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The tandem chain extension -aldol reaction of beta-keto esters

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The tandem chain extension -aldol reaction of beta-keto esters

Abstract
The Tandem Chain Extension-Aldol (TCEA) Reaction of beta-keto esters with aliphatic and aromatic aldehydes yields gamma-keto-beta'-hydroxy esters with significant syn-selectivity. A control Reformatsky reaction with a methyl 2-iodo-5,5-dimethyl-4-oxo-hexanoate 53 and methyl 2-iodo-5,5-dimethylhexanoate 65 indicates that the presence of a gamma-keto-functionality in the zinc-organometallic intermediate in the TCEA reactions is key to the syn-selectivity that is observed. The gamma-keto-functionality, through complexation to zinc, may direct the bias of the reaction toward a transition state that results in the syn-product. An investigation of the zinc-organometallic intermediate with Nuclear Magnetic Resonance Spectroscopy has supported the theory that the intermediate's gamma-keto-group is coordinated to zinc-species on the reaction mixture.

Use of protected alpha-hydroxyacetaldehydes in the TCEA reaction results in an erosion in the syn-selectivity of the TCEA reaction. A study, in which the steric bulk of the hydroxyacetaldehyde's protecting group was varied, has indicated that the erosion in syn-selectivity is likely due to complexation of the aldehydes hydroxy-functionality to zinc in the transition state of the TCEA reaction.

Finally, in an attempt to develop an approach toward the synthesis of CJ-12,954 114a, the TCEA reaction has been successfully applied to the synthesis of spiroketal units, via the generation of dihydroxy-keto synthons.

Keywords
Chemistry, Organic
THE TANDEM CHAIN EXTENSION-ALDOL REACTION OF β-KETO ESTERS

BY

Karelle S. Aiken
B.A., Williams College, 2000

DISSERTATION

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

Doctor of Philosophy
in
Chemistry

December, 2005
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DEDICATION

This thesis is dedicated to my parents,

Maria Aiken and Louis Aiken.

They dreamed of great things for their children and
began praying for us before we could even dream for ourselves.
The UNH Chemistry Department—Faculty and Staff: Thank you for providing a good environment for me to grow in knowledge of chemistry and also, to grow in character.

Dr. Zercher: Thank you for this adventure in chemistry. There’s nothing like observing and learning from a person who is consistent in drive and integrity.

My Committee: Drs. Carleton, Mayne, Greenberg and Johnson: Thank you for your invaluable input and for making the time to get me out of here!

Zercher group and UNH graduate students (past and present): You have set the pace for a high standard of work.

New England Board of Higher Education (NEBHE): Time spent at an Institute, a meeting or speaking with Joanne, Amanda and Emorcia was always valuable.

Andrews (of course), Ward 21, Williams, New Hampshire Friends: Because of your friendships, I am a wiser, smarter, kinder, more determined, and more of anything that is good!

My Family from NY to JA to Canada to Florida: Di support! Unu jus’ good. Words really cyaan express....

My Creator: You have and, You continue to sweetly surprise me. I ask for one thing but You always give me something greater, and more meaningful than I ever imagined.
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ABSTRACT

THE TANDEM CHAIN EXTENSION-ALDOL REACTION OF β-KETO ESTERS

By

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University of New Hampshire, December, 2005

The Tandem Chain Extension-Aldol (TCEA) Reaction of β-keto esters with aliphatic and aromatic aldehydes yields γ-keto-β'-hydroxy esters with significant syn-selectivity. A control Reformatsky reaction with a methyl 2-iodo-5,5-dimethyl-4-oxo-hexanoate 53 and methyl 2-iodo-5,5-dimethylhexanoate 65 indicates that the presence of a γ-keto-functionality in the zinc-organometallic intermediate in the TCEA reactions is key to the syn-selectivity that is observed. The γ-keto-functionality, through complexation to zinc, may direct the bias of the reaction toward a transition state that results in the syn-product. An investigation of the zinc-organometallic intermediate with Nuclear Magnetic Resonance Spectroscopy has supported the theory that the intermediate’s γ-keto-group is coordinated to zinc-species on the reaction mixture.

Use of protected α-hydroxyacetaldehydes in the TCEA reaction results in an erosion in the syn-selectivity of the TCEA reaction. A study, in which the steric bulk of the hydroxyacetaldehyde’s protecting group was varied, has indicated that the erosion in syn-selectivity is likely due to complexation of the aldehydes hydroxy-functionality to zinc in the transition state of the TCEA reaction.
Finally, in an attempt to develop an approach toward the synthesis of CJ-12,954 114a, the TCEA reaction has been successfully applied to the synthesis of spiroketal units, via the generation of dihydroxy-keto synthons.
CHAPTER I

INVESTIGATION OF THE ZINC-ORGANOMETALLIC INTERMEDIATE IN
THE SYN-SELECTIVE TANDEM CHAIN EXTENSION-ALDOL REACTION OF
β-KETO ESTERS

A. Introduction

1. The Chain Extension Reaction

Under the Furukawa cyclopropanation condition, a number of β-keto carbonyl compounds will undergo a chain extension, via the insertion of a methylene unit, to form γ-keto homologues. This zinc carbenoid-mediated chemistry was developed in the Zercher laboratory at the University of New Hampshire and it has been successfully used to chain extend β-keto amides, β-keto imides, β-keto phosphonates and β-keto esters.

Before the discovery of the zinc-mediated chain extension method, Bieraugel, Saigo, Reissig and Dowd separately developed methods for the synthesis of γ-keto carbonyl compounds, which are similar in one aspect of their mechanisms. All four methods proceed through the generation of a substituted cyclopropane intermediate, which eventually fragments to form the γ-keto carbonyl targets. The substituted cyclopropane intermediates in the methods of Bieraugel, Saigo and Dowd are derived from β-keto carbonyls, which are also the substrates in the Zercher’s method. In Reissig’s method, however, the substituted cyclopropane intermediate is generated from the exposure of a trimethylsilylenol ether to a carbenoid of an α-diazo ester.
Scheme 1: Bieraugel's Chain Extension Method

Scheme 2: Saigo's Chain Extension Method
Scheme 3: Reissig's Chain Extension Method

Scheme 4: Dowd's Chain Extension Method

The chain extension method by Zercher is believed to commence with the deprotonation of the β-keto carbonyl substrate to form an enolate 20 (Scheme 5). This enolate then performs nucleophilic substitution of the zinc-carbenoid species to give a methyl zinc intermediate 21. The methyl zinc intermediate 21 is believed to undergo an intramolecular addition into its keto group resulting in a zinc cyclopropanoate structure 22. It is proposed that similar to the other chain extension methods, the cyclopropanoate...
intermediate quickly fragments to a $\gamma$-keto zinc-organometallic intermediate 24, which upon protonation results in the $\gamma$-keto homologue 5 of the substrate.

\[ \text{Scheme 5: The Mechanism of the Carbenoid-Mediated Chain Extension Reaction of $\beta$-Keto Esters under the Furukawa Cyclopropanation Condition} \]

Using the hypothesis that the zinc-mediated chain extension reaction proceeds through a zinc-organometallic intermediate 24, one-pot tandem reactions were developed in order
to generate α-substituted γ-keto carbonyls. The tandem reactions are achieved by quenching the zinc-organometallic intermediate with electrophiles (Scheme 6). Excess carbenoid from a chain extension reaction, iodine, aldehydes, ketones and iminium ions have been employed as electrophiles. Notably, the tandem chain extension-iodination reactions generate α-iodinated targets, which can be further treated with a base to form α, β-unsaturated compounds 26. All three steps, the chain extension, iodination and elimination, are performed in a one-pot procedure, which has been called the tandem chain extension-oxidation-elimination reaction. The one-pot, tandem procedures have been employed as key steps in the generation of synthons and natural products.

The synthetic utility of the chain extension and tandem reactions has been illustrated by Zercher, Heim, and Minetto. The synthesis of ketomethylene isosteres has been accomplished through application of the chain extension and the tandem chain extension-aldol reaction. They have also used the tandem chain extension-oxidation-elimination reaction as a key step in the syntheses of (+)-Patulolide A 33 and (+)-Patulolide B 32, compounds with antifungal, antibacterial and anti-inflammatory activity. Heim et. al. has employed the chain extension chemistry to perform a ring expansion in the construction of the core 35 of Vibsanin E. Minetto et. al. has utilized the tandem chain extension-aldol reaction to build synthons for a microwave assisted Paal-Knorr reaction in the synthesis of pyrroles and furans.
Scheme 6: Tandem Chain Extension-Zinc Enolate Reactions with Various Electrophiles

average syn : anti 10 : 1
R' = O-alkyl

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Scheme 7: The Tandem Chain Extension-Elimination Reaction in the Synthesis of Patulolide A and Patulolide B

Scheme 8: The Carbenoid-Mediated Chain Extension Reaction in the Synthesis of the Core of Vibsanin E
Scheme 9: The Tandem Chain Extension-Aldol Reaction in the Synthesis of Pyroles and Furans

2. The Tandem Chain Extension-Aldol Reaction

β-Keto esters and β-keto amides have been employed in the tandem chain extension-aldol (TCEA) reaction with aromatic and alkyl aldehydes. The reaction with β-keto esters was extensively studied in order to investigate trends in its diastereoselectivity (Table 1). Typical TCEA reactions with β-keto esters were carried out at 0 °C, with five equivalents of carbenoid and one and half equivalents of the aldehyde relative to the substrate. The study revealed that at 0 °C, the reaction had an average syn : anti ratio of 10 : 1, which was further increased when the temperature was lowered to −78 °C (Table 1: entry 1). The increased syn : anti ratio at the lower
temperature is consistent with the belief that the TCEA reaction operates under kinetic control.

**Table 1:** The TCEA Reaction with β-Keto Esters

![Chemical structures](image)

| Entry | R'    | R''   | R'''  | Yield % | syn:anti  \\
|-------|-------|-------|-------|---------|-----------
| 1     | t-Bu  | OMe   | Ph    | 97      | 12:1      |
|       |       |       |       |         | 17:1 (-78 °C) |
| 2     | t-Bu  | OMe   | 3,4-(MeO)₂-C₆H₃ | 61      | 9:1       |
| 3     | 3,4-(MeO)₂-C₆H₃ | OEt   | 3,4-(MeO)₂-C₆H₃ | 57      | 7:1       |
| 4     | Me    | OMe   | t-Bu  | 85      | >20:1     |
| 5     | Me    | OMe   | Ph    | 61      | 15:1      |
| 6     | Me    | NPhMe | Me    | 46      | >5:1      |

A Zimmerman-Traxler transition state model has been proposed in order to explain the syn-selectivity of the TCEA reaction (Scheme 10). In the favored transition state, it is assumed that the aromatic or alkyl group of the aldehyde is in the pseudo-equatorial position while the enolate adopts a Z-configuration. Under kinetically controlled conditions, esters usually exhibit a preference for the formation of the E-enolate. The Zimmerman-Traxler transition state predicts that the E-enolate, contrary to the Z-enolate #, would bias the TCEA reaction toward the anti-diastereomer. Therefore, syn-selectivity.
of the kinetically controlled TCEA reaction with β-keto esters and amides (Table 1), suggests the presence of a common controlling feature that leads to Z-enolate formation.

![Scheme 10: The Zimmerman-Traxler Transition State Model for the TCEA Reaction](image)

In order to further probe the reason for preferred formation of the Z-enolate, the TCEA reaction was compared to a similar aldol reaction, the Reformatsky Reaction. The Reformatsky reaction, developed in 1887, also proceeds through a zinc-organometallic...
intermediate generated from the treatment of a α-halo ester with zinc (Scheme 11).\textsuperscript{18,19}

Unlike the TCEA reaction, however, a traditional Reformatsky reaction is only moderately diastereoselective. In general, the ratio of diastereomers in the reaction with aldehydes rarely surpasses 3:1 under kinetically controlled conditions.\textsuperscript{20} This moderate diastereoselectivity is most likely caused by an equilibrium involving 1,3-metallotropy, which results in the formation of both the E-enolate 41\textsubscript{a} and the Z-enolate 41\textsubscript{c}.\textsuperscript{21}

Significant stereoselectivity in Reformatsky reactions has only been achieved in a chiral environment---in the presence of a chiral auxiliary\textsuperscript{22} or when chirality exists in one of the substrates.\textsuperscript{23,24,25}

![Scheme 11: The Reformatsky Reaction](https://example.com/scheme11)

\[ \text{Scheme 11: The Reformatsky Reaction} \]
The structure of the Reformatsky intermediate has been determined from studies using NMR spectroscopy and X-ray crystallography.\textsuperscript{18,19} These results have shown that the intermediate exists as a dimer of a C-Zn bound species \textbf{41b}. Whether the TCEA intermediate is also dimeric is yet to be established, however, the main difference between the Reformatsky intermediate \textbf{41b} and the proposed chain extended intermediate \textbf{24}, is the presence of a $\gamma$-keto group. This keto group appears to be the source of the highly contrasting stereoselectivities that are exhibited by the two reactions. The $\gamma$-keto group in the chain extension intermediate \textbf{24} may facilitate the strong bias toward the formation of the Z-enolate in the transition state, through an association of the ketone's oxygen with the Zn-species.

\textbf{B. Results and Discussion}

In order to investigate the theory that the $\gamma$-keto group in the TCEA reaction of $\beta$-keto esters was responsible for the strong \textit{syn}-selectivity, a control study was proposed. It was envisioned that the control study would involve two Reformatsky reactions with $\alpha$-halo esters. Substrates for the reactions would only differ through the inclusion or absence of a $\gamma$-keto moiety. Strong support for the \textit{syn}-selective influence of the $\gamma$-keto group in the TCEA reaction would be gained if the Reformatsky reaction with the $\gamma$-keto substrate was significantly \textit{syn}-selective and the reaction with the non-keto substrate was effectively non-diastereoselective.
1. Synthesis of α-Halo-γ-Keto Ester

The tandem chain extension-iodination reaction was used to make the α-halo-γ-keto ester for the Reformatsky reaction. Iodination of the chain extension intermediate has been employed as a step in the synthesis of α, β-unsaturated γ-keto carboxylic acids in the tandem chain extension-oxidation-elimination reaction. A variety of substrates, such as β-keto esters and α-amino acid derived β-keto ester and β-keto amides, were successfully converted to their respective α, β-unsaturated homologues. Methyl acetoacetate, t-butyl acetoacetate, and methyl pivaloylacetate were some of the β-keto esters that proved to be suitable substrates for the elimination reaction. Hence, the α-iodo target of any of these compounds seemed to be accessible as potential substrates for the control studies. The chain extended-iodinated products of methyl acetoacetate 46 or t-butyl acetoacetate 49 were attractive for the control studies, because of the commercial availability of corresponding pentanoate esters. These pentanoate esters were considered to be appropriate starting material for the formation of α-iodo esters, which lacked γ-keto moieties.

The chain extended α-iodo homologues of both methyl acetoacetate and t-butyl acetoacetate were, however, shown to be unsuitable for the control studies. The tandem chain extension-iodination reaction of methyl acetoacetate produced a complex crude reaction mixture in which, over time, the iodo-target was converted to the chain extended material. Attempted purification and isolation of the iodinated target by flash column chromatography, were unsuccessful because the Si-gel appeared to facilitate the elimination of the α-iodo target 47 (Scheme 12). As a result, only the α, β-unsaturated homologue 48 was isolated after chromatography. The reaction with t-butyl acetoacetate
49 presented similar difficulties, in that, the α-iodo-target proved to be too unstable to isolate and store for future use. Due to the difficulty of isolation and storage of the α-iodo-γ-keto products of both methyl acetoacetate and β-butyl acetoacetate, methyl pivaloylacacetate was used to synthesize the α-iodo-γ-keto ester for the control studies.

The tandem chain extension-iodination of methyl pivaloylacacetate yielded a 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53 which could be purified by flash column chromatography in moderate yields, with only traces of the α, β-unsaturated homologue 55 and/or the simple chain extended product 54 being present. The isolated α-iodo product was unstable at room temperature and would undergo a significant amount of elimination within 24 hours. Cold temperatures greatly reduced the rate of elimination, and allowed for storage of the compound over longer periods. However, the material was usually used immediately after preparation.
With the α-iodo-γ-keto substrate in hand, suitable conditions for the Reformatsky reaction were developed. The TCEA reactions performed by Lai et al. \textsuperscript{11} were carried out at 0 °C, with four equivalents of the carbenoid and one and a half equivalents of aldehyde relative to the substrate. The reactions were also performed with a concentration of 0.08 M substrate in methylene chloride. Therefore, it was determined that the Reformatsky reactions would be performed in methylene chloride at 0 °C with a concentration of 0.08 M substrate. However, these conditions needed to be altered so that little or no the carbenoid was generated. Such conditions would be free of the
byproducts generated by decomposition of excess carbenoid and therefore, suitable for studies of the zinc-organometallic intermediate by NMR Spectroscopy.

2. Reformatsky Reaction with 2-Iodo-5,5-Dimethyl-4-Oxo-Hexanoic Acid Methyl Ester 53

Initial attempts to generate the zinc-organometallic intermediate at 0 °C from 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53 via zinc insertion were performed with zinc metal. However, the first reaction yielded chain extended material 54, starting material 53 and benzaldehyde, with negligible amounts of the aldol product. The conditions were altered by extending the reaction time and/or refluxing the reaction mixture; however, these changes were unsuccessful in increasing the extent to which the aldol reaction proceeded. For example, only starting material was recovered in even the most extreme conditions, reflux of the substrate in methylene chloride in the presence of zinc and benzaldehyde for twenty-four hours. All the results gathered from the studies with zinc metal indicated that either zinc insertion was slow and/or the aldol reaction was not taking place.

In order to find out if the solvent, methylene chloride, was having an effect on the rate of the reaction, the solvent was changed to THF. Frequently, Reformatsky reactions, with zinc metal, are carried out in THF under reflux.25 With reflux in THF, all of the starting material was consumed and a considerable amount of the simple chain extended product, was observed. Though aldol product was not observed, the presence of chain extended material, along with complete consumption of the substrate, indicated that zinc insertion was readily occurring. When compared to the attempts to perform the reaction
in methylene chloride, this result with THF suggested that zinc insertion via the zinc metal, was slow in methylene chloride.

In order to maintain the use of methylene chloride as the solvent in the control studies, the source of zinc was changed from the metal to diethyl zinc. With diethyl zinc, zinc insertion readily occurred at 0 °C and addition of benzaldehyde resulted in significant amounts of aldol product (Scheme 13). However, the syn : anti ratio of the aldol product was 3 : 1, far lower than the 12 : 1 ratio observed in the initial study of the TCEA reaction with methyl pivaloylacetate 52 and benzaldehyde (Table 1: entry 1).^{11}

Scheme 13: The Reformatsky Reaction for the Control Study with 2-Iodo-5,5-Dimethyl-4-Oxo-Hexanoic Acid Methyl Ester 53
It was thought that the identity of the X-group may affect the selectivity of the aldol reaction. When diethyl zinc is used as the source of Zn$^{2+}$ in Scheme 13, the X-group is believed to be an ethyl ligand. In the TCEA reaction (Scheme 10), however, the X-group could be either iodide or an iodomethyl group or another species that results from decomposition of the carbenoid. In effort to make the X-group of the zinc-organometallic intermediate the same as that in the TCEA reaction, methylene iodide was added to the reaction after zinc-insertion with diethyl zinc had occurred. The syn : anti ratio obtained for this reaction was 7 : 1. A ratio of 7 : 1, although not identical, was approaching the diastereoselectivity of the original methodology study of the TCEA reaction, 12 : 1 (Table 1: entry 1).11

3. Synthesis of 2-Iodo-5,5-Dimethylhexanoic Acid Methyl Ester 65

The substrate without the γ-keto group, 2-iodo-5,5-dimethylhexanoic acid methyl ester 65, was synthesized in a multi-step procedure which commenced with the reduction of methyl $t$-butylacetate 60 to 3,3-dimethylbutan-1-ol 61 (Scheme 14). The alcohol was oxidized to the aldehyde, which was employed in a Horner-Emmons reaction to yield the $\alpha,\beta$-unsaturated ester, 5,5-dimethylhex-2-enoic acid methyl ester 63. In the presence of a Pd-catalyst and hydrogen gas, the unsaturated ester was reduced to 5,5-dimethylhexanoic acid methyl ester 64. In the final step, the Reformatsky substrate, 2-iodo-5,5-dimethylhexanoic acid methyl ester 65, was generated from a quench of the lithium enolate of 5,5-dimethylhexanoic acid methyl ester 64 with iodine.
Scheme 14: The Synthesis of 2-Iodo-5,5-Dimethylhexanoic Acid Methyl Ester 65

4. Reformatsky Reaction with 2-Iodo-5,5-Dimethylhexanoic Acid Methyl Ester 65

The conditions used for the Reformatsky reaction with 2-iodo-5,5-dimethylhexanoic acid methyl ester 65 were the same as the conditions used for 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53 (Scheme 15). The reaction was run with 0.08 M of the substrate in methylene chloride. The substrate was dissolved in methylene chloride and treated with diethyl zinc, followed by methylene iodide. Treatment of the resulting zinc-intermediate with benzaldehyde resulted in aldol product in which the syn : anti ratio was 1 : 1, similar to the ratio observed in typical Reformatsky reactions. The stark contrast of absent diastereoselectivity compared to the 7 : 1 syn-selectivity of the Reformatsky reaction with the α-iodo-γ-keto ester 53, was consistent with proposal that the presence of
the γ-keto group in the TCEA intermediate was key to the *syn*-selectivity of the TCEA reaction (Table 2).

Scheme 15: The Reformatsky Reaction for the Control Study with 2-Iodo-5,5-Dimethylhexanoic Acid Methyl Ester 65

*syn : anti*

1 : 1

39%

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Table 2: The Control Reformatsky Reaction

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
<th>syn : anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td>58, 59</td>
<td>47</td>
<td>7:1</td>
</tr>
<tr>
<td>65</td>
<td>67, 68</td>
<td>39</td>
<td>1:1</td>
</tr>
</tbody>
</table>

5. An Investigation of the Zinc-Organometallic Intermediate with Nuclear Magnetic Resonance Spectroscopy

The investigation of the structure of the chain extension intermediate by Nuclear Magnetic Resonance Spectroscopy was pursued in an attempt to further elucidate the structure of the zinc-organometallic intermediate 24. These investigations would also offer some additional information:

i) If complexation were occurring, $^{13}$C-NMR spectra would exhibit resonances that corresponded to carbons of zinc-complexed keto- and the ester-carbonyls.

ii) Both $^1$H-NMR and $^{13}$C-NMR spectroscopy could be used to establish whether the intermediate was monomeric or dimeric, as in the Reformatsky reagent, or more complex in its overall structure.

iii) If they persisted for a reasonable amount of time, the existence of other intermediates, such as the hypothesized zinc cycloproanoate 22, could be observed by NMR spectroscopy.
i. Generation of the zinc-organometallic intermediate from 2-Iodo-5,5-Dimethyl-4-Oxo-Hexanoic Acid Methyl Ester 53

Initial attempts to generate the zinc-organometallic intermediate for spectroscopic studies were made with 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53. The substrate was treated with an undetermined amount of diethyl zinc in CD$_2$Cl$_2$ and the resulting reaction mixture was observed by NMR spectroscopy (Figure 1). The $^{13}$C- and $^1$H-NMR spectra for these studies showed signals corresponding to the substrate 53, diethyl zinc, and the intermediate 56, along with byproducts generated upon the zinc insertion into the carbon-halogen bond (Appendix).

In the $^1$H-NMR spectra, a singlet for protons in a pivaloyl group was easily identified at 1.19 ppm (Figure 1). Two triplets, for methylene units at 2.50 ppm and 2.76 ppm, indicated that immediately after the addition of diethyl zinc, the chain extended product, 5,5-dimethyl-4-oxo-hexanoic acid methyl ester 54, had formed. The singlets for pivaloyl groups in the $\alpha$-iodo-$\gamma$-keto substrate and the chain extended product occur at ~1.13 ppm. So, the signal at 1.19 ppm was assigned to a pivaloyl group of an intermediate. Another notable observation was the appearance of a broad signal at 2.23 ppm, which over time, decreased in intensity as the intensity of the signals for the chain extended material increased. This trend led to the assignment of the resonance at 2.23 ppm as a proton in the intermediate 56.
Figure 1: $^1$H-NMR spectra of the zinc organometallic intermediate generated from I. 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53; II. with diethyl zinc; III. with diethyl zinc and methylene iodide in CD$_2$Cl$_2$.

Further analysis of the 1 D $^1$H-NMR spectrum revealed that a broad singlet at 3.54 ppm integrated for 3 H's, relative to the signal at 2.23 ppm. The singlet at 3.54 ppm
appeared within a range of chemical shifts that is common to protons on the methoxy groups of methyl esters. Consequently, the signal at 3.54 ppm was tentatively assigned as the protons of the methyl ester in the chain extension intermediate 56 while the signal at 2.23 ppm was assigned as its methine proton α to the ester.

After insertion of diethyl zinc into the α-iodo-γ-keto substrate, the ligand on the zinc species of the intermediate 56 was most likely an ethyl ligand. However, in the carbenoid-mediated chain extension reaction the zinc-ligand is unknown, although an iodomethyl group, CH$_2$I, or another species that results from decomposition of the EtZnCH$_2$I carbenoid are possibilities. In an effort to determine if the structure of the intermediate 56 generated here is different from that for the carbenoid-mediated chain extension reaction, methylene iodide was added after the substrate was treated with diethyl zinc to generate 57a (Figure 1). With the addition of methylene iodide, the resonance at 2.23 ppm shifted downfield to 2.44 ppm. In addition, a signal, apparently buried under the quartet for ethyl iodide at 3.18 ppm, shifted downfield to 3.25 ppm. This signal integrated for 2 protons relative to the signal now at 2.44 ppm and it also decreased in intensity as the amount of chain extended product increased. Based on this trend, its integration and its chemical shift, the signal at 3.25 ppm was tentatively assigned to the protons of the methylene unit in the intermediate. The downfield shift of the signals for the methylene and methine protons of 57a relative to those of 56 indicated that the electron density around their nuclei had decreased. This decline in the electron density might be attributed to a change in a ligand on the intermediate's zinc.

Signals that corresponded to two other proposed intermediates, enolate 23 or cyclopropanoate 22, were not observed. Nevertheless, having identified signals that
corresponded to the methylene and methine protons in the intermediate, the results of the
$^1$H-NMR spectra, thus far, supported the theory that the intermediate was an open-chain
structure with a carbon-zinc bond. $^1$H-NMR experiments, however, did not reveal
whether the keto and ester group of the intermediate were complexed to zinc species.
This information would be obtained from $^{13}$C-NMR experiments.

The $^{13}$C-NMR spectra taken before and after the addition of methylene iodide were
similar, except for two features (Figure 2). Resonances for the methylene units of chain
extended product 54 at 31.7 ppm and 28.2 ppm were more intense after addition of CH$_2$I$_2$
than at the start of the experiment. However, this difference was likely the result of
quenching by a proton source, not as the result of methylene iodide addition. Another
significant difference was a downfield shift of a resonance at 32.7 ppm to 35.4 ppm upon
addition of CH$_2$I$_2$. The region in which these chemical shifts occurred and the change in
the chemical shift as a response to the change in the zinc species suggested that 32.7 ppm
(Et) and 35.4 ppm (CH$_2$I$_2$) corresponded to the methine-carbon bound to zinc in the
organometallic intermediate of the chain extension reaction.
Figure 2: $^{13}$C-NMR of the zinc-organometallic intermediate generated from I. 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53; II. with diethyl zinc; III. diethyl zinc and methylene iodide in CD$_2$Cl$_2$.

The $^{13}$C-NMR spectra of the intermediate, with the Et or the CH$_2$I$_2$-derived ligand on the zinc, had signals for the carbonyl-carbons of the ester and keto groups that were downfield of the signals for the same groups in the chain extended product 54. In the
chain extended product 54, resonances for the ester- and keto-carbons are at 173.7 ppm and 214.3 ppm, respectively. In the intermediate, the carbon of the ester-carbonyl resonated at 183.6 ppm, upon addition of diethyl zinc, and, 184.3 ppm, upon addition of CH$_2$I$_2$. In both cases, the resonance for the ketone carbon occurred at 228.6 ppm. Relative to the resonances of carbonyls in the chain extended product 54, the downfield shift of the carbonyl resonances in the intermediate 56 and 57a suggested that the intermediate’s carbonyl-oxygens were complexing to zinc species in the reaction mixture.

NMR spectroscopic investigation of the TCEA-like intermediate generated from Zn-insertion with 53 confirmed the existence of a C-Zn bound intermediate 57a in which the ester and keto carbonyls were complexed to Zn-species in solution.

During the NMR experiments, the formation of the chain extended product was an issue. A short lifetime of the intermediate generated from the α-iodo-γ-keto substrate 53 did not allow for long spectroscopic experiments. As a solution to this problem, a different approach to the intermediate was designed.

ii. Generation of the Zinc-Organometallic Intermediate from a Methyl β-Keto Ester

In the second approach, the intermediate was generated from a β-keto ester, methyl acetoacetate 46, using the chain extension reaction in which, two equivalents of carbenoid were used, instead of the traditional four or five equivalents. The lowered equivalents of carbenoid limited the amount of byproducts, propylzinc iodide and ethyl iodide, generated during carbenoid formation and decomposition. Intense signals from the byproducts would have obscured signals of interest.
To generate the intermediate, methyl acetoacetate 46 in CDCl₃, instead of CD₂Cl₂, was treated with two equivalents of diethyl zinc. After formation of the zinc enolate 70 was confirmed by NMR spectroscopy, two equivalents of methylene iodide were added to the mixture. Unfortunately, the resulting spectrum was more complicated than expected and the signals corresponding to the intermediate could not be assigned. Furthermore, a protic quench of the reaction mixture yielded crude material with a complex ¹H-NMR spectrum. The complexity of this spectrum indicated that treatment of methyl acetoacetate with the carbenoid resulted in other uncharacterized reactions in addition to chain extension. As a result, information relating to the intermediate formed in the chain extension reaction could not be obtained from the NMR experiments with methyl acetoacetate.

The substrate was changed from methyl acetoacetate to methyl pivaloylacetate 52a. Methyl pivaloylacetate 52a is one of the higher yielding substrates in the chain extension reaction.¹¹ The same method used with methyl acetoacetate was used to generate the intermediate from methyl pivaloylacetate: the addition of two equivalents of diethyl zinc to give the zinc enolate 70, followed by the addition of two equivalents of methylene iodide.

The spectra for the chain extension intermediate of methyl pivaloylacetate was similar to the spectra of the intermediate generated from zinc insertion with 2-iodo-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 53 (Figures 1 vs. 3; 2 vs. 4). There were however, slight differences in the chemical shifts of the signals in both the ¹H- and ¹³C-NMR spectra, possibly due to the change in solvent from CD₂Cl₂ to CDCl₃. In addition, chain extended material was not observed in these studies and it was determined that the
intermediate could last for as long as 25 hrs. after it was generated. Decomposition only occurred when a proton-source was introduced into the reaction mixture.

Use of a β-keto ester to generate the intermediate provided the opportunity to perform a deuterium-label experiment. In this experiment, the protons on the methylene unit of methyl pivaloylacetate were converted to the D-isotope by treatment of methyl pivaloylacetate with sodium carbonate in D$_2$O. The D-labeled substrate 52b was chain-extended and the intermediate 57b was observed by $^1$H- and $^{13}$C-NMR spectroscopy (Figures 3 & 4). Compared to the $^1$H-NMR spectrum of the non-labeled substrate, the $^1$H-NMR spectra of D-labeled intermediate 57b had diminished signals in the region of 2.66 ppm. The $^{13}$C-NMR resonance at 35.2 ppm also appeared to be somewhat diminished in the D-labeled case. The result with the D-label further supported the assignment of the resonances at 2.66 ppm ($^1$H-NMR) and 35.2 ppm ($^{13}$C-NMR) as the methine unit in the zinc-organometallic intermediate.
Figure 3: $^1$H-NMR spectra of the zinc-organometallic intermediate 57a/b generated with the carbenoid-mediated chain extension of I. methyl pivaloylacetate 52a; II. D-labeled methyl pivaloylacetate 52b
Figure 4: $^{13}$C-NMR spectrum of the zinc-organometallic intermediate 57a/b generated with the carbenoid-mediated chain extension of I. methyl pivaloylaceta 52a; II. D-labeled methyl pivaloylaceta 52b

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The stability of the intermediate was sufficient for investigations by 2D-NMR spectroscopy including HSQC experiments and COSY experiments. The COSY spectra of the intermediate 57a generated from methyl pivaloylacetate 52a, showed a correlation between the signal at 2.66 ppm and the broad, flattened signal at 3.25 ppm. This result supported the assumption that the signal in the region of 3.25 ppm corresponded to the methylene unit. The heteronuclear coupling experiment, HSQC, showed evidence for the correlation of signals in the $^1$H-NMR and $^{13}$C-NMR spectra at 2.66 ppm and 35.2 ppm, respectively. A correlation was also observed at 3.25 ppm ($^1$H-NMR) and 38.6 ppm ($^{13}$C-NMR). Based on these correlations, the signals at 35.2 ppm and 38.6 ppm were assigned as the carbons in the intermediate for the methine and the methylene units, respectively. The assignment of the resonances for these methylene and methine carbons was also supported by the results of DEPT-135 experiments. Other correlation by HSQC experiments were seen with:

i) 3.70 ppm and 54.0 ppm

ii) 1.24 ppm and 26.9 ppm

Based on the results of the 1D and 2D NMR experiments, the intermediate was fully characterized by $^1$H-NMR and $^{13}$C-NMR spectroscopy (Table 3).
Table 3: The chemical shift assignments for the zinc-organometallic intermediate 57a generated from the carbenoid-mediated chain extension of methyl pivaloylacetae 52a

<table>
<thead>
<tr>
<th>Nucleus</th>
<th>$^1$H NMR</th>
<th>13C NMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>57a</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>$\delta$/ppm</td>
<td>$\delta$/ppm</td>
<td>$\delta$/ppm</td>
</tr>
<tr>
<td>H1</td>
<td>1.24(s)</td>
<td>1.15(s)</td>
</tr>
<tr>
<td>-</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>-</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>H4</td>
<td>3.25</td>
<td>2.80</td>
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<tr>
<td>flat &amp; broad</td>
<td>(t)</td>
<td>C4</td>
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<td>H5</td>
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<tr>
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<td>(t)</td>
<td>C5</td>
</tr>
<tr>
<td>-</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>H7</td>
<td>3.70(s)</td>
<td>3.65(s)</td>
</tr>
</tbody>
</table>

6. Dynamic Nuclear Magnetic Resonance Spectroscopy

In the spectra of the zinc-organometallic intermediate 57a, the broadness of the signals at 2.66 ppm and 3.25 ppm in the $^1$H-NMR spectra and at 35.2 ppm, 38.6 ppm, 185.2 ppm and 230.4 ppm in the $^{13}$C-NMR, indicated that an interchange of various species of the zinc-organometallic intermediate 57a was being observed at room temperature. Dynamic NMR experiments were performed in order to determine whether the dynamic process
was intermolecular and/or intramolecular and to obtain additional information about the extent to which monomeric units of the intermediate were aggregating. The DNMR experiments involved variable temperature studies and variable concentration studies.

i. Variable Temperature

In the variable temperature studies, $^1$H-NMR spectra of the intermediate 57a were obtained at -45 °C, -15 °C, 0 °C, 15 °C and 19 °C (Figure 5), while $^{13}$C-NMR spectra were obtained at -15 °C, 0 °C, 15 °C and 19 °C. The $^{13}$C-NMR spectra acquired at various temperatures, did not exhibit significant differences. However, as the temperature was varied, with the $^1$H-NMR spectra conspicuous changes occurred in the resonances that corresponded to the methine and methylene protons in the intermediate 57a.
Figure 5: 1D $^1$H-NMR spectra of the zinc-organometallic intermediate 57a at 19 °C, 15 °C, 0 °C and -15 °C.

As the reaction mixture was cooled, changes in the methine and methylene resonances in the $^1$H-NMR spectra suggested that the intermediate existed as more than one type of species (Figure 5). The 2.66 ppm-signal, at 19 °C, decoalesced into two resonances at 2.71 ppm and 2.58 ppm, as the temperature was lowered to 0 °C. In addition, the broad
and flattened methylene signal at 3.25 ppm (19 °C) also decoalesced into two resonances at 3.71 ppm and 2.97 ppm. At −15 °C, the methine and methylene signals appeared as they did at 0 °C, though at slightly different chemical shifts.

At 0 °C and −15 °C, the methine resonance at 2.71 ppm appeared to be approaching the shape of a triplet, while the other signal at 2.58 ppm was broad and undefined. The signal at 2.71 ppm, relative to the resonance at 2.58 ppm, integrated for approximately 5 protons. This integral ratio indicated that the dominant species, ~83 % of the zinc-organometallic population corresponded to the resonance at 2.71 ppm while the other 17 % corresponded to the resonance at 2.58 ppm.

The methine and methylene resonances decoalesced at 0 °C. So, as the temperature was lowered, the interchange of the two groups of zinc-organometallic species was approaching a slow rate of exchange on the NMR time scale. With suitably low temperatures that induce slow exchange, it was expected that signals corresponding to the methine protons of the zinc-organometallic intermediate would be a number of well-defined triplets at chemical shifts ranging from ~2.71 ppm to ~2.58 ppm. In addition, if slow exchange were achieved, the number methine resonances would be directly related to the number of zinc-organometallic species that exists. However, when the temperature was lowered to −45 °C, proton-resonances for the intermediate became broadened and severely diminished. It was, therefore impossible to observe the intermediate at slow exchange on the NMR time scale.

The reduction in the strength of the signal at −45 °C was most likely due to an anisotropic effect in which, at cooler temperatures, tumbling of lager molecules in solution becomes so sluggish that the rate of relaxation of energetically excited nuclei is
strongly reduced. As a result, the resonances for the larger molecules are broadened and severely diminished.

At 0 °C and -15 °C, signals at 3.71 ppm and 2.91 ppm, each integrated for one proton relative to the sum of the integrals for the methine protons at 2.71 ppm and 2.58 ppm. In view of this integral ratio, the decoalescence of the resonance for the methylene protons at 3.25 ppm (19 °C) into resonances at 3.71 ppm and 2.91 ppm (0 °C), appeared to be a separation of signals for diastereotopic methylene protons, as opposed to signals representing different zinc-organometallic species. In theory, if slow exchange were accessible, these diastereotopic proton resonances would each become well defined with an ABX pattern.

The results of the DNMR experiments with variable temperatures indicated that at least two groups of interchanging species existed for the zinc-organometallic intermediate. However, these variable temperature studies could not be used to determine whether the interchanges were intramolecular and/or intermolecular. This type of information could, however, be obtained from NMR experiments with variable concentration.

ii. Variable Concentration

In the variable concentration experiment, the solution was made at a concentration of 0.36 M with respect to the substrate. The mixture was observed by ¹H-NMR spectroscopy and then diluted by a factor of 1/10 and observed again (Figure 6). As the sample was diluted, the broad resonances for the methylene protons of the intermediate,
3.57 ppm and 3.08 ppm (0.36M), further decoalesced into two sharper signals at 3.59 ppm and 3.03 ppm (0.036M).

The changes in the methylene resonance with dilution indicated that a dynamic process by which the intermediate was changing, involved intermolecular exchange. However, decoalescence of the methine signal at 2.72 ppm did not occur as it had in the variable temperature studies (Figures 5 & 6). Therefore, this experiment could not be used to verify whether or not the two species observed in the VT-studies were involved in an intermolecular and/or intramolecular exchange.

An attempt to further dilute the reaction to 0.0036M of the intermediate only resulted in a significant amount of quenching. Strong resonances for chain extended product at 2.84 ppm and 2.60 ppm were observed.
Figure 6: 1D $^1$H-NMR spectra of the zinc-organometallic intermediate 57a at 0.36M; 0.036M; 0.0036M

7. Reaction conditions and Syn-Selectivity

At the time of the variable concentration studies, intermediates that were generated for investigation by DNMR spectroscopy were routinely quenched with benzaldehyde. The results of various studies revealed that, in addition to the presence of the zinc-intermediate's $\gamma$-keto group functionality, the syn-selectivity of the tandem chain
extension-aldol (TCEA) reactions also depended on other factors, such as the equivalents of diethyl zinc and the concentration of the reaction mixture.

i. Concentration and Diastereoselectivity

The original study of the TCEA reaction was usually performed at a substrate-concentration of 0.08 M in methylene chloride. The aldol product of methyl pivaloylacetate and benzaldehyde in original study, had a syn : anti ratio of 12 : 1. In the NMR investigation of the zinc-organometallic intermediate generated from zinc carbenoid-mediated chain extension of methyl pivaloylacetate, the typical concentration of methyl pivaloylacetate was about 0.34 M in CDCl₃. In addition, the average syn : anti selectivity of the TCEA product generated in the NMR studies was ~7 : 1, syn-biased but significantly lower than the 12 : 1 ratio observed in the original study.

In order to determine if additional information about the intermediate could be obtained from reaction mixtures that were more dilute than the typical 0.34 M concentration, NMR investigations were performed with lower concentrations. One such study employed a concentration of 0.078 M of methyl pivaloylacetate in CDCl₃. In both the ¹H-NMR and ¹³C-NMR spectra, very little differences were observed between the reaction mixtures of 0.34 M and 0.078 M. However, upon addition of benzaldehyde to the 0.078M reaction mixture (NMR tube) a syn : anti selectivity of 11 : 1 was observed. This ratio was higher than the diastereomeric ratio of 7 : 1 at 0.34 M, and closer to the syn : anti ratio of 12 : 1 that was observed in the original study. An NMR experiment was also performed with a more dilute reaction mixture of 0.032 M. The TCEA product of

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this reaction had a syn : anti selectivity of 11 : 1, identical to the result of the 0.078M-study.

The diastereoselectivity of the mixtures for the NMR studies with various concentrations of the substrate indicated that concentration was an important factor in the selectivity of the TCEA reaction. However, the identical diastereoselectivity of the studies at 0.032 M and 0.078 M, also suggests a limit at which substrate-concentration will affect the diastereoselectivity of the TCEA product.

Changing the concentration may affect the extent to which the intermediate’s monomers 57a aggregate. Assuming that the intermediate 57a mimics the dimeric structure of the Reformatsky intermediate from the C-Zn bond through to the ester – carbonyl, more concentrated solution, 0.34M, would result in increased intermolecular aggregation as opposed to intramolecular aggregation via the keto carbonyl-zinc complexation which also directs the diastereoselectivity of the TCEA reaction. Therefore, erosion in syn-selectivity with the more concentrated reaction mixture, suggests that increased intermolecular aggregation of the intermediate 57a diminishes the bias of 57a toward formation of the Z-enolate in the transition state.

ii. Addition of THF and DME

A NMR investigation was undertaken in which an ethereal compound, tetrahydrofuran (THF) or dimethoxyethane (DME), was added to a CDCl₃-solution of the zinc-organometallic intermediate 57a. Ethereal solvents, via their lewis basic oxygen, were expected to compete with the intermediate’s keto moiety for complexation to the zinc species in the reaction mixture. NMR spectra were used to determine whether or not
some type of competition was occurring. In addition, the intermediate, in the presence of either THF or DME, was quenched with benzaldehyde and the diastereomeric ratio of the resulting aldol products determined from an NMR spectrum of the crude reaction mixture.

Four equivalents of DME relative to the methyl pivaloylacetate, were added after the generation of the zinc-organometallic intermediate 57a. Significant differences between the $^{13}$C-NMR spectra obtained with and, without DME were not observed. In the $^1$H-NMR spectra however, the methine signal found at 2.70 ppm (without DME) shifted upfield to 2.61 ppm (with DME) (Figure 7). The methylene signal became a more rounded and broad peak at 3.10 ppm after DME was added. The changes in the methine and methylene resonances may have been caused by a change in the zinc's ligand. In addition, an upfield shift of the $^1$H resonances of the methylene protons of ethyl and propyl zinc-ligands from ~0.50 ppm to ~0.25 ppm in the presence of DME further suggested that the electronic environment of the zinc-species had changed. However, the idea that DME was displacing the intermediate’s keto-moiety from zinc could not be confirmed, because the ketone’s $^{13}$C resonance for the intermediate was unaffected by the presence of DME.
After quenching the intermediate with benzaldehyde in the presence of DME, the resulting aldol product had a syn : anti ratio of 4.5 : 1. The TCEA product, generated from a NMR-reaction mixture in the absence of DME, typically exhibited a syn : anti ratio of 7 : 1. Thus, DME caused an erosion in the syn-selectivity of the TCEA reaction.
Though unconfirmed by NMR experiments, it likely that the DME effected the erosion in selectivity by competing with the keto-carbonyl of 57a for complexation to Zn-species in the reaction mixture.

With THF as an additive, significant changes occurred in the both $^1$H-NMR and $^{13}$C-NMR spectra. Two successive additions of THF were performed during this experiment. In the first addition 2.5 equivalents of THF relative to the starting material, were added and in the second addition another 2.9 equivalents of THF were added.

In the $^1$H-NMR experiments, a number of resonances were affected by the addition of THF. For the methine resonance, each addition of THF resulted in an upfield shift of the methine signal--2.69 ppm (without THF) to 2.58 ppm (2.5 eq THF) to 2.52 ppm (5.4 eq THF) (Figure 8). The chemical shifts for protons on THF typically occur at 3.73 ppm and 1.84 ppm in CDCl$_3$. However, in the presence of the intermediate, the chemical shifts for THF occurred downfield at 3.99 ppm and 1.97 ppm, with 2.5 equivalents of THF, and, 3.89 ppm and 1.89 ppm, with 5.4 equivalents of THF. As THF was added, the broad and flattened signal for the diastereotopic methylene protons at ~3.25 ppm resolved into two broad signals at 3.42 ppm and 3.04 ppm. The resonances for methylene units of the ethyl and propyl zinc-ligands also shifted upfield from ~0.50 ppm to ~0.30 ppm. The changes in the chemical shifts of the intermediate’s methine and the methylene protons of the ethyl and propyl zinc-ligands, and the unusual downfield location of the THF-resonances, indicated that THF was most likely complexing to zinc in the reaction mixture. In addition, the upfield shift of the THF resonances with 5.4 equivalents relative to the mixture with 2.5 equivalents indicates that in each case, the chemical shifts of the THF protons are a time-weighted average of the Zn-complexed and uncomplexed THF.
molecules—assuming that the mixture with 5.4 equivalents of THF would contain higher ratio of uncomplexed THF to Zn-complexed THF than the mixture with 2.5 equivalents THF.

Figure 8: $^1$H-NMR spectra of the zinc-organometallic intermediate 57a I. without THF; II. with 2.5 eq THF; III. with 5.4 eq THF
In the $^{13}$C-NMR spectra, the most obvious change was observed in the carbon-signal of the $\gamma$-keto-carbonyl (Figure 9). After 5.4 equivalents of THF were added to the reaction mixture, the ketone resonance at 230.4 ppm had diminished into the baseline of the $^{13}$C-NMR spectrum. In the chain extended product 54, the carbon resonance for the keto-carbonyl is at 214.3 ppm. As a result, ~214.3 ppm is assumed to be the theoretical chemical shift of the intermediate’s $\gamma$-keto-carbonyl if it were displaced from zinc. It may be that flattening of the intermediate’s ketone resonance at 230.4 ppm, in the presence of THF, is a dynamic phenomenon involving an averaging of the carbon resonances for the zinc-complexed keto-moiety at 230.4 ppm and the uncomplexed keto-moiety at ~214.3 ppm.
Figure 9: $^{13}$C-NMR spectra of the zinc-organometallic intermediate 57a I. without THF; II. with 2.5 eq THF; III. with 5.4 eq THF
The intermediate, in the presence of 5.4 equivalents of THF, was quenched with benzaldehyde. The syn : anti ratio of the TCEA product was 3.3 : 1, far lower than the 7 : 1 ratio observed in previous NMR experiments without additives, and similar to the diastereoselectivity of a typical Reformatsky reaction. Furthermore when 6.1 equivalents of THF were used, the diastereomeric ratio was further eroded to 2.3 : 1 (syn : anti). Thus THF, like DME, caused an erosion in the syn-selecitivity of the TCEA reaction.

The results of the NMR studies with THF were significant because the erosion in syn-selectivity of the TCEA reaction was corroborated with spectroscopic evidence for what appeared to be decomplexation of the intermediate's γ-keto-group from zinc. These results also showed that the resonance for the ester-carbonyl in 57a was unaffected by the presence of THF and therefore suggested that the ester-carbonyl-Zn complexation was stronger than the keto-carbonyl-zinc complexation.

iii. Diethyl Zinc as an Additive

In the studies with diethyl zinc as an additive, the zinc-organometallic intermediate was generated and then treated with an additional two equivalents of diethyl zinc. In the $^1$H-NMR spectra with additional diethyl zinc, the broad signal at 2.69 ppm became a sharp triplet at 2.65 ppm (Figure 10). In addition, the flat and broadened methylene resonance at 3.25 ppm sharpened somewhat into a broad signal at 3.36 ppm. This resonance integrated for two protons relative to methine triplet. The sharpening of both the methine and methylene resonances indicated that the additional equivalents of Et$_2$Zn
appear to facilitate an increased rate of exchange between the various species of the zinc-organometallic intermediate.

**Figure 10:** $^1$H-NMR spectra of I. the zinc-organometallic intermediate 57a; II. with an additional 2 equivalents of diethyl zinc

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The reaction mixture with the extra equivalents of diethyl zinc was quenched with benzaldehyde. The aldol product of this reaction mixture had a syn : anti selectivity of 9 : 1, slightly higher than the diastereomeric ratio of 7 : 1 without any additives. The role of the additional equivalents of zinc in the increased syn-selectivity of the TCEA reaction has not been determined.
CHAPTER II

TANDEM CHAIN EXTENSION-ALDOL REACTION BETWEEN β-KETO ESTERS AND PROTECTED α-HYDROXYACETALDEHYDES

A. Introduction

Aldol reactions are heavily utilized for carbon-carbon bond formation in organic synthesis. Aldol reactions can be base-catalyzed, acid-catalyzed or metal-mediated under catalytic or stoichiometric conditions. The metal-mediated reactions typically occur via the use of Lewis acids or via the formation of the metal enolate of the donor species. Some commonly used metal species are magnesium, lithium, titanium and zinc. The Reformatsky reaction is an example of a zinc-mediated aldol reaction in which, typically, the zinc enolate is formed by insertion of zinc into a carbon-halogen bond of a α-halo ester. Zinc metal, Zn-Cu couple, Zn/Ag-graphite and dialkyl zinc reagents have been used as sources of zinc in traditional Reformatsky reactions. Variations in the traditional Reformatsky reaction have also been accomplished through oxidative insertion of other metals into α-halo carbonyl starting materials.

Of particular interest with many aldol reactions is the incorporation of asymmetry in the formation of the carbon-carbon bond. Reformatsky reactions are only mildly diastereoselective. Many researchers have attempted to enhance the asymmetry of the reaction by taking advantage of the affinity that certain heteroatoms possess for complexing to Zn (II). Chelating moieties used to induce asymmetry have been
introduced as part of the substrate structure, or as part of a chiral ligand. Enhancement of asymmetry has also been accomplished by replacing zinc with other metal-species.

1. Chiral Ligands

Many of the ligands that are used in asymmetric Reformatsky reactions take advantage of the strong affinity of oxygen and nitrogen for binding to zinc. Guétté and colleagues with the use of (-)-sparteine 71, were the first group to report the use of a chiral ligand in the Reformatsky reaction (Figure 11). In the presence of (-)-sparteine 71, the aldol product derived from benzaldehyde and ethyl bromoacetate had an ee of 94%. Unfortunately, the yield for this reaction was only 21%. Since that time, a number of researchers have sought to design potential ligands with the goal of obtaining good enantiomeric excess, as well as acceptable yields in Reformatsky reactions.

Ribeiro and colleagues28 studied the effects of various carbohydrate-derived ligands. Their most successful result was obtained with a diol 72 derived from the open chain of D-mannitol, which induced the highest enantiomeric excess that was observed (Figure 11). The resulting aldol product, generated from the asymmetric Reformatsky reaction of ethyl bromoacetate and benzaldehyde, had a yield of 52% and an ee of 30%. Though low in enantioselectivity, this result was significant because the researchers were able to develop a ligand that induced a measurable amount of asymmetry and therefore, their observations could be used to increase their understanding of how the ligands induce asymmetry in Reformatsky reactions.
Emerson and coworkers also investigated the use of chiral carbohydrate-derived ligands 73 in Reformatsky reactions. These ligands, derivatives of 4,6-O-benzylidene-D-glucosamine, are also classified as amino alcohols (Figure 11). The highest enantiomeric excess in Emerson’s study was obtained with the carbohydrate derivative 73 in a Reformatsky reaction between t-butyl bromoacetate and benzaldehyde. The aldol product had a yield of 44 % and an ee of 42 %, which when compared to the study by Ribeiro was a slight improvement. \(^{28}\) \(^{1}\)H-NMR experiments revealed that the ligand was
most likely inducing asymmetry through the chelation of either the 4,6-oxygens or the N-2, O-3 amino alcohol to the organozinc intermediate.

Many other chiral amino alcohols that have been probed for stereoinduction in Reformatsky reactions are derived from naturally occurring amino acids (Figure 11). For example, Soai and colleagues studied S-(+)-DPMPM 74, which is derived from L-proline.30 With yields of 60–91% for the aldol products, the ligand 74 induced enantiomeric excess from 56% to 76% in the asymmetric Reformatsky reaction between tert-butyl bromoacetate and various aldehydes. In other studies, increased ee's were observed through use of an aminoalcohol 75 by Braun and coworkers. The researchers obtained optimal results with a yield of 61% and an ee of 84% from the asymmetric Reformatsky reaction between methyl bromodifluoroacetate and benzaldehyde.31a With the same ligand 75, Andrés and colleagues were able to access an ee of 83% with ethyl bromoacetate and 2-naphthaldehyde.31b Fujiwara and colleagues were able to obtain an ee of 90% through the use of a fluorinated ligand 76 with ethyl iodoacetate.31c Use of the iodo-ester allowed the researchers to perform the reaction at the low temperature of 30 °C, which helped to enhance the stereoinduction. The aldol product in this case was derived from benzaldehyde.

Other amino alcohols that have been used as chiral ligands, are cinchonidine 79 and an (+)-ephedrine-derivative 77 (Figure 11). A study by Andrés and colleagues employed the ephedrine-derivative 77.32 Optimal results of 78% ee with a yield of 56% were accessed with benzaldehyde and tert-butyl bromoacetate as the substrates. Cinchonidine 79 was employed in a Reformatsky reaction between tert-butyl bromoacetate and various heterocyclic aromatic ketones (Scheme 16). This study revealed that the structure of the
acceptor carbonyl as well as the equivalence of the ligand 79 determined the extent to which stereoinduction took place in the reaction. Imidazole or pyridine-based ketones in which the aromatic nitrogen was also ortho to the carbonyl exhibited high ee, 86 % to 97 %. When the heterocyclic nitrogen was further away from the carbonyl or when the ketone had an sp\textsuperscript{3}-hybridized amino group, the enantioselectivity was severely eroded.

Scheme 16: Asymmetric Reformatsky Reaction with Cinchonidine 79

2. Chelating Substrates

The incorporation of chelating heteroatoms in the structures of acceptor carbonyls has been used to introduce asymmetry into Reformatsky reactions. Examples are found in
Reformatsky reactions with chiral amino carbonyls and enantiopure Davis N-Sulfinylimine.

Pedrosa and colleagues obtained moderate diastereoselectivity when enantiomerically pure α-benzylamino aldehydes and α-Boc-amino aldehydes were used as acceptor carbonyls in a Reformatsky reaction with t-butyl bromoacetate (Scheme 17). In the studies with α-dibenzylamino aldehydes, the anti : syn ratio of the aldol product 82a-b ranged between 80 : 20 and 62 : 38. With the α-Boc-amino aldehydes, the anti : syn ratio was eroded to values between 1 : 2 and 1 : 1. The researchers proposed that an erosion in anti-selectivity occurred with the N-Boc substrate because the N-Boc-amino group is less basic than the dibenzylamino group.

\[
\begin{align*}
1. \text{BrZnCH}_2\text{CO}_2\text{tBu} & \\
2. \text{NH}_4\text{Cl/ H}_2\text{O} & \\
\text{R=CHO} & \xrightarrow{} \text{R=CO}_2\text{tBu} \\
\text{NR}^1\text{R}^2 & \text{OH} \\
\text{81} & \text{82a} & \text{82b} \\
\text{anti} & \text{anti} & \text{syn}
\end{align*}
\]

\[R^1 = R^2 = \text{Bn}; \text{anti : syn 1.6 : 1 to 4 : 1}\]
\[R^1 = \text{H}, R^2 = \text{Boc}; \text{anti : syn 1 : 2 to 1 : 1}\]

Scheme 17: Reformatsky Reaction with Chiral N-Substituted α-Amino Aldehydes

Lucas and colleagues investigated β and α-amino ketones in the Reformatsky reaction with various methyl α-bromo esters (Scheme 18; Table 14). The researchers determined that under kinetic control, the Reformatsky reaction between the α-amino
ketones and most of the methyl \( \alpha \)-bromo esters was \textit{anti}-selective. They also determined that the \textit{anti}-sense of the reaction was affected by the size of the R-group in the ester 83 and the nucleophilicity of the amino group in the ketone. In general, increased nucleophilicity of the amino group resulted in increased \textit{anti}-selectivity. The only exception to this rule occurred when the R-group was a \( t \)-butyl group. With \( R = tBu \), the \textit{anti}-sense of the reaction was significantly eroded with the \( \alpha \)-dimethylamino and \( \alpha \)-morpholine ketones and moreover, reversed with the \( \alpha \)-piperidino ketone.

A bicyclic transition state model was proposed to rationalize the results of Lucas' study (Scheme 18). It was proposed that the reaction was biased toward the formation of the \textit{anti}-isomer because, of the two possible transition states involving N-Zn complexation, 84b was the favored transition state.

When Lucas employed \( \beta \)-amino ketones, instead of \( \alpha \)-amino ketones, the general bias of the reaction was also toward the \textit{anti}-aldol product.\textsuperscript{34d} The selectivity of the \( \beta \)-amino studies was also rationalized with a bicyclic transition state model similar to 84a/b.
Scheme 18: The Bicyclic Transition State Model for the Reformatsky Reaction with α-Amino Ketones

Table 4: The Reformatsky Reaction with α-Amino Ketones

<table>
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<th>R</th>
<th>R¹ (% anti-isomer)</th>
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<tr>
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<tr>
<td>Me</td>
<td>75</td>
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</tr>
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<td>iPr</td>
<td>83</td>
</tr>
<tr>
<td>tBu</td>
<td>55</td>
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In an attempt to synthesize β-substituted α,α-difluoro-β-amino acids, a Reformatsky reaction was performed with Davis N-sulfinylimines 86 and ethyl bromodifluoroacetate (Scheme 19).³⁵ The researchers observed diastereomeric ratios that varied from 7 : 1 to
approximately 9 : 1. In order to explain the stereoselective bias of the reaction, a transition state model 87 was proposed. In this model, chelation of sulfinylimine-oxygen to the Zn (II) of the Reformatsky reagent directed the stereoselectivity of the reaction.

\[
\begin{align*}
\text{Scheme 19: Reformatsky Reaction between Davis N-Sulfinylimines and Ethyl Bromodifluoroacetate}
\end{align*}
\]

3. Anti-Selective Indium-Mediated Reformatsky-Type Reaction

Asymmetry has also been achieved in an untraditional Reformatsky reaction in which Babu and colleagues generated an indium enolate from the insertion of indium into the carbon-halogen bond of an ethyl α-alkyl-α-bromoacetate (Scheme 20). The results of this study were noteworthy because a significant degree of selectivity was obtained from
a reaction in which the conditions and the reagents in the reaction were completely achiral, akin to the TCEA reaction. The β-hydroxy-products, obtained in moderate to good yields of 60% to 99%, exhibited anti : syn ratios between 69 : 31 and 93 : 7. The researchers proposed that the reaction was occurring via a closed transition state in which the E-enolate of the ester was favored.

![Reaction Scheme](image)

**Scheme 20**: Indium-Mediated Diastereoselective Reformatsky-type Reaction

In conclusion, Reformatsky reactions are moderately diastereoselective.\(^{20,21,26}\) However, researchers have been able to increase the stereoselectivity of the reaction by taking advantage of the affinity that heteroatoms, such as O and N, possess for complexing to zinc. Chiral ligands and/or chelating substrates have been used to direct the diastereoselective bias of the Reformatsky reaction, as well as, in some instances, the
reaction's enantioselectivity. Stereoinduction has also been enhanced with the use of indium instead of zinc in a modified Reformatsky reaction.

B. Results

1. The TCEA reaction between t-butyldimethylsilyloxyacetaldehyde 93 and ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96

Lai performed a study in which t-butyldimethylsilyloxyacetaldehyde 93 was used as the electrophile in a TCEA reaction with ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96 (Scheme 21). Surprisingly, the aldol product from this reaction had a syn:anti ratio of 1:1, uncharacteristic of the average 10:1 ratio that had been obtained from the original TCEA study with aromatic and aliphatic aldehydes (Table 1). The stereochemistry of the aldol products, 95a and 95b, was determined by X-ray crystallography of their lactone-derivatives generated by treatment of the aldol product with fluoride. The TCEA reaction with 93 and 96 was repeated at a lower temperature of -78 °C. Treatment of the resulting crude product with fluoride generated only the anti-derived lactone, which indicated that the syn-TCEA product was never formed. Since the relative abundance of the anti-isomer generated in the TCEA reaction with t-butyldimethylsilyloxyacetaldehyde 93 increased when the temperature was lowered to -78 °C, the anti-isomer appears to be the kinetically favored product.

Assuming that the TCEA reaction was proceeding through a closed transition state with the Z-enolate of the ester, the reduced syn-selectivity of the reaction with 93 suggested a change in the facial selectivity of the aldehyde (Scheme 21). It was proposed that this change in facial selectivity was the result of silyloxy-group complexation to Zn.
(II) in the transition state. Therefore, if this model were correct, a protecting group that prevented the α-hydroxy-group of the acetaldehyde from complexing to zinc in the TCEA reaction would result in a syn-isomer being the major diastereomer in the TCEA product. Conversely, a protecting group that allowed complexation of the α-hydroxy-group of the acetaldehyde to zinc, would facilitate formation of the anti-isomer. The stereoinductive-effect of α-hydroxyacetaldehydes with protecting groups of varying steric bulk was probed using benzyloxyacetaldehyde, triiso-propylsilyloxyacetaldehyde and t-butyldiphenylsilyloxyacetaldehyde in the TCEA reaction.

Scheme 21: The Proposed Transition State for the TCEA Reaction with t-Butyldimethylsilyloxyacetaldehyde 93
2. Synthesis of Protected α-Hydroxyacetaldehydes

The protected α-hydroxyacetaldehydes were synthesized in two separate multistep procedures (Scheme 22). Each procedure began with the diprotection of 1,4-butenediol by treatment with sodium hydride and a halide of the protecting group. In the first procedure, the diprotected diol was epoxidized with *meta*-chloroperoxybenzoic acid (MCPBA). The epoxide was then cleaved with periodic acid to give the protected α-hydroxyacetaldehyde in fair to good yields. In the second procedure, the diprotected 1,4-butenediol was subjected to ozonolysis to provide the protected α-hydroxyacetaldehyde also in fair to good yields.

Scheme 22: Synthesis of the Protected α-Hydroxyacetaldehydes

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3. The TCEA Reaction with Protected α-Hydroxyacetaldehydes

With each of the synthesized aldehydes, tandem chain extension-aldol (TCEA) reactions were performed with two β-keto esters, methyl pivaloylacetate and ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96 (Table 5). The conditions of the original TCEA study were applied in this study with one exception--some of the reactions were performed at room temperature. The chain extension intermediate of each substrate was generated by treatment of the β-keto ester with four equivalents of carbenoid at 0 °C or at room temperature. The intermediate was subsequently reacted with one and a half equivalents of the protected α-hydroxyacetaldehyde. The integral ratios from the 1H-NMR spectra of the crude mixture of the TCEA products were used to determine the diastereomeric ratio.

With ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96, the diastereomers of the TCEA products of the α-silyloxyacetaldehydes were separated and then each converted to their respective lactones by treatment with fluoride (Scheme 23). The stereochemistry of each of the resulting lactones was determined by comparing NMR-spectra from this study to the fully characterized spectra of the lactone-isomers that were generated in Lai’s study. Once, the stereochemistry of the lactone-isomers was confirmed, this information was used to determine the stereochemistry of the respective TCEA products from which the lactones were derived. Finally, the syn : anti ratio of the TCEA reaction was determined from integral ratios in the 1H-NMR-spectra of the crude TCEA product mixture.
The diastereoselectivity of the TCEA reaction between BnO-acetaldehyde 99a and ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96 could not be determined because attempts to remove the Bn-protecting group were unsuccessful.

The stereochemistry of the TCEA products from methyl pivaloylacacetate 52a and the protected α-hydroxyacetaldehydes were identified by determining whether or not the isomer also existed as a hemiacetal. In the original TCEA studies (Table 1), it was noted that the syn-isomers of the products tend to exist as both the hemiacetal and 4-keto ester species while the anti-isomers tend to exist only as the 4-keto ester. Therefore, in this study with the α-hydroxyacetaldehydes 99a-c and methyl pivaloylacacetate 52a, isomers which existed as the hemiacetal 102a'-c' as well as the 4-keto ester 102a-c were assigned the syn-stereochemistry while isomers which only existed as the 4-keto ester 101a-c were assigned the anti-stereochemistry. Once the isomers were isolated and identified, the syn : anti ratio was determined using the integral ratios in the 1H-NMR spectra of the crude TCEA product mixtures.

The 1H-NMR spectra of the TCEA product generated with TIPSO-acetadehyde 99c and methyl pivaloylacacetate 52a was difficult to interpret. As a result, the syn : anti ratio of this product could not be determined.

In general the yields for the TCEA reactions in this study were low. Most of the material from these reactions was recovered as chain extended product of the respective β-keto ester due to the hygroscopic properties of the aldehydes. Residual water quenched the zinc-intermediate and provided the corresponding γ-keto ester.
Table 5: The TCEA Reaction with Protected α-Hydroxyacetalddehyde

\[
\begin{align*}
\text{a) } & \quad \text{ZnEt}_2/\text{CH}_2\text{I}_2 \\
\text{b) } & \quad \text{O} = \text{OP} \\
\end{align*}
\]

Table 5

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>R'</th>
<th>P</th>
<th>Product 101/102</th>
<th>syn : anti (101 : 102)</th>
<th>Yield % (101+102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52a</td>
<td>t-Bu</td>
<td>Me</td>
<td>Bn a</td>
<td>1 : 1</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDPS b</td>
<td>3 : 1</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIPS c</td>
<td>not determined</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>3,4- (CH\text{3})_2\text{C}_6\text{H}_5</td>
<td>Et</td>
<td>Bn d</td>
<td>not determined</td>
<td>&lt;57</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TBDPS e</td>
<td>1 : 3</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TIPS f</td>
<td>1 : 2</td>
<td>22</td>
<td></td>
</tr>
</tbody>
</table>

![Chemical structures of 102e-f and 101e-f](image)

Scheme 23: Deprotection of 102e-f and 101e-f

TBAF (2.5 eq), P = TIPS 50 % (cis- and trans-lactone)

TBDPS \leq 89 % (cis- and trans-lactone)

![Chemical structures of 103 and 104](image)

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A control study was also performed in order to probe whether the eroded syn-selectivity of the TCEA reaction with the α-hydroxyacetaldehydes was due to the uniqueness of the aldehyde and not due to overlooked differences in the reaction-conditions between the original TCEA study (Table 1) and this investigation. After generation of the chain extension intermediate from methyl pivaloylacetae, the reaction mixture was divided into two portions (Scheme 24). One portion of the intermediate mixture was quenched with benzaldehyde while the other portion was quenched with TBDPSO-acetaldehyde 99b. In the $^1$H-NMR spectra of the crude TCEA product the diastereomers exhibited a syn : anti ratio of 3.5 : 1, 102b : 101b, while only the syn-isomer 58 was observed in $^1$H-NMR spectra of the crude TCEA product of benzaldehyde. Since the same batch of intermediate gave TCEA products from each aldehyde with significant differences in the diastereomeric ratio, the result of the control study supported the hypothesis that the erosion in the syn-selectivity of the reaction with protected α-hydroxyacetaldehyde was due to the presence of the protected hydroxy-species in the aldehyde.
Scheme 24: The Control TCEA Reaction with Benzaldehyde and TBDPSO-acetaldehyde 99b

With the TIPS, Bn, TBDMS and TBDPS-protected α-hydroxyaldehydes, low syn : anti ratios were achieved in the TCEA investigation with methyl pivaloylacetae # # and ethyl 3-(3,4-dimethoxy-phenyl)-3-oxo-propanoate 96. This result suggests that the protected alcohols significantly affect the facial selectivity of the aldehyde. While the variation in stereoselectivity observed when using different protecting groups were not dramatic, the more sterically accessible oxygens did favor more anti product than the
more sterically encumbered oxygens (Table 5). This result is consistent with the theory that internal complexation of the oxygen with zinc directs the facial selectivity of the aldehyde and hence the stereoselectivity of the reaction. The role of the oxygen-zinc complexation in this study appears to be similar to the role of the nitrogen-zinc complexation in Lucas' study (Scheme 18), which demonstrated that an α-Lewis basic functionality in an acceptor carbonyl can direct the stereoselectivity of a traditional Reformatsky reaction.

An alternative explanation for the erosion in syn-selectivity with the α-hydroxyacetaldehyde could be found in two of the NMR-investigations of the zinc organometallic intermediate (Chapter 1). In these NMR studies, the treatment of the organometallic intermediate with DME or THF, followed by a quench with benzaldehyde, resulted in an aldol-product with eroded syn-selectivity. It was hypothesized that the erosion in stereoselectivity occurred because the ethereal solvents were affecting complexation of the intermediate’s keto-group to zinc (II) and therefore reducing the bias for Z-enolate formation in the transition state.

In the studies with the protected α-hydroxyacetaldehydes, the facial selectivity of the aldehyde may indeed have changed because of complexation between the zinc (II) and the silyloxy or benzyloxy group. In addition, however, this silyloxy or benzyloxy complexation with zinc (II) may have also disrupted the interaction between zinc and the intermediate’s keto-group. As a result, the bias toward Z-enolate-formation in the transition state would be weakened. It is, therefore, possible that in the TCEA reaction with the protected α-hydroxyacetaldehyde, none of the four possible transition state structures 105a-d is strongly favored (Scheme 25). Hence, the diastereoselectivity of the
TCEA reaction with the protected α-hydroxyacetaldehyde resembles that of a typical unselective Reformatsky reaction.

Scheme 25: The Four Transition State Structures for the TCEA Reaction
CHAPTER III

APPROACHES TOWARD THE SYNTHESIS OF CJ-12,954

A. Introduction

1. Basic Ring-Systems of Spiroketal

Most spiroketals can be classified as one of three basic ring systems: A, B and C (Figure 12). The A-ring system 106 is a 1,7-dioxaspiro[5.5]undecane. The B-ring system 107 is a 1,6-dioxaspiro[4.5]decane and the C-ring system is a 1,6-dioxaspiro[4.4]nonane 108. Examples of these ring systems can be found as core units in a number of natural products.

![Figure 12: The A, B and C Ring Systems of Spiroketals](image)

Spiroketal-based insect pheromones are amongst the simplest examples of spiroketals. These insect pheromones exhibit structural diversity with the incorporation of a simple alkyl chain α to either one or both of the oxygens. Chalcogran, for example, 2-ethyl-1,6-dioxaspiro[4.4]nonane, has one ethyl substituent. It has been isolated as 1 : 1 mixture of
diastereomers from a beetle, *Pityogenes chalcographus* (L.), a pest of the Norway spruce.\(^{39}\)

A common approach to spiroketals involves the use of dihydroxy keto synthons which are typically subjected to acidic conditions to facilitate dehydration and closure.\(^{38}\) With the TCEA reaction, the initial methodology study revealed that aldol products, mainly the *syn*-isomers, tend to exist as the hemiacetal as well as the opened-chain species.\(^{11}\) It therefore seems likely that the TCEA reaction of a hydroxy β-keto ester 109 to form a dihydroxy γ-keto synthon 110/111 can be applied to the synthesis of a spiroketal compound 112 - 113 (Scheme 26).

\[ 	ext{TCEA Reaction} \]

**Scheme 26:** Proposed Application of the TCEA reaction in the Synthesis of Spiroketals

2. Phthalide Extracts of the Basidiomycete *Phanerochaete velutina*

CJ-12,954 114a and six other phthalide compounds 114b - g were extracted from the basidiomycete *Phanerochaete velutina* (Figure 13).\(^{40}\) All of the compounds were shown
to have activity against *Helicobacter pylori*, the bacteria implicated in stomach ulcer formation. CJ-12,954 114a and CJ-13,014 114b, the only extracts with spiroketal moieties, were equivalent in activity against the bacteria and were determined to be the most potent of the seven compounds investigated.

![Chemical structures](image)

**Figure 13:** Structures of Phthalides 114a - g Extracted from *Phanerochaete Velutina*

Current treatment of ulcers employs one or a combination of the following:40
i) one or two broad-spectrum antibiotics in conjunction with a proton-pump inhibitor

ii) a bismuth salt.

However, relapse is common amongst ulcer sufferers and bismuth salts can be toxic. In addition, treatment over long periods typically results in drug resistance. A solution to combat the limitations in the current methods of treatment would be to develop an antibiotic that specifically targets *Helicobacter pylori*. As a result, the extracts from *Phanerochaete velutina* are potential leads for the development of drugs to treat ulcers.

At this time, of the seven phthalide-extracts, only the total synthesis of CJ-13,015 has been reported. Argade and Mondal synthesized CJ-13,015 in a multistep procedure that commenced with a Wittig reaction between 5-methylfurfural and (8-hydroxyoctyl)triphenylphosphonium bromide (Scheme 27). After hydrogenation, conversion of an alcohol to a bromide and an Sn2 reaction with lithiated 3,5-dimethoxyphthalide, the diketone functionality was released through acid hydrolysis. The researchers accomplished the total synthesis of (+)-CJ-13,015 in six steps with an overall yield of 65%.
Scheme 27: The Total Synthesis of CJ-13,015 114e

B. Results

We proposed that CJ-12,954 114a could be accessed using the TCEA reaction as the key step in the synthesis of the spiroketal unit. However, 2-methyl-1,6-dioxaspiro[4.4]nonane 118, a simpler synthetic target with a similar spiroketal-ring system, was first pursued in order to test the scope of the TCEA reaction and to develop reaction conditions that were most suitable for spiroketal synthesis. This spiroketal 118 is an analogue of the aggregation pheromone, Chalcogran, for the bark beetle.\textsuperscript{42} Retrosynthetic analysis, indicated that 118 could be accessed from the aldol product of the TCEA reaction between formaldehyde and 6-hydroxy-3-oxo-heptanoic acid methyl ester 120a/b (Scheme 28).
1. TCEA Reaction with 6-Hydroxy \( \beta \)-Keto Esters

The substrate \( 120a/b \) was obtained from the treatment of the dianion of methyl acetoacetate 46 with propylene oxide (Scheme 29). This hydroxy \( \beta \)-keto ester \( 120a/b \), if allowed to stand at room temperature, would undergo elimination to form (5-methyl-dihydro-furan-2-ylidene)-acetic acid methyl ester \( 123 \). Some of the target \( 120a/b \) would also undergo elimination during purification of the substrate with flash column chromatography using silica gel.

Compound \( 120a/b \), with its unprotected hydroxy group, was an unusual substrate for TCEA reaction because it had the free hydroxy-group. It seemed possible that the TCEA reaction conditions would be incompatible with the acidic proton and/or the hydroxyl functionality. Therefore, \( 120a/b \) was first probed to determine if it could efficiently chain extend with zinc-carbenoid. Treatment of \( 120a/b \) with carbenoid probably results in deprotonation of the hydroxyl as well as the methylene unit (Scheme 29). With a reaction time of three hours, treatment of \( 120a/b \) with four equivalents of zinc-carbenoid provided the chain extended product \( 124 \) in a yield of 50%. When seven equivalents of carbenoid were used, an increased yield of 60% was obtained and the reaction time was shortened to 1.5 hours. Since the hydroxy \( \beta \)-keto ester \( 120a/b \) could be chain extended in
moderate yields, it seemed possible that this compound would successfully undergo the TCEA reaction.

\[
\begin{align*}
a) \text{NaH (1.1 eq), } 0{^\circ}\text{C} \\
b) \text{nBuLi (1.1 eq), } -61{^\circ}\text{C} \\
c) \text{ } (2.0 \text{ eq})
\end{align*}
\]

\[
\begin{align*}
\text{46} & \rightarrow \text{38\%} \\
& \overset{-61{^\circ}\text{C to rt, 18 hr}}{\rightarrow} \text{120a} \rightarrow \text{120b}
\end{align*}
\]

\[
\begin{align*}
a) \text{Et}_2\text{Zn/CH}_2\text{I}_2 (X \text{ eq), t} \\
b) \text{NH}_4\text{Cl (aq)}
\end{align*}
\]

\[
\begin{align*}
X = 4, 50\%, t = 3\text{h} \\
7, 60\%, t = 1.5\text{h}
\end{align*}
\]

\[
\begin{align*}
\text{121} & \rightarrow \text{122} \\
& \rightarrow \text{123}
\end{align*}
\]

\[
\begin{align*}
\text{124}
\end{align*}
\]

**Scheme 29:** The Synthesis and Carbenoid-Mediated Chain Extension of 6-Hydroxy-3-Oxo-Heptanoic Acid Methyl Ester 120a/b

Investigations of the TCEA reaction with 120a/b was performed with three electrophiles, benzaldehyde, acetone and paraformaldehyde. Previous work by Lai\textsuperscript{11} and Hanson\textsuperscript{9} had demonstrated the utility of benzaldehyde and acetone in the TCEA reaction with unsubstituted \(\beta\)-keto esters. In the reaction between 120a/b and benzaldehyde, many fractions from the crude product were isolated by column chromatography. Fractions tentatively identified as the aldol product with traces of O-methylated products
accounted for 27% of the expected yield of the TCEA reaction. However, most of the material recovered from the TCEA reaction with benzaldehyde was a complicated mixture of products which were difficult to characterize.

Scheme 30: The TCEA Reaction of 120a/b with Benzaldehyde

In the TCEA reaction with 120a/b and acetone, the best results were obtained with ten equivalents of carbenoid instead of the typical four equivalents (Scheme 31). In addition to the spiroketal product 128, this reaction also produced chain extended product 124 and a spirolactone 127. It was impossible decipher between the structures of the spiroketal-derivative 128 and the hemiacetal(s) 126a - c of TCEA product with only the NMR spectra. Instead, in conjunction with the NMR spectra, the spiroketal's structure was determined by its IR spectrum which exhibited the absence of an OH-stretch that would occur with the hemiacetal 126 a - c. The structure of the spirolactone 127, was determined from its NMR spectra which exhibited a resonance at ~176 ppm for the carbonyl of the ester and the results of a reaction in which, upon treatment with concentrated aqueous hydrochloric acid in methanol, the spirolactone 127 was converted to the spiroketal 128.
The TCEA reaction between 120a/b and formaldehyde was attempted with both the gas and solid polymeric form of the electrophile. The reaction with paraformaldehyde provided the product in yields below 15% and a host of other compounds with structures that could not be identified. The reaction with the formaldehyde-gas yielded crude material which was refluxed with p-Toluenesulfonic acid in benzene in a Dean-Stark trap.
to effect spiroketal formation (Scheme 32). Purification of the crude product from the latter reaction gave the spiroketal product 129 in a yield of 28%. The rest of the material consisted of products from the TCEA reaction which were difficult to characterize. As an explanation for the low yields of reaction with formaldehyde, it was proposed that the unprotected hydroxy-group of 120a/b was participating in side-reactions that were responsible for the formation of a significant amount of the byproducts.

Scheme 32: The TCEA Reaction with 120a/b and Formaldehyde

The hydroxy-group of the 120a/b was protected with a TBDMS-group (Scheme 33) and the resulting compound 130 was treated with five equivalents of carbenoid to determine how efficiently the substrate chain extended under the carbenoid-mediated conditions. The chain extended product 131 was obtained in a crude yield of 96% without the need for further purification. Having confirmed that the hydroxyl-protected substrate participated in the chain extension reaction in excellent yields with the carbenoid, 130 was subjected to the TCEA reaction with paraformaldehyde which provided the TCEA product 132 in a yield of 85%. The compound 132 was treated with
TBAF in an effort to generate the diol required for formation of the spiroketal. However, this deprotection reaction produced the spirolactone 133.

Scheme 33: The TCEA Reaction with 130 and Paraformaldehyde

In order to suppress formation of the spirolactone 130 during removal of the TBDMS group, the methyl ester of the TCEA substrate was changed to a 6-buty l ester. 6-Butyl 6-
(tert-butyl-dimethyl-silyloxy)-3-oxo-heptanoate 135a was synthesized from tert-butyl acetoacetate in two steps following the same procedure used to synthesize 130 (Scheme 34). Chain extension of 135a provided the product in good yield and the TCEA reaction of 135a with paraformaldehyde provided the aldol product 137a in a yield of 66%. An attempt to convert the ester of 137a to the carboxylic acid by treatment with monohydrated p-TsOH in benzene resulted in formation of a mixture of compounds lacking the tert-Bu-group and/or the TBDMS group.

\[
\text{Scheme 34: The Chain Extension and TCEA Reactions of } 135a - b \text{ with Paraformaldehyde}
\]
In an effort to use a protecting group that was more resistant to cleavage under acidic conditions, \(\tau\)-butyldiphenylsilyl (TBDPS), instead of TBDMS, was used to protect the hydroxy-group (Scheme 34). Exposure of this new compound 135b to the carbenoid-mediated chain extension reaction conditions produced the desired \(\gamma\)-keto ester in an unoptimized yield of 53\%. The TCEA reaction with 135b and paraformaldehyde produced the aldol product 137b in a yield of 91\%.

2. Barton Decarboxylation

Decarboxylation was first attempted with diprotected material 138 because the diprotected substrate and its decarboxylated product 140 were relatively easy to isolate and characterize by NMR-spectroscopy (Scheme 35). Protection of the TCEA product was accomplished through the treatment of 137b with TBDPS-Cl and imidazole in DMF. The resulting diprotected compound 138 was refluxed with \(p\)-TsOH in benzene to yield 41\% of the desired acid 139, in addition to other compounds in which the TBPDS-group was lost.

Decarboxylation was achieved with a Barton procedure in which the acid 139 was treated with DCC and N-hydroxythiopyridinone to produce the N-oxy ester. The crude N-oxy ester was dissolved in THF and illuminated with a 150 W bulb in the presence of \(\text{Bu}_3\text{SnH}\) to yield the decarboxylated target 140 in a yield of 25\% over two steps.
Scheme 35: The Synthesis and Decarboxylation of the Diprotected TCEA Product 138


Having found a suitable substrate for the TCEA reaction and conditions for decarboxylation, the synthesis of 2-methyl-1,6-dioxaspiro[4.4]nonane 118 was pursued. A one-pot deprotection of both the TBDPS-group and the t-Bu-group of the TCEA product was attempted by stirring the substrate with Trifluoroacetic acid (TFA) in
methylene chloride. This reaction, however, produced a mixture of the spiroketal target and the spirolactone 133. Therefore, the removal of the TBDPS-group and the removal of the t-Bu ester was then performed in two steps. The TCEA product was first stirred with TBAF and the resulting crude mixture was treated with TFA. The Barton decarboxylation reaction with tributyltin hydride provided crude reaction material, for which observation by NMR spectroscopy and TLC analysis suggested that the target 118 had formed. However, pure 118 was never obtained because it could not be separated clearly from excess Bu$_3$SnH by column chromatography.

The chiral TBDPS-protected hydroxy keto ester was employed in a second attempt to synthesize 2-methyl-1,6-dioxaspiro[4.4]nonane 144 (Scheme 36). In this attempt, the hydrogen-radical source in the decarboxylation reaction was changed from Bu$_3$SnH to thiomercaptan. With this modification, the target 144 was successfully isolated from the crude reaction mixture in a yield of 42% over two steps. Some of the material from this reaction was also recovered as the carboxylic acid 143 which accounted for 26% of the substrate.

The successful synthesis of 2-methyl-1,6-dioxaspiro[4.4]nonane 144 with the TCEA reaction proved that this method was applicable to the synthesis of spiroketal units. This study also revealed that the TBDPS-protecting group on the hydroxy-substrate was the most suitable protecting group for the conversions that followed the TCEA reaction. Suitable reagents and conditions for the decarboxylation reaction were also identified.
Scheme 36: The TCEA-Synthesis of 2-Methyl-1,6-Dioxaspiro[4.4]Nonane 144

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4. Approaches toward the Synthesis of CJ-12,954 114a

i. First Synthetic Plan

Two approaches to CJ-12,954 were pursued. The first approach proposed that a phthalide unit 145 and a spiroketal unit 146 could be coupled together in a palladium-mediated reaction (Scheme 37). In addition, it was proposed that each of the units could be synthesized with tandem chain extension-zinc enolate reactions. The phthalide unit could be made from a Diels-Alder reaction between a 2,4-dimethoxy furan 148 and an α,β-unsaturated γ-keto ester 147 which was accessible from the tandem chain extension-oxidation-elimination reaction. The spiroketal 146 could be provided by a TCEA reaction between TMS-propynal 151 and 150.

Scheme 37: The Retrosynthetic Plan for the Synthesis of CJ-12,954 114a
The synthesis of 155 commenced with 152 and was accomplished in five steps. The TCEA product 153 of 152 and TMS-propynal 151 was deprotected with TBAF followed by treatment of the resulting product with TFA to form the carboxylic acid 154 (Scheme 38). The carboxylic acid was decarboxylated with the Barton procedure and purification of the crude reaction mixture provided a diastereomeric mixture of the volatile spiroketal 155 with TBDPSOH as a contaminant in an unoptimized yield of \( \leq 21 \% \).

The \( \alpha,\beta \)-unsaturated \( \gamma \)-keto ester 158 was synthesized in three steps. The procedure commenced with an \( \text{S}_2\) reaction between the dianion of methyl acetoacetate 46 and 3-bromopropyne to provide 3-oxo-hept-6-ynoic acid methyl ester 156 in 59 \% yield.

Scheme 38: The TCEA Synthesis of 155
Simple chain extension of 156 provided the chain extended product in quantitative yields without the need for further purification after the compound was isolated from the reaction mixture. The tandem chain extension-oxidation-elimination reaction of 156 did not proceed as smoothly, α,β-unsaturated product 158 was obtained in an unoptimized yield of 18%.

Scheme 39: The Synthesis and Tandem Chain Extension-Oxidation-Elimination Reaction of 158

An attempt was made to synthesize the 2,4-dimethoxyfuran 148 in two steps from tetronic acid 159 (Scheme 40). The tetronic acid 159 was first treated with methanol containing a catalytic amount of acetyl chloride to give the methyl tetronate 160 in an optimized yield of 54%. Many attempts were made to accomplish further substitution of
the methyl tetronate 160. However, these attempts were unsuccessful and so a new synthetic plan for CJ-12,954 114a was proposed.

\[
\text{Scheme 40: Attempted Synthesis of the 2,3-Dimethoxyfuran 148}
\]

**ii. Second Synthetic Plan**

The second retrosynthetic plan proposed that a key synthon for CJ-12,954 114a could be assembled in a TCEA reaction between a phthalide aldehyde 162 and a TBDPS-protected hydroxy β-keto ester 150 (Scheme 41). The resulting TCEA product 161 could be then be converted to CJ-12,954 114a via a TBDPS-deprotection, an ester hydrolysis and a decarboxylation reaction.

\[
\text{Scheme 41: The Second Retrosynthetic Plan for CJ-12,954 114a}
\]
The initial attempt to make the phthalide unit 162 followed a procedure by Clarke and colleagues in which they reported the regioselective carboxylation of 3,5-dimethoxybenzyl alcohol to form 3,5-dimethoxyphthalide in a 50 %-yield (Scheme 42).\(^4\) For this study, a simple model 167 with a secondary alcohol was first pursued (Scheme 43). The synthesis of 167 was attempted with a tandem alkylation-carboxylation of benzaldehyde 165. However, only the regioisomer 166 of the target 167 was obtained.

Scheme 42: Clarke's Synthesis of 3,5-Dimethoxyphthalide 164\(^4\)

\[
\text{a) nBuLi, THF} \\
\text{b) CO}_2 \\
\text{c) H}^+ \\
50\% \\
163 \rightarrow 164
\]

Scheme 43: Tandem Alkylation-Carboxylation of 3,5-Dimethoxybenzaldehyde
Another attempt to synthesize the phthalide unit was adapted from a procedure by Paradkar and colleagues. In Paradkar’s procedure, 3,5-dimethoxybenzyl acetate was regioselectively formylated in a Vilsmeier-Haack reaction to provide an aldehyde which was oxidized, deacetylated and cyclized to form 3,5-dimethoxyphtalide. We first studied Paradkar’s method with a model system involving a secondary acetate. With benzaldehyde as the starting material, 1-(3,5-dimethoxy-phenyl)-pentyl acetate was synthesized in a tandem alkylation-acetylation reaction (Scheme 44). The acetate was formylated and oxidized to the phthalide, 3-butyl-5,7-dimethoxy-3H-isobenzofuran-1-one, in two steps. The yields of these two steps were unoptimized and extremely low, but these yields were subsequently improved in the synthesis of the phthalide unit.

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Scheme 44: Synthesis of 3-Butyl-5,7-Dimethoxy-3H-Isobenzofuran-1-One 167
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The synthon 173 for the phthalide unit 162 was first synthesized with a Grignard reaction between 3,5-dimethoxybenzaldehyde and (7-bromo-heptyloxy)- tert-butyl-dimethyl-silane 172. The starting material 172 was synthesized in two steps from heptane-1,7-diol 170 (Scheme 45). The diol was refluxed with 48 % HBr (aq) in toluene to give the bromoalcohol 171 which was silated with TBDMS-chloride. The Grignard reaction between 171 and 165 was attempted in two solvents, THF and ether. Attempts to carry out the reaction in ether, both at room temperature and under reflux, resulted in recovery of the starting material. In THF, the reaction did not proceed at room temperature, however under reflux, the target 173 in addition to three byproducts 174 - 176 were produced. The byproducts were formed from reactions in which the aliphatic Grignard reagent was acting as a reducing reagent.
In order to avoid loss of material to the reduction reactions with the aliphatic Grignard, the starting materials were changed to 3,5-dimethoxybromobenzene 179 and 8-(tert-butyl-dimethyl-silyloxy)-octanal 178. The aldehyde 178 was synthesized in two steps from 1,8-octanediol 177 (Scheme 46). The diol was monoprotected with t-butyldimethylsilyl chloride and the resulting product was oxidized to the aldehyde 178 with pyridinium chlorochromate. The addition of the aldehyde 178 to a refluxing THF-suspension of 3,5-dimethoxyphenyl magnesium bromide provided the monoprotected alcohol 173 in a yield of 88 % (Scheme 47). This Grignard-procedure was used to
synthesize a number of other phthalide synthons 180 - 182 which were used at various points in this study.

Scheme 46: The Synthesis of 8-(tert-Butyl-Dimethyl-Silyloxy)-Octanal 178
Scheme 47: Syntheses of Phthalide Synthons
The first attempt to formylate the phenyl ring by application of a Vilsmeier-Haack formylation resulted in a mixture of products with and without the TBDMS-group. Since the TBDMS-group was not stable to the reaction conditions, the substrate was changed to the diacetylated diol 181 (Scheme 48). Though the target 183 was obtained with the diacetate 181, a significant amount of material was lost to the formation of byproducts 184 - 186. In order to avoid the elimination of the secondary acetate, the formylation was carried out at a lower temperature by refluxing the reaction mixture in methylene chloride (Scheme 48). The selectivity of the reaction toward formation of 183, as opposed to its regioisomer 184, was optimized by refluxing the reaction mixture at or below 45 °C—a mixture of the target 183 and the regioisomers 184 were isolated in a yield of 74 % with a ratio of 5 : 1 for 183 : 184 (regioisomers).

Once the conditions of the formylation reaction were established, oxidation to the phthalide was attempted with potassium permanganate in a solvent mixture of water and dioxane. Partial solubility of the substrate 181 in the dioxane/water mixture lead to extremely low yields. When the solvent was changed to a mixture of water and acetone, the oxidation proceeded in fair yields to provide the phthalide alcohol 187 (Scheme 48).
Scheme 48: Formylation of the Diacetate 181
iii. Synthesis of an Analogue of CJ-12,954 114a

While the conditions for the synthesis of the intact phthalide unit were being established, the TCEA reaction was carried out with the aldehyde-derivative 188 of 182. Treatment of the alcohol 182 with pyridinium chlorochromate provided the aldehyde 188 in a yield of 68% (Scheme 49).

\[
\text{PCC (3 eq or 1.5 eq), Celite, CH}_2\text{Cl}_2, \text{rt} \rightarrow \text{68%}
\]

Scheme 49: The Synthesis of 1-(3,5-Dimethoxy-Phenyl)-8-Oxo-Octyl Acetate 188

The TCEA product of the aldehyde 188 and the β-keto ester 152 was obtained in a yield of 82%. The TCEA product 189 was treated with TBAF and the resulting crude reaction mixture was stirred with anhydrous pTsOH to effect spiroketalization. The carboxylic acid 190 was provided by treatment of the t-butyl ester 189 with TFA. Notably, treatment of 189 with TFA resulted in the conversion of the acetoxy-group to a trifluoroacetoxy-group. The compound 190 was decarboxylated to provide an analogue 191 of CJ-12,954 in a yield of 32%. Attempts to formylate the spiroketal 191 with the Vilsmeier salt were unsuccessful.

iv. Synthesis of a Chiral Analogue of CJ-12,954

The absolute stereochemistry of CJ-12,954 114a is unknown but relative stereochemistry of the stereogenic centers in the spiroketal unit has been determined. In order to establish the stereochemical relationship within the natural product, the source of stereogony at each stereocenter must be chosen appropriately. In the asymmetric...
synthesis of CJ-12,954, the chirality of C-7 in this synthesis will be established with R-propylene oxide. The stereochemistry of C-2 will be established in the TCEA reaction with the use of a β-keto carbonyl-derivative of a chiral auxiliary and the chirality of the phthalide carbon will be controlled with an asymmetric reduction.

The chiral phthalide-aldehyde 196 was synthesized in seven steps beginning with the oxidation of the monoprotected alcohol 193 (Scheme 51). The resulting ketone 192 was asymmetrically reduced in the presence of (S)-(−)-2-Methyl-CBS-oxazaborolidine. After deprotection, the precursor-alcohol 195 was accessed with acetylation, formylation and oxidation reactions, according to procedures previously described in the synthesis of 187. An experiment with Chiral High Pressure Liquid Chromatography (HPLC) determined that the chiral alcohol 185 had an ee of 85%. Oxidation of the alcohol with pyridinium chlorochromate resulted in the chiral aldehyde 196 in a yield of 67%.
Scheme 51: Synthesis of chiral 7-(4,6-Dimethoxy-3-Oxo-1,3-Dihydro-Isobenzofuran-1-yl)-Heptanal 196
The chiral auxiliary chosen to introduce asymmetry into the TCA reaction was a camphorsultam. The ability for this auxiliary to induce asymmetry in the TCEA reaction was probed with β-keto carbonyl 198 of (L)10,2-camphorsultam and benzaldehyde. A total of three equivalents of carbenoid ensured complete conversion of the β-keto carbonyl 198 to the chain extended intermediate (Scheme 52). The intermediate was quenched with benzaldehyde to produce a mixture of TCEA isomers 200a - b with identical coupling constants for the β'-methine. This similarity in coupling constants suggested that the TCEA isomers had the same relative stereochemistry at their β'- and α-carbons. The isomers were produced in a ratio of 8:1, as determined by integration of the 1H-NMR spectrum of the crude reaction mixture. Their syn-stereochemistry was determined by the conversion of the major diastereomer to a known syn-methyl ester 201. If greater than three equivalents of carbenoid were used or if the reaction time after addition of benzaldehyde was extended beyond one minute, the TCEA product 200a - b would undergo O-methylation with excess carbenoid. This TCEA reaction also produced a cyclopropanol 199 of unidentified stereochemistry.
Scheme 52: The Synthesis of 198 and the TCEA with Benzaldehyde

The yield of the TCEA reaction with 198 was reduced due to formation of the cyclopropanol 200. The standard chain extension reaction with the substrate 198 also produced the cyclopropanol 199 in addition to the chain extended product 204 (Scheme 53). It is proposed that the cyclopropanol # arises from the reaction of the chain extended-organometallic intermediate with an extra equivalent of carbenoid. This
additional reaction with the carbenoid is most likely facilitated by chelation of zinc with an oxygen on the camphorsultam.

\[
\begin{align*}
198 & \xrightarrow{\text{a) } \text{Et}_2\text{Zn} / \text{CH}_2\text{I}_2 (3 \text{ eq}), 0^\circ \text{C to rt, 57 min}} 202a \\
203 & \xrightarrow{\text{Et}_2\text{Zn} / \text{CH}_2\text{I}_2} 202b \\
\text{c) conc NH}_4\text{Cl (aq)} & \quad \text{199 (19\%)} + 204 (39\%) \\
\end{align*}
\]

Scheme 53: The Chain Extension of 198

The hydroxy \(\beta\)-keto ester 213 for the asymmetric TCEA reaction was synthesized with the D-camphorsultam 208. A model to predict the stereochemical outcome of the TCEA
reaction with the 6-hydroxy-β-keto carbonyl of the camphorsultam was adapted from a Sn-enolate model developed by Oppolzer and colleagues (Figure 14). The D-camphorsultam was chosen because according to our model the chirality at the carbon of the newly formed C-O bond will result in the same relative stereochemistry at C-7 and C-2 that exists in the natural product 114a, assuming that the R-propylene oxide were used to establish the second stereocenter on the spiroketal.

The substrate 213 was synthesized from the condensation of R-γ-valerolactone 211 with the lithium enolate of the acetylated D-camphorsultam 209 (Schemes 54 & 55). The target 212 of this reaction was, however, acetylated by acyl-sultam 209 in the reaction mixture. Though the substrate 213 was obtained in a low yield, < 22 %, enough material was generated to carry out both a carbenoid-mediated chain extension reaction and the TCEA reaction.

![Figure 14: Model for the TCEA Reaction of 6-Hydroxy β-Keto Carbonyl of D-Camphorsultam 205](image-url)
Scheme 54: Synthesis of the Precursors 209 and 211

Scheme 55: The Synthesis of 213
The chain extension of 213 was performed with 4 equivalents of carbenoid (Scheme 56). The yield for this reaction was 42% of the expected mass for the regular chain extended product. The desired chain extended product 216 was isolated along with another compound. The molecular weight of the second compound, determined by mass spectrometry, was 14 mass units larger than the molecular weight of the chain extended product 216. Based on this MS-result and the NMR spectra of the isolated product mixture, the other compound was tentatively assigned as the 8-acetoxy-5-keto carbonyl 217. Since the chain extension of substrate 198 produced cyclopropanol 199, it is possible that a similar cyclopropanation reaction took place to provide intermediate 215. Fragmentation of 215 could provide access to the unanticipated product 217.
In the TCEA reaction with 213, the procedure had to be modified to avoid loss of material through formation of cyclopropanol or 5-keto carbonyl 217. This was done by carefully controlling the length of time in which the actylated auxiliary was exposed to carbenoid. After five minutes of stirring with the carbenoid, regardless of the presence of unreacted starting material, four equivalents of the aldehyde 196 was added to the reaction mixture. The crude TCEA product was converted to the carboxylic acid in one step by treating the material with lithium hydroxide. The yield for this reaction was 42%.
With the carboxylic acid in hand, a Barton Decarboxylation would be requires to access compound 220. An attempt to perform decarboxylation was unsuccessful. This attempt was however, performed under unoptimized conditions.

The applicability of the TCEA reaction in the synthesis of spiroketal units has been demonstrated with the syntheses of 144, 155 and 191 and their respective carboxylic acids and esters. In the approach toward the synthesis of CJ-12,954 114a, suitable chemistry has been developed for the synthesis of the phthalide unit 196. However, further study is necessary for developing a more efficient procedure to synthesize the chiral 6-hydroxy β-keto carbonyl.
CHAPTER IV

EXPERIMENTAL

A. General Experimental:

Unless noted otherwise, all reactions were run in oven-dried glassware and stirred with Teflon-coated stir-bars. The terms concentrated in vacuo or under reduced pressure refer to the use of a rotary evaporator or vacuum pump.

Solvents

Tetrahydrofuran (THF) was distilled from purple benzophenone ketyl prior to use. Benzene was distilled from calcium hydride prior to use. Methylene chloride (CH$_2$Cl$_2$) was distilled from P$_2$O$_5$ prior to use. Ethyl acetate (EtOAc) was purchased from Pharmco and distilled prior to use. Hexanes were purchased from Pharmco and distilled prior to use, pyridine was distilled from calcium hydride and stored over potassium hydroxide. Triethylamine (Et$_3$N) was stillled from potassium hydroxide.

Anhydrous, deoxygenated solvents were also accessed from a solvent purification system, SPS-400. SPS-400 was distributed by Innovative Technology Inc.. For reactions under anhydrous conditions, the following solvents were obtained from SPS-400: THF, Diethyl Ether, Toluene, Methylene Chloride, DMF, Methanol, Acetonitrile.
Reagents:

Diethylzinc was purchased both as a solution (1.0 M in hexanes) and neat from Aldrich. Methylene iodide (CH$_2$I$_2$) was purchased from Lancaster chemical companies. Non-oxidized copper wire was added as a stabilizer. Iodine was sublimed prior to use.

Chromatography:

Column chromatography was performed with Sorbent Technologies flash silica gel (32-63μm). Mobile phases were also noted.

Thin Layer Column Chromatography (TLC) was performed on EM Science F254 glass plates and visualized by UV and anisaldehyde stain.

Chiral High Performance Liquid Chromatography (HPLC) was performed with a Diacel Chiralpak ® AD-RH reverse phase column.

Spectroscopy:

Nuclear Magnetic Resonance (NMR) Spectroscopy was performed on a Bruker EM-360 operating at 360.130 MHz for $^1$H nuclei and 90.55 MHz for $^{13}$C nuclei, Varian Mercury operating at 399.130 MHz for $^1$H nuclei and 100.55MHz for $^{13}$C nuclei, and Varian Inova operating at 499.766 MHz for $^1$H nuclei and 125.679 MHz for $^{13}$C nuclei. All $^{13}$C and $^1$H-decoupled. Unless otherwise noted, all NMR experiments were carried out in deuterochlorofom (CDCl$_3$) solvent purchased from Cambridge Isotope Laboratory and stored over 4 Å molecular sieves or deutermethylene chloride (CD$_2$Cl$_2$) solvent purchased from Cambridge Isotope Laboratory. All chemical shifts are reported in parts
per million (ppm) and references to the resonance for CDCl₃ (¹H NMR δ 7.26 ppm; ¹³C NMR δ 77.16 (± 0.20) ppm). Unless otherwise noted, DEPT spectra are DEPT-135.

Infrared Spectroscopy was performed on an Avatar 360 FT-IR Thermo Nicolet Spectrometer.

Low Resolution Mass Spectroscopy was performed by
1. The University of New Hampshire Instrumentation Center on a Hewlett-Packard model 5988A GC/MS quadrupolar spectrometer equipped with a 25-meter methyl silicone (OV-I) capillary column
2. Hui Zhou and Weimin Lin on a ThermoFinnigan ion trap instrument fitted with electrospray ionization source (ESI) for MSⁿ analysis. The instrument was care of the Reinhold lab at the University of New Hampshire.

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected.

B. Preparation of Compounds for the Control Reformatsky Reaction

Methyl 2-Iodo-5,5-dimethyl-4-oxo-hexanoate (53)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a N gas-inlet, was charged with methylene chloride (40 mL) and methylene iodide (1.6 mL, 20.0 mmol) and then cooled in an ice-water bath (0 °C). Diethyl zinc (1M) in hexanes (20 mL, 20.0 mmol) was added and the resulting white suspension was stirred for 10 minutes. Methyl pivaloylacetate 52a (0.64 mL, 4.0 mmol) was added via syringe and the reaction was allowed to stir at 0 °C for 30 minutes at which time iodine (6.00 g, 23.7 mmol) was added to the mixture in a single portion. After a pink color developed and persisted for
more than 30 seconds, the mixture was treated with a saturated aqueous solution of sodium thiosulfate (40 mL). After the pink color disappeared, a concentrated aqueous solution of ammonium chloride (40 mL) was added to the stirring suspension. The resulting mixture was extracted twice with diethyl ether (2 x 70 mL). The combined organic layer was dried with sodium sulfate, filtered and concentrated on rotary evaporator. The crude oil was purified by flash column chromatography (10 % ethyl acetate in hexanes) to yield methyl 2-iodo-5,5-dimethyl-4-oxo-hexanoate 53 (1.0283 g, ≤ 86 %) as a yellow oil with traces of chain extended material, methyl 5,5-dimethyl-4-oxo-hexanoate 54, and the α,β-unsaturated ester methyl 5,5-dimethyl-4-oxo-hex-2-enoate 55. 53: 1H NMR (400 MHz, CD2Cl2, referenced to TMS 0.00 ppm) δ 4.57 (dd, 1H, J = 9.9, 5.0 Hz), 3.63 (s, 3H), 3.43 (dd, 1H, J = 18.2, 9.9), 3.07 (dd, 1H, J = 18.2, 5.0), 1.05 (s, 9H); 13C NMR (100 MHz, referenced to CD2Cl2 at 53.61 ppm) δ 213.1, 171.8, 53.0, 44.6, 43.8, 26.2, 12.3.

2-(Hydroxy-phenyl-methyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester (58/59)

An oven-dried round-bottomed flask, equipped with a stir bar and N2 gas-inlet, was charged with methyl 2-iodo-5,5-dimethyl-4-oxo-hexanoate 53 (0.1489 g, 0.50 mmol) in methylene chloride (2 mL) and cooled in an ice-water bath (0 °C). The solution was treated with diethyl zinc (1M) in hexanes (0.5 mL, 0.50 mmol) and after stirring for 10 minutes, the reaction mixture was treated with methylene iodide (0.04 mL, 0.50 mmol). After stirring for an additional 20 minutes, benzaldehyde (0.15 mL, 1.50 mmol) was added. After 1 hour, the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted twice with ethyl acetate (2 x 30 mL). The combined
organic layers was dried with sodium sulfate, decanted from sodium sulfate and concentrated on rotary evaporator. The oily residue was subjected to column chromatography (5% ethyl acetate in hexanes) to yield a mixture of the aldol products, 2-(hydroxy-phenyl-methyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 58/59, (0.0295 g, 21%) as a yellow oil. The syn:anti ratio resulting from the reaction, 7:1, was determined from integration of the $^1$H NMR spectrum of the crude product mixture. The identities of the products were confirmed by comparing NMR-spectra to results obtained by Lai et al. Methyl 5,5-dimethyl-4-oxo-hexanoate 54 was a byproduct of this reaction.

3,3-Dimethylbutanol (61)

A 250-mL round-bottomed flask equipped with a stir bar was charged with lithium aluminum hydride (0.7590 g, 20 mmol). The flask containing the solid was placed in an ice-water bath (0 °C), THF (160 mL) was added to the flask over 20 minutes in portions. Methyl t-butyl acetate 60 (2.6 g, 20 mmol) was added to the gray suspension and the flask was fitted with a condenser. The reaction mixture was allowed to warm to room temperature and then refluxed for two hours. The reaction was cooled to room temperature and deionized water (4 mL) was carefully added. This was followed by the addition of 2 N NaOH aqueous solution (4 mL) and finally, another addition of deionized water (10 mL). After stirring for 18 hours, sodium sulfate was added as a drying reagent to the solution containing a clump of white solid and the mixture was vacuum filtered through celite. The filtrate was concentrated under vacuum to yield 3,3-dimethylbutanol 61 (2.171 g, 83%) as a transparent colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.70
(distorted t, 2H, $J = 7.6$ Hz), 1.52 (distorted t, 2H, $J = 7.6$ Hz), 0.93 (s, 9H); $^{13}$C NMR (400 MHz) $\delta$ 60.3, 46.7, 29.9.

**Methyl 5,5-dimethylhex-2-enoate (63)**

An oven dried 250-mL round-bottomed flask was equipped with a stir bar and charged with methylene chloride (90 mL), 3,3-dimethylbutanol 61 (1.361 g, 10.39 mmol), N-methylmorpholine N-oxide (1.4043 g, 10.39 mmol) and crushed 4 Å molecular sieves (5 g). The suspension was cooled to 0 °C and then treated with tetra-N-propylammonium peruthenate (TPAP) (0.1825 g, 0.52 mmol). The reaction was monitored by thin layer chromatography and upon completion, filtered under vacuum through a plug of silica and celite. The filter cake was rinsed with THF (200 mL) and the combined methylene chloride and THF-filtrates containing 3,3-dimethylbutan-1-al 62 was used in the next step.

An oven-dried round-bottomed flask, equipped with a stir bar was charged with a solution of trimethylphosphonoacetate (3.78 g, 20.78 mmol) in THF (100 mL) at 0 °C under N$_2$ gas. This clear solution was treated with n-butyl lithium (2.5 M) in hexanes (8.31 mL, 20.78 mmol). After 30 minutes, the THF/methylene chloride solution of 3,3-dimethylbutan-1-al 62 was added to the reaction. The mixture was allowed to warm to room temperature and monitored by TLC. After completion of the reaction, approximately 1 hour, the reaction was quenched with saturated aqueous ammonium chloride (100 mL) and extracted with twice with diethyl ether (2 x 100 mL). The organic layer was dried over sodium sulfate, vacuum filtered through celite and concentrated on rotary evaporator. The crude oil was purified by flash column chromatography (1 %
ethyl acetate in hexane, R_f = 0.14) to yield a mixture of E and Z methyl 5,5-dimethylhex-
2-enoate 63 (0.9618 g, 59 %) as a colorless oil (E : Z; 8 : 1).

**E-isomer:** ^1^H NMR (400 MHz, CDCl_3) δ 6.96 (dt, 1H, J = 15.6, 7.8 Hz), 5.77 (d, 1H, 15.6 Hz), 3.69 (s, 3H), 2.05 (dd, 2H, J = 7.8, 1.0 Hz), 0.89 (s, 9H); ^1^C NMR (400 MHz) δ 167.1, 147.3, 122.9, 51.5, 46.9, 29.5.

**Z-isomer:** ^1^H NMR (400 MHz, CDCl_3) δ 6.27 (dt, 1H, J = 15.6, 7.7 Hz), 5.81 (d, 1H, J = 15.6 Hz), 3.66 (s, 3H), 2.06 (dd, 2H, J = 7.7, 1.6 Hz), 0.89 (s, 9H); ^1^C NMR (400 MHz) δ 167.1, 148.1, 120.6, 51.5, 42.4, 31.5.

**Methyl 5,5-dimethyl-hexanoate (64)**

A round-bottomed flask, equipped with a stir bar, was charged with a mixture E and Z isomers of methyl 5,5-dimethyl hex-2-enoate 63 (0.9618 g, 6.16 mmol) in THF (15 mL) and 10% Pd/C catalyst (0.0962 g). The black suspension was stirred under a blanket of N\_2 gas for approximately 10 minutes. With the N\_2 gas-inlet still connected with a positive nitrogen pressure present, the suspension was purged with H\_2 gas via a balloon. After a positive flow of H\_2 gas through the N\_2 gas-bubbler was observed, the N\_2 gas-inlet was removed and the reaction mixture was stirred with the balloon of H\_2 gas attached. After 18 hours, the balloon was removed and the suspension was filtered by gravity filtration. The filtrate was concentrated on a rotary evaporator to yield methyl 5,5-dimethylhexanoate 64 (0.6106 g, 63 %) as a colorless oil. ^1^H NMR (400 MHz, CDCl_3) δ 3.67 (s, 3H), 2.28 (t, 2H, J = 7.5 Hz), 1.59 (m, 2H), 1.19 (m, 2H), 0.89 (s, 9H); ^1^C NMR (400 MHz) δ 174.4, 51.6, 43.7, 35.0, 30.4, 29.4, 20.4.
Methyl 2-ido-5,5-dimethylhexanoate (65)

An oven-dried round-bottomed flask equipped with a stir bar was charged with diisopropylamine (1.01 mL, 7.20 mmol) in THF (5 mL). Under N₂ gas, the solution was cooled in an ice-water bath (0 °C) and treated with a n-butyl lithium (2.5 M) in hexanes (2.6 mL, 6.50 mmol). The resulting clear, pale yellow solution was allowed to stir for 30 minutes and then cooled to -78 °C. Methyl 5,5-dimethylhexanoate 64 (0.3845 g, 2.40 mmol) in THF (2 mL) was slowly added to the cooled solution and after 1 hour, a single portion of iodine (1.65 g, 6.50 mmol) was added to the enolate. After 18 hours, the reaction was quenched with concentrated sodium thiosulfate (15 mL) and allowed to stir until the pink color disappeared. Concentrated aqueous ammonium chloride (10 mL) was added to the resulting mixture, which was then extracted twice with ethyl ether (2 x 50 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated on a rotary evaporator to yield the crude product. The crude material was purified by column chromatography (100 % hexane) to yield methyl 2-ido-5,5-dimethylhexanoate 65 (0.3258 g, 48 %) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 4.24 (t, 1H, J = 7.6), 3.76 (s, 3H), 1.96 (m, 2H), 1.31 (m, 1H), 1.13 (m, 1H), 0.89 (s, 9H); ¹³C NMR (100 MHz) δ 172.2, 53.0, 43.7, 32.1, 30.5, 29.8, 21.6.

Methyl 2-(Hydroxy-phenyl-methyl)-5,5-dimethylhexanoate (67/68)

An oven-dried round-bottomed flask, equipped with a stir bar, was charged with methyl 2-ido-5,5-dimethyl-hexanoate 65 (0.1425 g, 0.50 mmol) in methylene chloride (5 mL) at 0 °C under N₂ gas. The solution was treated with diethyl zinc (1M) in hexanes (0.5 mL, 0.50 mmol) and after stirring for 10 minutes, the reaction mixture was treated
with methylene iodide (0.04 mL, 0.50 mmol). After stirring for an additional 20 minutes, benzaldehyde (0.15 mL, 1.50 mmol) was added. After 1 hour, the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted twice with ethyl acetate (2 x 30 mL). The combined organic layer was dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator. The oily residue was subjected to column chromatography (7.5 % ethyl acetate in hexanes) to yield a mixture of the aldol products, methyl 2-(hydroxy-phenyl-methyl)-5,5-dimethyl-hexanoate 67/68, (0.0524 g, 39 %). Byproducts of this reaction included methyl 2-iodomethyl-5,5-dimethyl-hexanoate and methyl 5,5-dimethylhexanoate 64. The syn:anti ratio of the aldol products, 1.6 : 1, was determined from integration of the resonance for the benzylic methine in the $^1$H NMR spectrum of the crude product.

67 and 68: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 – 7.28 (m, 10H), 4.92 (d, 1H, $J = 6.1$ Hz), 4.79 (d, 1H, $J = 7.7$ Hz), 3.68 (s, 3H), 3.57 (s, 3H), 2.96 (b, 1H), 2.80 (b, 1H), 2.73 – 2.63 (m, 2H), 1.85 - 1.48 (m, 4H), 1.39 – 1.22 (m, 2H), 1.02 (m, 2H), 0.83 (s, 9H), 0.78 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.9, 175.5, 142.1, 141.8, 128.6, 128.5, 128.1, 127.9, 126.5, 126.3, 75.4, 74.6, 53.9, 53.7, 51.8, 51.7, 41.8, 41.2, 30.4, 30.3, 29.3, 29.2, 24.8, 22.6.

C. Preparation of the Zinc-Organometallic Intermediate (57a):

Zinc-Organometallic Intermediate (57a)

An NMR-tube (WILMAD/LAG GLASS: 524 or 535-pp) was rinsed with acetone and hexane. After drying with a flow of N$_2$ gas, the NMR-tube was fitted with a rubber septum and a N$_2$ gas-inlet. A solution of methyl pivaloylacacetate 52a (37 µL, 0.24 mmol)
in deuterated chloroform (0.7 mL) was introduced into the NMR-tube. After observing
the clear solution by $^1$H and $^{13}$C-NMR spectroscopy and the mixture was again placed
under N$_2$-gas and treated with neat diethyl zinc (50 µL, 0.48 mmol). With addition of
diethyl zinc, the resulting mixture became warm, but soon cooled to room temperature.
An additional seal of parafilm treated with a drop of hexanes was wrapped around the
rubber septum. The zinc-enolate was observed by $^1$H and $^{13}$C-NMR spectroscopy. The
zinc-enolate mixture was placed under N$_2$ gas before treatment with methylene iodide
(39.3 µL, 0.48 mmol), the addition of which resulted in slight effervescence and warming
of the resulting pale yellow mixture. The parafilm used to wrap the tube was sealed
using a drop of hexanes and the pale yellow mixture was studied with various NMR-
experiments ($^1$H -NMR, $^{13}$C-NMR, 2D-NMR and D-NMR experiments).

**zinc-enolate of methyl pivaloylacetate (70):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.13 (s, 1H),
3.69 (s, 3H), 1.17 (s, 9H), 1.14 (t, 9H, $J =$ 8.1 Hz), 0.26 (q, 6H, $J =$ 8.1 Hz); $^{13}$C NMR
(100 MHz, CDCl$_3$) $\delta$ 196.0, 175.4, 85.9, 51.7, 40.1, 28.4, 10.8, 3.9 [ethane: $^1$H NMR
(400 MHz, CDCl$_3$) $\delta$ 0.85 (s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 6.8].

**zinc-organometallic intermediate (57a):** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.70 (s, 3H),
3.25 (flat b, 2H), 2.66 (b, 1H), 1.24 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 230.0, 184.9,
53.8, 44.1, 38.5, 34.9, 26.7; [ethyl iodide 69: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.17 (q, 2H,
$J =$ 7.5 Hz), 1.82 (t, 3H, $J =$ 7.5Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 20.7, -0.7];
[XZnCH$_2$I: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.69 (b); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -12.6
(b)].
D. Diprotection of 1,4-butenediol:

1,4-dibenzylxoy-2-butene (98a)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet, was charged with THF (100 mL) and sodium hydride (60 %) dispersed in oil, (5.201 g, 130 mmol). The white suspension was cooled in an ice water bath (0 °C) and treated with a drop-wise addition of distilled 1,4-butenediol 97 (3.20 mL, 38.86 mmol) via a syringe. Effervescence was observed. The resulting mixture was stirred for approximately 10 minutes, after which the translucent yellow solution was treated with benzyl bromide (14.0 mL, 118.0 mmol) and left to stir overnight. The reaction was quenched with deionized water and extracted three times with ether (3 x 70 mL). The combined organic extract was dried with magnesium sulfate, filtered to separate it from the magnesium sulfate and concentrated on a rotary evaporator. The excess benzyl bromide was collected by vacuum distillation (bp 45 °C, 1.30 mmHg). The residue was subjected to a silica plug which was first washed with hexane to remove grease and then washed with ether. The combined ether fractions were concentrated under vacuum to yield 1,4- dibenzylxoy-2-butene 98a (4.809 g, 46 %) as a pale yellow oil. \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.37 – 7.27 (m, 5H), 5.80 (t, 1H, \(J = 4.2\) Hz), 4.50 (s, 2H), 4.07 (d, 2H, \(J = 4.2\) Hz); \(^13\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 137.9, 128.9, 127.8, 127.1, 127.0, 71.5, 65.3.

1,4-bis(tert-butyldiphenylsilyloxy)-2-butene (98b)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet, was charged with THF (75 mL) and sodium hydride (60 %) dispersed in oil, (0.8731 g, 21.83 mmol). The white suspension was cooled in an ice-water bath (0 °C)
and treated with a drop-wise addition of distilled 1,4-butenediol 97 (0.75 mL, 9.69 mmol). Effervescence was observed. The resulting mixture was stirred for approximately 10 minutes, after which the translucent yellow solution was treated with tert-butylidiphenylchlorosilane (4.73 mL, 18.19 mmol) and left to stir for a minimum of 24 hours. The reaction was quenched with deionized water and extracted three times with ether (3 x 70 mL). The combined ether layer was dried with magnesium sulfate, filtered from the magnesium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to yield 1,4-di-tert-butyldiphenylsilyloxy-2-butene 98b (4.3387 g, 84 %).

\[ \text{H NMR} (360 \text{ MHz, CDCl}_3) \delta 7.73 - 7.70 (m, 4H), 7.49 - 7.39 (m, 8H), 5.73 (t, 1H, J = 4.3 Hz), 4.21 (m, 2H), 1.04 (s, 9H); \]
\[ \text{13C NMR} (90 \text{ MHz, CDCl}_3) \delta 135.7, 133.7, 130.0, 129.7, 127.8, 60.6, 26.9, 19.2. \]

1, 4 – bis(diisopropylsilox) – 2 – butene (98c)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet, was charged with THF (75 mL) and sodium hydride (60 %) dispersed in oil (1.245 g, 31.1 mmol). The white suspension was cooled in an ice-water bath (0 °C) and treated with a drop-wise addition of distilled 1,4-butenediol 97 (1.07 mL, 12.9 mmol). Effervescence was observed. The resulting mixture was stirred for approximately 10 minutes, after which the translucent yellow solution was treated with triisopropylchlorosilane (5.55 mL, 25.9 mmol) and left to stir for a minimum of 24 hours. The reaction was quenched with deionized water and extracted three times with ether (3 x 70 mL). The combined ether layer was dried with magnesium sulfate and concentrated under vacuum to yield 1,4-bis-triisopropylsilanyloxy-but-2-ene 98c (5.3747 g, ≤ 99 %).
E. General Procedure for Ozonolysis:

**tert-Butyldiphenylsilyloxyacetaldehyde (99b)**

An oven-dried round-bottomed flask equipped with a stir bar was charged with 1,4-di-tert-butyldiphenylsilyloxy-2-butene 98b (3.62 g, 6.07 mmol) in a mixture of methanol and methylene chloride (1 : 1, v : v) (50 mL). The flask was placed behind a blast-shield and the resulting yellow solution was cooled to an acetone-dry ice bath (−78 °C) and ozone was bubbled into the solution. When the mixture turned blue due to saturation with ozone, thiourea (5.07 g, 6.66 mmol) was added to the reaction. After stirring for one hour, the resulting yellow solution with a white precipitate was diluted with 100 mL of distilled water. The organic layer was collected and then washed twice with concentrated aqueous sodium bicarbonate (2 x 200 mL). The combined sodium bicarbonate-aqueous layers were extracted twice with ether (2 x 200 mL) and the combined ether layer was dried with magnesium sulfate and filtered from the magnesium sulfate. The dried ether solution was concentrated on a rotary evaporator to provide the crude product as a yellow residue. The residue was subjected to column chromatography (10 % ethyl acetate in hexanes) to provide the tert-butyldiphenylsilyloxyacetaldehyde 99b as a pale yellow oil (2.67 g, 74 %). \(^{1}H\) NMR (360 MHz, CDCl\(_3\)) \(\delta\) 9.73 (s, 1H), 7.69−7.67 (m, 4H), 7.47−7.39 (m, 6H), 4.24 (s, 2H), 1.13 (s, 9H); \(^{13}C\) NMR (90 MHz, CDCl\(_3\)) \(\delta\) 210.8, 135.6, 132.0, 130.2, 128.0, 70.1, 28.8, 19.4.
Triisopropylacetaldehyde (99c)

Column Chromatography (10 % ethyl acetate in hexanes)

Yellow oil, 60 %

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.71 (s, 1H), 4.23 (s, 2H), 1.13 - 1.06 (m, 21H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 202.9, 69.8, 17.9, 11.9.

F. General Procedure for the Epoxidation Reaction:

2,3-Bis-triisopropylsilanyloxymethyl-oxirane (100c)

A 250-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet, was charged with crude 1,4-bis-triisopropylsilanyloxy-but-2-ene (2.825 g, 6.00 mmol), methylene chloride (150 mL) and m-chloroperoxybenzoic acid (MCPBA) (80 %) in an aqueous dispersion (4.700 g, 27.2 mmol). After 18 hours, concentrated aqueous sodium thiosulfate (~200 mL) was added to the reaction mixture to quench excess MCPBA. The organic layer was separated from the aqueous layer and dried with magnesium sulfate followed by filtration from the drying agent. The organic layer was then concentrated on a rotary evaporator followed by a vacuum pump to provide 2,3-bis-triisopropylsilanyloxymethyl-oxirane 100c (2.426 g, $\leq$ 97 %) as a yellow oil. $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 3.85 (dd, 1H, $J = 11.5, 3.9$ Hz), 3.78 (dd, 1H, $J = 11.5, 5.6$ Hz), 3.13 (m, 1H), 1.12 - 1.03 (m, 21H); [impurity--MCPBA: aromatic region]; $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 62.2, 56.8, 17.9, 11.9 [impurity--MCPBA: aromatic region and 162 ppm].

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2,3-Bis-benzyloxymethyl-oxirane (100a)
yellow oil, crude ≤ 96 %
$^1$H NMR (360 MHz, CDCl$_3$) δ 7.29 – 7.23 (m, 5H), 4.55 (d, 1H, $J = 11.9$ Hz), 4.45 (d, 1H, $J = 11.9$ Hz), 3.63 (dd, 1H, $J = 11.3$, 3.6 Hz), 3.47 (dd, 1H, $J = 11.3$, 6.4 Hz), 3.20 (m, 1H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 137.6, 128.3, 127.6, 72.9, 67.9, 54.2.

2,3-Bis(tert-butylidiphenylsilyloxymethyl)oxirane (100b)
yellow oil, crude ≤ 99 %
$^1$H NMR (360 MHz, CDCl$_3$) δ 7.96 – 7.84 (m, 4H), 7.56 – 7.46 (m, 6H), 3.91 (m, 2H), 3.39 (m, 1H), 1.25 (s, 9H); $^{13}$C NMR (90 MHz, CDCl$_3$) δ 135.5, 133.1, 129.7, 127.7, 62.3, 56.6, 26.7, 19.1.

G. General Procedure for the Cleavage of Epoxides
Benzyloxyacetaldehyde (99a)
In an oven-dried round-bottomed flask, 2,3-bis-benzyloxymethyl-oxirane 100a (5.289 g, 23.2 mmol) was dissolved in THF (170 mL) and treated with periodic acid (6.680 g, 29.2 mmol) which was added in three portions. The resulting yellow suspension was stirred overnight for at least 18 hours. Upon completion, the reaction mixture was concentrated under vacuum to give a dark residue which was dissolved in ether (200 mL). The resulting ether solution was washed twice with water (2 x 150 mL) and dried with magnesium sulfate, filtered and concentrated on a rotary evaporator to provide an orange translucent oil. The oil was subjected to column chromatography (10 % ethyl acetate in hexanes) to provide pure benzyloxyacetaldehyde 99a (1.544 g, 22 %). $^1$H NMR
(360 MHz, CDCl₃) δ 9.59 (s, 1H), 7.29 – 7.15 (m, 5H), 4.51 (s, 2H), 3.98 (s, 2H); $^{13}$C NMR (90 MHz, CDCl₃) δ 200.4, 136.9, 128.6, 128.2, 128.0, 75.3, 73.6.

Triisopropylsilyloxyacetaldehyde (99c)

Column Chromatography (20 % ethyl acetate in hexanes)

Yellow oil, 66 %

**H. Tandem Chain Extension-Aldol Reaction with Protected α-Hydroxyacetaldehydes**

2-(2-Benzylxy-1-hydroxyethyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester (101a and 102a)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet, was charged with methylene chloride (60 mL), diethyl zinc (1M in hexanes (16.0 mL, 16.0 mmol) and methylene iodide (1.29 mL, 16.0 mmol). After ten minutes, the resulting white suspension was treated with methyl pivaloylacetate 52a (0.64 mL, 4.00 mmol) via a syringe, and the reaction mixture was stirred for an additional twenty minutes. Benzyloxyacetaldehyde 99a (0.9232 g, 6.15 mmol) dissolved in methylene chloride (10 mL) was added to the reaction mixture via a syringe. After one hour, the reaction was quenched with concentrated aqueous ammonium chloride (60 mL) and the resulting white suspension was extracted twice with an ethyl acetate-ether mixture (1:1, v : v) (2 x 250 mL). The combined organic layer was dried over magnesium sulfate, filtered to separate it from the magnesium sulfate and then concentrated on a rotary evaporator to give the crude product as an oil. The oil was subjected to column
chromatography (20 % ethyl acetate in hexanes) to provide *anti*-2-(2-benzyloxy-1-
hydroxyethyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 101a (0.1939 g, 15 %) and
*syn*-2-(2-benzyloxy-1-hydroxy-ethyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester
102a (0.1846 g, 14 %) and a mixture of the isomers (0.0357 g, 3 %) as oils.

*anti*-isomer 101a: \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.33 – 7.25 (m, 5H), 4.49 (bs, 2H), 3.93
(dt, 1H), 3.51 (s, 3H), 3.49 (m, 2H), 3.09 (m, 1H, \(J = 4.3\) Hz), 3.02 (dd, 1H, \(J = 17.6, 8.8\)
Hz), 2.73 (dd, 1H, \(J = 17.6, 4.3\) Hz), 1.08 (s, 9H); \(^13\)C NMR (90 MHz, CDCl\(_3\)) \(\delta\) 214.0,
173.9, 137.8, 128.5, 127.8, 73.5, 72.2, 70.7, 51.9, 44.07, 43.1, 35.8, 26.4.

*syn*-isomer 102a: \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.38 – 7.28 (m, 14.5H), 4.65 (d, 1H, \(J =
12.0\) Hz), 4.61 – 4.53 (m, 5H), 4.39 (dt, 1H, \(J = 8.2, 2.9\) Hz), 4.07 (m, 0.5H), 3.72 (s,
2.5H), 3.69 (s, 4H), 3.66 (s, 2.5H), 3.58 – 3.57 (m, 2H), 3.55 – 3.43 (m, 3H), 3.40 (bs,
1H), 3.09 (m, 1H), 3.03 (m, 1H), 2.81 (m, 1H), 2.67 (d, 0.5H, \(J = 5.2\)Hz), 2.33 (td, 1.5H,
\(J = 3.6,11.9\) Hz), 2.13 (m, 1.5H), 1.15 (s, 7.5H), 1.12 (s, 2H), 1.02 (s, 15H); \(^13\)C NMR
(90 MHz, CDCl\(_3\)) \(\delta\) 214.5, 175.9, 174.5, 173.7, 173.9, 173.7, 137.7, 137.4, 128.5, 128.4,
128.3, 127.9, 127.7, 127.6, 127.5, 126.9, 110.9, 110.6, 80.8, 77.5, 77.2, 76.8, 73.4, 73.2,
72.1, 71.3, 70.8, 70.2, 52.5, 52.1, 51.9, 45.2, 43.6, 43.5, 37.6, 37.5, 35.8, 34.7, 26.5, 25.7,
25.2, 25.2.

2-[2-(tert-Butyldiphenylsilanyloxy)-1-hydroxyethyl]-5,5-dimethyl-4-oxo-hexanoic

acid methyl ester (101b and 102b)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen
inlet, was charged with methylene chloride (60 mL), diethyl zinc (1M) in hexanes (16.0
mL, 16.0 mmol) and methylene iodide (1.29 ml, 16.0 mmol). After ten minutes, the
resulting white suspension was treated with methyl pivaloylacetate 52a (0.64 mL, 4.00 mmol) via a syringe and the reaction mixture was stirred for an additional twenty-five minutes. t-Butyldiphenylsiloxyacetalddehyde 99b (1.840 g, 6.15 mmol) dissolved in methylene chloride (10 mL) was added to the reaction mixture, via a syringe. After 70 minutes, the reaction was quenched with concentrated aqueous ammonium chloride (60 mL) and the resulting white suspension was extracted twice with an ethyl acetate-ether mixture (1:1, v:v) (2 x 250 mL). The combined organic layer was dried over magnesium sulfate, filtered to separate it from the magnesium sulfate and then concentrated on a rotary evaporator to give the crude product as an oil. The oil was subjected to column chromatography (5 % ethyl acetate in hexanes) to provide anti-2-[2-(tert-butyldiphenylsilanyloxy)-1-hydroxyethyl]-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 101a (0.4900 g, 26 %) and syn-2-[2-(tert-butyldiphenylsilanyloxy)-1-hydroxyethyl]-5,5-dimethyl-4-oxo-hexanoic acid methyl ester 102b (0.6900 g, 36 %) as oils.

anti-isomer 101b: \(^{1}H\) NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.73 - 7.61 (m, 4H), 7.45 - 7.38 (m, 6H), 3.91 (m, 1H), 3.70 (d, 2H, \(J = 5.4\) Hz), 3.62 (s, 3H), 3.22 (m, 1H, \(J = 4.6\) Hz), 3.07 (dd, 1H, \(J = 18.0, 9.2\) Hz), 3.02 (b, 1H), 2.73 (dd, 1H, \(J = 18.0, 4.6\) Hz), 1.14 (s, 9H), 1.09 (s, 9H); \(^{13}C\) NMR (90 MHz, CDCl\(_3\)) \(\delta\) 213.7, 173.9, 135.6, 132.9, 129.9, 127.8, 72.2, 65.8, 51.8, 44.0, 42.8, 35.8, 26.8, 26.5, 19.2.

syn-isomer 102b: \(^{1}H\) NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.76 - 7.72 (m, 9H), 7.70 - 7.65 (m, 6H), 7.48 - 7.39 (m, 23H), 4.46 (dd, 1H, \(J = 9.9, 4.7\) Hz), 4.34 (dt, 1.5H, \(J = 8.7, 3.1\) Hz), 4.04 (m, 1H), 3.87 (dd, 2H, \(J = 10.9, 3.4\) Hz), 3.84 (bs, 1H), 3.78 (dd, 2.5H, \(J = 4.0, 1.7\) Hz), 3.74 (s, 3.5H), 3.72 (d, 1.5H, \(J = 2.8\) Hz), 3.71 - 3.65 (m, 6.5H), 3.64 - 3.63 (m,
$3.5H$, $3.61 - 3.53$ (m, 2H), $3.24$ (dd, 1H, $J = 10.4, 5.5, 3.5$ Hz), $3.17$ (dd, 1H, $J = 9.5, 5.9, 3.8$ Hz), $3.07$ (dd, 1H, $J = 17.8, 9.0$ Hz), $3.03$ (s, 1.5H), $2.85 - 2.79$ (m, 2H, $J$(partial) = 3.6 Hz), $2.35$ (td, 2.5H, $J = 10.5, 3.1$ Hz), $2.22 - 2.12$ (m, 2.5H), $1.91$ (b, 0.5H), $1.16$ (s, H), $1.11$ (s, 25H) [impurity--hexanes : $^1H$ NMR (360 MHz, CDCl$_3$) δ 1.07, 0.91]; $^{13}C$ NMR (90 MHz, CDCl$_3$) δ 214.6, 176.7, 135.9, 135.7, 135.7, 130.0, 129.9, 129.9, 129.8, 127.9, 127.8, 111.0, 110.6, 82.3, 81.3, 77.2, 65.8, 64.9, 64.6, 52.6, 52.2, 52.0, 44.7, 43.4, 43.2, 37.6, 35.9, 34.8, 26.9, 26.7 25.3, 19.3.

2-(1-Hydroxy-2-triisopropylsilanyloxyethyl)-5,5-dimethyl-4-oxo-hexanoic acid methyl ester (101c and 102c)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet was charged with methylene chloride (60 mL), diethyl zinc (1M) in hexanes (16.0 mL, 16.0 mmol) and methylene iodide (1.29 mL, 16.0 mmol). After ten minutes, the resulting white suspension was treated with methyl pivaloylacetate 52a (0.64 mL, 4.00 mmol) and stirred for an additional twenty minutes. Triisopropylsilyloxyacetaldehyde 99c (1.555 g, 7.19 mmol) dissolved in methylene chloride (10 mL) was added to the reaction mixture, via a syringe. After one hour, the reaction was quenched with concentrated aqueous ammonium chloride (60 mL) and the resulting white suspension was extracted twice with an ethyl acetate-ether mixture (1:1, v:v) (2 x 250 mL). The combined organic layer was dried over magnesium sulfate, filtered to separate it from the magnesium sulfate and then concentrated on a rotary evaporator to give the crude product as an oil. The crude oil was subjected to column chromatography (5 % ethyl acetate in hexanes) to provide the anti- and syn-2-(1-hydroxy-2-triisopropylsilanyloxyethyl)-5,5-
dimethyl-4-oxo-hexanoic acid methyl ester 101c and 102c (combined yield: 0.517 g, 33 %) as yellow oils.

**syn**-isomer 101c: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.39 (td, 1H, $J= 7.2, 3.8$ Hz), 4.31 (dt, 4H, $J= 8.5, 2.3$ Hz), 3.93 (m, 1.5H), 3.90 (dd, 1.5H, $J = 10.5, 2.9$ Hz), 3.83 (dd, 1.5H, $J = 10.5, 3.9$ Hz), 3.77 (dd, 3H, $J = 10.6, 1$ Hz), 3.74 – 3.73 (m, 5H), 3.72 – 3.71 (m, 7.5H), 3.69 (s, 4.5H), 3.63 (dd, 1.5H, $J= 10.0, 6.2$ Hz), 3.52 (dd, 2H, $J = 19.9, 7.9$ Hz), 3.52 (dd, 0.5H, $J = 8.3, 3.8$ Hz), 3.47 (b, 1.5H), 3.18 (dd, 1H, $J = 10.5, 5.2, 3.2$ Hz), 3.11 – 3.05 (m, 2H), 2.32 (dd, 1H, $J = 20.8, 8.8$ Hz), 2.31, (dd, 1H, $J = 10.4, 3.0$ Hz), 2.14 – 2.07 (m, 2H), 1.19 – 1.12 (m, 18H), 1.09 – 1.05 (m, 72H), 1.02 – 1.01 (m, 24H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 214.7, 176.9, 174.1, 173.9, 111.0, 110.3, 82.1, 81.6, 71.7, 65.4, 64.4, 63.9, 52.5, 52.1, 51.9, 44.6, 44.1, 43.3, 42.6, 37.8, 37.6, 37.4, 35.8, 35.0, 26.6, 25.4, 25.3, 18.0, 11.9.

**4-(benzyloxy)-2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxybutyric acid ethyl ester (101d and 102d)**

An oven-dried 15-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet, was charged with methylene chloride (8 mL) and methylene iodide (0.32 mL, 4.00 mmol). The reaction mixture was cooled in an ice-water bath (0 °C) and then treated with diethyl zinc (1M) in hexanes (4.00 mL, 4.00 mmol). After ten minutes, the resulting white suspension was treated with ethyl 3,5-dimethoxybenzoyletacetate 96 (0.2522 g, 1.00 mmol) dissolved in methylene chloride in (1.19 mL) and the reaction mixture was stirred for an additional twenty minutes. Benzyloxyacetaldehyde 99a (0.2252 g, 1.50 mmol) dissolved in methylene chloride (1.50 mL) was added to the reaction mixture. After one
hour, the reaction was quenched with ammonium chloride (10 mL) and the resulting white suspension was extracted twice with ethyl acetate (2 x 50 mL). The combined organic layer was dried over sodium sulfate, decanted from the sodium sulfate and then concentrated under vacuum to give the crude product 4-(benzyloxy)-2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxybutyric acid ethyl ester \textbf{101d and 102d} (0.0552 g, <57 %) as a yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (d, 1H, $J = 8.4$ Hz), 7.50 (m, 1H), 7.328 - 7.28 (m, 5H), 6.86 (d, 1H, $J = 8.4$ Hz), 4.56 (d, 1H, $J = 12.0$ Hz), 4.54 (d, 1H, $J = 12.0$ Hz), 4.13 (q, 2H, $J = 7.2$ Hz), 4.08 (m, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.89 (m, 1H), 3.59 (d, 2H, 4.9 Hz), 3.49 (m, 1H), 3.29 (m, 1H), 3.02 (d, 1H, $J = 5.6$ Hz), 1.21 (t, 3H, $J = 7.2$ Hz);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.6, 173.7, 153.5, 149.1, 137.9, 129.9, 128.5, 127.9, 122.9, 110.2, 110.1, 73.6, 72.4, 70.9, 61.0, 56.2, 56.1, 43.6, 37.2, 14.2.

\textbf{4-(tert-butyl-diphenylsilanyloxy)-2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-butyr}ic acid ethyl ester \textbf{(101e and 102e)}

An oven-dried 15-mL round-bottomed flask equipped with a stir bar and a nitrogen inlet, was charged with methylene chloride (5 mL) and methylene iodide (0.16 mL, 2.0 mmol). The reaction mixture was cooled in an ice-water bath (0 °C) and then treated with diethyl zinc (1M) in hexanes (2.0 mL, 2.0 mmol). After ten minutes, the resulting white suspension was treated with ethyl 3,5-dimethoxybenzoylaceta\textit{e} 96 (0.1262 g, 0.5 mmol) dissolved in methylene chloride (~1 mL) and the reaction mixture was stirred for an additional twenty minutes. \textit{t}-Butyldiphenylsilyloxyacetaldehyde 99b (0.2238 g, 0.75 mmol) dissolved in methylene chloride (1.4 mL) was added to the reaction mixture.
After one hour, the reaction was quenched with ammonium chloride (3 mL) and the resulting white suspension was extracted twice with ethyl acetate (2 x 15 mL). The combined organic layer was dried over sodium sulfate, decanted from the sodium sulfate and then concentrated under vacuum to give the crude product as an oil. The oil was subjected to column chromatography (20% ethyl acetate in hexanes followed by 30% ethyl acetate in hexanes) to separate the aldol product from chain extended material. Column chromatography yielded a mixture of the isomers of 4-(tert-butylidiphenylsilyl-oxy)-2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-butyric acid ethyl ester 101e and 102e (0.0552 g, 20%). 

\[ ^1H \text{ NMR (500 MHz, CDCl}_3) \delta 7.71 - 7.63 \text{ (m, 10H), 7.61 (d, 0.75H, } J = 8.3 \text{ Hz), 7.60 (d, 0.75H, } J = 8.3 \text{ Hz), 7.58 (d, 0.5H, } J = 8.3 \text{ Hz), 7.57 (d, 0.5H, } J = 8.3 \text{ Hz), 7.51 (s, 1H), 7.50 (s, 1H), 7.50 (s, 1H), 7.44 - 7.34 (m, 15H), 6.88 (d, 1.5H, } J = 8.3 \text{ Hz), 6.87 (d, 1H, } J = 8.3 \text{ Hz), 4.12 - 4.06 (m, 6H), 3.98 (t, 3.98 - 3.93 (m, 7H), 3.91 (s, 6H), 3.89 (dd, 1H, } J = 5.3, 2.0 \text{ Hz), 3.87 (m, 1H), 3.76 - 3.71 (m, 4H), 3.67 (dd, 2H, } J = 19.1, 6.4 \text{ Hz), 3.48 (dd, 2H, } J = 18.0, 8.5 \text{ Hz), 3.44 (d, 0.5H, } J = 2.9 \text{ Hz), 3.34 (t, 0.5H, } J = 4.7 \text{ Hz), 3.32 - 3.29 (m, 1.5H), 3.28 - 3.24 (m, 2.5H), 3.17 (dd, 1H, } J = 17.4, 4.8 \text{ Hz), 2.99 (d, 1H, } J = 5.6 \text{ Hz), 2.82 (d, 2H, } J = 4.7 \text{ Hz), 1.18 (t, 2H, } J = 6.9 \text{ Hz), 1.16 (t, 4.5H, } J = 6.9 \text{ Hz), 1.07 (m, 18.5H); } ^{13}C \text{ NMR (125 MHz, CDCl}_3) \delta 197.2, 196.6, 173.6, 171.3, 153.5, 149.1, 149.1, 135.7, 132.9, 130.0, 129.8, 127.9, 122.9, 110.3, 110.1, 72.5, 71.9, 66.0, 65.9, 61.0, 60.5, 56.2, 56.1, 43.7, 43.2, 37.2, 36.1, 26.9, 21.2, 19.4, 14.2. \]
2-[2-(3,4-Dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-4-triisopropylsilanyloxybutyric acid methyl ester (101f and 102f)

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet, was charged with methylene chloride (5 mL) and methylene iodide (0.32 mL, 4.00 mmol). The reaction mixture was cooled in an ice-water bath (0 °C) and then treated with diethyl zinc (1M) in hexanes (4.00 mL, 4.00 mmol). After ten minutes, the resulting white suspension was treated with ethyl 3,5-dimethoxybenzoylacetate 96 (0.2522 g, 1.00 mmol) in methylene chloride (1mL) and stirred for an additional twenty minutes. Triisopropylsilyloxyacetaldehyde 99c (0.3246 g, 1.5 mmol) was dissolved in methylene chloride (6.5 mL) and the solution was added to the reaction mixture, via a syringe. After one hour, the reaction was quenched with ammonium chloride (10 mL) and the resulting white suspension was extracted twice with ethyl acetate (2 x 50 mL). The combined organic layer was dried over sodium sulfate, decanted from the sodium sulfate and then concentrated under vacuum to give the crude product as an oil. The oil was subjected to column chromatography (20 % ethyl acetate in hexanes) to separate the aldol product from chain extended material. The ethyl acetate-wash of the column provided an oily residue. The residue from the wash was subjected to another separation by column chromatography (30 %ethyl acetate in hexanes) to provide a mixture of the isomers of 2-[2-(3,4-Dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-4-triisopropylsilanyloxybutyric acid methyl ester 101f and 102f (0.1089 g, 22 %) as an oil. $^1$H NMR (500 MHz, CDCl$_3$) $^\delta$ 7.64 (td, 1H, $J = 8.5, 2.0$ Hz), 7.52 (m, 1H), 6.88 (d, 1H, $J = 8.4$ Hz), 4.17 (q, 2H, $J = 7.1$ Hz), 4.00 (m, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.80 (dd, 0.5H, $J = 9.9, 4.1$Hz), 3.78 (d, 0.5H, $J = 6.5$ Hz), 3.68 (dd, 0.5H, $J = 10.0, 6.6$ Hz), 3.58 – 3.47 (m, 1H), 3.80 (dd, 0.5H,
$J = 17.7, 4.2 \text{ Hz}$, 3.31 (m, 0.5H), 3.22 (m, 1H), 3.01 (d, 0.5H, $J = 5.0 \text{ Hz}$), 2.87 (d, 0.5H, $J = 4.6 \text{ Hz}$), 1.25 (t, 1H, $J = 7.1 \text{ Hz}$), 1.24 (t, 2H, $J = 7.1 \text{ Hz}$), 1.15 – 1.06 (m, 14H), 1.05 – 1.04 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 197.4, 196.8, 173.8, 173.6, 153.6, 149.2, 130.1, 123.2, 122.9, 110.5, 110.3, 110.2, 110.1, 72.5, 71.7, 65.5, 65.0, 60.9, 56.1, 55.9, 43.8, 43.2, 37.1, 36.2, 18.0, 14.2, 11.9.

3-[2-(3,4-Dimethoxyphenyl)-2-oxo-ethyl]-4-hydroxy-dihydro-furan-2-one (103 and 104)

**Deprotection of TIPS-group**

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet, was charged with ethyl 2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-4-triisopropylsilanyloxy-butanotate 101f and 102f (0.1089 g, 0.23 mmol), THF (7 mL) and tetrabutylammonium fluoride (1M) in THF (0.23 mL, 0.23 mmol). The resulting translucent orange mixture was stirred at room temperature. After 2 hours, the mixture is diluted with deionized water (7 mL) and extracted three times with ethyl acetate (3 x 20 mL). The combined organic extract was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide a yellow oil as the residue. The residue was subjected to column chromatography to provide the cis-3-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-4-hydroxy-dihydro-furan-2-one 104 (0.0202 g, 31 %) and trans-3-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-4-hydroxy-dihydro-furan-2-one 103 (0.0121 g, 19 %) as yellow oils. $^1$H NMR spectroscopy indicated that in the crude reaction mixture the ratio of the trans-lactone : cis-lactone, 103 : 104, was 1 : 2.
trans 103: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67 (dd, 1H, $J = 8.5$, 2.0 Hz), 7.53 (d, 1H, $J = 2.0$ Hz), 6.92 (d, 1H, $J = 8.5$ Hz), 4.70 (b, 1H), 4.58 (dd, 1H, $J = 9.1$, 7.5 Hz), 4.44 (m, 1H), 4.09 (dd, 1H, $J = 8.9$, 7.8 Hz), 4.01 (dd, 1H, $J = 18.4$, 2.5 Hz), 3.97 (s, 3H), 3.94 (s, 3H), 3.12 (dd, 1H, $J = 18.4$, 10.9 Hz), 3.03 (ddd, 1H, $J = 10.6$, 7.8, 2.3 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.5, 176.5, 154.5, 149.4, 128.8, 123.8, 110.3, 110.2, 72.9, 71.8, 56.3, 56.2, 44.6, 38.9.

cis 104: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.68 (dd, 1H, $J = 8.4$, 2.0 Hz), 7.53 (d, 1H, $J = 2.0$ Hz), 6.91 (d, 1H, $J = 8.4$ Hz), 4.81 (dd, 1H, $J = 5.8$, 4.2 Hz), 4.47 (dd, 1H, $J = 10.5$, 4.8 Hz), 4.38 (d, 1H, $J = 10.5$ Hz), 3.97 (s, 3H), 3.94 (s, 3H), 3.58 (dd, 1H, $J = 17.8$, 3.3 Hz), 3.42 (dd, 1H, $J = 17.8$, 10.5 Hz), 3.15 (ddd, 1H, $J = 10.5$, 5.8, 3.3 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 197.6, 177.5, 154.2, 149.3, 129.3, 123.5, 110.3, 110.2, 74.9, 69.2, 56.3, 56.2, 41.9, 32.9.

Deprotection of TBDPS-group

An oven-dried 250 ml round-bottomed flask equipped with a stir bar and a nitrogen inlet was charged with ethyl 2-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-3-hydroxy-4-t-butyldiphenylsilanyloxy-butanotate 101e and 102e (0.0552 g, 0.10 mmol), THF (3 mL) and tetrabutylammonium fluoride (1M) in THF (0.11 mL, 0.11 mmol). The resulting translucent orange mixture is stirred at room temperature. After 2 hours, the mixture is diluted with deionized water (5 mL) and extracted three times with ethyl acetate (3 x 10 mL). The combined organic extract was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide a yellow oil as the residue. The residue is subjected to column chromatography to provide cis-3-[2-(3,4-
dimethoxyphenyl)-2-oxo-ethyl]-4-hydroxy-dihydro-furan-2-one \textbf{104} (0.0088 g, 30 \%) and 
trans-3-[2-(3,4-dimethoxyphenyl)-2-oxo-ethyl]-4-hydroxy-dihydro-furan-2-one \textbf{103} (\leq 0.0144 g, \leq 49 \%) as yellow oils. \textsuperscript{1}H NMR spectroscopy indicated that in the crude reaction mixture the ratio of the trans-lactone : cis-lactone, \textbf{103} : \textbf{104}, was 1: 3.

I. Syntheses of Spiroketalts and the Corresponding Synthons

6-Hydroxy-3-oxo-heptanoic acid methyl ester (120a/b)

An oven-dried 250 mL-round-bottomed flask equipped with a stir bar and N\textsubscript{2} gas-inlet, was charged with sodium hydride in a 60 \% oil dispersion (0.90 g, 22.50 mmol) in THF (80 mL) and cooled in an ice-water bath (0 °C). The white suspension was treated with methyl acetoacetate \textbf{46} (2.16 mL, 20.0 mmol) via a syringe and stirred for 30 minutes. The reaction was cooled in a chloroform-dry ice bath (–63 °C) and n-butyl lithium (< 2.5 M\textsuperscript{1}) in hexanes (20 mL, < 50.0 mmol), via syringe, was added over 30 seconds to the mixture which turned from yellow to an intense orange color as the dianion formed. After 45 minutes, racemic-propylene oxide (5 mL, 71.50 mmol) was added in one portion via a syringe to the orange reaction mixture and the reaction was allowed to warm to room temperature. After 18 hours, the reaction was quenched with a solution of saturated aqueous ammonium chloride (20 mL) and extracted three times with ethyl acetate (3 x 70 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to yield an oily orange residue. This crude material was subjected to flash column chromatography (10 \% ethyl acetate in hexanes) to provide 6-hydroxy-3-oxo-heptanoic acid methyl ester

\textsuperscript{1} The n-butyl lithium was originally 2.5M in hexanes but over time, the solution became more dilute because of exposure to moisture. In this reaction, the actual concentration of the n-butyl lithium solution was unknown. This reaction requires at least 1.1 eq of n-butyl lithium relative to the \beta-keto ester.
120a/b (1.3496 g, 38 %), a mixture of open-form, hemiacetal and enol, as a pale, orange oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.52 (s, 2H), 4.40 (s, 1H), 4.37 (m, 2H, J = 6.3 Hz), 4.21 (m, 1H), 3.83 (m, 0.5H), 3.73 (s, 10.5H), 3.49 (s, 1H), 2.81 - 2.71 (m, 7H, J = 15.6 Hz), 2.25 - 2.13 (m, 3H), 2.09 - 1.99 (m, 3H), 1.95 - 1.78 (m, 4.5H), 1.69 (m, 1.5H), 1.48 (m, 2H), 1.33 (d, 3H, J = 6.2 Hz), 1.21 (d, 7.5H, J = 6.2 Hz); enol, opened-chain, hemiacetal: $^{13}$C NMR (100 MHz) δ 203.3, 172.2, 167.9, 103.1, 77.4, 75.0, 66.9, 52.4, 51.9, 49.2, 44.3, 44.1, 39.5, 38.5, 37.4, 32.6, 32.3, 31.9, 23.7, 22.8, 21.2.

7-Hydroxy-4-oxo-octanoic acid methyl ester (124)

A 100-mL oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet, was charged with methylene iodide (1.13 mL, 14.0 mmol) in methylene chloride (18 mL) at 0 °C. The solution was cooled in an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (14.0 mL, 14.0 mmol). After 10 minutes, the resulting white suspension was treated with 6-hydroxy-3-oxo-heptanoic acid methyl ester 120a/b (0.3351 g, 1.92 mmol) dissolved in methylene chloride (2 mL) via a syringe. The ice-water bath was allowed to warm to room temperature during the reaction and the reaction was monitored by TLC to ensure that the starting material had completely reacted. After 90 minutes, the reaction was quenched with saturated aqueous ammonium chloride. The resulting mixture was extracted twice with ethyl acetate (2 x 50 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to give an oily residue. The residue was subjected to flash column chromatography (20 % ethyl acetate in hexanes, followed by 50 % ethyl acetate in
hexanes) to provide 7-hydroxy-4-oxo-octanoic acid methyl ester 124 as a pale yellow oil (0.2316 g, 60 %).

Opened-chain: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta 3.80 (m, 1H), 3.68 (s, 3H), 2.76 (d, 2H, \( J = 6.6 \) Hz), 2.64 – 2.59 (m, 4H), 1.79 (m, 1H), 1.69 (m, 1H, \( J = 7.0 \) Hz), 1.20 (d, 3H, \( J = 6.2 \) Hz), (resonances for hemiacetal: \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta 4.34, 4.13, 2.09 – 1.86, 1.31, 1.29 \); opened-chain and hemiacetal: \( ^13C \) NMR (100 MHz, CDCl\(_3\)) \( \delta 209.8, 173.5, 106.1, 74.9, 67.5, 53.7, 52.0, 39.2, 37.7, 37.3, 35.7, 35.6, 32.8, 32.6, 32.3, 29.8, 27.9, 23.9, 22.9, 21.2, 17.3

2,2,7-Trimethyl-1,6-dioxa-spiro[4.4]nonane-3-carboxylic acid methyl ester (128)

An oven-dried round-bottomed flask equipped with a stir bar and N\(_2\)-gas inlet, was charged with methylene iodide (1.6 mL, 20.00 mmol) in methylene chloride (100 mL). The solution was cooled in an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (20 mL, 20.0 mmol). After 10 minutes, the resulting white suspension was treated with 6-hydroxy-3-oxo-heptanoic acid methyl ester 120a/b (0.3497 g, 2.00 mmol) dissolved in methylene chloride (5 mL). The ice-water bath was allowed to warm to room temperature during the reaction. After stirring for one hour, acetone\(^2\) (0.22 mL, 1.3 mmol) was added. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) after one hour and extracted three times with ethyl acetate (1 x 100 mL, 2 x 50 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator. The resulting oily residue was subjected to flash column chromatography to yield products eluted in the following order: i. mixture of 4 diastereomers of the aldol product, 2,2,7-trimethyl-1,6-dioxa-

\(^2\) The acetone was distilled from calcium hydride and stored over sieves to ensure that it was dry.
spiro[4.4]nonane-3-carboxylic acid methyl ester 128 (0.1790 g, 39 %) as a yellow oil, ii. the chain extended product, 7-hydroxy-4-oxo-octanoic acid methyl ester 124 (0.0452g, 8%) and iii. an oil consisting of a mixture of products in which the spirolactone 127 was the major product: 3-(1-hydroxy-1-methyl-ethyl)-7-methyl-1,6-dioxa-spiro[4.4]nonan-2-one # with impurities (0.1287 g, ≤ 30 %). The structure of the spirolactone 127 was determined with $^1$H NMR and $^{13}$C NMR spectroscopy in which the $^1$H NMR spectrum exhibited a diminished resonance for the methyl unit of the MeO-ester in the region of 3.60 – 3.80 ppm and the $^{13}$C NMR spectra exhibited resonances at ~ 178.5 ppm for the lactone’s carbonyl and 116.5 – 116.7 ppm for the quaternary C.

mixture of 4 spiroketal diastereomers #: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.27 – 4.03 (m 4H), 3.70 (s, 12H), 3.22 (dd, 1H, $J$ = 12.0, 7.1 Hz), 3.20 (dd, 1H, $J$ = 12.0, 7.1 Hz), 2.89 – 2.84 (m, 1.5H), 2.79 (dd, 0.75 H, $J$ = 10.7, 6.7 Hz), 2.77 (dd, 0.75 H, $J$ = 10.7, 6.9 Hz), 2.48 (dd, 1H, $J$ = 12.8, 11.9 Hz), 2.45 (dd, 1.5H, $J$ = 12.2 Hz), 2.26 (dd, 1H, $J$ = 13.2, 8.0 Hz), 2.25 (dd, 1H, $J$ = 13.4, 8.7 Hz), 2.16 (dd, 1H, $J$ = 12.8, 7.1 Hz), 2.14 –1.92 (m, 14 H), 1.89 – 1.82 (m, 1H), 1.76 – 1.65 (m, 2.5 H), 1.51 (s, 4H), 1.49 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.29 (d, 4H, $J$ = 6.1 Hz), 1.28 (d, 3H, $J$ = 6.2 Hz), 1.22 – 1.19 (m, 12H), 1.08 (s, 3 H), 1.06 (s, 4H) [contains hexanes: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.88 (t), 1.26 (m)]; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.8, 171.9, 171.8, 113.8, 113.6, 113.5, 113.3, 82.2, 82.1, 82.0, 76.1, 75.8, 74.6, 73.9, 53.8, 52.9, 52.8, 51.8, 53.1, 53.0, 52.0, 39.5, 39.2, 39.0, 38.7, 38.6, 36.7, 35.4, 32.5 (overlap: 2C), 32.2, 31.9, 32.1, 30.7, 29.5, 29.2, 24.9, 24.8, 24.2, 23.9, 23.0, 22.9, 21.4, 21.3; IR (film) 2974, 1740

reference: a single isomer #: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.22 (m, 1H, $J$ = 6.1 Hz), 3.70 (s, 3H), 3.22 (dd, 1H, $J$ = 12.0, 7.1 Hz), 2.48 (dd, 1H, $J$ = 12.8, 11.9 Hz), 2.16 (dd,
$^1$H, $J = 12.8, 7.1$ Hz), 2.11 – 1.99 (m, 4H), 1.49 (s, 3H), 1.20 (d, 3H, $J = 6.1$ Hz), 1.08 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.8, 113.5, 82.3, 73.9, 52.9, 51.9, 38.8, 35.5, 31.9, 30.7, 24.9, 21.3.

**Methyl-1,6-dioxaspiro[4.4]nonane-3-carboxylic acid methyl ester (129)**

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with methylene iodide (0.43 mL, 5.30 mmol) in methylene chloride (10 mL) at 0 °C. The solution was treated with diethyl zinc (1M) in hexanes (5 mL, 5.00 mmol). After 10 minutes, the resulting white suspension was treated with 6-hydroxy-3-oxo-heptanoic acid methyl ester 120a/b (0.0955 g, 0.55 mmol) in methylene chloride (1 mL) via a syringe. After stirring for one hour, the reaction was treated with formaldehyde gas for 45 minutes. The formaldehyde gas was generated by heating paraformaldehyde that had been dried with the drying pistol (solvent: benzene; pressure: 1 mmHg). After treating the reaction mixture with formaldehyde gas, the reaction was allowed to stir for an additional hour and then quenched with saturated aqueous ammonium chloride (20 mL) and extracted three times with ethyl acetate (3 x 20 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator.

The reaction was repeated at the identical scale and the combined crude material from both reactions was dissolved in benzene (20 mL) and treated with p-toluenesulfonic acid monohydrate (0.2853 g, 1.50 mmol). The mixture was refluxed in a Dean-Stark trap for 18 hours. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator to provide an oily residue. The residue was subjected to flash column

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chromatography (5% ethyl acetate in hexanes) to provide a mixture of diastereomers, \( dr \) 2:1, 7-methyl-1,6-dioxa-spiro[4.4]nonane-3-carboxylic acid methyl ester 129 as a pale yellow oil (0.0564 g, 28%).

**mixture of diastereomers:** \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \( \delta \) 4.21 – 4.00 (m, 2.5 H): [4.15 (dd, \( J = 8.6, 8.6 \) Hz )], 3.97 (dd, 0.5H, \( J = 8.8, 6.1 \) Hz), 3.69 (s, 3H), 3.32 (dddd, 0.7H, \( J = 14.4, .5, 5.8, 5.2 \) Hz), 3.12 (dddd, 0.3H, \( J = 17.1, 10.5, 8.3, 6.7 \) Hz), 2.44 (dd, 0.5H, \( J = 13.5, 6.6 \) Hz), 2.27 (dd, 0.5H, \( J = 8.4, 4.6 \) Hz), 2.26 – 2.21 (m, 1H: [2.24 (dd, \( J = 8.6, 2.6 \) Hz )]), 2.13 – 2.00 (m, 2H), 1.70 (m, 1H), 1.46 (m, 1H), 1.27 (d, 1H, \( J = 6.1\)Hz), 1.26 (d, 0.5H, \( J = 6.2\)Hz), 1.20 (d, 1H, \( J = 6.1\)Hz), 1.19 (d, 0.5H, \( J = 6.2\)Hz), [impurity: hexanes, n-hexanes: \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\) \( \delta \) 0.88 (t), 1.26 (m)]; \(^13\text{C} \text{NMR (100 MHz, CDCl}_3\) \( \delta \) 174.5, 174.4, 174.3, 174.1, 115.3, 115.1, 114.8, 76.6, 76.5, 74.7, 74.6, 68.7, 68.6, 67.9, 67.7, 53.6, 52.2, 52.1, 43.4, 43.1, 42.9, 38.9, 38.8, 38.7, 38.0, 36.6, 36.1, 35.6, 34.6, 32.6, 32.5, 32.1, 32.0, 31.8, 22.8, 30.0, 29.8, 29.5, 23.0, 21.3, 21.2, [impurity: hexanes, n-hexanes: \(^13\text{C} \text{NMR (100 MHz, CDCl}_3\) \( \delta \) 14.1, 22.7, 31.6]. IR (film) 3458 (broad), 2967, 1739.

**6-(tert-Butyldimethylsilanyloxy)-3-oxo-heptanoic acid methyl ester (130)**

An oven-dried round-bottomed flask equipped with a stir bar and N\(_2\) gas-inlet, was charged with 6-hydroxy-3-oxo-heptanoic acid methyl ester 120a/b (1.391 g, 7.90 mmol) in DMF (15 mL). The resulting clear solution was treated with imidazole (0.5912 g, 8.70 mmol) and then with tert-butyldimethylchlorosilane (0.874 g, 8.70 mmol). After stirring for 24 hours at room temperature, the reaction mixture was diluted with distilled water (50 mL). The resulting aqueous mixture was extracted with hexanes (3 X 70 mL).
combined organic extracts were dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue. The residue was subjected to flash column chromatography (2 % ethyl acetate in hexanes) to yield 6-(tert-butyldimethylsilyl oxy)-3-oxo-heptanoic acid methyl ester 130 (1.411 g, 64 %) as a transparent, pale yellow oil.

β-keto ester: $^1$H NMR (400 MHz, CDCl$_3$) δ 3.80 (m, 1H), 3.74 (s, 3H), 3.48 (d, 1H, $J$ = 15.5 Hz), 3.44 (d, 1H, $J$ = 15.5 Hz), 2.69 - 2.53 (m, 2H), 1.74 (m, 1H), 1.55 (m, 1H), 1.13 (d, 3H, $J$ = 6.1 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); open chain and enol : $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.1, 167.9, 67.4, 52.7, 49.4, 39.4, 36.3, 33.2, 26.2, 24.0, 18.4, -4.0, -4.5.

7-(tert-Butyldimethylsilyl oxy)-4-oxo-octanoic acid methyl ester (131)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with methylene iodide (0.21 mL, 2.50 mmol) in methylene chloride (10 mL). The flask was placed in an ice-water bath (0 °C) and the solution was treated with diethyl zinc (1M) in hexanes (2.5 mL, 2.50 mmol). After 10 minutes, the resulting white suspension was treated, via a syringe, with 6-(tert-butyldimethylsilyl oxy)-3-oxo-heptanoic acid methyl ester 130 (0.1436 g, 0.50 mmol) dissolved methylene chloride (1 mL). The progress of the reaction was monitored by TLC and after 30 minutes the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and extracted twice with ethyl acetate (2 x 20 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary
evaporator followed by a vacuum pump to give 7-(tert-butyldimethylsilyloxy)-4-oxo-octanoic acid methyl ester 131 as a yellow oil (0.1455g, 96 %).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.82 (m, 1H), 3.68 (s, 3H), 2.74 (dt, 2H, $J = 6.9, 6.2$ Hz), 2.60 - 2.45 (m, 4H), 1.75 (ddd, 1H, $J = 13.8, 6.4, 4.4$ Hz), 1.65 (ddd, 1H, 13.8, 6.3, 6.0 Hz), 1.12 (d, 3H, $J = 6.1$ Hz), 0.88, (s, 9H), 0.045 (s, 3H), 0.035 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 209.2, 173.6, 67.8, 52.1, 39.0, 37.4, 33.4, 28.0, 26.2, 24.0, 18.4, -4.1, -4.5.

7-(tert-Butyldimethylsilyloxy)-2-hydroxymethyl-4-oxo-octanoic acid methyl ester (132)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with methylene iodide (0.81 mL, 10.0 mmol) in methylene chloride (45 mL) and then cooled in an ice-water bath (0 °C). The solution was treated with diethyl zinc (1M) in hexanes (10 mL, 10.0 mmol). After 10 minutes, the resulting white suspension was treated, via a syringe, with 6-(tert-butyldimethylsilyloxy)-3-oxo-heptanoic acid methyl ester 130 (0.5761 g, 1.99 mmol) in methylene chloride (5 mL). After stirring for 30 minutes, the reaction was treated with solid paraformaldehyde (0.2400 g, 8.00 mmol) which was added in one portion. After two hours, the reaction was quenched with saturated aqueous ammonium chloride (20 mL) and extracted three times with ethyl acetate (3 x 50 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide crude product as a white oily suspension. The crude product was subjected to flash column chromatography (3 % ethyl acetate in hexanes) to provided diastereomers and
hemiacetal forms of 7-(tert-butyldimethylsilanyloxy)-2-hydroxymethyl-4-oxo-octanoic acid methyl ester 132 (combined: 0.5610 g, 85 %) as pale yellow oils: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.89 – 3.74 (m, 3H), 3.71 – 3.68 (m: 3 x s, 3H), 3.09 (m, 1H, $J = 6.0$ Hz), 2.91 (dt, 1H, $J = 17.9$, 7.0 Hz), 2.74 (td, 1H, $J = 10.6$, 6.1 Hz), 2.60 – 2.45 (m, 2H), 1.78 – 1.58 (m, 2H), 1.12 (d, 3H, $J = 6.0$ Hz), 0.88 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (100 MHz) $\delta$ 209.1, 174.6, 67.8, 63.1, 52.4, 42.8, 41.1, 39.3, 33.4, 26.2, 24.0, 18.4, -4.1, -4.5.

(6R)-6-Hydroxy-3-oxo-heptanoic acid tert-butyl ester (134)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with THF (100 mL) and sodium hydride (60 %) in an oil dispersion (1.60 g, 39.1 mmol). The resulting white suspension was cooled by transferring the flask to an ice-water bath (0 °C). The white suspension was treated with t-butyl acetoacetate 49 (5.00 mL, 30.0 mmol). After 30 minutes, the reaction was cooled in an acetone-dry ice bath (–78 °C) and n-butyl lithium (2.5 M) in hexanes (18.00 mL, 45.00 mmol) was added by syringe in a 30 seconds time period. The mixture turned from yellow to a deep orange color as the dianion formed. After 45 minutes, $R$-propylene oxide (3.16 mL, 45.00 mmol) was added. After 18 hours, the reaction was quenched with a solution of saturated aqueous ammonium chloride (70 mL) and extracted three times with ethyl acetate (1 x 100 mL, 2 x 70). The combined organic layers was dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator to yield an oily orange residue. Flash column chromatography (15 % ethyl acetate in hexanes, $R_f$(134) = 0.1, to collect starting material #, followed by 30 % ethyl acetate in hexanes to collect the
product #) was performed on the residue to yield (6R)-6-hydroxy-3-oxo-heptanoic acid tert-butyl ester 134 (4.67 g, 72 %) as a pale, orange oil.

(The above procedure was also used to synthesize the achiral 6-hydroxy-3-oxo-heptanoic acid tert-butyl ester # by using racemic propylene oxide instead of R-propylene oxide. The yields for this reaction were similar.)

β-keto ester and hemiacetal: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.66 (s, 2H), 4.54 (s, 1H), 4.35 (m, 2.5H, $J = 6.4$ Hz), 4.17 (m, 1.5H, $J = 6.4$ Hz), 3.81 (broad, 1H), 3.37 (s, 2H), 2.72 - 2.57 (m, 10H), 2.18 (ddd, 2.5H, $J = 13.2, 8.5, 6.6$ Hz), 2.10 (m, 1.5H), 2.02 (m, 4H), 1.91 - 1.59 (m, 10H), 1.47 (m: multiple s, 45H), 1.32 (d, 4.5H, $J = 6.2$ Hz), 1.21 (d, 10.5H, $J = 6.2$ Hz); $^{13}$C NMR (100 MHz) $\delta$ 204.2, 171.7, 171.5, 104.3, 82.4, 82.1, 82.0, 77.6, 77.6, 75.2, 67.5, 50.9, 45.4, 39.5, 39.0, 37.9, 32.8, 32.4, 32.1, 28.5, 24.1, 23.2.

6-(tert-Butyldimethylsilyloxy)-3-oxo-heptanoic acid tert-butyl ester (135a)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with 6-hydroxy-3-oxo-heptanoic acid tert-butyl ester (1.139 g, 5.30 mmol) in DMF (10 mL). The resulting clear solution was treated with imidazole (0.3947 g, 5.80 mmol) and tert-butyldimethylchlorosilane (0.8739 g, 5.80 mmol). After stirring for 24 hours, distilled water (20 mL) was added. The resulting aqueous mixture was extracted three times with hexanes (3 x 50 mL). The combined organic extracts were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue. Flash column chromatography (3 % ethyl acetate in hexanes) was performed on the residue to yield 135a (1.499 g, 85 %) as a pale, transparent, yellow oil. β-keto ester 135a: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.84 (m, 1H), 3.36 (d, 1H $J = 15.3$ Hz), 3.28 (m, 1H), 3.20 (s, 2H), 2.75 (m, 10H), 2.15 (ddd, 2.5H, $J = 13.2, 8.5, 6.6$ Hz), 2.01 (m, 1.5H), 1.90 - 1.59 (m, 10H), 1.48 (m: multiple s, 45H), 1.33 (d, 4.5H, $J = 6.2$ Hz), 1.21 (d, 10.5H, $J = 6.2$ Hz).
3.35 (d, 1H, J = 15.3 Hz), 2.59 (m, 2H), 1.70 (m, 2H), 1.47 (s, 9H), 1.12 (d, 3H, J = 6.1 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 203.5, 166.6, 81.9, 67.5, 50.8, 39.0, 32.9, 28.0, 25.9, 23.8, 18.2, -4.3, -4.6.

7-(tert-Butyldimethylsilanyloxy)-4-oxo-octanoic acid tert-butyl ester (136a)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with methylene iodide (0.21 mL, 2.50 mmol) and methylene chloride (7 mL). The flask was placed in an ice-water bath (0 °C) to cool the solution and the solution was treated with diethyl zinc (1M) in hexanes (2.50 mL, 2.50 mmol) via a syringe. After 10 minutes, the resulting white suspension was treated with 6-(tert-butyldimethylsilanyloxy)-3-oxo-heptanoic acid t-butyl ester 135a (0.1579 g, 0.48 mmol) dissolved methylene chloride (1mL). The progress of the reaction was monitored by TLC and after 60 minutes the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted twice with ethyl acetate (2 x 20 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to give 7-(tert-butyldimethylsilanyloxy)-4-oxo-octanoic acid t-butyl ester 136a as a yellow oil (0.1391 g, 84 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.80 (m, 1H), 2.65 (m, 2H), 2.56 –2.42 (m, 4H), 1.75 – 1.56 (m, 2H), 1.41 (s, 9H), 1.09 (d, 3H, J = 6.1 Hz), 0.85 (s, 9H), 0.02, (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (100 MHz) $\delta$ 209.4, 172.4, 80.8, 67.9, 39.1, 37.5, 33.4, 29.5, 28.4, 26.2, 24.0, 18.4, -4.1, -4.5.
7-(tert-Butyldimethylsilanyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester (137a)

An oven-dried round-bottomed flask equipped with a stir bar and N₂ gas-inlet, was charged with methylene iodide (1.22 mL, 15.1 mmol) and methylene chloride (47 mL). The solution was cooled with an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (15 mL, 15.0 mmol) via a syringe. After 10 minutes, the resulting white suspension was treated, via a syringe, with 6-(tert-butyldimethylsilanyloxy)-3-oxo-heptanoic acid tert-butyl ester 135a (0.9893 g, 2.99 mmol) dissolved in methylene chloride (3 mL). After 45 minutes, reaction mixture was treated with the solid paraformaldehyde (0.3600 g, 12.0 mmol) which was added in one portion. After 2 hours, the reaction was quenched with a drop-wise addition of saturated aqueous ammonium chloride (20 mL) and extracted three times with ethyl acetate (3 x 70 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide the crude product as a white oily suspension. The crude product was subjected to column chromatography (5 % ethyl acetate in hexanes to isolate the more nonpolar products, followed by 50 % ethyl acetate in hexanes to isolate the material consisting mainly of the 4-keto ester). The target, 7-(tert-butyldiphenylsilanyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester 137a, was isolated as two species: i. a species which consisted mainly of the hemiacetal with traces of O-methylated material and ii. a species which consisted mainly of the 4-keto ester (hemiacetal: 0.2942 g, 26 %; 4-keto ester: 0.4536 g, 40 %) as a pale yellow oils.
Species with Hemiacetal as the major component; partial characterization 137a: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.01 (m), 3.84 (m), 3.62 - 3.42 (m), 3.18 (m), 3.01 - 2.85 (m), 2.48 (m), 2.25 - 1.57 (m), 1.439 (s, 9H), 1.12 (d, 3H, \(J = 6.1\) Hz), 0.88 (s, 9H).

Species with 4-keto ester as the major component 137a: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.82 (m, 1H), 3.76 (dd, 1H, \(J = 11.1, 5.5\) Hz), 3.73 (dd, 1H, \(J = 11.1, 5.0\) Hz), 2.97 (m, 1H), 2.84 (dd, 0.5H, \(J = 17.7, 7.0\) Hz), 2.82 (dd, 0.5H, \(J = 17.7, 6.7\) Hz), 2.68 (dd, 0.5H, \(J = 17.7, 6.1\) Hz), 2.66 (dd, 0.5H, \(J = 17.7, 6.3\) Hz), 2.73 - 2.63 (m, 1H), 2.60 - 2.44 (m, 2H), 1.78 - 1.54 (m, 2H), 1.5 (s, 9H), 1.12 (d, 3H, \(J = 6.1\) Hz), 0.88 (s, 9H), 0.08 - 0.04 (m, 6H) [partial characterization of hemiacetal: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.42 - 3.89 (m), 3.29 (m), 3.07 (m), 2.22 (m), 2.03 (m), 1.89 - 1.79 (m)]; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 209.0, 173.3, 81.5, 67.6, 63.1, 43.5, 41.1, 39.1, 33.2, 28.1, 25.9, 23.8, 18.2, -4.3, -4.6.

6-(tert-Butyldiphenylsilyloxy)-3-oxo-heptanoic acid tert-butyl ester (135b)

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and N\(_2\) gas-inlet was charged with 6-hydroxy-3-oxo-heptanoic acid tert-butyl ester 134 (4.67 g, 21.6 mmol) in DMF (20 mL). The resulting clear solution was treated with imidazole (1.89 g, 27.9 mmol) and tert-butyldiphenylchlorosilane (5.54 mL, 21.6 mmol). After 24 hours, the reaction was diluted with deionized water (40 mL). The resulting aqueous mixture was extracted three times with hexanes (3 x 60 mL). The combined organic extracts were dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue. Flash column chromatography (5 % ethyl acetate in hexanes, \(R_f(135b) = 0.15\)) was performed on the residue to yield 135b (9.82 g,
81 %) as a pale, transparent, yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66 (d, 4H, 8.0 Hz), 7.36 – 7.34 (m, 6H), 3.90 (m, 1H), 3.27 (d, 1H, \(J = 15.3\) Hz), 3.23 (d, 1H, \(J = 15.3\) Hz) 2.59 (ddd, 1H, \(J = 17.5, 9.3, 5.7\) Hz), 2.51 (ddd, 1H, \(J = 17.5, 9.3, 6.0\) Hz), 1.73 (m, 2H), 1.45 (s, 9H), 1.07 – 1.05 (m, 12H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.3, 166.5, 135.9, 134.8, 129.7, 127.7, 81.9, 68.5, 50.6, 38.6, 32.6, 28.0, 27.1, 23.2, 19.3.

7-(tert-Butyldiphenylsilanyloxy)-4-oxo-octanoic acid tert-butyl ester (136b)

An oven-dried round-bottomed flask equipped with a stir bar and \(N_2\) gas-inlet was charged with methylene iodide (0.21 mL, 2.50 mmol) in methylene chloride (3.0 mL). The flask was placed in an ice-water bath (0 °C) to cool the solution and the solution was treated with diethyl zinc (1M) in hexanes (2.5 mL, 2.50 mmol) via a syringe. After 10 minutes, the resulting white suspension was treated with 6-(tert-butyldiphenylsilanyloxy)-3-oxo-heptanoic acid \(t\)-butyl ester 135b (0.2273 g, 0.50 mmol) dissolved methylene chloride (1 mL) via a syringe. The progress of the reaction was monitored by TLC and after 60 minutes the reaction was quenched with saturated aqueous ammonium chloride (5 mL) and extracted twice with ethyl acetate (2 x 10 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to give 7-(tert-butyldiphenylsilanyloxy)-4-oxo-octanoic acid \(t\)-butyl ester 136b as a yellow oil with TBDPSOH as an impurity (0.1252g, 53 %). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.73 – 7.71 (m, 4H), 7.68 – 7.65 (m, 6H), 7.45 - 7.35 (m, 17H), 3.89 (m, 1H), 2.67 – 2.53 (m, 3H), 2.51 – 2.37 (m, 3H), 1.79 – 1.65 (m, 2H), 1.43 (s, 9H), 1.07 (m, 12H) [impurity
TBDPSOH: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.05 (s, 17H); $^{13}$C NMR (125 MHz) $\delta$ 209.2, 172.2, 136.0, 129.7, 127.7, 60.7, 68.9, 38.5, 37.3, 33.1, 29.3, 28.3, 27.1, 23.3, 19.4; [impurity TBDPSOH: $^{13}$C NMR (125 MHz) $\delta$ 135.9, 129.6, 127, 826.7, 19.2].

7-(tert-Butyldiphenylsilyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester (137b)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet, was charged with 6-(tert-butyldiphenylsilyloxy)-3-oxo-heptanoic acid tert-butyl ester 135b (1.8118 g, 4.00 mmol) in methylene chloride (50 mL). The solution was cooled with an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (20 mL, 20.0 mmol), via a syringe. Gas evolution was observed. After 10 minutes, the mixture was treated with methylene iodide (1.62 mL, 20.0 mmol). After 30 minutes, the resulting white suspension was treated with the solid paraformaldehyde (0.600 g, 20.0 mmol) which was added in one portion. After three hours, the reaction was quenched with saturated aqueous ammonium chloride (40 mL) and extracted three times with ethyl acetate (3 x 70 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide the crude product as a white oily suspension. The crude product was passed through a Si-plug (30% ethyl acetate in hexanes) to provide 7-(tert-butyldiphenylsilyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester 137b (1.8185 g, 91%) as a pale yellow oil:

4-keto ester and hemiacetal 137b: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 –7.65 (m, 17H), 7.45 –7.35 (m, 25H), 4.22 – 3.94 (m, 3.5H), 3.88 (m, 4H), 3.76 – 3.67 (m, 6.5H), 3.30 (m, 1H), 3.20 (m, 1H), 2.93 (m, 3H), 2.75 (dd, 2H, $J = 17.6, 6.9$ Hz), 2.67 (dd, 2.5H, $J =$
7-(tert-Butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid tert-butyl ester (138)

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and N\textsubscript{2} gas-inlet was charged with 7-(tert-butyldiphenylsilyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester 137\textsubscript{b} (0.9061 g, 1.82 mmol) in DMF (10 mL). The resulting clear solution was treated with imidazole (0.1486 g, 2.18 mmol) and tert-butyldiphenylchlorosilane (0.47 mL, 1.82 mmol). After stirring for 24 hours, the reaction was diluted with deionized water (10 mL). The resulting aqueous mixture was extracted three times with hexanes (3 x 30 mL). The combined organic extracts was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue. Flash column chromatography (2 % ethyl acetate in hexanes followed by 30 % ethyl acetate in hexanes) was performed on the residue to yield 7-(tert-butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid tert-butyl ester 138 (0.7641 g, 62 %) as a pale, transparent, yellow oil.\textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.71 – 7.65 (m, 8H), 7.47 – 7.35 (m, 12H), 3.91 (m, 2H), 3.74 (dt, 1H, \(J = 9.8, 4.6\) Hz), 3.04 – 2.86 (m, 2H), 2.58 – 2.36 (m, 4H), 1.73 (m, 2H), 1.46 (s, 9H), 1.08 (s, 21H), [impurity: TBDPSOH: \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.76 – 7.73 (m), 7.47 – 7.35 (m), 1.09 (s)]; \textsuperscript{13}C NMR (90 MHz, CDCl\textsubscript{3}) \(\delta\) 209.1, 172.5, 135.9, 135.7,
7-(tert-Butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid (139)

An oven-dried round-bottomed flask was equipped with a stir bar and N\textsubscript{2} gas-inlet and a condenser. The flask was charged with 7-(tert-butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid tert-butyl ester 138 (0.7641 g, 1.04 mmol), anhydrous \textit{p}-toluenesulfonic acid (0.0534 g, 0.31 mmol) and toluene (10 mL). The mixture was refluxed for approximately 6 hours. After cooling the reaction mixture to room temperature, the solvent was evaporated under vacuum to yield a brown residue. The residue was subjected to column chromatography (10% ethyl acetate in hexanes) to provide 7-(tert-butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid 139 as a yellow oil (0.2931 g, 41%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.67–7.61 (m, 10H), 7.39–7.35 (m, 14H), 3.88 (m, 2H), 3.78 (m, 1H), 3.10 (m, 1H), 2.87 (td, 1H, \( J = 18.1, 8.1 \) Hz), 2.61–2.33 (m, 3H), 1.69 (m, 2H), 1.05–1.03 (m, 21H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 208.9, 178.1, 136.1, 136.0, 135.8, 134.9, 130.1, 129.9, 128.0, 68.9, 64.1, 42.7, 40.6, 38.8, 33.1, 27.3, 27.0, 25.9, 23.5, 19.5.

1,7-Bis-(tert-butyldiphenylsilyloxy)-octan-4-one (140)

An oven-dried round-bottomed flask was wrapped in aluminum foil and equipped with a stir bar and N\textsubscript{2} gas-inlet. The flask was charged with 7-(tert-butyldiphenylsilyloxy)-2-(tert-butyldiphenylsilyloxymethyl)-4-oxo-octanoic acid
139 (0.0711 g, 0.10 mmol) in methylene chloride (2 mL) and N-hydroxythiopyridinone (0.0133 g, 0.11 mmol) followed by dicyclohexylcarbodiimide (0.0222 g, 0.11 mmol). After 1 hour, the mixture was filtered through a pipette plugged with glass wool into a vial wrapped in aluminum foil. A white residue and a pale yellow filtrate were collected. The pale yellow filtrate was evaporated on a rotary evaporator without heating, in the vial wrapped in aluminum foil. The crude residue was analyzed by $^1$H and $^{13}$C NMR spectroscopy to ensure that the N-hydroxy ester had formed. The presence of the N-hydroxy ester was confirmed by the presence of the ester’s carbonyl-resonance at ~ 176 ppm in the $^{13}$C NMR spectrum of the crude product (The starting material # exhibited a more downfield shift of ~ 178.1 ppm for carbonyl-resonance of the carboxylic acid.).

An oven-dried 100-mL round-bottomed flask was wrapped with aluminum foil and equipped with a stir bar and N$_2$ gas inlet. The flask was charged with the crude N-hydroxy ester of 139 dissolved in THF (11.2 mL) and tributyltin hydride (0.32 mL, 1.19 mmol) which was added via a syringe. The foil wrapping was removed and the flask was illuminated with a 150 W-lamp. After 18 hours, the solvent was evaporated on a rotary evaporator to provide a crude yellow oily residue. The residue was subjected to column chromatography (pure hexanes to isolate excess tributyltin hydride followed by 10% ethyl acetate in hexanes). The target, 1,7-bis-(tert-butyldiphenylsilyloxy)-octan-4-one 140 was isolated as a yellow oil (0.0161 g, 25%).

$^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.68 – 7.64 (m, 8H), 7.44 – 7.32 (m, 12H), 3.88 (m, 1H), 3.64 (t, 2H, $J$ = 6.1 Hz), 2.51 – 2.30 (m, 4H), 1.81 – 1.64 (m, 4H), 1.05 (s, 21H); $^{13}$C NMR (90 MHz, CDCl$_3$) $\delta$ 210.9, 136.0, 135.9, 135.7, 134.8, 134.3, 133.9, 129.8, 129.7, 127.8, 127.7, 127.6, 68.1, 65.2, 39.2, 38.6, 33.1, 29.9, 27.2, 27.0, 26.8, 23.4, 19.4.
Dioxospiro[4.4]nonane (144)

Part 1: Formation of the carboxylic acid 143

An oven-dried 100-mL round-bottomed flask, equipped with a stir bar and N₂ gas-inlet, was charged with 7-(tert-butyldiphenylsilyloxy)-2-hydroxymethyl-4-oxo-octanoic acid tert-butyl ester 141 (2.655 g, 5.33 mmol) and THF (12 mL). The resulting pale yellow solution was treated with tetrabutylammonium fluoride (1M) in THF (13.3 mL, 13.3 mmol). The reaction was monitored by TLC and after approximately 2 hours, the dark orange reaction mixture was diluted with distilled water (20 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 x 60 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to provide the crude product as a yellow oil which consisted of TBDPS-F and the deprotected aldol product.

The crude product mixture from above was dissolved in methylene chloride (10.9 mL) and transferred to oven-dried 100-mL round-bottomed flask equipped with a stir bar and N₂ gas-inlet. The resulting solution was treated with trifluoroacetic acid, TFA, (13.1 mL, 170.6 mmol). After 20 minutes, the reaction mixture was evaporated on rotary evaporator. The resulting residue was diluted with methylene chloride (3 mL) and benzene (1 mL) and the resulting mixture was evaporated on a rotary evaporator. The dilution and evaporation process with methylene chloride and benzene was repeated three times. The resulting brown residue was subjected to column chromatography (10 % ethyl acetate in hexanes to separate TBDPS-F followed by 10 % methanol in ethyl acetate to isolate the carboxylic acid 143). The carboxylic acid 143 was isolated as a yellow oil.
(0.8289 g, 76%). The carboxylic acid exhibited a resonance for the carbonyl at ~178 ppm in its $^{13}$C NMR-spectrum.

Part 2: Barton Decarboxylation

A 20-mL scintillation vial equipped with a stir bar, 24/40 septum and N$_2$ gas-inlet, was charged with 7-hydroxy-2-hydroxymethyl-4-oxo-octanoic acid 143 (0.2249 g, 1.23 mmol) and methylene chloride (5.15 mL). The vial was wrapped in aluminum foil and treated sequentially with N-hydroxythiopyridinone (0.1569 g, 1.24 mmol) and dicyclohexylcarbodiimide (DCC) (0.2547 g, 1.24 mmol), in the order mentioned. After 2 hours, the reaction mixture was subjected to gravity filtration and the resulting filtrate was collected in an oven-dried round-bottomed flask wrapped in aluminum foil. The filtrate was concentrated on a rotary evaporator with a room temperature water bath to provide a gray solid consisting of the N-hydroxythiopyridinone ester and traces of DCC and TBDPSOH. The presence of the N-hydroxythiopyridinone ester was determined from the $^1$H NMR and $^{13}$C NMR of the crude product mixture. In the $^{13}$C NMR spectrum in particular, the carbonyl of the ester had a resonance that was shifted upfield of the carbonyl-resonance for the carboxylic acid 143.

Wrapped in aluminum foil, the round-bottomed flask containing the crude N-hydroxythiopyridinone ester was equipped with a stir bar, septum and a N$_2$ gas-inlet and charged with methylene chloride (30 mL). $t$-Butylmercaptan (1.42 mL, 12.3 mmol) was added via a syringe. The resulting mixture was cooled in an ice-water bath (0 °C). The foil was removed and the reaction mixture was illuminated with a lamp (150 W). Throughout the reaction, the ice-water bath temperature was maintained between 0 - 5 °C. After 1 hour and 30 minutes, the reaction mixture was concentrated on a rotary
evaporator and the residue was subjected to column chromatography to provide 2-methyl-1,6-dioxo-spiro[4.4]nonane 144 (0.741 g, 42 %) and recovered material consisting mainly of the carboxylic acid 143 (0.0600 g, < 26 %).

[NB.: 1. The pyridine byproduct of this reaction may be isolated with the target 144 after column chromatography, this mixture can be dissolved in methylene chloride and treated with aqueous HCl (5M). After ~ 30 minutes of stirring at room temperature, extraction with a low-boiling organic solvent can be performed to retrieve the target 144. 2. The spiroketal 144 has a low boiling point and therefore, solvent should be removed without heating at pressures greater than 20 mmHg]

2 isomers: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.21 (m, 1.5H, $J = 6.4$ Hz), 4.12 (m, 1H), 3.99 (m, 1H), 3.92 (m, 1.5H), 3.86 (m, 1.5H), 3.81 (m, 1H), 2.18 – 1.47 (m, 20H), 1.22 (d, 3H, $J = 6.1$ Hz), 1.30 (d, 4.5H, $J = 6.1$ Hz) [contains impurities: hexanes: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.26 (m), 0.88 (t, 3H) and TBDPSOH-phenyl resonances: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.72 – 7.63 (m), 7.44 – 7.36]; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 114.9, 114.8, 76.2, 74.3, 67.1, 36.5, 35.5, 35.4, 35.1, 32.8, 32.2, 24.9, 24.6, 21.3; [contains impurities: hexanes: $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 31.6, 22.7, 14.1 and TBDPSOH].

2-[5-(tert-Butyldiphenylsilanyloxy)-2-oxo-hexyl]-3-hydroxy-5-trimethylsilyl-pent-4-ynoic acid tert-butyl ester (153)

An oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet was charged with 6-(tert-butyldiphenylsilanyloxy)-3-oxo-heptanoic acid tert-butyl ester 152 (1.810 g, 3.99 mmol) in methylene chloride (40 mL). The solution was cooled with an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (20 mL, 20.0 mmmol),
via a syringe. Gas evolution was observed. After 10 minutes, the mixture was treated with methylene iodide (1.61 mL, 20.0 mmol). After 30 minutes, the resulting white suspension was treated with the 3-trimethylsilylpropynal (0.86 mL, 6.0 mmol) via a syringe. The reaction was monitored by TLC, and after 20 minutes the reaction was quenched with saturated aqueous ammonium chloride (40 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide the crude product as an oil. The crude product was subjected to column chromatography (10 % ethyl acetate in hexanes) to provide 2-[5-(tert-butyldiphenylsilanyloxy)-2-oxo-hexyl]-3-hydroxy-5-trimethylsilyl-pent-4-ynoic acid tert-butyl ester 152 (combined: 1.435 g, 60 %) as a pale yellow oil:

opened chain and hemiacetal: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.73- 7.67 (m, 17H), 7.44 – 7.06 (m, 25H), 4.61 (m, 3H), 3.91 (m, 4H), 3.14 (m, 4H), 3.06 (m, 1.5H), 2.92 (dt, 3H, $J$ = 17.6, 8.8 Hz), 2.87 – 2.73 (m, 3H), 2.64 – 2.42 (m, 9H), 1.74 (m, 10H), 1.63 (m, 3H), 1.45 (s, 24H), 1.06 (s, 40H), 0.18 (s, 7H), 0.17 (s, 23H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 208.9, 171.4, 136.2, 135.1, 129.9, 127.9, 91.1, 82.3, 69.1, 63.6, 47.4, 40.1, 39.2, 33.2, 31.1, 28.3, 27.4, 23.5, 19.6, 9.7, 0.22.

**2-Ethynyl-7-methyl-1,6-dioxaspiro[4.4]nonane (155)**

Part 1: Formation of the carboxylic acid 154

An oven-dried 100-mL round-bottomed flask, equipped with a stir bar and N$_2$ gas-inlet, was charged with 2-[5-(tert-butyldiphenylsilanyloxy)-2-oxo-hexyl]-3-hydroxy-5-trimethylsilyl-pent-4-ynoic acid tert-butyl ester 153 (1.719 g, 3.00 mmol) and THF (15
mL). The resulting pale yellow solution was treated with tetrabutylammonium fluoride (1M) in THF (7.5 mL, 7.5 mmol). The reaction was monitored by TLC and after 2 hours, the dark orange reaction mixture was diluted with deionized water (20 mL). The resulting aqueous mixture was extracted three times with ethyl acetate (3 x 60 mL). The combined organic layers was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to provide the crude product as a yellow oil which consisted of TBDPS-F, TMS-F and the fully-desilated aldol product.

The crude product mixture from above was dissolved in methylene chloride (4.10 mL) and transferred to a 20-mL scintillation vial equipped with a stir bar, 24/40 septum and a N₂ gas-inlet. The resulting solution was treated with trifluoroacetic acid, TFA, (4.91 mL, 64 mmol). After 20 minutes, the reaction mixture was evaporated on rotary evaporator. The resulting residue was diluted with methylene chloride (3 mL) and benzene (1 mL) and the resulting mixture was evaporated on a rotary evaporator. The dilution and evaporation process with methylene chloride and benzene was repeated three times. The brown residue was subjected to column chromatography (10 % ethyl acetate in hexanes to isolate TBDPS-F followed by 10 % methanol in ethyl acetate to isolate the carboxylic acid 154). The carboxylic acid 154 was isolated as a yellow oil (0.6301 g, 61 %). The carboxylic acid exhibited a resonance for the carbonyl at ~178 ppm in its 13C NMR-spectrum.

Part 2: Barton Decarboxylation

A 20-mL scintillation vial equipped with a stir bar, 24/40 septum and N₂ gas-inlet, was charged with 2-ethynyl-7-methyl-1,6-dioxa-spiro[4.4]nonane-3-carboxylic acid 154...
(0.3881 g, 1.37 mmol) and methylene chloride (5.00 mL). The vial was wrapped in aluminum foil and the solution was treated sequentially with N-hydroxythiopyridinone (0.1784 g, 1.37 mmol) and dicyclohexylcarbodiimide (0.2835 g, 1.37 mmol). After 2 hours, the reaction mixture was subjected to gravity filtration through a pipette plugged with glass wool. The resulting filtrate was collected in a 100-mL oven-dried round-bottomed flask wrapped in aluminum foil. With the flask wrapped in aluminum foil, the filtrate was concentrated on a rotary evaporator with a room temperature water bath to provide a gray solid consisting of the N-hydroxythiopyridinone ester and traces of DCC and t-butyldiphenyl and trimethylsilyl-byproducts. The presence of the N-hydroxythiopyridinone ester was determined from the 1H NMR and 13C NMR of the crude product mixture. In the 13C NMR spectrum, the carbonyl of the ester had a resonance that was shifted upfield of the carbonyl in the carboxylic acid 154.

Wrapped in aluminum foil, the flask containing the crude N-hydroxythiopyridinone ester was equipped with a stir bar, septum and a N2 gas-inlet. Methylene chloride (30 mL) and t-butyldercaptan (1.59 mL, 13.7 mmol) were added to the flask, in the order mentioned. The resulting mixture was cooled in an ice-water bath (0 °C). The foil was removed and the reaction mixture was illuminated with a lamp (150 W). Throughout the reaction, the ice-water bath temperature was maintained between 0 - 5 °C. After 1 hour and 30 minutes, the reaction mixture was concentrated on a rotary evaporator and the residue was subjected to column chromatography (10 % ethyl acetate in hexanes) to provide a mixture of 2-ethynyl-7-methyl-1,6-dioxa-spiro[4.4]nonane 155, the byproduct bispyridine disulfide and traces of silyl compounds. The spiroketal 155 has a low boiling point and therefore, evaporation of the organic solvent was performed on a rotary
evaporator with a room temperature water bath. The pressure on the rotary evaporator was never less than 40 mmHg.

The bispyridine-byproduct was removed by dissolving the mixture in methylene chloride and washing the resulting solution with concentrated aqueous HCl. After the acidic wash, the organic layer was washed with concentrated aqueous sodium bicarbonate, deionized water and brine in the order mentioned. The neutralized organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator with a room temperature water bath and a pressure above ~40 mmHg. The target, 2-ethynyl-7-methyl-1,6-dioxa-spiro[4.4]nonane, was provided as a yellow oil (0.0469g, <21 %) with the silyl-byproducts as impurities.

4 isomers: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.77 (ddd, 2H, $J = 7.3, 5.1, 2.1$ Hz), 4.70 (ddd, 3H, $J = 7.8, 5.8, 2.1$ Hz), 4.66 – 4.59 (m, 2H), 4.33 (m, 1H, $J = 6.4$ Hz), 4.26 – 4.12 (m, 6H), 2.46 – 2.44 (4 x s, 7H), 2.42 – 2.33 (m, 6H), 2.29 – 1.89 (m, 50 H), 1.82 – 1.68 (m, 4H), 1.53 – 1.42 (m, 8H), 1.34 (d, 2H, $J = 6.2$), 1.29 (d, 7H, $J = 6.2$ Hz), 1.22 (d, 4H, $J = 5.9$ Hz), 1.21 (m, 8H, $J = 6.1$ Hz); [impurity: TBDPSOH: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.73 – 7.71, 7.42 – 7.25, 1.07]; $^{13}$C NMR (100 MHz) δ 115.8, 115.6, 115.5, 84.9, 84.8, 84.2, 83.9, 77.6, 76.8, 74.8, 73.1, 72.9, 72.7, 67.7, 67.6, 66.9, 66.1, 37.1, 36.6, 36.0, 35.6, 35.5, 35.4, 35.1, 34.9, 33.0, 32.9, 32.8, 32.7, 32.6, 32.4, 32.1, 32.0, 23.1, 22.9, 21.6, 21.4; [impurity: TBDPSOH: $^{13}$C NMR (125 MHz, CDCl$_3$) δ 135.1, 129.9, 127.9, 26.9].

7-Bromoheptanol (171)

A 250-mL flask equipped with a stir bar and reflux condenser was charged sequentially with 1,7-heptanediol (0.7 mL, 5 mmol), toluene (20 mL) and aqueous HBr
(48%) (0.85 mL, 7.5 mmol). The reaction mixture was heated to reflux. After 20 hours, the reaction was cooled to room temperature and diluted with ether (50 mL). The resulting mixture was washed twice with aqueous sodium bicarbonate (5%) (2 x 20 mL) and then once with brine (20 mL). The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator. Column chromatography (10% ethyl acetate in hexanes followed by 20% ethyl acetate in hexanes) of the residue provided 7-bromoheptanol 171 (0.764 g, 78%) as a yellow oil. 

\[ \text{H NMR (500 MHz, CDCl}_3 \text{)} \delta 3.65 (\text{td, 2H, } J = 6.6, 1.8 \text{ Hz}), 3.41 (\text{td, 2H, } J = 6.8, 1.1 \text{ Hz}), 1.87 (\text{m, 2H}), 1.70 (\text{b, 1H}), 1.57 (\text{m, 2H}), 1.45 (\text{m, 2H}), 1.39 - 1.34 (\text{m, 4H}); \text{C NMR (125 MHz)} \delta 63.1, 34.2, 32.9, 28.8, 28.4, 25.9. \]

(7-Bromoheptyloxy)-tert-butyldimethylsilane (172) 

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and N\textsubscript{2} gas-inlet was charged with 7-bromoheptanol 171 (4.727 g, 24.2 mmol), methylene chloride (73 mL), N, N-dimethylaminopyridine (catalytic amount), tert-butyldimethylchlorosilane (4.390 g, 29.1 mmol) and freshly distilled triethylamine (6.80 mL, 48.9 mmol). After 24 hours, the reaction was quenched with aqueous HCl (1N) (30 mL). The resulting mixture was extracted with diethyl ether (1 x 100 mL, 1 x 50 mL). The combined organic layers were washed twice with concentrated aqueous sodium bicarbonate (2 x 60 mL), once with deionized water (60 mL) and once with brine (60 mL). The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and evaporated on a rotary evaporator. The resulting yellow oil was subjected to column chromatography (0.5% ethyl acetate in
hexanes) to provide (7-bromoheptyloxy)-*tert*-butyldimethylsilane 172 (6.585 g, 87 %) as a transparent, colorless oil.

\[^1\text{H} \text{NMR} \ (500 \text{ MHz, CDCl}_3) \delta 3.59 \ (t, \ 2\text{H}, J = 6.5 \text{ Hz}), \ 3.99 \ (t, \ 2\text{H}, J = 6.9 \text{ Hz}), \ 1.85 \ (m, \ 2\text{H}), \ 1.51 \ (m, \ 2\text{H}), \ 1.43 \ (m, \ 2\text{H}), \ 1.36 – 1.30 \ (m, \ 4\text{H}), \ 0.89 \ (s, \ 9\text{H}), \ 0.04 \ (s, \ 6\text{H}); \ ^{13}\text{C} \text{NMR} \ (125 \text{ MHz}) \delta 63.5, 34.3, 33.1, 33.0, 28.9, 28.5, 26.3, 25.9, 18.7, -4.9.

8-(*tert*-Butyldimethylsilanyloxy)octanal (178)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and N\textsubscript{2} gas-inlet was charged with 1,8-octanediol (23.79 g, 160 mmol), imidazole (5.45 g, 80 mmol) and DMF (150 mL). The mixture was stirred until all the solids completely dissolved to form a transparent, colorless solution. The solution was treated with *tert*-butyldimethylchlorosilane (12.05 g, 80 mmol). After stirring under nitrogen for 24 hours, the reaction was diluted with deionized water (80 mL) and extracted with hexanes (3 x 150 mL). The combined organic extracts were dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator to yield 8-(*tert*-butyldimethylsilanyloxy)octanol as a transparent colorless oil as the crude product (25.87 g). The crude material was used in the next step.

An oven-dried 250-mL round-bottomed flask, equipped with a stir bar and nitrogen gas inlet was charged with crude material of 8-(*tert*-butyldimethylsilanyloxy)-octanol (8.67 g), celite (14.35 g) and methylene chloride (135 mL). The mixture was cooled to 0 °C and treated with pyridinium chlorochromate (PCC) (10.79 g, 50.1 mmol). After 30 minutes, the black suspension was treated with hexanes (100 mL). The resulting mixture was vacuum filtered through celite and the filter cake was washed with hexanes (50 mL).
The combined filtrate was concentrated on a rotary evaporator resulting in a black residue. The black residue was treated with hexanes (150 mL) and the resulting suspension was filtered under vacuum through celite. The filtrate was concentrated on a rotary evaporator to give a thick black oil. The oil was subjected to flash column chromatography (10 % ethyl acetate in hexanes, R_f = 0.5) to yield the aldehyde, 8-(tert-butyl(dimethyl)silyloxy)octanal 178 (7.26 g, < 35 %) as a transparent, colorless oil with 1,8-bis-(tert-butyl(dimethyl)silyloxy)octane as an impurity. ^1H NMR (400 MHz, CDCl_3) \( \delta \) 9.76 (s 1H), 3.60 (t, 2H, \( J=6.7 \) Hz), 2.43 (q, 2H, \( J=7.2 \) Hz), 1.62 (m, 2H), 1.51 (m, 2H), 1.33 (m, 6H), 0.89 (s, 9H), 0.056 (s, 6H); ^13C NMR (100 MHz) \( \delta \) 202.9, 63.3, 44.0, 32.9, 29.3, 26.1, 22.2, 18.5, -5.1.

8-(tert-Butyl(dimethyl)silyloxy)-1-(3,5-dimethoxyphenyl)-octan-1-ol (173)

A 250-mL oven-dried round-bottomed flask, equipped with a stir bar, a condenser and a nitrogen gas-inlet, was charged with magnesium (0.6247 g, 26.0 mmol), a few crystals of iodine (catalytic amounts) and THF (15 mL). The mixture was heated to reflux and then, via a syringe with an 8-inch needle, treated with 3,5-dimethoxybromobenzene 179 (5.651 g, 26.0 mmol) dissolved in THF (15 mL). This solution was added drop-wise, via a syringe. During addition of the 3,5-dimethoxybromobenzene, the purple reaction solution became transparent and developed a pale yellow color. After 45 minutes, when most of the magnesium had reacted, the refluxing mixture was treated with a drop-wise addition of 8-(tert-butyldimethyl)silyloxy)octanal 178 (5.728 g, 22.1 mmol) dissolved in THF (15 mL) via a syringe with an 8-inch needle. The progress of this reaction was monitored by TLC. After 3 hours, the reaction was cooled to room temperature and then
further cooled in an ice-water bath (0 °C). The reaction was quenched with aqueous HCl (1 M) (15 mL). After approximately five minutes after the addition of the aqueous HCl, the mixture was extracted with ethyl acetate (3 x 90 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to give a the thick brown oil. The oil was subjected to flash column chromatography (10 % ethyl acetate in hexanes) to yield 8-(tert-butyldimethylsilanyloxy)-1-(3,5-dimethoxy-phenyl)octan-1-ol 173, (7.698 g, 88 %) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 6.45 (s, 2H), 6.31 (s, 1H), 4.53 (t, 1H, $J$ = 5.8 Hz), 3.74 (s, 6H), 3.54 (t, 2H, $J$ = 6.6 Hz), 2.04 (broad, 1H), 1.76 – 1.58 (m, 2H), 1.45 (t, 2H, $J$ = 6.6 Hz), 1.36 (m, 1H), 1.28 – 1.18 (m, 7H), 0.85 (s, 9H), 0.00 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.1, 147.9, 104.1, 99.6, 74.9, 63.6, 55.6, 39.3, 33.2, 29.8, 29.7, 26.2, 26.1, 18.7, -4.9.

1-(3,5-Dimethoxyphenyl)octane-1,8-diol (180)

A 250-mL oven-dried round-bottomed flask equipped with a stir bar and nitrogen gas-inlet was charged with magnesium (0.3659 g, 15.2 mmol), a few crystals of iodine (catalytic amount) and THF (12 mL). The flask was fitted with a condenser and the mixture heated. Once the purple solution started to reflux, 3,5-dimethoxybromobenzene 179 (3.309 g, 15.0 mmol) dissolved in THF (12 mL) was added drop-wise via a syringe with an 8-inch needle. During addition of the 3,5-dimethoxybromobenzene, the purple solution became transparent and colorless. After 45 minutes, when most of the magnesium had reacted, the refluxing mixture was treated with a drop-wise addition of 8-(t-butyldimethylsilanyloxy)octanal 178 (3.548 g, 13.7 mmol), via a syringe with an 8-
inch needle. After 4 hours, the reaction was cooled to room temperature and then further cooled in an ice-water bath (0 °C). The cooled mixture was treated with aqueous HCl (1 M) (15 mL) and stirred for 4 hours. The resulting mixture was periodically observed with TLC. Upon completion of the reaction, the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried with sodium sulfate, decanted from sodium sulfate and concentrated on a rotary evaporator to give a thick brown oil. The oil was subjected to flash column chromatography (10 % ethyl acetate in hexanes, Rf (180) = 0.1, followed by 70 % ethyl acetate in hexanes to collect the product) to yield a yellow solid 1-(3,5-dimethoxyphenyl)octane-1,8-diol 180 (2.558 g, < 66 %) with traces of an uncharacterized phenyl impurity. [NB: The pure compound is white with mp 57 – 59 °C.]; 1H NMR (400 MHz, CDCl3) δ 6.50 (d, 2H, J = 2.3 Hz), 6.37 (t, 1H, J = 2.3 Hz), 4.59 (dd, 1H, J = 7.3, 5.8 Hz), 3.79 (s, 6H), 3.63 (dd, 2H, J = 10.8, 6.3 Hz), 1.89 (b, 1H), 1.82 - 1.65 (m, 2H), 1.63 (m, 1H), 1.55 (m, 2H), 1.42 (m, 1H), 1.31 (m, 7H); 13C NMR (100 MHz, CDCl3) δ 160.9, 147.7, 103.9, 99.4, 74.9, 63.2, 55.5, 39.1, 32.9, 29.6, 29.4, 25.9, 25.8.

8-acetoxy-1-(3,5-dimethoxyphenyl)octyl acetate (181)

An oven-dried 100-mL round-bottomed flask, equipped with a stir bar and nitrogen gas inlet was charged with 1-(3,5-dimethoxyphenyl)octane-1,8-diol 180 (1.84 g, 6.45 mmol) dissolved in distilled pyridine (10.5 mL, 128.2 mmol). The pale yellow solution was treated with a catalytic amount of dimethylaminopyridine and then cooled in an ice-water bath (0 °C). At this temperature, acetic anhydride (12.1 mL, 128.2 mmol) was added via a syringe and the reaction mixture was allowed to warm to room temperature.

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After 3 hours, the mixture was again cooled in an ice-water bath (0 °C) and deionized water (20 mL) was added slowly at a rate that prevented the reaction mixture from heating and foaming as the water was added. Extraction was performed with ether (3 x 80 mL). Aqueous washes of the combined organic layers were performed in the following order: i. once with water (40 mL), ii. twice with aqueous HCl (1 M) (2 x 40 mL) [NB. The ether- mixture was stirred for ~10 mins. with the aqueous HCl-washes in order to effectively remove the pyridine], iii. three times with concentrated aqueous sodium carbonate (3 x 40 mL). Once effervescence was no longer observed with the addition of the concentrated aqueous sodium bicarbonate, the organic layer is washed with water (40 mL), and brine (40 mL), dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by drying on a vacuum pump to yield 8-acetoxy-1-(3,5-dimethoxyphenyl)octyl acetate 181 (2.06 g, 86 %) as a yellow oil. If pyridine was still present after evaporation of the solvent, repeat the three aqueous washes. The 8-acetoxy-1-(3,5-dimethoxyphenyl)octyl acetate 181 is stored over 4 Å MS sieves before being subjected to the Vilsmeier-Haack reaction. \(^1\)H NMR (400 MHz, CDCl₃) δ 6.47 (s, 2H), 6.38 (s, 1H), 5.64 (t, 1H, \(J = 7.3\) Hz), 4.04 (t, 2H, \(J = 5.5\) Hz), 3.79 (s, 6H), 2.08 (s, 3H), 2.05 (s, 3H), 1.87 (m, 1H), 1.74 (m, 1H), 1.61 (m, 2H), 1.36 - 1.29 (m, 8H); \(^{13}\)C NMR (100 MHz) δ 171.5, 170.6, 160.9, 143.5, 104.8, 99.7, 76.2, 64.8, 55.5, 36.5, 29.4, 29.3, 28.8, 26.0, 25.6, 21.5, 21.2.
8-acetoxy-1-(2-formyl-3,5-dimethoxyphenyl) octyl acetate (183)

8-acetoxy-1-(4-formyl-3,5-dimethoxyphenyl) octyl acetate (184)

An oven-dried 10-mL round-bottomed flask, equipped with a stir bar, a condenser and nitrogen gas inlet, was charged with freshly acquired DMF (1.08 mL, 13.9 mmol) and methylene chloride (2.5 mL), each via a syringe. At room temperature, the solution of DMF was treated with freshly distilled phosphorus oxychloride (1.08 mL, 11.6 mmol), via syringe with an 8-inch needle. As the Vilsmeier salt formed, the solution turned yellow, became hot and boiled. Once the flask cooled to room temperature, it was placed in an ice-water bath (0 °C) and 8-acetoxy-1-(3,5-dimethoxyphenyl)octyl acetate 181 (1.4130 g, 3.85 mmol) in methylene chloride (2.5 mL) was added via syringe. Once addition of 181 was complete, the reaction, which became a deep red color, was warmed to room temperature and then heated in an oil bath at 45 °C for 12 hours (overnight). The mixture was cooled to room temperature and then the excess Vilsmeier salt was decomposed by pouring the reaction mixture into an Erlenmeyer flask containing saturated aqueous sodium acetate (15 mL). Extraction was performed with ethyl acetate (2 x 60 mL). The combined organic layers were dried with sodium sulfate and concentrated on a rotary evaporator to give a thick dark brown oil. This residue was vacuum filtered through a plug of silica and celite, which was washed with 50 % ethyl acetate in hexanes (200 mL). The filtrate was concentrated to give a mixture of regioisomers, 8-acetoxy-1-(2-formyl-3,5-dimethoxyphenyl)octyl acetate 183 and 8-acetoxy-1-(4-formyl-3,5-dimethoxyphenyl)octyl acetate 184 (5 : 1, 183 : 184) (1.1231, 74 %) as a yellow oil. A second wash of the filter cake with 50 % ethyl acetate in hexanes
(200 mL) provided only the regioisomer, 8-acetoxy-1-(4-formyl-3,5-dimethoxy-phenyl)-octyl acetate 184 (0.1869 g, 16 %), as a yellow oil.

8-Acetoxy-1-(2-formyl-3,5-dimethoxyphenyl)octyl acetate 183 \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.5 (s, 1H), 6.60 (d, 1H, \(J = 2.3 \text{ Hz}\)), 6.56 (dd, 1H, \(J = 8.8, 3.1 \text{ Hz}\)), 6.37 (d, 1H, \(J = 2.3 \text{ Hz}\)), 4.04 (t, 2H, \(J = 6.7 \text{ Hz}\)), 3.88 (s, 3H), 3.87 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.77 (m, 1H), 1.69 – 1.55 (m, 3H), 1.56 – 1.26 (m, 8H); \(^{13}\text{C} NMR\) (125 MHz, CDCl\(_3\)) \(\delta\) 189.8, 171.2, 170.1, 165.1, 148.3, 115.4, 102.9, 96.2, 72.8, 64.6, 55.9, 55.4, 36.5, 39.1, 28.5, 25.8, 21.2, 20.9.

8-Acetoxy-1-(4-formyl-3,5-dimethoxyphenyl)octyl acetate 184 (partial characterization):

\(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 10.45 (s, 1H), 6.50 (s, 2H), 5.64 (dd, 1H, \(J = 7.9, 5.7 \text{ Hz}\)), 4.04 (td, 2H, \(J = 6.7, 2.5 \text{ Hz}\)), 3.89 (s, 6H), 2.11 (s, 3H), 2.08 (s, 3H), 1.86 (m, 1H), 1.75 (m, 1H), 1.61 (m, 2H), 1.47 – 1.23 (m, 8H).

3-(7-Hydroxyheptyl)-5,7-dimethoxy-3H-isobenzofuran-1-one (187)

A 250-mL round-bottomed flask equipped with a stir bar was charged with a solution an isomeric mixture of 8-acetoxy-1-(2-formyl-3,5-dimethoxyphenyl)octyl acetate 183 and 8-acetoxy-1-(4-formyl-3,5-dimethoxyphenyl)octyl acetate 184 (0.636, 1.61 mmol) and an acetone-water solvent mixture (total volume: 82 mL ; 1 : 1, v : v). The pale yellow solution placed in an oil bath at 50 °C and potassium permanganate (0.3195 g, 2.02 mmol) in a suspension of a minimal volume of acetone was added in portions. The flask was then fitted with a condenser and the temperature of the oil bath was increased to 80 °C. The purple reaction mixture was refluxed at 80 °C for 12 hours. The mixture was cooled to room temperature and the acetone was removed on the rotary...
evaporator. The resulting aqueous residue was basified with 5% aqueous sodium bicarbonate (35 mL) and extracted with ether (50 mL). The aqueous layer was acidified with concentrated aqueous HCl and extracted three times with ether (3 x 50 mL). The combined organic extracts were concentrated on a rotary evaporator and the resulting residue was dissolved in THF (20 mL). The THF solution was treated with 5% aqueous sodium hydroxide (20 mL) and stirred at room temperature. After 2 hours, the flask was fitted with a condenser and the mixture was refluxed for 1 hour. The cloudy mixture was cooled to room temperature, acidified with concentrated sulfuric acid and then heated for 30 minutes in an oil bath at 50 °C. The final mixture was extracted with ether (2 x 40 mL). The combined ether extracts were washed with concentrated aqueous sodium bicarbonate (20 mL), water (20 mL) and brine (20 mL) in the order listed. The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to yield 3-(7-hydroxyheptyl)-5,7-dimethoxy-3H-isobenzofuran-1-one 187 (0.1485 g, 30%) as an off-white solid. [NB: In order to obtain a melting point, a portion of 187 was purified. The pure compound is a white solid and the melting point was determined to be 102 - 106 °C]; $^1$H NMR (400 MHz, CDCl$_3$) δ 6.42 (s, 2H), 6.41 (s, 1H), 5.30 (dd, 1H, $J=8.0, 3.6$ Hz), 3.95 (s, 3H), 3.89 (s, 3H), 3.63 (t, 2H, $J=6.6$ Hz), 1.99 (m, 1H), 1.69 (m, 1H), 1.57-1.22 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 168.7, 166.9, 159.8, 155.3, 107.1, 98.8, 97.6, 80.1, 63.1, 56.2, 56.1, 34.9, 32.8, 29.4, 29.3, 25.8, 24.7.

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7-(4,6-Dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl) heptanal (196)

An oven-dried 25-mL round-bottomed flask, equipped with a stir bar and nitrogen gas-inlet was charged with 3-(7-hydroxyheptyl)-5,7-dimethoxy-3H-isobenzofuran-1-one 187 (0.2322 g, 0.75 mmol), celite (a few milligrams), 4 Å MS (a few pellets) and methylene chloride (3.2 mL). The mixture treated with pyridinium chlorochromate (0.2434 g, 1.13 mmol). After one hour and thirty minutes of stirring at room temperature, the black suspension was treated with hexanes (20 mL). The resulting mixture was vacuum filtered through celite and the filter cake was washed with hexanes (40 mL). The combined filtrate was concentrated on a rotary evaporator resulting in a black residue. Hexanes (20 mL) were added to the black residue and the resulting suspension was vacuum filtered through celite. The filtrate was concentrated to give a thick brown oil. The oil was subjected to column chromatography to provide 7-(4,6-dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-heptanal 196 (0.1547 g, 67 %) as an off-white solid which was used immediately after it was dried in the TCEA reaction.

\[ \text{H NMR (400 MHz, CDCl}_3 \text{)} \delta 9.69 (s, 1H), 6.36 (s, 2H), 5.23 (dd, 1H, } J = 7.7, 3.4\text{Hz), 3.89 (s, 3H), 3.84 (s, 3H), 2.36 (t, 2H, } J = 7.3 \text{ Hz), 1.95 (m, 1H), 1.67 - 1.27 (m, 9H); } \]
\[ \text{C NMR (100 MHz, CDCl}_3 \text{)} \delta 202.7, 168.5, 166.7, 159.6, 155.0, 106.8, 98.6, 97.5, 79.8, 55.9, 43.8, 34.6, 29.0, 28.9, 24.4, 21.9. \]

Acetic acid 1-(3,5-dimethoxyphenyl)-8-hydroxyoctyl ester (182)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar was charged with magnesium (0.58 g, 24.0 mmol.), a few crystals of iodine and THF (17 mL). The flask was fitted with a condenser and \( \text{N}_2 \) gas-inlet and the purple suspension was
refluxed. A solution of 3,5-dimethoxybromobenzene 179 (5.21 g, 24.0 mmol) in THF (17 mL) was added drop-wise to the refluxing solution. Within five minutes, the solution changed from purple to a colorless solution. After 45 minutes when most of the magnesium had reacted, the refluxing mixture was treated with a drop-wise addition of 8-(tert-butyldimethylsilanyloxy)octanal 178 (5.16 g, 20.0 mmol) in THF (17 mL). After an additional 4 hours of reflux, the reaction mixture was cooled to room temperature and treated with acetyl chloride (1.10 mL, 28.8 mmol). The reaction was stirred for another 2 hours and then treated with deionized water (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue as the crude product, acetic acid 8-(tert-butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)octyl ester 182a. The product was used in the next step without further purification.

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and N₂ gas-inlet was charged with acetic acid 8-(tert-butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)octyl ester 182a was dissolved in THF (70 mL) and treated with tetrabutylammonium fluoride (1M) in THF (45 mL, 45.0 mmol). After three hours, the reaction was diluted with deionized water (50 mL). The resulting mixture was extracted with ethyl acetate (3 x 70 mL). The combined organic extracts were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to yield a yellow oily residue as the crude product. The residue was subjected to flash column chromatography (15 % ethyl acetate in hexanes followed, by 7 % ethyl acetate in
hexanes) to yield acetic acid 1-(3,5-dimethoxyphenyl)-8-hydroxyoctyl ester 182b (5.93 g, ≤ 91 %) as a yellow oil with traces of uncharacterized impurities.

**Acetic acid 8-(tert-butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)octyl ester 182a:** 
$^1$H NMR (400 MHz, CDCl$_3$) δ 6.46 (s, 2H), 6.37 (s, 1H), 5.63 (t, 1H, $J$ = 7.0 Hz), 3.78 (s, 6H), 3.58 (t, 2H, $J$ = 6.6 Hz), 2.07 (s, 3H), 1.86 (m, 1H), 1.74 (m, 1H), 1.48 (m, 2H), 1.27 – 1.21 (m, 8H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.5, 160.9, 143.5, 104.7, 99.6, 76.2, 63.4, 55.4, 36.5, 32.9, 29.5, 29.4, 26.1, 25.9, 25.6, 21.4, 18.5, -5.1.

**Acetic acid 1-(3,5-dimethoxyphenyl)-8-hydroxyoctyl ester 182b:** 
$^1$H NMR (400 MHz, CDCl$_3$) δ 6.43 (d, 2H, $J$ = 2.2 Hz), 6.34 (t, 1H, $J$ = 2.2 Hz), 5.60 (dd, 1H, $J$ = 7.6, 6.2 Hz), 3.75 (s, 6H), 3.56 (m, 2H), 2.04 (s, 3H), 1.82 (m, 1H), 1.71 (m, 1H), 1.49 (m, 2H) 1.29 – 1.23 (m, 8H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.5, 160.8, 143.3, 104.4, 99.5, 76.1, 62.8, 55.3, 36.3, 32.7, 29.3, 25.6, 25.4, 21.3.

**Acetic acid 1-(3,5-dimethoxy-phenyl)-8-oxo-octyl ester (188)**

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and nitrogen gas-inlet was charged with acetic acid 1-(3,5-dimethoxyphenyl)-8-hydroxyoctyl ester 182 (2.39 g, 7.35 mmol), celite (5.00 g) and methylene chloride (50 mL). The mixture was treated with pyridinium chlorochromate (2.38 g, 11.1 mmol), which was added in one portion. After 3 hours of stirring at room temperature, the black suspension was treated with hexanes (100 mL). The resulting mixture was vacuum filtered through celite and the filter cake was washed with hexanes (50 mL). The combined filtrate was concentrated on a rotary evaporator resulting in a black residue. Hexanes were added to

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the black residue and the resulting suspension was vacuum filtered through celite. The filtrate was concentrated to give a thick brown oil. The oil was subjected to vacuum filtration through a plug of celite and silica. The plug was washed with 40% ethyl acetate in hexanes (1000 mL). The filtrate was concentrated on a rotary evaporator followed by a vacuum pump to yield acetic acid 1-(3,5-dimethoxyphenyl)-8-oxo-octyl ester 188 (1.63 g, 68%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.75 (broad s, 1H), 6.46 (s, 2H), 6.37 (s, 1H), 5.64 (t, 1H, $J=7.0$ Hz), 3.78 (s, 6H), 2.40 (t, 2H, $J=7.4$ Hz), 2.06 (s, 3H), 1.80 (m, 1H), 1.74 (m 1H), 1.61 (m, 2H), 1.32-1.24 (m, 6H); $^{13}$C NMR (100 MHz) $\delta$ 202.9, 170.6, 160.9, 143.4, 104.7, 99.7, 76.2, 55.5, 44.0, 36.4, 29.3, 29.2, 25.5, 22.2, 21.5.

10-Acetoxy-2-[5-(tert-butyldiphenylsilyloxy)-2-oxo-hexyl]-10-(3,5-dimethoxyphenyl)-3-hydroxydecanoic acid tert-butyl ester (189)

An 250-mL oven-dried round-bottomed flask equipped with a stir bar and N$_2$ gas inlet was charged with (6R)-6-(tert-butyldiphenylsilyloxy)-3-oxo-heptanoic acid tert-butyl ester 152 (3.503 g, 7.71 mmol) in methylene chloride (77 mL). The solution was cooled in an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (38.5 mL, 38.5 mmol) via a syringe. Evolution of gas was observed. After 10 minutes, the mixture was treated with acetic acid 1-(3,5-dimethoxy-phenyl)-8-oxo-octyl ester 188 (2.981 g, 9.25 mmol) dissolved in methylene chloride (3 mL). After fifteen minutes, the reaction was carefully quenched with ammonium chloride (30 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried.

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with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evilorator to provide the crude product as an oil. The crude product was subjected to column chromatography to provide 10-acetoxy-2-[5-(tert-butylidiphenylsilyloxy)-2-oxo-hexyl]-10-(3,5-dimethoxyphenyl)-3-hydroxydecanoic acid tert-butyl ester 189 (4.976 g, 82 %) as a pale yellow oil:

Mixture of isomers: $^1$H NMR (500 MHz, CDCl$_3$) δ 7.70 – 7.67 (m, 4H), 7.43 – 7.34 (m, 6H), 6.47 (d, 2H, $J$ = 2.0 Hz), 6.37 (t, 1H, $J$ = 2.0 Hz), 5.64 (t, 1H, $J$ = 6.8 Hz), 4.19 – 4.15 (m, 1H), 4.14 – 4.02 (m, 1H), 3.93 – 3.87 (m, 2H), 3.78 (s, 6H), 2.98 – 2.29 (m, 3H), 2.07 (s, 3H), 1.97 – 1.24 (m, 23H), 1.05 (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.4, 208.9, 176.1, 175.8, 175.3, 173.4, 173.4, 172.9, 1.72, 7, 172.5, 170.4, 160.9, 143.4, 135.9, 134.9, 134.8, 134.7, 134.5, 134.4, 134.3, 129.7, 129.6, 127.7, 127.6, 127.5, 106.8, 106.6, 104.6, 99.6, 82.8, 82.4, 82.2, 81.9, 81.6, 81.5, 81.4, 81.3, 80.9, 80.8, 77.4, 76.1, 71.9, 71.8, 69.7, 68.9, 55.4, 49.7, 46.2, 45.0, 41.6, 39.6, 39.5, 39.4, 39.2, 38.9, 38.7, 36.4, 36.0, 35.9, 35.3, 35.1, 35.0, 34.9, 34.2, 34.1, 34.0, 33.9, 33.8, 33.0, 32.1, 29.4, 28.2, 28.1, 25.5, 23.3, 21.4, 19.4.

**Trifluoroacetic acid 1-(3,5-dimethoxyphenyl)-7-(7-methyl-1,6-dioxa-spiro[4.4]non-2-yl)heptyl ester (191)**

Part 1: Formation of the carboxylic acid 190

An oven-dried 100-mL round-bottomed flask, equipped with a stir bar and $N_2$ gas-inlet, was charged with 10-acetoxy-2-[5-(tert-butylidiphenylsilyloxy)-2-oxo-hexyl]-10-(3,5-dimethoxyphenyl)-3-hydroxydecanoic acid tert-butyl ester 189 (4.832 g, 6.11 mmol) and THF (10 mL). The resulting pale yellow solution was treated with
tetrabutylammonium fluoride (1M) in THF (18.5 mL, 18.5 mmol). The reaction was monitored by TLC and after approximately 2 hours, the dark orange reaction mixture was diluted with deionized water (10 mL). The resulting aqueous mixture was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator followed by a vacuum pump to provide the crude product as a yellow oil which consisted of TBDPS-F and the deprotected aldol product.

The product mixture generated above was dissolved in THF (50 mL) and transferred to oven-dried 250-mL round-bottomed flask equipped with a stir bar, reflux condenser and N$_2$ gas-inlet. The resulting solution was treated with anhydrous p-toluenesulfonic acid (1.146 g, 6.11 mmol) and then heated to reflux. After 18 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL) and washed successively with aqueous concentrated sodium bicarbonate (20 mL), deionized water (20 mL) and brine (20 mL). The combine organic extracts were dried with sodium sulfate, decanted from the sodium sulfate and evaporated on a rotary evaporator followed by a vacuum pump. The crude product was isolated as an oil which also consisted of TBDPS-F.

The product mixture generated above was dissolved in methylene chloride (11.8 mL) and transferred to oven-dried 100-mL round-bottomed flask equipped with a stir bar and N$_2$ gas-inlet. The resulting solution was treated with trifluoroacetic acid (TFA) (14.1 mL, 183.3 mmol). After 20 minutes, the solvent was removed through use of the rotary evaporator. The resulting residue was diluted with methylene chloride (3 mL) and benzene (1 mL) and the resulting mixture was evaporated on a rotary evaporator. The

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dilution and evaporation process with methylene chloride and benzene was repeated three times. The resulting brown residue was subjected to column chromatography (20 % ethyl acetate in hexanes remove the TBDPS-F, followed by 10 % methanol in ethyl acetate to isolate the carboxylic acid #). The carboxylic acid 190 was isolated as a dense brown oil (2.917 g, 69%). The carboxylic acid exhibited a resonance for the carbonyl at ~178 ppm in its $^{13}$C NMR-spectrum.

Part 2: Barton Decarboxylation

A 100-mL round bottomed-flask equipped with a stir bar and $N_2$ gas-inlet, was charged with 2-[7-acetoxy-7-(3,5-dimethoxyphenyl)heptyl]-7-methyl-1,6-dioxa-spiro[4.4]nonane-3-carboxylic acid 190 (2.012 g, 2.74 mmol) and methylene chloride (30.0 mL). The flask was wrapped in aluminum foil and treated with $N$-hydroxythiopyridinone (0.3581 g, 2.74 mmol) and dicyclohexylcarbodiimide (0.5655 g, 2.74 mmol), in the order mentioned. After 2 hours, the reaction mixture was subjected to gravity filtration and the resulting filtrate was collected in an oven-dried round-bottomed flask wrapped in aluminum foil. The filtrate was concentrated on a rotary evaporator with a room temperature water bath to provide a gray solid consisting of the $N$-hydroxythiopyridinone ester and traces of DCC. The presence of the $N$-hydroxythiopyridinone ester was determined from the $^1$H NMR and $^{13}$C NMR of the crude product mixture. In the $^{13}$C NMR the ester carbonyl was shifted upfield of the carbonyl in the carboxylic acid 190.

Wrapped in aluminum foil, the flask containing the crude $N$-hydroxythiopyridinone ester was equipped with a stir bar and a $N_2$ gas-inlet. Methylene chloride (73 mL) and $t$-butylmercaptan (3.18 mL, 2.74 mmol) were added separately to the flask by syringe. The
resulting mixture was cooled in an ice-water bath (0 °C). The foil was removed and the reaction mixture was illuminated with a lamp (150 W). Throughout the reaction, the ice-water bath temperature was maintained between 0 - 5 °C. After 1 hour and 30 minutes, the reaction mixture was concentrated on a rotary evaporator. The residue was dissolved in hexanes (90 mL), filtered by gravity and the filtrate was concentrated on a rotary evaporator. The resulting residue was subjected to column chromatography (5 % ethyl acetate in hexanes, Rf(191) = 0.0, followed by 50 % ethyl acetate in hexanes) to provide trifluoroacetic acid 1-(3,5-dimethoxyphenyl)-7-(7-methyl-1,6-dioxa-spiro[4.4]non-2-yl)heptyl ester 191 (0.4340 g, 32 %).

Partial characterization: 1H NMR (400 MHz, CDCl3) δ 6.47 (d, 2H, J = 2.1 Hz), 6.42 (t, 1H, J = 2.1 Hz), 5.77 (t, 1H, J = 7.0 Hz), 4.26 – 3.87 (m, 3H), 3.79 (s, 6H), 3.72 (m, 4H), 3.36 – 3.19 (m, 2H), 2.17 – 1.08 (m, 23H, [spectra shows 38H. This is larger due to impurity]; partial characterization: 13C NMR (100 MHz) δ 161.1, 157.1(m, CO), 140.7, 118.8 (CF3), 116.1 (CF3), 114.8, 114.6, 114.6, 114.4, 113.3 (CF3), 110.4 (CF3), 104.5, 100.4, 80.9, 79.9, 77.9, 75.8, 74.2, 73.9, 55.5, 37.5, 37.64, 36.8, 36.6, 36.5, 36.2, 35.9, 36.8, 35.7, 35.7, 35.3, 35.2, 32.97, 32.3, 31.9, 30.9, 30.3, 30.1, 29.5, 29.2, 26.0, 25.8, 25.7, 25.3, 23.1, 22.9, 21.4, 21.3. [impurity—TBDPS-unit: 13C NMR (100 MHz) δ 127.8]

8-(t-butyldimethylsilylxyloxy)-1-(3,5-dimethoxyphenyl)octan-1-one (192)

An oven-dried 250-mL round-bottomed flask equipped with a stir bar and nitrogen gas-inlet, was charged with 8-(t-butyldimethylsilylxyloxy)-1-(3,5-dimethoxyphenyl)octan-1-ol 173 (3.382 g, 8.52 mmol), methylene chloride (50 mL), 4 Å molecular sieves (5.00
g) and celite (5.00 g). The mixture was stirred for three minutes in order to completely
dissolve the alcohol. Pyridinium chlorochromate (2.939 g, 13.64 mmol) was added
to the flask in one portion and the resulting opaque, brown mixture was stirred under
nitrogen for 30 minutes. Stirring for longer than 30 minutes resulted in lower yield due
to cleavage of the t-butyldimethylsilyl group and formation of a keto aldehyde. Ether (50
mL) was added to the reaction mixture and brown suspension was vacuum filtered
through fresh celite. The filtrate was concentrated and the residue, a brown oil, was
vacuum filtered through a plug of silica and celite, which was washed with 10 % ethyl
acetate in hexanes (500 mL), (Rf = 0.43). The filtrate was concentrated with the use of a
rotary evaporator, followed by a vacuum pump to yield 8-(t-butyldimethylsilanyloxy)-1-
(3,5-dimethoxy-phenyl) octan-1-one 192 (2.853 g, 85 %) as a pale yellow oil. 1H NMR
(400 MHz, CDCl3) δ 7.04 (s, 2H), 6.59 (s, 1H), 3.78 (s, 6H), 3.55 (t, 2H, J = 6.6 Hz),
2.86 (t, 2H, J = 7.4 Hz), 1.67 (m, 2H, J = 7.0 Hz), 1.46 (m, 2H, J = 7.0 Hz), 1.40 – 1.20
(m, 6H), 0.85 (s, 9H), 0.00 (s, 6H); 13C NMR (100 MHz, CDCl3) δ 200.3, 161.0, 139.2,
106.1, 105.2, 63.5, 55.7, 38.9, 33.0, 29.5, 26.2, 25.9, 24.6, 18.6, -5.1.

(1R)-8-(tert-Butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)-octan-1-ol (193)
An oven-dried 250-mL round-bottomed flask equipped with a stir bar and nitrogen
gas-inlet, was charged with (S)-2-methyl-CBS-oxazaborolidine (1M) in toluene (1.35
mL, 1.35 mmol), via a syringe, methylene chloride (1.35 mL) and borane dimethylsulfide
complex (1.29 mL, 13.52 mmol), in the order mentioned. After 10 minutes, the reaction
mixture was cooled in an acetonitrile-dry ice bath (-43 °C). As a solution in methylene
chloride (5 mL), 8-(t-butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)octan-1-one 192
(5.335 g, 13.5 mmol) was added to the cooled reaction mixture over three hours. After addition of the ketone was complete, the reaction mixture was stirred for an additional 2 hours. Throughout the reaction, the temperature of the acetonitrile-dry ice bath was maintained below –20 °C. The reaction was quenched with the addition of methanol (20 mL) and the resulting mixture was allowed to warm to room temperature. The mixture was diluted with ethyl acetate (100 mL) and successively washed with water (40 mL) and brine (40 mL). The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator. The residue was subjected to column chromatography to provide 8-((tert-butyldimethylsilanyloxy)-1-(3,5-dimethoxyphenyl)octan-1-ol 193 (4.094 g, 76 %) as a yellow oil.

This alcohol 193 was further converted to the chiral 3-(7-hydroxy-heptyl)-5,7-dimethoxy-3H-isobenzofuran-1-one 195. The ee of the chiral hydroxyl phthalide 195 was probed with chiral high pressure liquid chromatography (HPLC): ee 85 % [Mobile phase: 100 % methanol; retention time: 2.45 min (area: 90 %), 4.82 (area: 7.343 %)]

1-(10,10-Dimethyl-3,3-dioxo-3\textsuperscript{6}-thia-4-aza-tricyclo[5.2.1.0\textsuperscript{1,5}]dec-4-yl)-butane-1,3-dione (198)

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet was charged with (+)-L-2,10-camphorsultam 197 (2.00 g, 9.3 mmol) in THF (20 mL). The colorless, transparent solution was cooled in an ice-water bath (0 °C) and treated with n-butyl lithium (2.5 M) in hexanes (4.46 mL, 11.2 mmol) via a syringe. After 10 minutes, diketene (0.86 mL, 11.2 mmol) was added by syringe to the pale yellow mixture. After 1 hour, the reaction was quenched with concentrated aqueous
ammonium chloride (10 mL) and the mixture was extracted with ethyl acetate (2 x 70 mL). The combined organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated with the use of a rotary evaporator. The resulting brown residue was subjected to flash column chromatography (10 % ethyl acetate in hexanes) to provide 1-(10,10-Dimethyl-3,3-dioxo-3\textsubscript{6}-thia-4-aza-tricyclo[5.2.1.0\textsubscript{1,5}]dec-4-yl)-butane-1,3-dione \textbf{198} as a white solid (2.67 g, 96 %) with enol and keto forms. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 13.18 (s, 0.3H), 5.65 (s, 0.3H), 4.02 (d, 0.7H, \( J = 16.8 \) Hz), 3.88 (m, 1H), 3.67 (d, 0.7H, \( J = 16.8 \) Hz), 3.49 (d, 1H, \( J = 13.8 \) Hz), 3.42 (d, 1H, \( J = 13.8 \) Hz), 2.29 – 2.15 (m, 3H), 2.07 (m, 1H), 2.00 (s, 1H), 1.89 (m, 3H), 1.42 (m, 1H), 1.34 (m, 1H), 1.16 (s, 1H), 1.14 (s, 2H), 0.96 (s, 1H), 0.95 (s, 2H).

\textbf{1-(10,10-Dimethyl-3,3-dioxo-3\textsubscript{6}-thia-4-aza-tricyclo[5.2.1.0\textsubscript{1,5}]dec-4-yl)-2-(hydroxyphenyl-methyl)-pentane-1,4-dione (200a/b)}

An oven-dried 50-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet was sequentially charged with methylene chloride (8.70 mL) and methylene iodide (0.18 mL, 2.20 mmol). The resulting solution was cooled in an ice-water-bath (0 °C) and treated with diethyl zinc (1M) in hexanes (2.00 mL, 2.00 mmol). The resulting white suspension was treated with a methylene chloride (2 mL) solution of 1-(10,10-dimethyl-3,3-dioxo-3\textsubscript{6}-thia-4-aza-tricyclo[5.2.1.0\textsubscript{1,5}]dec-4-yl)-butane-1,3-dione \textbf{198} (0.3046 g 1.02 mmol). The progress of the reaction was monitored by TLC and after 30 minutes another equivalent of carbenoid was added to drive the reaction to completion by first adding diethyl zinc (1M) in hexanes (1.0 mL, 1mmol) using a syringe, followed by methyl iodide (0.10 mL, 1.2 mmol) also added with a syringe. After the starting material

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was no longer visible by TLC, the reaction mixture was treated with benzaldehyde (0.16 mL, 1.5 mmol). After stirring with the aldehyde for 1 minute, the reaction was quenched with concentrated aqueous ammonium chloride (10 mL). [NB. Longer reaction times with aldehyde resulted in O-methylated product.] The resulting mixture was extracted with ethyl acetate (3 x 70 mL). The combined organic layer was dried with sodium sulfate, decanted from the sodium sulfate and then concentrated on a rotary evaporator to provide a yellow oil. The yellow oil was subjected to flash column chromatography (10 % ethyl acetate in hexanes) to provide the two syn-isomers of the aldol product 1-(10,10-Dimethyl-3,3-dioxo-3\(\lambda^5\)-thia-4-aza-tricyclo[5.2.1.0\(\lambda^1,5\)]dec-4-yl)-2-(hydroxy-phenyl-methyl)-pentane-1,4-dione 200a/b as an oily solid (0.1483 g, \(\leq\) 35 %) and the cyclopropanol, 1-[2-(10,10-Dimethyl-3,3-dioxo-3\(\lambda^5\)-thia-4-aza-tricyclo[5.2.1.0\(\lambda^1,5\)]dec-4-yl)-2-hydroxy-cyclopropyl]-propan-2-one, 199 as a pale yellow oil (0.0689 g, \(\leq\) 21 %).

**major isomer 200a or 200b:** ¹H NMR (500 MHz, CDCl₃) δ 7.43 – 7.25 (m, 20H), 5.28 (d, 3H, \(J=5.5\) Hz), 5.22 (d, 1H, \(J=9.1\) Hz), 4.92 (s, 2H), 4.01 (m, 2H), 3.90 (m, 3H), 3.82 (m, 4H), 3.48 (s, 1H), 3.47 (d, 3H, \(J=13.8\) Hz), 3.40 (d, 3H, \(J=13.8\) Hz), 3.36 (d, 1H, \(J=13.8\) Hz), 3.32 (d, 1H, \(J=13.8\) Hz), 3.02 (m, 3H), 2.78 (s, 1H), 2.57 (dd, 1H, \(J=12.4, 6.5\) Hz), 2.46 (m, 2H), 2.40 (dd, 3H, \(J=13.7, 9.7\) Hz), 2.32 (dd, 3H, \(J=13.7, 3.9\) Hz), 2.12 (s, 3H), 2.12 –1.91 (8H), 1.94 –1.74 (m, 15H), 1.66 (s, 6H), 1.65 (s, 3H), 1.41 –1.25 (m, 13H), 1.02 (s, 9H), 0.94 (s, 9H), 0.86 (s, 3H), 0.73 (s, 3H); ¹³C NMR (125 MHz) δ 207.5, 175.5, 172.5, 172.2, 141.5, 140.4, 140.0, 128.7, 128.4, 128.3, 128.1, 126.7, 126.3, 126.2, 106.1, 105.8, 86.6, 84.3, 73.9, 65.6, 65.4, 65.3, 53.4, 53.2, 53.2, 52.5, 49.2,
1-[2-(10,10-Dimethyl-3,3-dioxo-3\(^{6}\)-thia-4-aza-tricyclo[5.2.1.0\(^1\).5\)]dec-4-yl)-2-hydroxy-cyclopropyl]-propan-2-one (199): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.86 (dd, 1H, \(J = 4.6, 8.1\) Hz), 3.68 (s, 1H), 3.18 (s, 2H), 2.80 (dd, 1H, \(J = 17.1, 5.8\) Hz), 2.54 (dd, 1H, \(J = 17.1, 8.6\) Hz), 2.22 (s, 3H), 2.11 (m, 1H), 1.94 – 1.82 (m, 5H), 1.38 – 1.24 (m, 2H), 1.17 (dd, 1H, \(J = 9.9, 5.7\) Hz), 1.06 (s, 3H), 0.93 (s, 3H), 0.61 (dd, 1H, \(J = 6.7, 5.9\) Hz); \(^{13}\)C NMR (100 MHz) \(\delta\) 208.1, 65.7, 64.0, 50.9, 49.3, 47.9, 45.2, 42.2, 35.8, 32.9, 30.2, 26.9, 20.7, 20.2, 18.1, 17.9. \([^{1}\)H and \(^{13}\)C NMR spectra also exhibit resonances for ethyl acetate.]

1-(10,10-Dimethyl-3,3-dioxo-3\(^{6}\)-thia-4-aza-tricyclo[5.2.1.0\(^1\).5\)]dec-4-yl)-pentane,1,4-dione (204)

An oven-dried 50-mL round-bottomed flask, equipped with a stir bar and a nitrogen gas-inlet was charged with methylene iodide (0.28 mL, 3.47 mmol) and methylene chloride (8.7 mL). The resulting solution was cooled in an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (3 mL, 3.00 mmol), via a syringe. The resulting white suspension was treated, via a syringe, with a methylene chloride (2 mL) solution of 198 (0.2973 g 0.99 mmol). The progress of the reaction was monitored by TLC. After 57 minutes, the reaction was quenched with concentrated aqueous ammonium chloride (20 mL). The resulting mixture was extracted with ethyl acetate (2 x 70 mL). The combined organic layer were dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide the residue as a yellow oil. The residue was subjected to flash column chromatography (20 % ethyl acetate in
hexanes) to provide the chain extended product, 1-(10,10-Dimethyl-3,3-dioxo-3\(\lambda^6\)-thia-4-aza-tricyclo[5.2.1.0\(2\),5\]dec-4-yl)-pentane-1,4-dione, 204 (0.1211 g, 39 %) as a yellow oil and the cyclopropanol, 1-[2-(10,10-Dimethyl-3,3-dioxo-3\(\lambda^6\)-thia-4-aza-tricyclo[5.2.1.0\(1\),5\]dec-4-yl]-2-hydroxy-cyclopropyl]-propan-2-one, 199 (0.0607 g, 19 %) as a yellow oil.

1-(10,10-Dimethyl-3,3-dioxo-3\(\lambda^6\)-thia-4-aza-tricyclo[5.2.1.0\(1\),5\]dec-4-yl)-pentane-1,4-dione 204: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.86 (dd, 1H, \(J = 6.6, 5.5\) Hz), 3.50 (d, 1H, \(J = 13.7\) Hz), 3.44 (d, 1H, \(J = 13.7\) Hz), 3.06 (m, 1H), 2.92 – 2.85 (m, 2H), 2.72 (m, 1H), 2.19 (s, 3H), 2.02 (dd, 1H, \(J = 13.8, 7.8\) Hz), 1.96 – 1.87 (m, 4H), 1.41 (dd, 1H, \(J = 10.0, 9.2\) Hz), 1.34 (dd, 1H, \(J = 9.2, 8.9\) Hz), 1.21 (s, 3H), 0.98 (s, 3H); \(^{13}\)C NMR (125 MHz) \(\delta\) 206.19, 170.7, 65.2, 52.9, 48.6, 47.8, 44.7, 38.3, 37.5, 32.8, 29.7, 29.4, 26.5, 20.8, 19.9.

(N-Acetyl)-(2R)-bornane-10,2-sultam (209)

An oven-dried 100-mL round-bottomed flask equipped with a stir bar and a nitrogen gas-inlet was charged with (-)-D-2,10-camphorsultam 208 (3.229 g, 15.0 mmol) in THF (30 mL). The colorless, transparent solution was cooled in an ice-water bath (0 °C) and treated with \(n\)-butyl lithium (2.5 M) in hexanes (9.00 mL, 22.5 mmol). After 10 minutes, acetyl chloride (1.70 mL, 22.5 mmol) was added to the pale yellow mixture, via a syringe. After 30 minutes, the reaction was quenched with deionized water (20 mL). After 10 minutes, the mixture was extracted with ethyl acetate (2 x 70 mL). The combined organic layer was washed successively with concentrated aqueous sodium bicarbonate (30 mL), deionized water (30 mL) and brine (30 mL). The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated with the
use of a rotary evaporator followed by vacuum pump to provide (N-acetyl)-(2R)-bornane-10,2-sultam 209 (3.995 g, quantitative) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.84 (dd, 1H, $J$ = 7.6, 4.9 Hz), 3.49 (d, 1H, $J$ = 13.8 Hz), 3.42 (d, 1H, $J$ = 13.8 Hz), 2.39 (s, 3H), 2.14 (m, 1H), 2.07 (dd, 1H, $J$ = 13.7, 7.9 Hz), 1.95 -1.86 (m, 3H), 1.40 (m, 1H), 1.31 (m, 1H), 1.15 (s, 3H), 0.96 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.7, 65.3, 52.9, 48.5, 47.9, 44.8, 38.5, 32.9, 26.6, 23.3, 20.9, 20.0.

**Acetic acid 6-(10,10-dimethyl-3,3-dioxo-3\textsuperscript{\lambda}-thia-4-aza-tricyclo[5.2.1.0\textsuperscript{1,5}]dec-4-yl)-1-methyl-4,6-dioxo-hexyl ester (213)**

An oven-dried 100-mL round-bottomed flask, equipped with a stir bar and a nitrogen gas-inlet, was charged with THF (14 mL) and diisopropylamine (1.79 mL, 12.7 mmol), via a syringe. The resulting solution was cooled in an ice-water bath (0 °C) and treated with n-butyl lithium (5.96 mL, 10.6 mmol), via a syringe. After 10 minutes, (N-acetyl)-(2R)-bornane-10,2-sultam 209 (2.275 g, 8.80 mmol) dissolved in THF (15 mL) was added to the transparent, pale yellow solution over 90 minutes using a syringe pump. Thirty minutes after the addition of N-acetyl)-(2R)-bornane-10,2-sultam 208 was completed, the reaction mixture was treated with $R$-$\gamma$-valerolactone 211 (0.42 mL, 4.42 mmol). After 18 hours, the reaction was quenched with concentrated aqueous citric acid (10 mL) and extracted with ethyl acetate (3 x 60 mL). The organic extract was washed once with deionized water (60 mL) and once with brine (60 mL). The organic extract was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a rotary evaporator to provide the residue as a yellow oil. The residue was subjected to flash column chromatography (10 % ethyl acetate in hexanes to isolate the more nonpolar
impurities and byproducts, \( R_2(209) = 0.0 \), followed by 30 % ethyl acetate in hexanes to isolate the product) to provide acetic acid 6-(10,10-dimethyl-3,3-dioxo-3\( ^6 \)-thia-4-aza-tricyclo[5.2.1.0\( 1,5 \)]dec-4-yl)-1-methyl-4,6-dioxo-hexyl ester 213 (0.3893 g, 22 %), as a yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.88 (m, 1H, \( J = 6.1 \) Hz), 3.98 (d, 1H, \( J = 16.7 \) Hz), 3.87 (dd, 1H, \( J = 7.7, 4.9 \) Hz), 3.66 (d, 1H, \( J = 16.7 \) Hz), 3.48(d, 1H, \( J = 13.9 \) Hz), 3.40 (d, 1H, \( J = 13.9 \) Hz), 2.57 (td, 1H, \( J = 7.9, 2.0 \) Hz), 2.25 (m, 2H), 2.03 (s, 1H), 2.01 (s, 2H), 1.94 – 1.80 (m, 6H), 1.49 – 1.32 (m, 4H), 1.22 (d, 1H, \( J = 6.1 \) Hz), 1.20 (d, 2H, \( J = 6.1 \) Hz), 1.15 (s, 1H), 1.13 (2H), 0.96 (s, 1H), 0.958 (s, 2H); [partial characterization: \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 201.4 (ketone), 170.8 (ester), 164.7 (amide), 70.1 (ester-methine)].

**Acetic acid 7-(10,10-dimethyl-3,3-dioxo-3\( ^6 \)-thia-4-aza-tricyclo[5.2.1.0\( 1,5 \)]dec-4-yl)-1-methyl-4,7-dioxo-heptyl ester (216)**

An oven-dried 10-mL round-bottomed flask, equipped with a stir bar and a nitrogen gas-inlet, was charged with acetic acid 6-(10,10-dimethyl-3,3-dioxo-3\( ^6 \)-thia-4-aza-tricyclo[5.2.1.0\( 1,5 \)]dec-4-yl)-1-methyl-4,6-dioxo-hexyl ester 213 (0.0759 g, 0.19 mmol) and methylene chloride (2 mL). The resulting solution was cooled in an ice-water bath (0 °C) and treated with diethyl zinc (1M) in hexanes (0.76 mL, 0.76 mmol). Gas evolution was observed. After 10 minutes, the reaction mixture was treated with methylene iodide (0.07 mL, 0.86 mmol). The progress of the reaction was monitored by TLC. After 30 minutes, the reaction was quenched with concentrated aqueous ammonium chloride (5 mL). The resulting mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic layer was dried with sodium sulfate, decanted from the sodium sulfate and
concentrated on a rotary evaporator to provide the residue as a yellow oil. The residue was subjected to flash column chromatography to provide a mixture of the 4-keto sulfonamide 216 and a compound tentatively assigned as the 5-keto sulfonamide 217 (0.03297 g, < 42 % for the 4-keto sulfonamide 216), as a yellow oil. m/z 427.20 (5-keto sulfonamide 217), 413.17 (4-keto sulfonamide 216). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.87 (m, 2H, \(J = 6.2\) Hz), 3.89 (distorted t, 1H, \(J = 7.2\) Hz), 8.34 (dd, 1H, \(J = 7.7, 4.8\) Hz), 3.67 (m, 0.5H), 3.59 (dd, 0.5H, \(J = 10.1, 5.4\) Hz), 3.53 – 3.38 (m, 5H), 3.12 – 2.99 (m, 2H), 2.98 – 2.90 (m, 1H), 2.80 (ddd, 1H, \(J = 17.9, 7.9, 4.9\) Hz), 2.69 (ddd, 1H, \(J = 17.9, 6.3, 5.4\) Hz), 2.58 – 2.36 (m, 5H), 2.17 – 2.09 (m, 2H), 2.08 – 2.02 (m, 3H), 2.02 – 2.01 (m, 6H), 1.94 – 1.73 (m, 10H), 1.44 – 1.30 (m, 6H), 1.27 – 1.17 (m, 12H), 1.15 (s, 2H), 0.96 (s, 6H), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 207.4, 207.2, 206.4, 175.1, 170.9, 170.8, 70.3, 70.2, 65.4, 65.3, 65.2, 53.1, 52.9, 48.7, 48.5, 47.9, 47.8, 45.7, 44.8, 44.7, 44.4, 41.7, 38.7, 38.6, 38.5, 36.6, 35.7, 32.9, 29.7, 29.6, 29.5, 26.6, 21.4, 21.0, 20.9, 20.2, 20.1, 20.0, 18.2, 6.6

2-(6-Acetoxy-2-oxo-heptyl)-9-(5,7-dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl)-3-hydroxy-nonanoic acid (219)

Part 1: The TCEA reaction

An oven-dried 10-mL round-bottomed flask was equipped with a stir bar and a nitrogen gas-inlet. The flask was charged with methylene chloride (1.00 mL) and acetic acid 6-(10,10-dimethyl-3,3-dioxo-3,6-thia-4-aza-tricyclo[5.2.1.0\(^{1.5}\)]dec-4-yl)-1-methyl-4,6-dioxo-hexyl ester 213 (0.0527 g, 0.13 mmol). The resulting solution was cooled in an ice-water-bath (0 °C) and treated with diethyl zinc (1M) in hexanes (0.53 mL, 0.53
mmol), via a syringe. Gas evolution was observed. After 10 minutes, the resulting solution was treated with methylene iodide (0.04 mL, 0.53 mmol). After 5 minutes, \(R-7-(4,6\text{-Dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl})\text{heptanal 196 (0.1619 g, 0.53 mmol)}\) as a solution in methylene chloride (1.00 mL) was added. The progress of the reaction was monitored by TLC. After complete consumption of the starting material \(213\) was observed by TLC, the reaction was quenched with concentrated aqueous citric acid (5 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried with sodium sulfate, decanted from the sodium sulfate and then concentrated on a rotary evaporator to provide a yellow oil. The yellow oil was subjected to flash column chromatography (30 % ethyl acetate in hexanes to isolate most of the unreacted aldehyde, \(R_f(218) = 0.0\), followed by 60 % ethyl acetate in hexanes) to provide a mixture of \(R-7-(4,6\text{-Dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl})\text{heptanal 196}\) and the target Acetic acid \(14-(5,7\text{-dimethoxy-3-oxo-1,3-dihydro-isobenzofuran-1-yl})\text{-7-(10,10-dimethyl-3,3-dioxo-3\(\lambda^6\)-thia-4-aza-tricyclo[5.2.1.0\(1,5\)]decane-4-carbonyl)-8-hydroxy-1-methyl-5-oxo-tetradecyl ester 218\) as an oil.

Part 2: Synthesis of the Carboxylic acid 219

The isolated mixture of the aldehyde 196 and the aldol product 218 was dissolved in a mixture of THF and deionized water (10 mL, 1: 1, v : v), and treated with lithium hydroxide (> 0.003 g, > 0.13 mmol). The reaction was monitored by TLC. The reaction was left to stir overnight. The basic mixture was extracted with ether (7 mL) to isolate excess aldehyde 196. The aqueous mixture was then acidified with aqueous concentrated sulfuric acid and then extracted three times with ether (3 x 10 mL). The organic layer was dried with sodium sulfate, decanted from the sodium sulfate and concentrated on a
rotary evaporator followed by a vacuum pump to provide the carboxylic acid 219 (0.0200 g, 30%) as an oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.41 (s, 2H), 5.29 (m, 1H, $J=3.8$ Hz), 4.29 - 4.08 (m, 2H), 3.93 (s, 3H), 3.89 (s, 3H), 3.02 (m, 0.5H), 2.78 (m, 0.5H), 2.41 - 2.56 (m, 9H), 1.56 - 1.29 (m, 8H), 1.28 - 1.18 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.6, 178.1, 176.02, 168.9, 166.9, 159.8, 155.4, 114.5, 107.0, 98.8, 97.6, 81.9, 80.2, 75.2, 70.2, 56.1, 49.5, 48.8, 39.9, 38.9, 37.0, 36.4, 35.2, 34.9, 34.6, 34.0, 33.4, 32.6, 32.1, 30.4, 39.8, 29.3, 28.9, 25.8, 25.3, 24.6, 24.5, 23.1, 21.1.


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Chemical shifts in CD$_2$Cl/CDCl$_3$ for reagents and byproducts from the generation of the zinc-organometallic intermediate for NMR Spectroscopy

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