mass

Elements Used:
C: 0-100  H: 0-100  N: 0-10  O: 0-10

GCT_6681 28 (1.833) Cm (28:34-1:9x3.000)

TOF MS EI+

Element:
C: 0-100  H: 0-100  N: 0-10  O: 0-10

Minimum: -1.5
Maximum: 150.0

Mass  Calc. Mass  m/z  PPM  DBE  i-FIT  Formula
169.1106  169.1103  0.3  1.8  3.0  58.7  C9 H15 N O2

m/z: 169.1103
Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 150.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron ions.
172 formula(s) evaluated with 2 results within limits (all results up to 1000) for each mass

Elements Used:
C: 0-100  H: 0-100  N: 0-10  O: 0-10

Nick Arnsta, NAA183

m/z: 183.1259
Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 150.0
Element prediction: Off

Monoisotopic Mass, Odd and Even Electron Ions
77 formula(e) evaluated with 1 results within limits (all results (up to 1000) for each mass)
Elements Used:
C: 0-100  H: 0-100  N: 0-10  O: 0-10
GCT_6679 25 (1.633) Cm (24:29-1:5x3.000)

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Elemental Composition Report

Single Mass Analysis (displaying only valid results)
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 150.0
Element prediction: Off

Monoisotopic Mass; Odd and Even Electron Ion
88 formula(s) evaluated with 1 results within limits (all results (up to 1000) for each mass)

Elements Used:
C: 0-100  H: 0-100  N: 0-10  O: 0-10
GCT_6680 24 (1.567) Cm (24-4.7x3.000)  Nick Arnista, NAA139
TOF MS EI+

<table>
<thead>
<tr>
<th>Mass</th>
<th>Calc. Mass</th>
<th>m/z</th>
<th>PPM</th>
<th>DBE</th>
<th>I-PIE</th>
<th>Formula</th>
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<tr>
<td>139.0999</td>
<td>139.0997</td>
<td>0.2</td>
<td>1.4</td>
<td>3.0</td>
<td>6.5</td>
<td>C8 H13 N O</td>
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