The tandem zinc-mediated chain extension-iodomethylation reaction and its applications

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The tandem zinc-mediated chain extension-iodomethylation reaction and its applications

Abstract
A tandem zinc-mediated chain extension-iodomethylation reaction was developed and used to generate various alpha-iodomethyl gamma-keto esters, amides and imides. The yields for formation of alpha-iodomethyl gamma-keto esters were higher than alpha-iodomethyl gamma-keto amides. beta-Keto amides with bulky substituents on the amide bond were not good substrates for the zinc-mediated chain extension-iodomethylation reaction. Use of a chiral beta-keto imide provided a facile means to effectively control the stereochemistry at the alpha-position of the extended chain with this methodology.

A palladium-catalyzed cross-coupling reaction was used to install different functional groups at the alpha-carbon site of an -iodomethyl gamma-keto ester and imide. Reactions between alpha-iodomethylated gamma-keto compounds and aromatic iodides or an alkenyl bromide were performed successfully in modest yields. However, iodophenol and 1-fluoro-4-iodobenzene did not provide products when reacted with the alpha-iodomethylated product under the same reaction conditions.

Other applications of the alpha-iodomethyl gamma-keto ester were studied in an effort to attach different alkyl groups to the alpha-position, including thiolation and nucleophilic alkylation.

The alpha-substituted gamma-keto esters or imides can be designed to contain functionality that mimics the side chain of amino acids in a ketomethylene peptide isostere.

Keywords
Chemistry, Organic

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THE TANDEM ZINC-MEDIATED CHAIN EXTENSION-IODOMETHYLATION REACTION AND ITS APPLICATIONS

BY

QINGLIN PU
B.S., Nanjing University of Science and Technology, 1990

THESIS

Submitted to the University of New Hampshire
in Partial Fulfillment of the
Requirements for the Degree of

Master of Science
in
Chemistry

September, 2007
This thesis has been examined and approved.

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August 15, 2007  
Date
DEDICATION

This thesis is dedicated to Dingsong and Andy who have given me their wonderful love, support and encouragement throughout my graduate time at UNH. I will forever be grateful for that. I also wish to dedicate this thesis to my family in China, who are always standing with me throughout my entire struggle.
ACKNOWLEDGEMENTS

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<tr>
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<tbody>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Pmb</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>carbobenzylxy</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>CDI</td>
<td>carbonyldiimidazole</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyle</td>
</tr>
</tbody>
</table>
ABSTRACT

THE TANDEM ZINC-MEDIATED CHAIN EXTENSION-IODOMETHYLATION REACTION AND ITS APPLICATIONS

By

QINGLIN PU

University of New Hampshire, September, 2007

A tandem zinc-mediated chain extension-iodomethylation reaction was developed and used to generate various α-iodomethyl γ-keto esters, amides and imides. The yields for formation of α-iodomethyl γ-keto esters were higher than α-iodomethyl γ-keto amides. β-Keto amides with bulky substituents on the amide bond were not good substrates for the zinc-mediated chain extension-iodomethylation reaction. Use of a chiral β-keto imide provided a facile means to effectively control the stereochemistry at the α-position of the extended chain with this methodology.

A palladium-catalyzed cross-coupling reaction was used to install different functional groups at the α-carbon site of an α-iodomethyl γ-keto ester and imide. Reactions between α-iodomethylated γ-keto compounds and aromatic iodides or an alkenyl bromide were performed successfully in modest yields. However, iodophenol and 1-fluoro-4-iodobenzene did not provide products when reacted with the α-iodomethylated product under the same reaction conditions.
Other applications of the α-iodomethyl γ-keto ester were studied in an effort to attach different alkyl groups to the α-position, including thiolation and nucleophilic alkylation.

The α-substituted γ-keto esters or imides can be designed to contain functionality that mimics the side chain of amino acids in a ketomethylene peptide isostere.
CHAPTER I

INTRODUCTION

Chain Extension Chemistry

Chain extension methodology provides opportunities for organic chemists to lengthen existing carbon chains to a desired chain length. The versatility of chain extension reactions have been shown in the preparation of a variety of building blocks for bioorganic chemistry research. The generation of 1,4-dicarbonyl compounds is of great interest in these research fields. Most common methods of chain extension leading to the 1,4-dicarbonyl functionality involve the intermediacy of a donor-acceptor cyclopropane, which is defined by an electron donating group (alkoxyl or amino) and an electron withdrawing group (ester, amide, phosphonate, imide, etc) being present on two adjacent carbons of a cyclopropane ring. A number of different ways to form 1,4-dicarbonyl compounds, especially \( \gamma \)-keto esters via donor-acceptor cyclopropane, have been reported. A brief review of the various chain extension reactions is described below.

**Bieräugel's Method**

Bieräugel and coworkers\(^1\) reported the first chain extension method used to convert \( \beta \)-keto esters \( 1 \) to \( \gamma \)-keto esters \( 5 \) in 1974. As a result of the reaction between a \( \beta \)-keto ester and a secondary amine, an enamine ester \( 2 \) was formed. When the Simmons- Smith reagent\(^2\) was added to the enamine, 2-aminocyclopropane ester \( 3 \) was generated. This donor-acceptor cyclopropane was believed to be the intermediate preceding formation of the ring-opened species imine \( 4 \) in this reaction. A \( \gamma \)-keto ester was
produced after hydrolysis of the imine intermediate (Scheme 1). Although low yields in the conversion of various β-keto esters led to limited applications for this method, Bieräugel’s strategy was the first method reported to pursue chain extension reaction with a donor-acceptor cyclopropane.

\[
\begin{align*}
&\text{1} \quad \text{NHR}_2 \quad \text{2} \\
&\quad \text{Zn-Cu, EtI} \quad \text{3} \\
&\quad \text{H} \\
&\quad \text{CH}_2\text{I}_2 \\
&\quad \text{4} \\
&\text{5} \\
&\quad \text{NH}_4\text{Cl} \quad \text{H}_2\text{O} \\
&\quad \text{6} \\
&\quad \text{7} \\
&\quad \text{8} \\
&\quad \text{9} \\
&\quad \text{10} \\
&\quad \text{11} \\
&\quad \text{12}
\end{align*}
\]

Scheme 1. Bieräugel’s Method for Formation of γ-Keto Esters 5

Saigo’s Method

Saigo and coworkers modified Bieräugel’s method through the formation of a trimethylsilyl (TMS) enol ether 6, and applied this strategy to a series of β-keto esters and β-diketones (Scheme 2). When the TMS enol ether was trapped with the Simmons-Smith reagent, two different TMS protected cyclopropyl alcohol intermediates 8 and 10 appeared to have been formed in the process of the reaction. Multiple additions of the methylene groups took place and the formation of an unexpected mixture of carboxylic acids 11 and 12 were isolated after saponification. No unsubstituted γ-keto ester was
formed in this multi-step process, most likely due to migratory aptitude of the silicon.

\[
\begin{align*}
\text{TMSO} & \quad \longrightarrow \quad \text{O} \quad \text{OTMS} \\
\text{R} & \quad \text{O} \quad \text{OR'} \\
\begin{array}{c}
\text{6} \\
\text{7} \\
\text{8}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{a) KOH/CH}_3\text{OH} \\
\text{b) H}_3\text{O}^+ \\
\text{TMSO} \quad \longrightarrow \quad \text{O} \quad \text{OR'} \\
\text{R} & \quad \text{O} \quad \text{Zn/Cu} \\
\begin{array}{c}
\text{9} \\
\text{10} \\
\text{11} \\
\text{12}
\end{array}
\end{align*}
\]

**Scheme 2.** Saigo’s Method for Formation of γ-Keto Acids 11 and 12

**Dowd’s Method**

Dowd and coworkers developed a different strategy for the formation of γ-keto esters from substituted β-keto esters in which a free radical-mediated ring expansion reaction was involved (Scheme 3). The substituted β-keto ester starting material 13, which was prepared by addition of an α-substituted β-keto ester with methylene dibromide, was treated with tri-\(n\)-butyltin hydride in the presence of AIBN to generate a radical intermediate 14. This radical species was proposed to attack the adjacent carbonyl

---

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group to form a donor-acceptor cyclopropanoxy radical 15, followed by fragmentation to generate an ester stabilized radical 16. Capture of a hydrogen atom from tri-n-butyltin hydride completed the formation of the product and continued the radical chain reaction.

Dowd’s method has been shown to provide access to a variety of chain extended or ring-expanded products, especially for the formation of five to eight-membered rings. The targeted compound was always an α-substituted γ-keto ester, for this methodology was not applicable to α-unsubstituted β-keto esters. The most likely explanation is that competing E2 reactions would take place through the removal of an acidic proton on the α-position of 13 (R' = H) during the alkylation of starting β-keto ester.

Scheme 3. Dowd’s Method for Formation of γ-Keto Esters 17
Reissig’s Method

Reissig’s research group developed a [2+1]-cycloaddition strategy in which a carbenoid derived from methyl diazoacetate in the presence of copper (II) acetylacetonate was trapped with a silyl enol ether 18 to generate a cyclopropane intermediate 19. Fluoride promoted the fragmentation of the cyclopropane ring and offered the γ-keto ester 5. Although a different starting material, which was derived from a ketone species rather than β-keto ester, was used in this method, the common donor-acceptor cyclopropane was involved in the formation of the γ-keto ester. This was a complementary chain extension reaction to previous methods.

![Chemical Diagram](https://example.com/diagram.png)

Scheme 4. Reissig’s Method for Formation of γ-Keto Ester 5

Zinc-carbenoid-mediated Chain Extension

A zinc-mediated chain extension methodology has been developed by Zercher’s research group. The chain extension reaction utilizes Furukawa-modified Simmons-Smith cyclopropanation conditions for the preparation of γ-keto esters from α-unsubstituted β-keto esters. The proposed mechanism of this zinc-mediated chain

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extension is believed to involve formation of a donor-acceptor cyclopropane (Scheme 5). Deprotonation of the β-keto ester by diethyl zinc or the zinc carbenoid (ethyl(iodomethyl)zinc) derived from Et₂Zn and CH₂I₂ results in the formation of the zinc enolate 20, which has been confirmed as an intermediate by NMR studies and production of ethane gas as a byproduct of enolate formation.⁷ Direct alkylation of the zinc enolate with the carbenoid EtZnCH₂I could provide the zinc intermediate 21. The cyclopropyl alkoxide intermediate 22 is assumed to be generated through an intramolecular cyclization, but no direct evidence supports the presence of this cyclopropane intermediate, possibly due to its rapid fragmentation to an oligomeric zinc species 23, which bears structural and reactivity similarity to a Reformatsky intermediate. Quenching with an acid, such as aqueous ammonium chloride solution produced an α-unsubstituted γ-keto ester 5. This one-pot method is more efficient and is easier to perform than the previously reported chain extension methods, which usually involved multi-step sequences. The efficiency of the zinc-mediated chain extension reaction is unaffected by the presence of olefin functionality.⁶
This zinc-mediated chain extension reaction has been successfully applied to a variety of functionalities such as β-keto amides 25, phosphonates 27 and imides 29 (Scheme 6). These substrates work with the zinc carbenoid in a similar pattern compared to β-keto esters. Although the zinc carbenoid method works inefficiently with α-substituted β-keto dicarbonyl substrates, tandem zinc-mediated chain extension reactions provide attractive approaches to target the desired α-substituted γ-keto compounds.
Scheme 6. Chain Extension of $\beta$-Keto Amides, Phosphonates and Imides

Recently Xue and his coworkers reported a modified zinc-mediated chain extension reaction for the generation of $\alpha$-unsubstituted 1,4-diketones 32 from $\alpha$-unsubstituted 1,3-diketones 31 by using a different organozinc carbenoid (CF$_3$CO$_2$ZnCH$_2$I).$^9$ This carbenoid was prepared by treatment of the original carbenoid (EtZnCH$_2$I) with trifluoroacetic acid (Scheme 7). The proposed mechanism by Xue and coworkers, which still involved in generation of the cyclopropane intermediate, was based on analogy to Zercher's proposed mechanism. Both aromatic and aliphatic 1,3-diketones were employed to give corresponding 1,4-diketone products in moderate yields. No desired compounds were observed in the reactions of $\alpha$-substituted $\beta$-diketones and excess...
amount of zinc carbenoid resulted in formation of 1,2-disubstituted cyclopropyl alcohols. This carbenoid has also been applied to the ring expansion of β-keto lactones.\textsuperscript{9a}

\[ R_1\text{CO}_2R_2 \xrightarrow{\text{a): CF}_3\text{CO}_2\text{ZnCH}_2\text{I}} R_1\text{CH}_2\text{CO}_2R_2 \]

\[ R_1\text{CO}_2R_2 \xrightarrow{\text{b): aq. NH}_4\text{Cl}} R_1\text{CH}_2\text{CO}_2R_2 \]

**Scheme 7.** Xue's Chain Extension Reaction for the Formation of 1,4-Diketones \textbf{32}

**Tandem Chain Extension Methylation Reaction**

Based upon the practical limitation of zinc-mediated chain extension in the direct formation of α-substituted γ-keto esters and amides from α-substituted β-keto esters, Zercher and Hilgenkamp reported a variation on the chain extension reaction that provided a useful solution to this limitation.\textsuperscript{7,10} This approach was utilized to produce α-methylated γ-keto esters and amides in modest yields. In order to facilitate methylation, trimethylsilylchloride (TMSCl) was added prior to quenching the reaction mixture (Scheme 8). The trimethylsilyl group appeared to aid fragmentation of the proposed dimeric species and formation of an activated intermediate, which could be TMS-ketene acetal species \textbf{33} or trimethylsilyloxyacyclop propane \textbf{34}. Either intermediate could act as a nucleophile and attack the electrophilic carbenoid, which was present in excess in the reaction, and provide a zinc homoenolate intermediate \textbf{35}. When quenched with an acid, the α-methyl γ-keto esters \textbf{36} were obtained.
Scheme 8. Proposed Mechanism of Chain Extension Methylation Reaction

In an effort to test the efficiency of the tandem chain extension α-methylation reaction, several β-keto esters or amides were exposed to the reaction conditions. The desired α-methylated γ-keto esters and tertiary amides were obtained in yields ranging from 57% to 73% after column chromatography. The data suggests that the methylation reaction was not hindered by the existence of a bulky substituent or aromatic ring on the ester or amide functionality.

Table 1. Preparation of α-Methyl γ-Keto Esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CH₃</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>tBu</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td>CH₂Ph</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>C₆H₅</td>
<td>Et</td>
<td>70</td>
</tr>
</tbody>
</table>
In contrast to the good yields of α-methylated γ-keto esters, secondary β-keto amides, such as N-cyclohexyl 3-oxo-butanamide 37, provided low yields of the corresponding α-methylated γ-keto amides 38 (Scheme 9). α-Unsubstituted γ-keto amides 39 were the major products of the reaction. A proposed explanation for these results, which was supported by deuterium labeling studies, is that the secondary β-keto amide proton partially quenches the dimeric zinc species before its conversion to TMS-ketene acetal species 33 or trimethylsilyloxy cyclopropane 34.

Scheme 9. Synthesis of a Secondary α-Methyl γ-Keto Amide 39

Tandem chemistry has been explored to expand the applications of the zinc-mediated chain extension reactions. For example, trapping the intermediate zinc enolate 24 with a halogen as an electrophile, followed by elimination with an amine base, provides an α,β-unsaturated γ-keto ester 41. Chain extension-aldol reactions, which involve the reaction between the zinc enolate 24 and various aldehydes provide the predominant \textit{syn}-aldol products 40, with stereoselectivity much greater than in the typical
Reformatsky reaction (Scheme 10).\textsuperscript{12}

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{ZnX} \\
\text{R} \quad \text{OR'}
\end{array}
\begin{array}{c}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{OR'}
\end{array}
\begin{array}{c}
\text{O} \\
\text{R} \quad \text{OR'}
\end{array}
\end{array}
\end{equation}

\textbf{Scheme 10. Applications of the Chain Extension Reaction}

\textbf{Introduction to Peptide Isosteric Replacements}

Over the past two decades, the utility of 1,4-dicarbonyl compounds as components of novel bioactive agents such as peptide inhibitors has been explored.\textsuperscript{13,14} Peptide mimetics can be designed to mimic or block the bioactivity of natural peptides or enzymes. For example, peptide isosteres have been widely used as inhibitors of aspartic acid proteases (such as renin\textsuperscript{15}), cysteine proteases\textsuperscript{16} and serine proteases.\textsuperscript{17} The cleavage of a normal peptide bond is described briefly in Scheme 11.\textsuperscript{18} Peptide isosteres are generated when the amide bonds of a peptide are replaced by other functional groups of similar size that are hydrolytically stable. In these cases peptide isosteres are capable of maintaining similar binding properties as the natural peptide, but are not easily enzymatically degraded.\textsuperscript{19} Therefore, design and synthesis of peptidomimetics are crucial components of bioorganic and medicinal chemistry research. A number of functional
groups have been used to mimic the structure of peptide bonds, including ketomethylene 46,20 hydroxyethylene 47,21 alkenes 4822 and difluoroketomethylene groups 4923 (Figure 1).

\[\text{Scheme 1. Hydrolysis of a Peptide Chain}\]
Figure 1. Isoteric Replacements of Peptide Amino Bonds

Previous Methods for Preparing Ketomethylene Isosteres

The ketomethylene replacement has proven to be effective in inhibition of a variety of enzymatic systems, such as HIV protease, arginine aminopeptidases, angiotensin-converting enzyme (ACE), human rhinovirus (HRV) 3C protease, and retroviral protease. This type of isostere has been incorporated in synthetic drugs (i.e. Ruprintrivir), as well as being observed as a key functionality in naturally-occurring protease inhibitors (i.e. Arphamenines). Many approaches to the generation of ketomethylene isosteres have been investigated, and a brief review on this area is provided below.

One common method reported for the formation of ketomethylene isosteres involves reactions of a Grignard reagent 51 (Scheme 12). The Grignard reagent derived from a chiral propyl bromide 50 was reacted with an N-protected protected amino acid derivative, normally amino aldehyde 52, to generate intermediate alcohol 53. Protection of the secondary hydroxyl group by acetylation was followed by removal of
the benzyl ether by hydrogenolysis, which provided a primary alcohol. This alcohol was oxidized to the corresponding acid 55 using ruthenium chloride and coupled with other amino acid derivatives. Cleavage of the acetyl group and further oxidation provided the protected ketomethylene-containing isostere 57. However, the oxidation process was troublesome and racemization often occurred due to the presence of amino aldehydes.

Scheme 12. Synthesis of Ketomethylene Isosteres Using Grignard Reagents

Hoffman and his coworkers developed another synthetic approach to ketomethylene isosteres. The key step in this approach was the formation of a γ-keto ester through direct alkylation of a β-keto ester. The β-keto ester 59 was prepared by treating...
the lithium enolate of $t$-butyl acetate with an activated derivative of amino acid 58. Addition of sodium hydride to the $\beta$-keto ester resulted in the formation of the enolate, which was exposed to ethyl bromoacetate. Alkylation of the $\beta$-keto ester provided the $\alpha$-substituted $\gamma$-keto ester. Cleavage of the $t$-butyl ester and decarboxylation by treatment with trifluoroacetic acid (TFA) provided the $\gamma$-keto ester 60. Hydrolysis with lithium hydroxide and coupling with proline methyl ester gave the ketomethylene-containing peptide chain 61 (Scheme 13).

Scheme 13. Synthesis of Ketomethylene Isosteres through Alkylation of $\beta$-Keto Esters

Another similar strategy was illustrated by the same authors using scalemic alkylation agents 2-triflyloxy esters 63, which allowed the incorporation of the $\alpha$-substitution. Since tert-butyl $\beta$-keto esters could be deprotected and decarboxylated easily under acidic conditions, the $t$-butyl esters were used in alkylation reactions to improve overall yields in this modified method. Alkylation of $t$-butyl $\beta$-keto esters 62
with 2-triflyloxy esters 63 followed by treatment of the crude alkylation product by TFA, followed by LiOH gave γ-keto acids 66. The resulting γ-keto acids were coupled to chiral α-methylbenzylamine 67 to provide peptide isosteres 68 (Scheme 14). This chiral alkylation methodology offered high enantioselectivities for preparation of α-alkylated γ-keto esters and acids, however, the deficiency of the suitable chiral alkylation reagents limits the application of this method.

![Chemical structures](image)

Scheme 14. Synthesis of Ketomethylene Isosteres Using Chiral Alkylating Reagents

Another synthetic approach to ketomethylene isosteres, which was reported by Lygo and Rudd in 1995, involved the use of a β-keto sulfone intermediate. The Boc-protected amino acid ester derivative 69 was reacted with a dianion derived from methylphenylsulfone to generate the desired sulfone 70, which could undergo the reaction with bromoacetate derivatives 71 to provide β-keto sulfone intermediate 72.
Direct reduction using samarium iodide (SmI₂) in a mixture of THF and MeOH afforded the ketomethylene tripeptide isosteres 73 (Scheme 15). Although this short route allowed for formation of peptide isosteres that were related to HIV protease inhibitors, epimerization was still observed during the base-catalyzed coupling reaction.

![Chemical structures](image)

**Scheme 15.** Synthesis of Ketomethylene Isosteres through a β-Keto Sulfone

As described above, generation of ketomethylene-containing peptide mimics often requires lengthy and demanding synthetic sequences. Control of stereochemistry of the α-carbon side chain has also been shown to be a challenge in most of these synthetic approaches. Recently Zercher and coworkers demonstrated a simple and efficient zinc carbenoid-mediated method that facilitates the conversion of β-keto esters to γ-keto esters and allows for the potential incorporation of α-side chain functionality. N-Protected amino acids 74 were subjected to a neutral C-acylation reaction through intermediate acyl imidazoles to provide the corresponding β-keto esters 75. The target γ-keto esters 76 were
formed in good yields via a zinc-mediated chain extension reaction. Cleavage of the benzyl ester by hydrogenolysis, followed by EDC coupling with the methyl ester of phenylalanine yielded the tripeptide mimic 77 (Scheme 16) as a single diastereomer. No epimerization of amino acid stereocenters was observed by chiral HPLC study.

Scheme 16. Synthesis of Ketomethylene-containing Tripeptide Isosteres through Zinc-mediated Chain Extension Reaction

Application of tandem reaction processes, including tandem chain extension-aldol and chain extension-methylation reactions, has provided access to $\alpha$-substituted ketomethylene isosteres. Through appropriate selection of starting materials and subsequent manipulation of the tandem reaction products, $\alpha$-side chains that mimic natural amino acid side chains have been produced (Scheme 17).33
Scheme 17. Preparation of an a-Substituted γ-Keto Imide 80 through Tandem Chain Extension–aldol Reaction

Although many approaches have been used for the synthesis of ketomethylene isosteric replacements, satisfactory results have not been obtained in all cases. The zinc carbenoid-mediated chain extension reaction provides an opportunity to synthesize ketomethylene isosteres via a novel synthetic route; however, efficient mimicry of the peptide backbone requires a substituent, normally an alkyl group, at the a-carbon site. Furthermore, control of this a-stereocenter is essential to the efficient formation of the isostere. The diversity of side chains required in ketomethylene isosteres suggests that a variety of routes are required for the incorporation of the side chain. Development of an efficient methodology for the preparation of ketomethylene isosteres of peptide bonds that facilitates the stereocontrolled incorporation of diverse side-chain functionality has become an urgent priority in this research area.
RESULTS AND DISCUSSION

Zinc-mediated Chain Extension-iodomethylation

The utility of the zinc-mediated chain extension reaction has expanded recently to the preparation of ketomethylene-containing peptide isosteric replacements. As expressed in chapter I, the zinc-mediated chain extension methylation reaction provides the ability to incorporate an α-methyl substituent in γ-keto esters and amides through treatment of the intermediate zinc enolate equivalent with excess carbenoid and catalytic TMS-Cl. Since information gained from previous experimental data indicates that nucleophilic character is present in the zinc homoenolate, treatment with iodine provides the opportunity to generate α-iodomethyl γ-keto esters (or amides). The opportunity to perform subsequent chemistry leading to the formation of various α-substituted γ-keto esters (amides) is presented due to reactivity of the iodomethyl group. The zinc-mediated chain extension-iodomethylation reaction derived from chain extension methylation reaction is shown in Scheme 18.

Scheme 18. Zinc-mediated Chain Extension-iodomethylation Reaction

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Synthesis of α-Iodomethyl γ-Keto Esters

The chain extension-iodomethylation reaction was first conducted on β-keto esters. Three representative β-keto esters (methyl pivaloylacetate, benzyl acetoacetate, and t-butyl acetoacetate) were chosen as substrates for the chain extension-iodomethylation reaction. Based upon previous optimization of the conditions for the chain extension methylation reaction investigated by Hilgenkamp, the iodomethylation reaction was performed on the substrates using a similar procedure. Exposing β-keto esters to five equivalents of carbenoid derived from the reaction system, followed by addition of catalytic trimethylsilylchloride (0.2 equivalents) and excess iodine, provided the desired α-iodomethyl γ-keto esters in satisfactory yields after purification by column chromatography. The results showed that the efficiency of chain extension-iodomethylation is not hindered by the presence of a bulky or aromatic group on the ester oxygen, which is consistent with the results found in the chain extension methylation reaction.

| Table 2. Preparation of α-Iodomethyl γ-Keto Esters |
|---|---|---|---|---|
| Entry | R | R' | Product (Yield) |
| 1 | t-Butyl | CH₂ | 82 (58%) |
| 2 | CH₃ | t-Butyl | 83 (62%) |
| 3 | CH₃ | CH₂Ph | 84 (60%) |

From a 1H NMR investigation of the crude reaction mixtures, five compounds were
observed in the reaction of methyl pivaloylacate. Those compounds were identified as the targeted \( \alpha \)-iodomethyl \( \gamma \)-keto ester 82, \( \beta \)-iodomethyl \( \gamma \)-keto ester 85, \( \alpha \)-iodo \( \gamma \)-keto ester 86, \( \alpha \)-methyl \( \gamma \)-keto ester 87 and simple chain-extended product \( \gamma \)-keto ester 88. The small amount of compound 86 was believed to result from

\[
\begin{align*}
\text{82} & \quad \text{85} & \quad \text{86} \\
\text{87} & \quad \text{88}
\end{align*}
\]

Figure 2. Products in the Crude Mixture of Iodomethylation Reaction on Methyl Pivaloylacate

the chain extended \( \gamma \)-keto ester by treatment with iodine prior to quench with saturated ammonium chloride solution. This result was probably due to the inefficiency of the chain extension methylation reaction. An easy way to enhance the methylation was to increase the reaction time after addition of TMSI to the reaction mixture from 30 min to 60 min. The compounds 86 and 88 were not observed in the \( ^1 \text{H} \) NMR spectrum of the crude mixture after this change was made. The \( \alpha \)-methyl \( \gamma \)-keto ester 87 could be eliminated from the reaction mixture by increasing the equivalents of iodine from 2.0 to
5.0 and extending the iodonation time to 10 min after the appearance of a constant purple color of reaction mixture.

The most interesting byproduct, observed in preparation of the α-iodomethyl γ-keto ester of methyl pivaloylacetate, was the β-iodomethyl γ-keto ester 85. The compound was hard to separate from the α-iodomethyl γ-keto ester 82 by column chromatography. When comparing NMR spectra of compounds 82 and 85, a minor difference was the chemical shift of the methine proton adjacent to the iodomethyl group. The proton of 82 was shifted slightly upfield, while the methine proton in 85 was slightly downfield due to its location nearer to the ketone carbonyl group. A proposed mechanism to explain the appearance of compound 85 in the chain extension-iodomethylation reaction is illustrated in Scheme 19.

An assumption is made that the starting β-keto ester has not completely finished undergoing the chain extension reaction before addition of TMS chloride to the reaction mixture. This means it is possible for remaining β-keto ester enolate to react with TMSCl, which leads to the formation of TMS enol ether 6. This intermediate could be converted to the constitutional isomer 7 because of the migrating ability of silicon. After reacting with the zinc carbenoid, the TMS-protected cyclopropyl alcohol intermediate 8 could be presented in the reaction mixture. This hypothesis is similar to Saigo's chain extension method described in chapter I (Scheme 2). Fragmentation of intermediate 8 provides a chain extended zinc species 90. Reaction of 90 with TMS chloride and excess carbenoid would provide the homoenolate 92, which could be converted to β-iodomethyl γ-keto ester 93 by introduction of iodine to the reaction.
Scheme 19. Proposed Mechanism of Formation of β-Iodomethyl γ-Keto Esters 93

In order to test this hypothesis, the chain extension time of the reaction was increased from 10 min to 30 min. This modification was used to allow all of the starting compound β-keto ester to be consumed completely before addition of trimethylsilyl chloride to the reaction. Use of thin layer chromatography (TLC) technique can effectively monitor the degree of starting material consumption in the reaction. It was observed from the $^1$H NMR spectrum of the crude reaction mixture that the amount of byproduct β-iodomethyl γ-keto ester dramatically decreased, which supported this proposed mechanism. However, no further evidence confirms the existence of the intermediates in this type of iodomethylation reaction.
Synthesis of \( \alpha \)-Iodomethyl \( \gamma \)-Keto Amides

Based on the successful formation of \( \alpha \)-iodomethyl \( \gamma \)-keto esters, the zinc-mediated chain extension iodomethylation was studied with \( \beta \)-keto amides as the starting materials. Considering the inefficiency of the chain extension methylation for secondary \( \beta \)-keto amides,\(^8\) tertiary \( \beta \)-keto amides were viewed as more suitable starting materials for this study. The selected \( \beta \)-keto amides were not commercially available, so they were prepared by the reaction of diketene with various amines (Scheme 20).\(^{34}\)

\[
\begin{align*}
\text{NH} & + \text{H}_2\text{O, rt} \rightarrow \text{N} \rightarrow \text{O} \rightarrow \text{O} \\
\text{NH} & + \text{NaHCO}_3 \rightarrow \text{N} \rightarrow \text{O} \rightarrow \text{O}
\end{align*}
\]

**Scheme 20.** The Reaction of Diketene with Different \( \beta \)-Keto Amides

The first \( \beta \)-keto amide utilized in the iodomethylation reaction was \( N,N \)-diisopropyl-3-oxo-butyramide 94, which was derived from \( N,N \)-diisopropylamine. Surprisingly, no desired product \( \alpha \)-iodomethyl \( \gamma \)-keto amide 96 was observed in the crude reaction mixture when it was subjected to the iodomethylation conditions. Only \( \alpha \)-iodo \( \gamma \)-keto amide 97 and the chain extended product 98 were observed (Scheme 21).
Attempts were made to produce the iodomethylation product of the β-keto amide, including a modification in the amount of catalytic trimethylsilylchloride (TMSCl) from 0.2 equivalents to 1.0 equivalents, as well as lengthening the reaction time for methylation from 45 min to 90 min. ¹H-NMR spectra of the crude reaction mixture showed the major product was still the α-iodo γ-keto amide 97. The desired α-iodomethyl chain-extended product was not formed. As discussed before, the role of the trimethylsilylchloride in the tandem chain extension methylation reaction is believed to promote fragmentation of the dimeric species 23 and generate an activated nucleophile. Another more powerful electrophilic TMS-source TMSOTf was used to promote the formation of α-methyl γ-keto amide. This effort resulted in slightly higher yield of the α-iodo compound 97, yet no iodomethylated material was obtained.

In addition to N,N-diisopropyl-3-oxo-butyramide 94, the iodomethylation reaction was performed with another β-keto amide substrate, 1-(1,3-dioxobutyl) pyrrolidine 95, derived from pyrrolidine. The desired compound α-iodomethyl γ-keto amide 99 was

**Scheme 21.** The Iodomethylation Reaction with N,N-Diisopropyl-3-oxo-Butyramide 94
observed in the crude mixture, but the α-iodo γ-keto amide 100 was still present in the reaction mixture. The target compound 99 derived from pyrrolidine β-keto amide 95 was isolated by column chromatography in only 12% yield (Scheme 22). Although similar modifications applied to the reaction of the diisopropylamide substrate were also carried out with 95, no improvement in yield was achieved.

Scheme 22. The Iodomethylation Reaction with 1-(1,3-Dioxobutyl) pyrrolidine 95

Based on all of the information obtained from the experiments, it was concluded that the tandem zinc-mediated chain extension-iodomethylation reaction does not work efficiently with some β-keto amides; however, this does not mean that all β-keto amides would be unreactive, since earlier work by Hilgenkamp demonstrated that some β-keto amides, such as an N,N-dimethyl-3-oxobutyramide, can be converted to the desired α-methyl γ-keto amides using the tandem chain extension-methylation reaction. A likely explanation for the failure of N, N-diisopropyl β-keto amide 94 and pyrrolidine β-keto
amide 95 in the iodomethylation reaction is that the methylation reaction is somehow hindered by the presence of bulky amide substituents. The steric hindrance may obstruct the ability of the amide carbonyl to form the TMS enol ether by reaction with TMSCl.

Synthesis of α-Iodomethyl γ-Keto Imides

In an effort to broaden the scope of the zinc-mediated chain extension iodomethylation reaction, the methodology was applied to a β-keto imide starting material, derived from an oxazolidinone precursor. Oxazolidinones derived from chiral amino acids are frequently referred to as Evans' auxiliaries, which have been used widely for asymmetric synthesis. The utility of chiral oxazolidinone β-keto imides in the zinc-mediated chain extension-aldol reactions has been investigated by Lai and Lin. Incorporation of the chiral oxazolidinone onto an amino acid-derived starting material has proven to be effective for formation of the chiral β-keto imide used for diastereoselective chain extension-aldol reactions. We felt the chiral auxiliary would be attractive for the control of stereochemistry at the α-carbon of iodomethylation products.

Before introducing the chiral auxiliary β-keto imide to this study, an achiral oxazolidinone β-keto imide was exposed to the chain extension iodomethylation reaction conditions. The β-keto imide 101 can be generated in a yield of 36% through reaction between diketene and oxazolidinone in the presence of strong base n-butyl lithium. The iodomethylated compound 102 was isolated by column chromatography in 31% yield (Scheme 23).
Scheme 23. Preparation of an Oxazolidinone β-Keto Imide 101 and Its Iodomethylated Product 102

Previous studies reported by Lin\textsuperscript{36b} showed that one predominant cyclopropanol derivative was separated from the crude mixture when the chain extension-aldol reaction was performed on a peptide-derived β-keto imide. A similar phenomenon occurred in the chain extension-iodomethylation of the oxazolidinone β-keto imide. The interpretation was that the imide functional group enhanced the formation of a TMS-enol ether intermediate 104 due to its ability to react with the TMS group, which was available in the reaction system, while the imide carbonyls chelated with zinc (II) in the chain extension-aldol reaction. The proposed mechanism involves spontaneous alkylation of the TMS-enol ether 104 with the excess carbenoid.
If the cyclopropyl alcohol was formed via this mechanism, the cyclopropyl alcohol could be easily formed when performing the methylation reaction. The existence of TMS chloride might promote formation of the TMS enol ether intermediate, which could attack the zinc carbenoid to generate the cyclopropyl alcohol derivative through an intramolecular cyclization process. Experimental data (Scheme 25) showed that the ratio of methylated product 108 to cyclopropanol 107 decreased significantly with the increasing amount of catalytic TMS chloride equivalents. This indicated that TMS chloride played an important role in promoting the formation of the byproduct cyclopropyl alcohol. Furthermore, evidence also depicted that longer reaction time for the methylation helped to generate the cyclopropyl side product. Limiting the amount of...
TMS chloride and limiting the reaction time would be necessary to maximize the yield of the desired iodomethylated compound and reduce cyclopropanol formation.

\[ \text{Scheme 25. Chain Extension Methylation on an Oxazolidinone } \beta\text{-Keto Imide 101} \]

Control of stereochemistry at the \( \alpha \)-carbon site is both essential and a challenge in the preparation of ketomethylene isosteres. In order to achieve stereo-controlled \( \alpha \)-substitution, an approach which utilized a chiral \( \beta \)-keto imide was undertaken. Reduction of the amino acid L-phenylalanine 109 with borane dimethylsulfide followed by sequential reactions with triphosgene and diketene, provided the chiral \( \beta \)-keto imide 112. The chiral \( \beta \)-keto imide was exposed to the same conditions as used in the iodomethylation reaction of compound 101. The synthetic route to a chiral \( \alpha \)-iodomethyl \( \gamma \)-keto imide is illustrated on Scheme 26.

From integration of the \(^1\)H NMR spectrum of the crude reaction mixture, it was found that the ratio of diastereoisomers of \( \alpha \)-iodomethyl \( \gamma \)-keto imide 113 was over 5 to 1, indicating that the chiral auxiliary of the \( \beta \)-keto imide controls the stereochemistry at the \( \alpha \)-position in the chain extension iodomethylation reaction. However, the yield of compound 113 was only 26%.
Scheme 26. Synthesis of α-Iodomethyl γ-Keto Imide 113 through Chain Extension

Iodomethylation Reaction

As anticipated before, due to the similarity with the achiral β-keto imide, a considerable amount of cyclopropyl alcohol 114 was also isolated by column chromatography from the reaction mixture in a yield of 28%. The diastereoisomeric cyclopropanols were produced in a ratio (dr) of over 19:1. In agreement with the previous result that the TMSCl promotes the formation of cyclopropyl alcohol, the yield of isolated compound 114 was increased to 41% when the amount of TMSCl was increased from 0.2 equivalents to 1.0 equivalents. Another modification to increase the yield of cyclopropyl alcohol 114 was to lengthen the reaction time of the methylation prior to the addition of iodine to the reaction mixture. The data showed that the yield of compound 114 increased when the methylation time was changed from 1 hr to 2 hr. In the meantime
the amount of iodomethylated compound 113 decreased to a similar degree.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound 113</th>
<th>Compound 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMSCl = 0.2 equiv</td>
<td>Methylation: 1 hr</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>Methylation: 2 hr</td>
<td>23%</td>
</tr>
<tr>
<td>TMSCl = 1.0 equiv</td>
<td>Methylation: 1 hr</td>
<td>20%</td>
</tr>
</tbody>
</table>

It is unclear what factors effectively control the stereoselectivity of the cyclopropyl alcohol formation. In another words, it is unclear which diastereomer converts faster to the cyclopropanol. When treating the compound 96 with diethylzinc for a couple of hours, no cyclopropyl alcohol 114 was observed in the reaction mixture.

One predominant isomer of the cyclopropanol 114 was obtained using the chiral β-keto imide as the starting material. Since the cyclopropyl alcohol is a solid, it will be possible to identify the relative configurations of the product by X-ray crystallographic analysis. Efforts to grow an X-ray quality crystal are underway. Fragmentation of the cyclopropane ring in 114 might provides access to a chiral homoenolate, which would be of great interest on organic synthesis. Interest in the cyclopropyl alcohol may also be found in its use as a sp$^3$-hybridized transition state mimic for peptide hydrolysis.
Incorporation of Side Chain on α-Carbon Site of an α-Iodomethyl γ-Keto Ester

1) Palladium-catalyzed Cross-coupling Reaction

As described above, efficient formation of peptide isosteres requires that appropriate functional groups be installed as side chains. Preferably, these side chains will have identical functionality and stereochemical orientation with those found in the natural amino acids system. The successful preparation of α-iodomethylated γ-keto esters provided an iodomethyl group at the α-carbon site. This iodomethyl substituent was proposed to be useful for the α-side chain mimics due to the high reactivity of iodide. A strategy in which transmetallation-coupling reaction would be utilized to attach a variety of carbon skeletons to the α-iodomethyl group was proposed.

A transmetallation-coupling reaction, also called cross-coupling, involves the reaction between an organometallic reagent R-M with an organic compound R’-X, where X is a leaving group activated by a transition metal like palladium or nickel.37

\[ \text{R-M} + \text{R'-X} \xrightarrow{\text{Pd or Ni}} \text{R-R'} \]

Scheme 27. Metal-catalyzed Cross-coupling Reaction

Due to the central importance of coupling reactions in the formation of new carbon-carbon bonds in organic synthesis, cross-coupling reactions have been investigated intensively over the last thirty years.38 Many transition metals are capable of promoting and catalyzing this type of reaction, including palladium, copper, nickel and iron. Palladium has proved to be the most broadly employed and powerful catalyst for
facilitating carbon-carbon bond formation through a variety of cross-coupling reactions. Palladium-catalyzed cross-coupling reactions would be expected to facilitate the goal of incorporating α-side chains that mimic those found in nature. Generally, iodides and bromides have been used as the organic acceptors (carbon electrophile) in Pd-catalyzed cross coupling reactions. A variety of metals, including tin, zinc, aluminum, boron or silicon, can be employed as the organometallic donors in this type of reaction. To investigate the Pd-catalyzed cross-coupling reaction on the iodomethylated γ-keto product 82, a Negishi coupling reaction was utilized to this study. The palladium complex tris (dibenzylideneacetone)dipalladium was selected as the catalyst in collaboration with the tri-(o-tolyl)phosphine ligand. Zinc metal also was introduced to make the organozinc compound from the iodomethylated material 82. Since aryl iodides are generally more reactive than bromides or chlorides with the zero valent palladium complex, different sp²-hybridized iodides were employed in this study. The Pd-catalyzed Negishi cross-coupling reaction is considered to proceed via a catalytic cycle, as summarized in Scheme 28.
Scheme 28. Proposed Mechanism of Pd-catalyzed Negishi Coupling Reaction

The procedure was carried out by exposing the α-iodomethyl γ-keto ester 82 to the mixture of zinc dust (1.4 equiv.) and a small amount of iodine in DMF at 0 °C for 30 min under a nitrogen atmosphere to produce a solution of an intermediate organozinc reagent. The iodobenzene derivative (1.2 equiv.), tris (dibenzylideneacetone)dipalladium(0) (0.05 equiv.), and tri-(o-tolyl)phosphine (0.2 equiv.) were added to the reaction mixture. The reaction mixture was heated to 60 °C and stirred for 5 h with the cross-coupling reaction taking place through the action of the palladium catalyst. In order to investigate the generality of the cross-coupling reaction with the chain extended system, different sp²-hybridized iodides were used in the cross-coupling reaction. Some of these compounds were selected since they possess similar functional groups to those found in the skeleton of peptide inhibitors, such as Ruprintrivir, and natural amino acids, like L-leucine.
Scheme 29. Preparation of α-Alkylated γ-Keto Ester via Pd-catalyzed Negishi Coupling Reaction

The first effort to form an α-alkylated γ-keto ester through a Pd-catalyzed Negishi-coupling reaction utilized α-iodomethyl γ-keto ester 82 and iodobenzene (Scheme 29). The desired α-alkylated compound was separated successfully from the crude mixture after column chromatography. Compound 115 can be used to mimic the side chain of the amino acid phenylalanine. Compared with the organic synthesis procedure reported by Jackson et al\textsuperscript{42}, in which a similar procedure was used (Scheme 30) to produce a coupling product from 35% to 39% yield, the 30% yield for the formation of the α-alkylated γ-keto ester 115 is not unexpected.
Another aromatic iodide derivative, 1-chloro-4-iodobenzene was also employed in this type of cross-coupling reaction with the same α-iodomethyl γ-keto ester 82. Pure α-alkylated γ-keto ester 116 was obtained in a 25% yield.

Since the organozinc intermediate, which would be used in the following cross-coupling reaction, was generated in the methylation process without addition of iodine, in order to simplify the steps of these reactions, an one-step of chain extension methylation-Pd-catalyzed cross-coupling reaction was attempted. Toluene was used as a solvent in the chain extension methylation reaction instead of dichloromethane. The cross-coupling reaction was preformed between the unisolated organozinc intermediate and iodobenzene under similar conditions. No desired α-alkylated compound 115 was obtained by column chromatography. The major product was α-methylated γ-keto ester 36. It indicated the cross-coupling does not take place under this one-step procedure (Scheme 31).
The α-alkylated γ-keto ester that was incorporated with iodophenol, which could mimic the side group of the amino acid tyrosine, was expected to be generated through the Pd-catalyzed cross-coupling reaction. Because the acidic proton on iodophenol would quench the zinc intermediate generated in-situ by zinc insertion of α-iodomethyl γ-keto ester 82, protection of the OH group was required. tert-Butyldimethylsilyl chloride was used to protect the iodophenol (Scheme 32) in the study.\textsuperscript{44}

The effort to produce compound 119 (Scheme 33) in the cross-coupling reaction was failed. No targeted compound was observed in the crude reaction mixture or after...
column separation. When compound 82 was only treated with zinc dust and a small amount of iodine, the α-methyl γ-keto ester 87 was generated from the aqueous quench of the organozinc intermediate. This study indicated that the zinc insertion process was successful in the first step of the reaction. Some modifications were attempted in the cross-coupling reaction, including increasing the reaction time from 5 h to 24 h, and using an acetyl protecting group (with better electron withdrawing capability) instead of the TBDMS group. No evidence for the formation of the target compound in the reaction mixture was found. The oxygen donates electron density to the aromatic ring, which may play a role in hindering palladium insertion into the iodophenol, thus resulting in the failure of new carbon-carbon bond formation.

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{I} \\
\text{O}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{Pd_{2}db}_{3}, \text{P(o-Tol)_{3}} \\
\text{DMF, 60°C}
\end{array}
\rightarrow
\begin{array}{c}
\text{OPG}
\end{array}
\]

\text{PG} = \text{TBDMS 119 or Acetyl 120}

\text{Scheme 33. Attempted Preparation of α-Alkylated γ-Keto Ester with Protected Iodophenol via Pd-catalyzed Cross-coupling Reaction}

In addition to the study of the α-iodomethylated γ-keto ester 82, the Pd-catalyzed cross-coupling reaction between α-iodomethyl γ-keto imide 102 and iodobenzene was also studied. The same procedure was followed as described above (Scheme 34). The desired coupled compound 121 was successfully isolated from the crude reaction mixture in a yield of 23%.
Scheme 34. Preparation of α-Alkylated γ-Keto Imide 119 via Pd-catalyzed Negishi Coupling Reaction

In order to expand the scope of the cross-coupling reaction as applied to the α-iodomethylated γ-keto ester system, another substrate, 2-bromopropene, was utilized. The reaction with α-iodomethyl γ-keto ester 82 followed a similar procedure as described for the aryl iodides. Since 2-bromopropene has a low boiling point (42-47 °C), careful control of reaction conditions was required. The desired α-alkylated γ-keto ester 122 was successfully obtained in a 25% yield. Because the compound 122 incorporated a new carbon-carbon double bond in its molecular structure, it was possible to further manipulate the α-substituent. Treatment of 122 with hydrogen in the presence of palladium on carbon provided compound 123, which was easily isolated by column chromatography using a pipette. Compound 123 contains a side chain that effectively mimics the side chain of the amino acid leucine. All of the information gained from these methodological studies suggests that the zinc-mediated chain extension-iodomethylation product provides an opportunity to incorporate a substituent at the α-carbon site of the extended chain, thereby facilitating the regio-controlled α-substitution for the efficient mimicry of peptide systems.
2) Attempted Synthesis of a Ketomethylene Isostere

Based upon the successful results from the study on the chain extension iodomethylation methodology and in order to demonstrate the utility of the tandem chain extension-iodomethylation chemistry, the preparation of ketomethylene isostere 124, which is a key component of peptide inhibitor Ruprintrivir 125, was proposed. The proposed synthetic approach is illustrated in Scheme 36.

Figure 3. The Ketomethylene Isostere 124 and Ruprintrivir 125
L-Valine was selected as starting material for the synthesis of target 124. Since tandem chain extension-iodomethylation reactions are sensitive to the presence of a proton source, which would quench the enolate and/or homoenolate prior to the introduction of iodine, appropriate protection of the amino acid is required. Previous studies on the protection of amino acids were carried out by Tryder and Lin. A variety of protecting groups used for amino acids have been shown to be tolerated in the chain extension reaction; therefore, an effective two-step protection sequence was developed. The first step involved protection with a para-methoxybenzyl group (Pmb) through treatment of L-valine with p-anisaldehyde, followed by reduction using sodium borohydride. The Pmb-protected amino acid 126 was produced in a good yield. However, the nucleophilic nitrogen atom was assumed to be incorportible with the electrophilic carbenoid used in the chain extension reaction, so further protection on the amino group was needed. The carbobenzyloxy (Cbz) group is a very common protecting group for amino acids in peptide synthesis, and was believed to be suitable for protecting the amine group to its electron withdrawing character. Incorporation of the Cbz group onto the Pmb-protected amino acid 126 proceeds in an aqueous sodium hydroxide solution, which is used to scavenge the HCl generated from the reaction of Cbz chloride and amine. The N-protected amino acid 127 was obtained in a good yield.
Scheme 36. Attempted Synthetic Approach to a Ketomethylene Isostere 124

In this synthetic route to target compound 124, the key step was to prepare the desired chiral β-keto imide 129 that could be used as a substrate in the zinc-mediated chain extension-iodomethylation and Pd-catalyzed cross-coupling reaction. The generation of the β-keto imide from amino acid was performed through a modified Claisen condensation using a method developed by Lin (Scheme 38). Activation of the protected-valine through treatment with carbonyl diimidazole at room temperature in

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THF formed acyl imidazole 132. Then the acyl imidazole solution was transferred to another solution, in which the N-acetylated oxazolidinone 128 had been deprotonated by lithium diisopropylamide (LDA) to form an enolate intermediate. The chiral β-keto imide 129 was generated in a reasonable yield. The preparation of compound 128 is shown in Scheme 37.

```
\[
\begin{array}{c}
\text{O} & \text{NH}_2 & \text{Bn} \\
\text{HO} & & \\
\text{BF}_3 \cdot \text{OEt}_2 & \text{BH}_3 \cdot \text{SMe}_2 & \text{HO} & \text{Bn} & \text{NH}_2 \\
\end{array}
\]

D-phenylalanine

\[
\begin{array}{c}
\text{O} & \text{NH} & \text{Bn} \\
\text{HO} & & \\
\text{CH}_3\text{COCl} & \text{n-BuLi} & \text{O} & \text{NH} & \text{Bn} \\
\end{array}
\]

128

Scheme 37. Preparation of Compound 128 from D-phenylalanine

Self-condensation of compound 128 during treatment with LDA occurs under these reaction conditions, so slow addition of compound 128 to the LDA solution was crucial to achieve efficient formation of 129. On the other hand, the acidic character of 129 presents ability to quench the enolate intermediate. The imidazole byproduct 133, generated from the activation of the acid, can also act as a proton source to consume the enolate during the reaction process, so in order to maximize the yield of chiral β-keto imide 129 a 3:1 ratio of enolate intermediate 134 to protected acid 132 was required.
Scheme 38. Synthesis of Chiral β-Keto Imide 129 through a Modified Claisen Condensation Reaction

The zinc-mediated chain extension-iodomethylation reaction was conducted on the chiral β-keto imide 129 to generate the corresponding α-iodomethyl γ-keto imide 130 in a yield of 46% under the same conditions as used with previous β-keto imides. The $^1$H NMR spectrum of the purified compound 130 was difficult to interpret, due to the coexistence of rotamers and diastereomers. The $^{13}$C NMR spectrum revealed an upfield peak (chemical shift δ 4.7), which corresponded to a carbon attached to an iodine atom. This peak was characteristic in all of the α-iodomethylated γ-keto compounds prepared in this study. Evidence from the MS spectrum (ESI) also strongly supported the conclusion that 130 was indeed obtained through the iodomethylation reaction, in which the value of the largest peak (m/z 749) was consistent with the molecular weight (726) of 130 plus a sodium ion (23). The ratio of diastereoisomers and absolute configuration of the α-carbon is still unknown. Further study on the stereo-controlled iodomethylation is needed.

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required.

Unfortunately no cross-coupling product 131 was generated when compound 130 was reacted with 1-fluoro-4-iodobenzene. The complicated structure of compound 130 might be a factor in inhibiting the coupling reaction. Therefore the α-iodomethyl γ-keto ester 82 was used in a cross-coupling reaction with 1-fluoro-4-iodobenzene (Scheme 39). No coupling product 135 was observed in this reaction, although the side products α-hydroxymethyl γ-keto ester 136 and tri-(o-tolyl)phosphine oxide 137 were shown to be present in the reaction mixture by NMR and MS spectroscopy. These results suggest that 1-fluoro-4-iodobenzene does not participate in this cross-coupling reaction; however further investigation of this question needs to be carried out in the future.

Scheme 39. Attempted Synthesis of α- Alkylated γ-Keto Ester 135 with 1-Fluoro-4-Iodobenzene and Side Products 136 and 137
3) Other Applications

As described earlier in chapter II, the anticipated high reactivity of the iodide formed in the product of zinc-mediated chain extension-iodomethylation reaction could be used to attach different groups to the α-position, thereby mimicking the side chain of natural amino acids such as cysteine and glutamic acid.

A previous attempt to make a ketomethylene peptide mimic with cysteine-like side chain was made by Emerald Wilson in the Zercher research group. The data showed the α-iodomethyl γ-keto ester 82 did not react with thiourea to make an isothiuronium salt 138, which presumably could have been converted to a cysteine derivative 139. The methylated material 87 was identified by $^1$H NMR as well as other byproducts (Scheme 40).

![Scheme 40. Attempted Formation of Isothiuronium Salt 138](image)

Alternative nucleophilic sulfur reagents were investigated for the preparation of the compound 139 in the present study, including sodium sulfide and sodium hydrogen...
sulfide. The literature reports that several pathways have been used for the preparation of thiols from iodides.\textsuperscript{47} Since sulfur-containing compounds are easily oxidized and thiols are excellent nucleophiles, excess amounts of Na\textsubscript{2}S or NaSH (10 equiv.) were employed in these thiolation reactions to avoid the formation of thioether \textbf{140} and dimeric species \textbf{141}. Unfortunately, the major compound identified by \textsuperscript{1}H NMR and MS (ESI) analyses was the thioether \textbf{140} rather than the desired compound \textbf{139}. The isolated yield of \textbf{140} was about 28-30\%. The minor dimeric form of compound \textbf{141} was isolated from the crude mixture, which was readily converted to \textbf{139}. The limited solubility of the sodium salts slowed its participation as a nucleophile, while the thiolate intermediate was nicely soluble; therefore formation of \textbf{140} was difficult to avoid. Modifications, including an attempt to increase the solubility of Na\textsubscript{2}S by using more solvent (DMF) or by using a solvent mixture of DMF and H\textsubscript{2}O did not result in any improvement.

\textbf{Scheme 41.} Formation of Thioether \textbf{140} and Dimeric Species \textbf{141} of Compound \textbf{139}

Due to the unsatisfactory result described above, an alternative approach to the incorporation of a sulfur on the side chain was attempted. Treatment of iodide \textbf{82} with potassium thioacetate provided the acetyl-protected thiol \textbf{142}.\textsuperscript{48} Conversion of the
protected sulfur compound 142 to the target compound 139 was attempted through removal of the acetyl group using sodium methoxide in a methanol solution (Scheme 42). Surprisingly, no desired compound 139 was observed in the crude mixture. The presence of compounds 140 and 141 were identified by mass spectrum. Moreover, compound 139 was not observed from mass spectral data of the crude reaction mixture during the reaction period. Although the acetyl group was never successfully removed in this study, its removal is well preceded. This strategy of iodide displacement with a sulfur nucleophile provides access to the peptide isosteres with cysteine-like side chains

Scheme 42. Attempted Formation of Compound 139 Using Protected Sulfur Compound 142

The product of the tandem zinc-mediated chain extension-iodomethylation reaction could also be used to install a carboxylate functionality on the α-carbon site of the extended chain through nucleophilic alkylation. An initial study on this application was conducted through the use of dimethyl malonate. The dimethyl malonate was treated with a strong base and reacted with the α-iodomethyl γ-keto ester 82 to generate α-alkylated compound 143, which could be converted to compound 144 by further decarboxylation (Scheme 43). The decarboxylated product would mimic the side group of glutamic acid.

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The compound 141 was successfully obtained using this strategy; however, the coexistence of three methyl ester groups in the same molecule provides a challenge for the subsequent ester cleavage and decarboxylation. The use of an alternative malonate reagent with easily removable ester groups, such as benzyl t-butyl malonate, would be preferred for improving selectivity in the ester cleavage and decarboxylation.

Scheme 43. Nucleophilic Alkylation on Compound 82

In summary, the products formed in the tandem chain extension iodomethylation reaction could be utilized in subsequent chemistry, which provides a facile means to form side chains suitable for peptide isosteric replacements.
CHAPTER III

CONCLUSION

A new efficient methodology for the preparation of α-substituted γ-keto esters, amides and amino acid-derived imides has been developed. A tandem zinc-mediated chain extension-iodomethylation reaction, which is derived from the zinc-mediated chain extension methylation reaction, has been successfully applied to a variety of β-keto esters, amides and imides. This one-pot approach containing three distinct steps facilitates the efficient preparation of ketomethylene isosteres, which are proven inhibitors for various enzymatic systems. The yields for the formation of α-iodomethyl γ-keto esters were higher than for the formation of α-iodomethyl γ-keto amides. β-Keto amides with bulky groups on the amide bond did not react efficiently under the zinc-mediated chain extension-iodomethylation reaction conditions.

Evidence showed that exposure of a chiral β-keto imide to the chain extension-iodomethylation reaction conditions provides an α-iodomethyl γ-keto product with high diastereoselectivity (de>80%). Furthermore, one predominant isomer of a cyclopropane product was obtained from the chiral β-keto imide. When an increase in the amount of catalytic TMSCl was used, an improved yield of the cyclopropanol was realized. The absolute configuration of the α-position of the cyclopropanol isomer has not been assigned. These data indicate that a chiral β-keto imide promotes the stereocontrolled incorporation of substituents at the α-position of the extended chain.
It is believed that the mechanism of the zinc-mediated chain extension -iodomethylation reaction involves a donor-acceptor cyclopropane intermediate, which fragments to provide a zinc enolate intermediate. Exposure of the zinc enolate to TMS-CI promotes the formation of a reactive TMS enol ether, which reacts with another equivalent of the zinc carbenoid to generate a zinc homoenolate. This zinc homoenolate can be utilized in further tandem reaction processes to generate products which possess an appropriately positioned α-side chain for the effective mimicry of peptide bonds. Different substrates were successfully incorporated to generate α-sustituted γ-keto esters and imides in modest yields.

In one application of the homoenolate-derived product, a palladium-catalyzed cross-coupling reaction was used to derivitize the α-iodomethylated product. The cross-coupling reaction facilitated the incorporation of an α-substitution suitable for peptide isosteres; however, some aromatic halides, including iodophenol and 1-fluoro-4-iodobenzene, did not react with the α-iodomethylated product in this palladium-catalyzed cross-coupling reaction.

The α-iodomethylated products were utilized as substrates in other applications, such as thiolation and nucleophilic alkylations, to attach different alkyl groups at the α-position.
CHAPTER IV

EXPERIMENTAL SECTION

1. General Experimental

Unless otherwise noted, all reactions were run in oven-dried glassware and stirred with teflon-coated magnetic stir-bars. The term *concentrated under reduced pressure* refers to the use of a rotary-evaporator or vacuum pump.

a) Solvents

Methylene chloride (CH$_2$Cl$_2$), tetrahydrofuran (THF), diethyl ether (Et$_2$O), $N,N$-dimethylformamide (DMF) and methanol were dried by passing the solvent through a column of aluminia or molecular sieves using an Inovative Technology Inc. solvent delivery system. Ethyl acetate (EtOAc) and hexanes used for chromatography were purchased from Pharmco and distilled prior to use.

b) Reagents

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Diethylzinc was purchased both as a solution (1.0 M in hexane) and neat. Methylene iodide (CH$_2$I$_2$) was purchased from Lancaster Chemical. Non-oxidized copper wire was added as a stabilizer. Iodine was sublimed prior to use.
Trimethylsilylchloride (TMS-Cl) was distillated from calcium hydride under a nitrogen environment and stored over 4 Å sieves.

Tris(dibenzylideneacetone)dipalladium(0) and tri-(o-tolyl)phosphine were purchased from Aldrich Chemical Co. and used without further purification. Palladium 10% on carbon was purchased from Aldrich Chemical Co. and used without purification.

c) Chromatography

Column chromatography was performed with Sorbent Technologies flash silica gel (32-63μm). The mobile phase was prepared as noted in the individual experimental section. Thin Layer Chromatography (TLC) was carried out on EM Science F254 glass plates and visualized by UV and anisaldehyde or KMnO₄ stains.

d) Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy was performed on Varian Mercury operating at 399.768 MHz for ¹H nuclei and 100.522 MHz for ¹³C nuclei, and Varian Inova operating at 499.766 MHz for ¹H nuclei and 125.679 MHz for ¹³C nuclei. All ¹³C are ¹H-decoupled. Unless otherwise noted, all NMR experiments were carried out in deuterochloroform (CDCl₃) solvent purchased from Cambridge Isotope Laboratory and stored over 4 Å sieves. All chemical shifts are reported in parts per million (ppm) downfield of tetramethylsilane (TMS) internal standard.
Mass Spectrometry (Electronic Scanning Ionization) was performed on a Thermo Finnigan LCD instrument. Mass Spectrometry (Matrix Assisted Laser Desorption Ionization) was performed on an Axima instrument. Infrared spectroscopy was performed on a Nicolet 205 Fourier Transform spectrometer.

e) Experimentation

Melting points were determined using an Electrothermal 9100 digital melting point apparatus and are uncorrected. Optical rotations were conducted using a Rudolph Research AUTOPOL III automatic polarimeter in specified solution and concentrations are given in g/mL.

2. Preparation of α-Iodomethyl γ-Keto Esters

2-Iodomethyl-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 82

An oven-dried, one-necked, 50-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with 15 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and methylene iodide (0.32 mL, 4.0 mmol) was added dropwise into the flask. Diethyl zinc (4.0 mL, 1.0 M in hexane, 4.0 mmol) was added slowly to the reaction mixture at 0 °C over two min. The resulting white suspension was stirred for 10 min, and then methyl pivaloylacetate (0.16 mL, 1.0 mmol) was added rapidly. After the
solution was stirred for 30 min, trimethylsilylchloride (25 µL, 0.2 mmol) was added in one portion by micro-syringe. The mixture was allowed to stir for 45 min at room temperature followed by the addition of iodine (1.269 g, 5.0 mmol) to the reaction mixture. The reaction mixture quickly became a pink suspension and was stirred for 10 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×15 mL), and brine (3×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 30 torr). The residue was purified by column chromatography on silica (30:1, hexane: ethyl acetate, Rf = 0.16) to yield 0.128 g (41%) of 2-iodomethyl-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 82 as a clear yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.73 (s, 3 H), 3.45 (dd, J = 6.0, 10.0 Hz, 1 H), 3.38 (dd, J = 5.4, 10.0 Hz, 1 H), 3.20 (m, 1 H), 3.11 (dd, J = 7.0, 17.9 Hz, 1 H), 2.80 (dd, J = 5.4, 18.0 Hz, 1 H), 1.18 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 213.3, 172.5, 52.6, 44.3, 42.0, 39.2, 26.8, 6.3; IR (neat, cm$^{-1}$): 2967, 1738, 1705, 1477, 1366, 1232.

2-Iodomethyl-4-oxo-pentanoic acid tert-butyl ester 83

An oven-dried, one-necked, 50-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with 15 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and methylene iodide (0.32 mL, 4.0 mmol) was added dropwise into
the flask. Diethyl zinc (4.0 mL, 1.0 M in hexane, 4.0 mmol) was added slowly to the reaction mixture at 0 °C over two min. The resulting white suspension was stirred for 20 min, and then \( \text{t-butyl acetoacetate (0.17 mL, 1.0 mmol) was added rapidly. After the solution was stirred for 30 min, trimethylsilylchloride (25 \mu L, 0.2 mmol) was added in one portion by micro-syringe. The mixture was allowed to stir for 45 min at room temperature followed by the addition of iodine (1.269 g, 5.0 mmol) to the reaction mixture. The reaction mixture quickly became a pink suspension and was stirred for 10 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×15 mL), and brine (3×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 30 torr). The residue was purified by column chromatography on silica (15:1, hexane: ethyl acetate, \( R_f = 0.15 \)) to yield 0.201 g (63%) of 2-iodomethyl-4-oxo-pentanoic acid tert-butyl ester 83 as a clear yellow liquid. \(^1\text{H NMR (400 MHz, CDCl}_3\)) \( \delta \) 3.46 (dd, \( J = 5.6, 9.9 \text{ Hz, 1 H} \)), 3.35 (dd, \( J = 4.4, 9.9 \text{ Hz, 1 H} \)), 3.07 (m, 1 H), 3.00 (dd, \( J = 5.5, 17.6 \text{ Hz, 1 H} \)), 2.62 (dd, \( J = 5.0, 17.6 \text{ Hz, 1 H} \)), 2.20 (s, 3H), 1.46 (s, 9 H); \(^{13}\text{C NMR (100 MHz, CDCl}_3\)) \( \delta \) 206.0, 170.8, 82.0, 45.3, 42.5, 30.4, 28.1, 7.3.
2-Iodomethyl-4-oxo-pentanoic acid benzyl ester 84

An oven-dried, one-necked, 50-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with 15 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and methylene iodide (0.32 mL, 4.0 mmol) was added dropwise into the flask. Diethyl zinc (4.0 mL, 1.0 M in hexane, 4.0 mmol) was added slowly to the reaction mixture at 0 °C over two min. The resulting white suspension was stirred for 10 min, and then benzyl acetoacetate (0.18 mL, 1.0 mmol) was added rapidly. After the solution was stirred for 30 min, trimethylsilylchloride (25 μL, 0.2 mmol) was added in one portion by micro-syringe. The mixture was allowed to stir for 45 min at room temperature followed by the addition of iodine (1.269 g, 5.0 mmol) to the reaction mixture. The reaction mixture quickly became a pink suspension and was stirred for 10 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with diethyl ether (3×10 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×15 mL), and brine (3×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 30 torr). The residue was purified by column chromatography on silica (25:1, hexane: ethyl acetate, \( RF = 0.21 \)) to yield 0.208 g (58%) of 2-iodomethyl-4-oxo-pentanoic acid benzyl ester 84 as a clear yellow liquid. \(^1H\) NMR (400 MHz, CDCl\(_3\)) δ 7.36 (s, 5 H), 5.15-5.14 (m, 2 H), 3.48 (dd, \( J = 7.5, 11.4 \) Hz, 1 H), 3.39 (dd, \( J = 4.6, 10.1 \) Hz, 1 H), 3.23 (m, 1 H), 3.06 (dd, \( J = 60 \))
3. Preparation of β-Keto Amides

\textit{N, N-Diisopropyl-3-oxo-butyramide 94}

An one-necked, 50-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was charged with 15 mL of deionized water. \textit{N,N-Diisopropylamine} (2.8 mL, 20 mmol) and diketene (2.3 mL, 30 mmol) were added into the reaction flask. The reaction mixture was stirred at room temperature for 4 h, quenched with 10 mL of saturated citric acid solution, and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2×10 mL), and brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (9:1, hexane: ethyl acetate, \( R_f = 0.25 \)) to yield 1.54 g (42%) of \textit{N,N-diisopropyl-3-oxo-butyramide 94} as a clear orange liquid. The dicarbonyl was in equilibrium with the enol form. \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 3.49 (s, 2 H), 2.26 (s, 3 H), 1.40 (d, \( J = 6.8 \) Hz, 6 H), 1.19 (d, \( J = 6.7 \) Hz, 6 H); enol form: \( \delta \) 5.10 (s, 1 H), 1.96 (s, 3 H), 1.40 (d, \( J = 6.8 \) Hz, 6 H), 1.19 (d, \( J = 6.7 \) Hz, 6 H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \( \delta \) 203.3, 165.7, 52.6, 50.0, 46.2, 30.2, 20.9, 20.6.
1-Pyrrolidin-1-yl-butane-1,3-dione 95

A two-necked, 100-mL round-bottomed flask equipped with a reflux condenser and magnetic stir-bar was charged with 30 mL of deionized water, sodium bicarbonate (2.52 g, 30.0 mmol) and pyrrolidine (1.7 mL, 20.0 mmol). Diketene (2.3 mL, 30.0 mmol) was added to the flask dropwise. The reaction mixture was allowed to heat to 50 °C in water bath, and stirred for 2 h. The reaction was stirred at room temperature overnight, then quenched with 10 mL of saturated citric acid solution, extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with saturated sodium bicarbonate solution (2×10 mL), and brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (ethyl acetate, Rf = 0.51) to yield 0.62 g (20%) of 1-pyrrolidin-1-yl-butane-1,3-dione 95 as a clear orange liquid. Enol form was also present. ¹H NMR (400 MHz, CDCl₃) δ 3.49-3.40 (m, 6 H), 2.29 (s, 3 H), 2.00-1.85 (m, 4 H); enol form: δ 4.99 (s, 1H), 3.49-3.40 (m, 4 H)), 1.95 (s, 3 H), 2.00-1.85 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃) δ 202.6, 165.1, 51.5, 47.3, 45.9, 30.5, 26.1, 24.6, enol form: δ 174.2, 170.4, 88.9, 46.2, 45.0, 26.0, 21.7. IR (neat, cm⁻¹): 2975, 2880, 1717, 1626, 1454, 1361.
4. Preparation of a chiral $\beta$-Keto imide

1-((S) 4-Benzyl-2-oxo-oxazolidin-3-yl)-butane-1,3-dione 112

An oven-dried, one-necked, 100-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with a solution of (S)-4-benzyl-oxazolidin-2-one (1.4 g, 8.0 mmol) in 50 mL of anhydrous tetrahydrofuran. The THF solution was cooled to -78 °C and n-butyl lithium (4.0 mL, 10.0 mmol of a 2.5 M solution in hexane) was added dropwise to the flask. After the completion of the addition, the reaction mixture was warmed to 0 °C for 10 min. The mixture was cooled to -78 °C again, and diketene (1.23 mL, 16.0 mmol) was added slowly to the mixture. The resultant orange solution was maintained at -78 °C for an additional 30 min after the addition was complete, and then allowed to stir at 0 °C for 2 h. The mixture was quenched with 15 mL of saturated NH$_4$Cl solution and concentrated under reduced pressure (25 °C, 18 torr) to remove the solvent THF. The residue was extracted by methylene chloride (3×20 mL), and the combined organic layers were washed with sat. NaHCO$_3$ solution (2×20 mL) and brine (3×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (4:1, hexane: ethyl acetate, $R_f = 0.14$) to yield 0.80 g (38%) of 1-((S) 4-benzyl-2-oxo-oxazolidin-3-yl)-butane-1,3-dione 112 as a light yellow solid, mp 67-68.5 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.22 (m, 5 H), 4.72 (m, 1 H), 4.25-4.16 (m, 2 H), 4.11-4.06 (m, 2 H), 3.37 (dd, $J = 3.4$, 13.5 Hz, 1 H), 2.80 (dd, $J = 9.6$, 13.5 Hz, 1 H), 2.29 (s, 3 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 201.1, 166.6, 153.9, 135.3, 129.7, 129.2, 127.6, 66.6, 55.2, 51.6, 38.4, 30.4; enol form: $\delta$ 180.5, 153.9, 135.3, 129.7, 129.2, 127.6, 90.1, 66.3, 54.9, 38.4, 22.4.

5. Preparation of $\alpha$-Iodomethyl $\gamma$-Keto Imides

2-Iodomethyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1,4-dione

An oven-dried, one-necked, 100-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with 1-(2-oxo-oxazolidin-3-yl)-butane-1,3-dione (0.346 g, 2.0 mmol) dissolved in 30 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and diethyl zinc (10.0 mL, 1.0 M in hexane, 10.0 mmol) was added slowly to the flask at 0 °C over two min to form an enolate. The reaction mixture was stirred for 15 min, and then methylene iodide (0.48 mL, 6.0 mmol) was added into the flask. An additional portion of methylene iodide (0.32 mL, 4.0 mmol) was added to the reaction mixture at 0 °C after 15 to 20 min. The resulting solution was stirred for 30 min, and trimethylsilylchloride (50 $\mu$L, 0.4 mmol) was added by micro-syringe in one portion. The mixture was allowed to stir for 30 min at room temperature followed by the addition of iodine (2.58 g, 10.0 mmol) to the reaction mixture. The reaction mixture quickly became a pink suspension and was stirred for 10 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with ether acetate (5×20 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×25 mL), and brine...
(3×25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 20 torr). The residue was purified by column chromatography on silica (2:1, hexane: ethyl acetate, Rf = 0.16) to yield 0.101 g (31%) of 2-iodomethyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1,4-dione 102 as a yellow solid. mp 71-75 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.50-4.42 (m, 2 H), 4.31 (m, 1 H), 4.12-3.97 (m, 2H), 3.39 (dd, J = 5.4, 10.2 Hz, 1H), 3.32 (dd, J = 6.5, 10.1 Hz, 1H), 3.16 (dd, J = 9.9, 18.1 Hz, 1H), 2.75 (dd, J = 4.1, 18.0 Hz, 1H), 2.18 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 206.1, 172.3, 153.4, 62.4, 46.6, 42.9, 39.0, 29.9, 4.4.

3-[1-Hydroxy-2-(2-oxo-propyl)-cyclopropyl]-oxazolidin-2-one 107 and 2-Methyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1, 4-dione 108

An oven-dried, one-necked, 100-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with 1-(2-oxo-oxazolidin-3-yl)-butane-1,3-dione (0.171 g, 1 mmol) dissolved in 15 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and diethyl zinc (5.0 mL, 1.0 M in hexane, 5.0 mmol) was added slowly to the flask at 0 °C over two min to form an enolate. The reaction mixture was stirred for 15 min, and then methylene iodide (0.24 mL, 3.0 mmol) was added into the flask. An additional portion of methylene iodide (0.16 mL, 2.0 mmol) was added to the reaction mixture at 0 °C after 15 to 20 min. The resulting solution was stirred for 30 min, and trimethylsilylchloride (50 μL, 0.4 mmol) was added by micro-syringe in one portion. The
mixture was allowed to stir for 45 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with ether acetate (3×20 mL). The combined organic layers was washed with brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure (25 °C, 20 torr). The residue was purified by column chromatography on silica (2:1, hexane: ethyl acetate, \( R_f = 0.08 \)) to yield 0.06 g (30%) of 3-[1-hydroxy-2-(2-oxo-propyl)-cyclopropyl]-oxazolidin-2-one \( 107 \) as a colorless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.28-4.16 (m, 2 H), 3.76-3.66 (m, 2 H), 2.56 (dd, \( J = 4.1, 17.4 \text{ Hz} \), 1 H), 2.35 (dd, \( J = 8.8, 18.2 \text{ Hz} \), 1 H), 2.09 (s, 3 H), 1.64-1.59 (m, 2 H), 1.18 (m, 1 H), 0.78 (t, \( J = 6.9 \text{ Hz} \), 1 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 209.1, 158.2, 65.2, 62.8, 43.4, 42.3, 30.3, 20.9, 20.5; IR (neat, cm\(^{-1}\)): 3442(b), 2927, 1775, 1699, 1390, 1227, 1039.

A compound 2-methyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1, 4-dione \( 108 \) was also isolated from the crude reaction mixture by column chromatography on silica (2:1, hexane: ethyl acetate, \( R_f = 0.16 \)) in a 22% yield (0.043 g) as a colorless liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.43-4.30 (m, 2 H), 4.41-3.95 (m, 3 H), 3.10 (dd, \( J = 10.3, 18.1 \text{ Hz} \), 1 H), 2.53 (dd, \( J = 4.1, 18.2, 1 \text{ H} \), 2.14 (s, 3 H), 1.18 (d, \( J = 7.0 \text{ Hz} \), 3 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 207.1, 176.8, 153.4, 62.2, 47.4, 42.9, 33.3, 29.8, 17.3. IR (neat, cm\(^{-1}\)): 1775, 1698, 1392, 1264,1202.
An oven-dried, one-necked, 50-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was cooled to room temperature under a nitrogen atmosphere, and charged with a solution of 1-((S)-4-benzyl-2-oxo-oxazolidin-3-yl)-butane-1,3-dione 112 (0.261 g, 1.0 mmol) in 15 mL of methylene chloride. The solvent is cooled to 0 °C in an ice bath and diethyl zinc (5.0 mL, 1.0 M in hexane, 5.0 mmol) was added slowly to the flask at 0 °C over two min to form an enolate. The reaction mixture was stirred for 15 min, and then methylene iodide (0.24 mL, 3.0 mmol) was added into the flask. An additional portion of methylene iodide (0.16 mL, 2.0 mmol) was added to the mixture at 0 °C after 15 to 20 min. The resultant solution was stirred for 30 min, and trimethylsilylchloride (25 µL, 0.2 mmol) was added by micro-syringe in one portion. The mixture was allowed to stir for 30 min at room temperature followed by adding iodine (1.265 g, 5.0 mmol) to the reaction. The reaction mixture quickly became a pink suspension and was stirred for 10 min, quenched with 10 mL of saturated aqueous ammonium chloride, and extracted with ether acetate (3×20 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×15 mL) and brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (3:1, hexane: ethyl acetate, \( R_f = 0.28 \)) to yield 0.11 g (26%) of 1-((S)-4-Benzyl-2-oxo-oxazolidin-3-yl)-2-iodomethyl-pentane-1,4-dione 113 as a light
yellow liquid of two diastereoisomers with a ratio of 2.5:1. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$
7.33-7.20 (m, 5 H), 4.80-4.67 (m, 1 H), 4.31-4.16 (m, 3 H), 3.42 (d, $J = 5.5$ Hz, 2 H),
3.36-3.33 (m, 1 H), 3.20 (dd, $J = 10.1$, 18.1 Hz, 1 H), 2.87-2.69 (m, 2 H), 2.19 (s, 3 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.0, 172.0, 153.3, 140.9, 129.6, 129.2, 127.7, 66.8,
55.5, 46.4, 40.0, 38.5, 37.8, 29.9, 4.9; MS (MALDI): calcd for C$_{16}$H$_{18}$O$_4$N (M$^+$-I)
288.2782: found, 287.7.

The compound 1-((S)-4-Benzyl-2-oxo-oxazolidin-3-yl)-pent-2-ene-1,4-dione was
also present in the reaction mixture. Resonances observed for this compound: $^1$H NMR
(400 MHz, CDCl$_3$) $\delta$ 8.0 (d, $J = 15.9$ Hz, 1 H), 7.1 (d, $J = 15.9$ Hz, 1 H); $^{13}$C NMR (100
MHz, CDCl$_3$) $\delta$ 198.1, 164.4, 135.1, 27.8.

The crude reaction mixture was also purified by column chromatography on silica
(1:1, hexane: ethyl acetate, $R_f = 0.12$) to produce 0.08 g (28%) of one predominant
stereoisomer of (S)-4-Benzyl-3-[1-hydroxy-2-(2-oxo-propyl)-cyclopropyl]-oxazolidin-2-
one 114 as a colorless crystal, mp 102-103 °C; [$\alpha$]$^{25}_D = +4.8$ (c = 0.0053 g/mL, CHCl$_3$).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.25 (m, 5 H), 4.75 (s, 1 H), 4.22 (m, 1 H), 4.07-3.98
(m, 2 H), 3.54 (dd, $J = 3.8$, 13.4 Hz, 1H), 2.83 (dd, $J = 4.5$, 18.4 Hz, 1 H), 2.71-2.62 (m, 2
H), 2.22 (s, 3 H), 1.54 (m, 1 H), 1.38 (dd, $J = 5.9$, 10.1 Hz, 1 H), 0.96 (t, $J = 6.2$ Hz, 1 H);
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 208.5, 157.8, 136.7, 129.7, 129.2, 127.1, 66.9, 64.8, 57.6,
42.1, 38.4, 30.2, 21.8, 19.6. IR (KBr, cm$^{-1}$): 3317 (b), 3029, 2921, 1745, 1603, 1413,
1246. MS (MALDI): calcd for C$_{16}$H$_{19}$O$_4$N (M$^+$ +Na$^+$) 312.1871: found, 312.1; calcd for
C$_{16}$H$_{19}$O$_4$N (M$^+$ +K$^+$) 328.3000: found, 328.1.

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6. Preparation of α-Alkylated γ-Keto Esters

2-Benzyl-5, 5-dimethyl-4-oxo-hexanoic acid methyl ester 115

A mixture of zinc dust (0.09 g, 1.4 mmol) and iodine (2.0 mg, 0.005 mmol) was placed into an oven-dried, 25-mL round-bottomed flask equipped with a rubber septum and magnetic stir bar. The flask was allowed to cool to room temperature under nitrogen gas. Dimethylformamide (1 mL) was added via syringe into the flask, followed by the addition of a solution of iodobenzene (0.224 g, 1.1 mmol) in 4 mL of DMF dropwise by syringe. The reaction mixture was stirred at 0 °C (ice bath) for 30 min. The ice bath was removed and the septum was replaced with a reflux condenser after 2-iodomethyl-5, 5-dimethyl-4-oxo-hexanoic acid methyl ester 82 (0.312 g, 1.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (45 mg, 0.05 mmol) and tri-o-tolylphosphine (60 mg, 0.2 mmol) were added. The reaction mixture was heated to 60 °C and stirred for 5 h. The resulting black mixture was decanted to an Erlenmeyer flask containing 10 mL of deionized water. An additional 5 mL of saturated citric acid solution was added in order to break the emulsion. The mixture was extracted with diethyl ether (3×10 mL), and the combined organic layers were washed with deionized water (2×10 mL) and brine (2×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (30:1, hexane: ethyl acetate, Rf = 0.14) to yield 0.79 g (30%) of 2-benzyl-5,5'-dimethyl-4-oxo-hexanoic acid methyl ester 115 as a clear orange liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 (t, $J = 6.9$ Hz, 2H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 2.46 (s, 3H), 2.45 (s, 3H).
7.4 Hz, 2 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.13 (d, J = 6.8 Hz, 2H), 3.61 (s, 3 H), 3.14 (m, 1H), 2.99 (dd, J = 6.6, 13.5 Hz, 1 H), 2.92 (dd, J = 9.0, 18.2 Hz, 1 H), 2.72 (dd, J = 8.3, 13.6 Hz, 1 H), 2.56 (dd, J = 4.6, 18.1 Hz, 1 H), 1.08 (s, 9 H); 13C NMR (100 MHz, CDCl3) δ 214.3, 175.6, 138.8, 129.4, 129.1, 126.8, 51.9, 44.1, 42.2, 37.9, 26.6; IR (neat, cm⁻¹): 2966, 1736, 1704, 1476, 1366, 1230; MS (ESI): calcd for C₁₆H₂₂O₃ (M⁺ +Na⁺) 285.1919: found, 285.1.

2-(4-Chloro-benzyl)-5, 5-dimethyl-4-oxo-hexanoic acid methyl ester 116

A mixture of zinc dust (0.09 g, 1.4mmol) and iodine (2.0 mg, 0.005 mmol) was placed into an oven-dried, 25-mL round-bottomed flask equipped with a rubber septum and magnetic stir bar. The flask was allowed to cool to room temperature under nitrogen gas. Dimethylformamide (1 mL) was added via syringe into the flask followed by dropwise addition of a solution of 1-chloro-4-iodobenzene (0.3.0 g, 1.26 mmol) in 4 mL of DMF. The reaction mixture was stirred at 0 °C (ice bath) for 30 min. The ice bath was removed and the septum was replaced with a reflux condenser after 2-iodomethyl-5, 5-dimethyl-4-oxo-hexanoic acid methyl ester 82 (0.312 g, 1.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (45.0 mg, 0.05 mmol) and tri-o-tolylphosphine (60 mg, 0.2 mmol) were added. The reaction mixture was heated to 60 °C and stirred for 5 h. The resulting black mixture was decanted to an Erlenmeyer flask containing 10 mL of deionized water. An additional 5 mL of saturated citric acid solution was added in order to break the emulsion. The mixture was extracted with
diethyl ether (3×10 mL), and the combined organic layers were washed with deionized water (2×10 mL) and brine (2×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (20:1, hexane: ethyl acetate, Rf = 0.18) to yield 0.075 g (25%) of 2-(4-chloro-benzyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 116 as a clear orange liquid. ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, J = 8.6 Hz, 2 H), 7.09 (d, J = 8.3 Hz, 2 H), 3.62 (s, 3 H), 3.15 (m, 1 H), 2.96 (dd, J = 7.0, 11.9 Hz, 1 H), 2.92 (dd, J = 8.5, 18.0 Hz, 1 H), 2.71 (dd, J = 7.8, 13.8 Hz, 1 H), 2.54 (dd, J = 4.9, 18.1 Hz, 1 H), 1.09 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ 214.0, 175.6, 137.3, 132.6, 130.5, 128.8, 52.1, 44.3, 42.2, 38.5, 36.6, 26.6; IR (neat, cm⁻¹): 2967, 1736, 1704, 1492, 1169.

**tert-Butyl-(4-iodo-phenoxy)-dimethyl-silane 117**

Into an oven-dried, 50-mL round-bottomed flask purged under N₂ and equipped with a rubber septum and magnetic stir bar were placed iodophenol (1.1 g, 5.0 mmol), t-butyldimethylsilyl chloride (1.2 g, 7.5 mmol) and 12 mL of pyridine. The reaction mixture was heated to 45 °C (water bath) and stirred for 4 h. The resultant solution was extracted by diethyl ether (3×15 mL) and neutralized by 1N HCl solution (2×10 mL), then washed with brine (3×20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography using pure ether acetate as the mobile phase (Rf = 0.8) to yield 0.73 g (44%) of tert-butyl-(4-iodo-phenoxy)-dimethyl-silane as a colorless liquid. ¹H NMR
(400 MHz, CDCl₃) δ 7.32 (d, J = 8.6 Hz, 2 H), 6.42 (d, J = 8.6 Hz, 2 H); 0.86 (s, 9 H), 0.07 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 160.1, 142.75, 126.9, 88.1, 30.1, 22.7, 0.0.

**Acetic acid 4-iodo-phenyl ester 118**

Into an oven-dried, 50-mL round-bottomed flask purged under N₂ and equipped with a rubber septum and magnetic stir bar were placed iodophenol (1.1 g, 5.0 mmol), acetic anhydride (0.7 mL, 7.5 mmol) and 10 mL of pyridine. The reaction mixture was allowed to stir at room temperature for 12 h. The resultant solution was extracted by diethyl ether (3×20 mL). The combined ether layers were washed with brine (3×15 mL) and neutralized by 1N HCl solution (2×10 mL), then washed with brine (2×15 mL) again, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (20:1, hexane: ethyl acetate, Rᵣ = 0.25) to yield 1.14 g (87%) of acetic acid 4-iodo-phenyl ester as a white solid. Mp 36-38 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.68 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 2.28 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 150.7, 138.8, 124.0, 90.1, 21.3; IR (KBr, cm⁻¹): 3083, 2264, 1980, 1758, 1577, 1479, 1368.

**2-Benzyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1, 4-dione 121**

A mixture of zinc dust (0.09 g, 1.4 mmol) and iodine (2.0 mg, 0.005 mmol) was placed into an oven-dried, 25-mL round-bottomed flask equipped with a rubber septum and magnetic stir bar. The flask was allowed to cool to room temperature under nitrogen gas. Dimethylformamide (1 mL) was added via syringe into the flask followed by the
dropwise addition of a solution of iodobenzene (0.224 g, 1.1 mmol) in 4 mL of DMF. The reaction mixture was stirred at 0 °C (ice bath) for 30 min. The ice bath was removed and the septum was replaced with a reflux condenser after 2-iodomethyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1, 4-dione 102 (0.325 g, 1.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (45 mg, 0.05 mmol) and tri-o-tolyl phosphine (60 mg, 0.2 mmol) were added. The reaction mixture was heated to 60 °C and stirred for 5 h. The resulting black mixture was decanted to an Erlenmeyer flask containing 10 mL of deionized water. An additional 5 mL of saturated citric acid solution was added in order to break the emulsion. The mixture was extracted with ether acetate (3×10 mL), and the combined organic layers were washed with deionized water (2×10 mL) and brine (2×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (1:1, hexane:ethyl acetate, Rf = 0.47) to yield 0.066 g (24%) of 2-benzyl-1-(2-oxo-oxazolidin-3-yl)-pentane-1,4-dione 121 as a white solid. mp 108-111 °C; 1H NMR (400 MHz, CDCl3) δ 7.30-7.27 (m, 5 H), 4.45-4.30 (m, 3 H); 4.05 (dd, J = 6.7, 9.4 Hz, 1 H), 3.93 (dd, J = 6.9, 9.3 Hz, 1 H), 3.09 (dd, J = 5.1, 13.1 Hz, 1 H), 3.03 (dd, J = 10.7, 18.0 Hz, 1 H), 2.51 (dd, J = 10.0, 13.1 Hz, 1 H), 2.45 (dd, J = 3.5, 18.3 Hz, 1 H), 2.07 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 207.2, 175.7, 153.4, 138.2, 129.4, 128.7, 126.9, 62.2, 44.4, 42.9, 40.2, 37.9, 29.9. IR (KBr, cm⁻¹): 2921, 1773, 1715, 1480, 1395, 1263.
5, 5-Dimethyl-2-(2-methyl-allyl)-4-oxo-hexanoic acid methyl ester 122

A mixture of zinc dust (0.09 g, 1.4 mmol) and iodine (2.0 mg, 0.005 mmol) was placed into an oven-dried, 25-mL round-bottomed flask equipped with a rubber septum and magnetic stir bar. The flask was allowed to cool to room temperature under nitrogen gas. Dimethylformamide (1 mL) was added via syringe into the flask followed by the dropwise addition of a solution of 2-bromo-1-propene (0.30 g, 1.26 mmol) in 4 mL of DMF. The reaction mixture was stirred at 0 °C (ice bath) for 30 min. The ice bath was removed and the septum was replaced with a reflux condenser after 2-iodomethyl-5, 5-dimethyl-4-oxo-hexanoic acid methyl ester 82 (0.312 g, 1.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (45 mg, 0.05 mmol) and tri-o-tolylphosphine (60 mg, 0.2 mmol) were added. The reaction mixture was heated to 60 °C and stirred for 5 h. The resulting black mixture was decanted to a Erlenmeyer flask containing 10 mL of deionized water. An additional 5 mL of saturated citric acid solution was added in order to break the emulsion. The mixture was extracted with diethyl ether (3×10 mL), and the combined organic layers were washed with deionized water (2×10 mL) and brine (2×10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (20:1, hexane: ethyl acetate, \( R_f = 0.15 \)) to yield 0.075 g (12%) of 5,5-dimethyl-2-(2-methyl-allyl)-4-oxo-hexanoic acid methyl ester 122 as a clear orange liquid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.79 (s, 1 H), 4.69 (s, 1 H), 3.66 (s, 3 H), 3.07 (m, 1 H), 2.92 (dd, \( J = 9.3, 18.1 \) Hz, 1 H), 2.58 (dd, \( J = 4.2, 18.1 \) Hz, 1 H), 2.38 (dd, \( J = 6.8, \)
14.2 Hz, 1 H), 2.14 (dd, J = 8.5, 14.6 Hz, 1 H), 1.79 (s, 3 H), 1.14 (s, 9 H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 214.4, 175.9, 142.8, 113.2, 51.9, 44.2, 40.5, 38.4, 38.1, 26.5, 21.9.

7. Preparation of Compound 124

{(S)-2-(4-Methoxy-benzylamino)-3-methyl-butyric acid 126}

To a 250-mL round-bottomed flask containing a solution of L-valine (12.42 g, 106 mmol) in 50 mL of 2.0 M NaOH was added p-anisaldehyde (12.7 mL, 104.0 mmol) in one portion. The reaction mixture was allowed to stir at room temperature for 30 min, cooled to 0 °C and sodium borohydride (1.6 g, 42.0 mmol) was added in small portion. After an additional 30 min, a second portion of p-anisaldehyde (6.8 mL, 56.0 mmol) was added into the mixture and kept stirring for 1 h, then a second portion of sodium borohydride (1.6 g, 42.0 mmol) was added and after 4 h the mixture was neutralized with 1 N HCl to PH 6. The resulting white precipitate was collected by filtration, washed with cold water and air-dried for 2 h. The solid was dissolved in 100 mL of 1 M NaOH and extracted with diethyl ether (2\times 50 mL). The aqueous layer was neutralized with 1 N HCl to PH 6. The resulting white solid was collected by filtration and dried under reduced pressure to yield 14.6 g (58%) of (S)-2-(4-methoxy-benzylamino)-3-methyl-butyric acid 126 as a white powder. mp 244-247 °C; \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}/TFA) \delta 7.42 (d, J = 8.8 Hz, 2 H), 7.00 (d, J = 8.8 Hz, 2 H), 4.12 (s, 2 H), 3.78 (s, 3 H), 3.72 (s, 1 H), 2.32-2.27 (m, 1 H), 1.03 (d, J = 7.0 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}):
MHz, DMSO-d$_6$/TFA) δ 169.7, 159.6, 132.7, 123.5, 117.5, 64.3, 54.9, 50.4, 29.1, 18.9, 18.8; IR (KBr, cm$^{-1}$): 3447 (b), 2962, 1602, 1515, 1454, 1322, 1254, 1221, 1177.

(S)-2-[Benzyloxy carbonyl-(4-methoxy-benzyl)-amino]-3-methyl-butyric acid 127

Pmb-protected L-valine 126 (1.19 g, 5.0 mmol) was dissolved in the 20 mL of 1 N NaOH and 20 mL of THF. The mixture was kept stirring at room temperature for 30 min, then cooled to 0 °C and benzyloxy carbonyl chloride (0.69 mL, 5.0 mmol) was added in one portion. The reaction was vigorously stirred overnight. The resulting mixture was washed with ether (2×15 mL) and acidified with conc. HCl to pH 1. The resulting cloudy solution was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (2×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.93 g (50%) of compound 127 as a light yellow oily liquid. The compound exists as a mixture of 2 rotameric forms.$^1$H NMR (400 MHz, CDCl$_3$) δ 10.0 (bs, 1 H), 7.37-6.77 (m, 9 H), 5.17 (s, 2 H), 4.53-4.44 (m, 2 H), 3.99 (m, 1 H), 3.72 (s, 3 H), 2.42-2.26 (m, 1 H), 1.01-0.68 (m, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 176.2, 174.6, 159.1, 157.7, 136.4, 130.4, 130.1, 129.4, 128.7, 128.5, 128.4, 128.2, 113.9, 68.3, 68.1, 65.4, 55.4, 50.8, 27.9, 20.4, 19.6; IR (neat, cm$^{-1}$): 3500-2837 (b), 2964, 1736, 1700, 1613, 1513, 1458, 1247.
[4-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-(S)-1-isopropyl-2,4-dioxo-butyl]-(4-methoxy-benzyl)-carbamic acid benzyl ester 129

An oven-dried, 10-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar was purged under nitrogen, and charged with 4 mL of anhydrous tetrahydrofuran, compound 127 (0.381 g, 1.0 mmol, in 1 mL of anhydrous THF), and 1,1-carbonyldiimidazole (0.18 g, 1.1 mmol) in order. In a separate oven-dried, 50-mL round-bottomed flask, equipped with a rubber septum and magnetic stir-bar under nitrogen, were charged with 15 mL of anhydrous tetrahydrofuran and diisopropylamine (0.57 mL, 4.0 mmol). The solution was allowed to cool to 0 °C (ice bath) and n-butyl lithium (1.9 mL, 4.0 mmol, 2.1 M in hexane solution) was added. After stirring for 10 min, the reaction mixture was cooled to -78 °C (dry ice in acetone bath), (R)-3-acetyl-5-benzyl oxazolidin-2-one (0.88 g, 4.0 mmol, in 5 mL of anhydrous THF) was added over 30 min using a syringe pump. The acyl imidazole solution was transferred to the 50-mL flask containing the enolate solution using syringe quickly. The reaction was quenched with 5 mL of 1N HCl solution after stirring at -78 °C for 30 min. The solution was extracted with diethyl ether (3×10 mL), and the combine ether layers were washed with 10 mL of sat.NaHCO₃ solution to remove the acid. The organic layer was washed with 5 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (3:1, hexane: ethyl acetate, Rₓ = 0.28) to yield 0.337 g (59%) of compound 129 as a light yellow oily mixture. [α]²⁵_D = -85.0 (c = 0.006 g/mL, CHCl₃), ¹H
NMR (400 MHz, CDCl₃) δ 7.32-7.03 (m, 12 H), 6.79-6.69 (m, 2 H), 5.17-5.04 (m, 2 H), 4.73-4.49 (m, 2 H), 4.18-4.00 (m, 4 H), 3.89-3.60 (m, 1 H), 3.70-3.69 (m, 3 H), 3.29-3.20 (m, 1 H), 2.72-2.63 (m, 1 H), 2.38-2.23 (m, 1 H), 0.93-0.80 (m, 3H), 0.72-0.64 (m, 3 H);

¹³C NMR (100 MHz, CDCl₃) δ 200.2, 166.8, 159.5, 156.5, 153.5, 136.4, 135.5, 131.1, 130.4, 129.7, 129.2, 128.8, 128.4, 127.5, 114.1, 71.1, 68.1, 66.4, 55.5, 55.2, 49.9, 49.1, 48.6, 37.5, 27.3, 26.7, 21.6, 20.8, 19.1; IR (neat, cm⁻¹): 3029, 2962, 1779, 1697, 1611, 1512, 1454, 1359, 1247; MS (ESI): calcd for C₃₃H₃₆O₇N₂ (M⁺ +Na⁺) 596.3569: found, 595.1.

[5-((R)-4-Benzyl-2-oxo-oxazolidin-3-yl)-4-iodomethyl-(S)-1-isopropyl-2,5-dioxo-pentyl]- (4-methoxy-benzyl) -carbamic acid benzyl ester 130

An oven-dried, one-necked, 100-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar with a flow of nitrogen was cooled to room temperature, and charged with compound 129 (0.26 g, 0.45 mmol) dissolved in 8 mL of methylene chloride. The solvent was cooled to 0 °C in an ice bath and diethyl zinc (2.3 mL, 1.0 M in hexane, 2.3 mmol) was added slowly to the flask at 0 °C over 1 min to form an enolate. The reaction mixture was stirred for 15 min, and then methylene iodide (0.11 mL, 1.38 mmol) was added into the flask. An additional portion of methylene iodide (0.07 mL, 0.87 mmol) was added to the reaction mixture at 0 °C after 30 min. The resulting solution was stirred for 30 min, and trimethylsilylchloride (12.5 µL, 0.2 mmol) was added by micro-syringe in one portion. The mixture was allowed to stir for 1 h at 0 °C followed by
the addition of iodine (0.57 g, 2.25 mmol) to the reaction. The reaction mixture quickly became a pink suspension and stirred for 10 min, quenched with 5 mL of saturated aqueous ammonium chloride, and extracted with ether acetate (3×15 mL). The combined organic layers were washed with saturated sodium thiosulfate solution (2×10 mL), and brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (5:1, hexane: ethyl acetate, Rf = 0.27) to yield 0.15 g (46%) of compound 130 as a orange oily liquid. 1H NMR (400 MHz, CDCl3) δ 7.49-7.06 (m, 12 H), 6.86-6.76 (m, 25.5 Hz, 2 H), 5.27-5.20 (m, 2 H), 4.70-4.59 (m, 1 H), 4.51-4.40 (m, 1 H), 4.28-4.11 (m, 4 H), 4.04-3.86 (m, 1 H), 3.80 (s, 3 H), 3.34-3.25 (m, 1 H), 3.17-3.02 (m, 2 H), 2.89-2.69 (m, 2 H), 2.60-2.33 (m, 2 H), 1.00-0.73 (m, 6 H); 13C NMR (100 MHz, CDCl3) δ 205.4, 171.8, 159.4, 155.6, 153.8, 136.4, 135.4, 130.8, 129.9, 129.1, 128.3, 128.1, 127.6, 114.2, 69.3, 68.5, 66.5, 60.6, 58.1, 55.4, 48.2, 43.8, 38.4, 30.2, 26.2, 21.5, 19.6, 4.7; MS (ESI): calcd for C35H39O7N2I (M+ +Na+) 749.5965: found, 749.1.

8. Preparation of α-Methylthiolated γ-Keto Esters

2-(2-Methoxycarbonyl-5,5-dimethyl-4-oxo-hexylsulfanylmethyl)-5,5-dimethyl-4-oxo-hexanoid acid methyl ester 140

Into an oven-dried, one-necked, 25-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar with a flow of nitrogen were placed sodium sulfide
Na$_2$S (0.78 g, 10.0 mmol) and 9 mL of $N, N$-dimethylformamide. The solution was for 20 min at room temperature. The yellow suspension was allowed to cooled in a -15 °C (dry ice in ethylene glycol) and compound 82 (0.312 g, 1.0 mmol, in 1 mL of DMF) was added to the reaction mixture which was stirred for 5 h. The reaction was quenched with 2 mL of sat. NH$_4$Cl solution. The DMF and water were removed under reduced pressure (50 °C, 18 torr). The residue was extracted with diethyl ether (3×15 mL) and the combined organic layers were washed with brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (6:1, hexane: ethyl acetate, R$_f$ = 0.09) to yield 0.09 g (25%) of compound 140 as a light yellow liquid. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.67 (s, 6 H), 3.11-3.04 (m, 2 H), 3.02-2.98 (m, 2 H), 2.85-2.75 (m, 4 H), 2.67-2.61 (m, 2 H), 1.13 (s, 18 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 213.8, 174.3, 52.2, 44.2, 42.4, 37.7, 34.0, 26.6; IR (neat, cm$^{-1}$): 2967, 1737, 1703, 1476, 1366, 1202. MS (MALDI): calcd for C$_{20}$H$_{34}$O$_6$S (M$^+$ +Na$^+$) 425.6160; found, 425.6.

2-Acetylsulfanylmethyl-5,5-dimethyl-4-oxo-hexanoid acid methyl ester 142

Into an oven-dried, one-necked, 10-mL round-bottomed flask equipped with a rubber septum and magnetic stir-bar with a flow of nitrogen were placed potassium thioacetate (0.23 g, 2.0 mmol), compound 82 (0.312 g, in 1 mL of tetrahydrofuran, 1.0 mmol) and 4.0 mL of tetrahydrofuran. The light yellow suspension was allowed to stir overnight at room temperature. The resultant brown suspension was extracted with diethyl ether (3×15 mL).
mL) and the organic layer was removed using a pipette. The combined ether extracts were washed with brine (3×15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (15:1, hexane: ethyl acetate, Rf = 0.10) to yield 0.17 g (65%) of 2-acetyl sulfanyl methyl-5,5-dimethyl-4-oxo-hexanoid acid methyl ester 142 as an orange liquid. 1H NMR (400 MHz, CDCl3) δ 3.63 (s, 3 H), 3.16 (dd, J = 8.0, 15.6 Hz, 1 H), 3.08-3.02 (m, 2 H), 2.96 (dd, J = 7.2, 18.0 Hz, 1 H), 2.64 (dd, J = 4.2, 17.8 Hz, 1 H), 2.27 (s, 3 H), 1.08 (s, 9 H); 13C NMR (100 MHz, CDCl3) δ 213.8, 194.9, 173.8, 52.3, 44.1, 40.3, 37.5, 30.5, 30.2, 26.6.
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