Tandem zinc-carbenoid mediated chain extension-aldol chemistry of beta-carbonyl imides

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Abstract
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Due to the extended chain extension reaction times, reduction of aldehydes was observed during attempted aldol reactions. A chain extension aldol protocol, specific for the application to malonyl diimides, was developed to reduce the appearance of products resulting from the reduction of the respective aldehyde.

Keywords
Chemistry, Organic
TANDEM ZINC-CARBENOID MEDIATED CHAIN EXTENSION-ALDOL CHEMISTRY OF β-CARBONYL IMIDES

BY

Timothy J. Henderson
B.S., University of New Hampshire, 2006

THESIS

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

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Professor of Chemistry

8/04/09
Date
DEDICATION

This thesis is dedicated to my mother, Christine Henderson, and my uncle, Skip Thomas. Without their influence and patience, I would not be the person that I am today. I will forever be grateful for their support and guidance.
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I would like to acknowledge Dr. Zercher for his patience and guidance. He is a truly gifted and dedicated educator and I owe a large part of my understanding of chemistry to him.

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ABSTRACT

TANDEM ZINC-CARBENOID MEDIATED CHAIN EXTENSION ALDOL CHEMISTRY OF β-CARBONYL IMIDES

by

Timothy J. Henderson

University of New Hampshire, September, 2009

Synthetic sequences to prepare γ-methoxy β-keto imides and malonyl diimides were investigated in an effort to expand the scope of the tandem zinc-mediated chain extension aldol reaction. The chain extension-aldol reaction of the γ-methoxy β-keto imide proceeded smoothly, although low stereoselectivity of the reaction was observed. The chain extension of malonyl diimides were slow when compared to traditional substrates. The chain extension-aldol reaction of malonyl diimides provided γ-lactones with moderate yield and selectivity in a one-pot reaction sequence.

Due to the extended chain extension reaction times, reduction of aldehydes was observed during attempted aldol reactions. A chain extension aldol protocol, specific for the application to malonyl diimides, was developed to reduce the appearance of products resulting from the reduction of the respective aldehyde.
CHAPTER I

INTRODUCTION

Zinc Carbenoid-Mediated Chain Extension Reaction

The zinc carbenoid-mediated chain extension reaction was discovered during the attempted synthesis of 2 from 1 by Zercher and co-workers (Scheme 1).\textsuperscript{1} Instead of production of 2 being observed under the standard cyclopropanation conditions, an additional reaction occurred in which a methylene unit was inserted between the adjacent carbonyls.\textsuperscript{1} This protocol has been shown to be an efficient one-pot method for the generation of γ-keto amides (3),\textsuperscript{2} esters (4),\textsuperscript{1} and phosphonates (5)\textsuperscript{3} from their respective β-keto starting materials (Scheme 2).

![Scheme 1- Discovery of the zinc-mediated chain extension reaction](image-url)
Scheme 2- Zinc-carbenoid mediated chain extension reaction with β-keto amides, esters, and phosphonates

The proposed reaction mechanism (Scheme 3) begins with deprotonation of the β-keto carbonyl species 6 by diethyl zinc or preformed carbenoid 7, which results in the formation of an initial zinc enolate 8. Alkylation of the zinc-enolate intermediate is proposed to follow, forming a zinc homoenolate species 9. 3-exo-trig Cyclization results in the formation of 10, which is then followed by donor-acceptor ring fragmentation to give a latent zinc enolate species 11. Aqueous work-up produces the γ-keto homologue 12. The latent zinc enolate species has been shown to have similar qualities to the Reformatsky intermediate.\(^4\) Alkylation of the latent enolate with carbenoid, which is present in excess under standard chain extension conditions, is not typically observed with β-keto esters or amides, but does present a challenge with β-keto imides.\(^5-7\)
Scheme 3- Proposed mechanism of the chain extension reaction.

This facile generation of the γ-keto carbonyl framework was applied to synthesis of ketomethylene isosteres as potential protease inhibitors. The ketomethylene isostere (13) mimics a peptide backbone (14) through substitution of an amide nitrogen with a methylene unit (Figure 1). Initial synthetic approaches to the generation of ketomethylene isosteres utilizing the chain extension reaction did not allow the formation of isosteres with α-substituents (Scheme 4). The desire to mimic the α-substituent found in the natural peptide backbones inspired the development of synthetic strategies that take advantage of the regioselective generation of nucleophilic character found in the Reformatsky-like zinc enolate intermediate (11).

Figure 1- Peptide and ketomethylene isostere backbones
Tandem Protocols

A variety of tandem reaction protocols have been developed. The Reformatsky-type intermediate 11 has been treated sequentially with molecular iodine and base to generate an α,β-unsaturated-γ-keto ester or amide (15). Compounds of this type have been functionalized at the α-position through regioselective conjugate addition.10-12

The zinc enolate intermediate (11) has also been alkylated with excess carbenoid in the presence of catalytic trimethylsilylchloride, which resulted in the generation of an intermediate homoenoenate (16). The intermediate homoenoenate could be quenched with a proton source to generate α-methyl γ-keto carbonyls13 or molecular iodine to generate α-iodomethyl γ-keto carbonyls (17). The regioselective formation of α-iodomethyl γ-keto carbonyls (17) resulted in their use as attractive coupling precursors to a variety of amino acid side chains.14,15
Scheme 5- Utility of the latent zinc enolate intermediate

Treatment of the latent zinc enolate intermediate (11) with either an aldehyde or ketone initiates a tandem aldol process, which resulted in the regiocontrolled incorporation of a side chain $\alpha$ to the ester.\(^{16,17}\)
Tandem Zinc-Mediated Chain Extension Aldol Reaction

The tandem aldol variant of the chain extension reaction, when applied to β-keto amides or esters, generates a new carbon-carbon bond and two contiguous stereocenters producing anti (18) or syn (19) diastereomers. The syn and anti aldol products can exist in equilibrium with their respective hemiacetal forms (20 and 21) producing another possible mixture of diastereomers. The complicated mixture of constitutional and stereoisomers in the crude reaction mixture presents unique challenges for characterization.

Relative Stereoselectivity

One common model used to explain stereoselectivity of aldol reactions is the Zimmerman-Traxler transition state model. The Zimmerman-Traxler model for explaining stereoselectivity of aldol reactions assumes a closed transition state, where one equivalent of the metal counter-ion is used to both stabilize the enolate as well as activate the aldehyde towards nucleophilic attack. The reactants in this transition state model adopt a pseudo-chair conformation. The aldehyde is proposed to approach the enolate in a fashion by which the R group of the aldehyde adopts a pseudo-equatorial orientation to avoid the pseudo-1, 3-diaxial interactions that would result from approach of the aldehyde where the R group adopts a pseudo-axial orientation. Based upon this model, the main determinant of the syn or anti product is the initial enolate geometry. E-Enolates in this transition state hypothesis would favor formation of the anti
stereochemistry as a major product, whereas Z-enolates would favor formation of the *syn* product as the major isomer.

Scheme 6- Zimmerman-Traxler closed transition state models
The tandem chain extension aldol reaction has been shown to be syn selective for both amides and esters (Table 1). The syn selectivity is consistent with a closed transition state model involving Z enolates. While ester enolates are rarely biased in favor of a Z-geometry, complexation with the γ-keto functionality appear to aid in the preference for a Z-enolate (Scheme 6). The influence of the γ-keto functionality was confirmed in a model study that compared the stereoselectivities of the Reformatsky reaction involving the zinc enolate generated from the α-halo γ-keto ester (22) versus the aldol reaction of the zinc enolate generated from the α-halo ester (23) (Scheme 7). Another result from this model study showed that the ligand on the zinc also plays a role in the stereoselectivity of the reaction.

Table 1- Selected chain extension aldol reactions and their stereoselectivities
Scheme 7- Model study showing dependence on γ-keto functionality and ligand

The cyclopropane fragmentation included in the chain extension aldol reaction may also influence the uncommon syn-selectivity observed and/or Z-selective enolate formation. Saigo and coworkers studied the fragmentation of donor-acceptor cyclopropanes 24a-b to zwitterionic species 25a-b.19 As part of their study, it was shown that this zwitterionic intermediate could trap aldehydes to ultimately isolate γ-lactones (26). The lactonization was subsequently induced by catalytic p-TsOH. Since the stereochemistry of the γ-lactone is generated in the initial aldol reaction, cis (26) would be derived from the anti-aldol product and trans (26) would come from the syn-aldol product. In a study of a variety of Lewis Acids capable of chelation, the aldol stereoselectivity was demonstrated to typically favor formation of the anti product. However when zinc (II) bromide, magnesium (II) bromide and diethyl aluminum chloride
were used as Lewis acid, the reaction selectivity favored syn-aldol product formation.\textsuperscript{19}

This selectivity was proposed to be a consequence of the conformation adopted by the donor-acceptor cyclopropane upon fragmentation to the enolate zwitterion (25).\textsuperscript{19}

\begin{align*}
\text{E-fragmentation conformer} & \quad \text{Z-fragmentation conformer} \\
\text{a } & \quad \text{b }
\end{align*}

\textbf{Scheme 8- Saigo and coworkers donor-acceptor cyclopropane fragmentation aldol reaction}

The tandem chain extension aldol reaction of a chiral $\beta$-keto imide produced a reaction mixture that was dominated by production of the \textit{anti}-aldol isomer (Table 1).\textsuperscript{17}

Since generation of a $E$-enolate of the $\gamma$-keto imide homologue would be disfavored due to developing $A^{1,3}$-strain (Figure 2), this result is inconsistent with a $Z$-enolate reacting through a closed transition state. However the result is consistent with a transition state hypothesis proposed by Heathcock.\textsuperscript{20} Heathcock proposed an open transition state model
that operated when two equivalents of Lewis acids are used. One Lewis acid serves to stabilize the enolate, while the other is used to activate the aldehyde towards nucleophilic attack. In this model the enolate approaches the aldehyde in a fashion that places the imide enolate anti-periplanar to the oxygen of the aldehyde. The facial selectivity of the aldehyde is oriented in a way that minimizes the steric interactions that would be observed between the side chain of the enolate and the Lewis acid activating the aldehyde. The Lewis acid is believed to activate the aldehyde by complexing trans to the phenyl group (Figure 3). The facial selectivity of the enolate is influenced by the stereochemistry of the isopropyl substituent.

![Figure 2- Enolate geometries of \(\gamma\)-keto imide](image)

![Figure 3- Open transition state precursors to anti and syn aldol products of the aldol reaction](image)
Complex Diastereoselectivity

The tandem chain extension aldol methodology has been applied towards the stereoselective formation of $\alpha$-substituted ketomethylene peptide isosteres through the use of chiral auxiliaries. A variety of amino acids were initially probed to identify an auxiliary that could facilitate absolute diastereoselectivity in the aldol reaction. Proline was identified as an efficient director of absolute stereochemistry, likely due to its uniquely rigid structure. The relative diastereocontrol ($\text{syn/anti}$) of the reaction with the proline auxiliary was discovered to be consistent with that of typical amides under the chain extension protocol. The absolute stereocontrol of the aldol reaction using the (L)-proline auxiliary resulted in the formation of stereocenters that mimicked those found in natural amino acid side chains. One problem with the widespread applicability of the proline auxiliary would be the harsh conditions required to cleave the amide bond. An ideal chiral auxiliary would be one that could be cleaved readily under more moderate conditions.

A variety of chiral oxazolidinone derivatives have also been probed to explore the relative efficiency of stereo-induction. The absolute stereoselectivity of the oxazolidinone chiral auxiliaries under chain extension aldol conditions was identified to be consistent with work previously reported using chiral oxazolidinones in traditional aldol reactions involving chelating metals. The imide functionality can be readily cleaved by treatment with lithium peroxide and these conditions do not affect $\alpha$-stereocenters. Before the zinc-carbenoid tandem chain extension aldol reaction can be
applied to β-keto carbonyl systems, a better understanding of the relative stereoselectivity (syn/anti) of the reaction needs to be acquired.

In an effort to understand the relative stereoselectivity (syn/anti) that was produced from the chain extension aldol reaction of the chiral β-keto imide with benzaldehyde, an achiral β-keto imide was subjected to the tandem zinc-mediated chain extension aldol conditions. The anti aldol product was observed as the major product. The stereochemical assignments were based solely on the vicinal coupling constants between the carbinol proton and the α-methine proton. These assignments are supported by trends observed in spectroscopic data in the literature that compare data from both the anti (27) and syn (28) structures. According to the trends the syn-aldol products have lower vicinal coupling constants than anti-aldol products. This can be rationalized by examining the conformations available for the diastereomeric products (Scheme 9). The conformations which allow for the possibility of hydrogen bonding should lower the energy of those respective conformers. Both the syn and anti aldol products possess two conformers (anti-a,b and syn-a,c) that foster hydrogen bonding, however, anti-a is the only hydrogen-bonding conformer that places the vicinal hydrogens antiperiplanar to each other, thereby increasing the coupling constant \(^3J_{HH}\). The challenge in the application of this characterization strategy to the chain extension aldol products is the difficulty in assigning the proton resonances in the NMR spectra to the carbinol and α-methine protons of the open-chained product in the presence of the hemiacetal equilibria.
Another complicating feature is that aldol products often strongly favor the closed hemiacetal form(s).

\[ \text{anti 27} \]

\[ \text{syn 28} \]

Scheme 9- Conformer analysis of aldol products

\textbf{γ-Butyrolactones}

γ-Butyrolactone derivatives and their respective stereoselective syntheses have been investigated widely. In addition to being the framework of natural products, including the paraconic acids (Figure 4), γ-butyrolactones have been demonstrated to possess biological activity, such as anti-fungal,\textsuperscript{26} anti-tumor\textsuperscript{27} and anti-bacterial activities.\textsuperscript{28} As a result, γ-lactones have become the target of synthetic methodology investigations and a wide variety of stereoisomeric derivatives of these γ-lactones are well studied in the literature.\textsuperscript{29-31}
The ability to convert zinc-mediated chain extension aldol products of β-carbonyl imides to γ-lactones would simplify characterization and be an attractive method for the assignment of syn and anti stereoselectivity that results from the aldol reaction. One method to convert chain extension aldol products of γ-heteroatom β-keto carbonyls to γ-lactones is through application of a CAN-mediated oxidative cleavage process that was recently discovered (Scheme 10). The oxidative cleavage requires the presence of both the γ-heteroatom and hemiketal. This method for the formation of γ-lactones has proven to be clean and efficient. To apply this method as a tool in the investigation of the diastereoselectivity of the chain extension aldol reaction, synthesis of γ-methoxy β-keto imide 29a would need to be developed.

When the methyl ester 29b (Scheme 10) was treated under chain extension aldol conditions with various aldehydes, a significant drop in syn-selectivity was observed when compared to β-keto esters that lack the γ-heteroatom. This loss of selectivity could be due to competitive complexation involving the δ-methoxy functionality thereby compromising the selective formation of the Z-enolate. The use of an imide functional
group should strongly bias formation of a Z-enolate; nevertheless, competitive complexation with the γ-methoxy functionality would complicate the analysis of the stereocontrol. In addition, an understanding of the role γ-heteroatoms play in determining the syn/anti stereochemistry was needed.

\[
\begin{align*}
R^1 & \quad R^2 \\
29 & \quad \xrightarrow{1) \text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2} \quad \text{HO}_2\text{O} \text{R}^\text{II} \quad \xrightarrow{\text{CAN, H}_2\text{O, MeCN}} \quad \text{O}_2\text{O} \text{R}^\text{II}
\end{align*}
\]

Scheme 10- CAN oxidative cleavage protocol

When β-keto imide 32 was treated under chain extension conditions, 33 was observed (Scheme 11).\textsuperscript{22} This product was attributed to organozinc intermediate 34 reacting with a second equivalent of carbenoid to form 35. A 3-exo-trig cyclization then would occur to form cyclopropoxide 36, which is not as susceptible to fragmentation as a donor-acceptor cyclopropane. Isolation of 33 indicated that the imide functionality was electrophilic enough to participate in cyclopropane formation, therefore substitution of the ketone for an imide functionality appeared to be possible in the chain extension reaction. It is worth noting that substitution of the ketone with an ester functionality (as found in a malonate diester) was not suitable for a successful chain extension reaction.
When compound 37 was exposed to the carbenoid, a chain extended product was observed. When the intermediate enolate was exposed to aldehyde or a ketone, production of \( \gamma \)-lactone 38 was also observed through an intramolecular cyclization and expulsion of the oxazolidinone from the tetrahedral intermediate. The regioselective incorporation of the aldehyde and expulsion of the oxazolidinone indicated that generation of an ester enolate 39 was formed instead of the imide enolate. This is consistent with the proposed formation of the donor-acceptor cyclopropane involving the imide carbonyl, followed by fragmentation to form 39 (Scheme 12). When achiral \( \alpha \)-carboxy ester imides (40) were subjected to tandem zinc-mediated chain extension aldol conditions, \( \text{trans} \) lactones (41), which come about from the anticipated \( \text{syn} \) aldol, were observed as major products (Scheme 13). While this approach to \( \gamma \)-lactones appears efficient, the function of the ester enolate is limited, in that control of absolute stereochemistry is not practical when utilizing ester enolates.

To extend this study to the formation of \( \gamma \)-lactone utilizing chiral imide enolates, both carbonyl groups would need to be imides, one to provide the imide enolate and one serving as the ketone-surrogate in the chain extension reaction. The ability to generate \( \gamma \)-lactones through a one-step reaction scheme should be advantageous when compared to the longer method involving the CAN-mediated oxidative cleavage.
Scheme 11- Over alkylation observed with β-keto imide systems

Scheme 12- One-pot method of generating γ-lactones 38

Scheme 13- Generation of γ-lactone esters 41
CHAPTER II

RESULTS AND DISCUSSION
Scheme 12- One-pot method of generating γ-lactones 38

Scheme 13- Generation of γ-lactone esters 41
Scheme 15- Synthesis of compound 42

Previous syntheses of β-keto imides (47) utilized diketene. In order to adapt this strategy to the synthesis of γ-methoxy β-keto imide 42, a mixed diketene 48 would have been required. A synthetic sequence was designed that involved generation of an acylated Meldrum’s acid adduct (49), which has been shown to be a mixed diketene equivalent. The acylated Meldrum’s acid adduct was prepared in a similar fashion to that described by Yonemitsu and coworkers. The Meldrum’s acid adduct was prepared by treatment of Meldrum’s acid, readily available from malonic acid, with methoxyacetyl chloride in the presence of pyridine. The difficulty in the purification of Meldrum’s acid adducts necessitated the use of the Meldrum’s acid adduct in an impure form, which led to characterization challenges and low yields. The presence of the Meldrum’s acid adduct was eventually confirmed by refluxing crude 49 in methanol which produced methyl 4-methoxyacetoacetate. Structural assignment of the methyl 4-methoxyacetoacetate was made by comparison to NMR data available from Aldrich. After the presence of the Meldrum’s acid adduct in the crude reaction mixture was
confirmed, the adduct was refluxed in toluene with oxazolidinone. Compound 42 was generated in a yield of 10% from Meldrum's acid.

Scheme 16- Synthesis of β-keto imide and retrosynthetic analysis of γ-methoxy β-keto imide

When 42 was treated under tandem chain extension aldol conditions with benzaldehyde, the crude product mixture was carried forward to the CAN oxidative cleavage reaction without purification in an effort to maintain the diasteromeric ratio generated in the initial aldol reaction. Treatment of the aldol products (50 and 51) with ceric ammonium nitrate gave a mixture (1.2:1) of diastereomeric products 52 with a mass
recovery of 88% (based on MW of the anticipated aldol product). The low diastereoselectivity can be attributed to an influence of the \( \gamma \)-methoxy functionality.\(^{32}\) In an effort to identify the diastereomers, the \( \gamma \)-lactones 52 were treated with sodium methoxide to generate \( \gamma \)-lactones 53, for which characterization data is known in the literature.\(^{37}\) Since the stereocenters of the aldol products have been shown to remain unaffected throughout the CAN oxidative cleavage process,\(^{22,32}\) the stereocenters in the \( \gamma \)-lactone are established in the initial aldol reaction. The \textit{trans} lactone would come from the \textit{syn} aldol adduct and the \textit{cis} lactone would come about from an \textit{anti} aldol adduct. The sodium methoxide method of oxazolidinone cleavage resulted in isolation of one methyl ester diastereomer, which indicated that epimerization at the \( \alpha \)-site to the ester had occurred. The low mass recovery (18\% based on the expected ester product) could also indicate selective degradation of one ester lactone diastereomer. The major product of the cleavage, which was believed to be a result of the epimerization, was identified as the \textit{trans} isomer. This method of imide cleavage had been shown to work inconsistently under similar circumstances.\(^6\)
Scheme 18- Chain extension aldol and subsequent CAN oxidation of γ-methoxy β-keto imide

The relatively low stereoselectivity of the reaction showed that this method of studying the stereoselectivity of the tandem zinc-mediated chain extension aldol reaction of β-keto imides could be compromised due to the γ-methoxy substituent. Previous zinc-mediated chain extensions involving the β-keto γ-methoxy ester framework were also less diastereoselective than their traditional β-keto ester counterparts. This loss of stereoselectivity in β-keto γ-methoxy methyl esters have been rationalized by competitive chelation of the zinc by the γ-keto and δ-methoxy functionalities in the formed zinc enolate. This competitive mode of complexation was proposed to compromise the bias towards the Z enolate, thereby resulting to a diminished preference for syn aldol product.
The loss of stereoselectivity in the chain extension aldol reaction of the β-keto γ-methoxy imide would not likely be a result of this competitive complexation. Since the zinc-mediated chain extension aldol reaction of the β-keto γ-methoxy imide does not likely involve an E-enolate due to steric interactions, diminishment of the chelation biasing the Z-enolate should not dramatically affect the enolate’s influence on stereoselectivity observed in the aldol reaction. The anti selectivity observed in the chain extension aldol of β-keto imide (47) was rationalized by use of an open transition state model (Figure 3). Application of this model to γ-methoxy β-keto imide 42 leads to two possible reactive conformer models 55 and 56 (Figure 7). A reaction that proceeds through conformation 55 would lead to the anti aldol product, while 56 would lead to the syn aldol product. The influence of the δ-methoxy substituent on the reduced stereoselectivity of these type of aldol reactions is not fully understood. A substrate that lacks the γ-methoxy substitution has been reported to proceed with high antiselectivity, and the sole difference between 42 and 47 is the presence or absence, respectively, of the
methoxy substituent. However, it is apparent that methoxy substituent is playing a role in the stereoselectivity.

istency.

![Figure 6-β-Keto imide analogue](image)

**Figure 6-β-Keto imide analogue**

![Figure 7-Open transition state model of the enolate generated under tandem chain extension-aldol protocol of γ-methoxy β-keto imide](image)

**Figure 7-Open transition state model of the enolate generated under tandem chain extension-aldol protocol of γ-methoxy β-keto imide**

The attempted methoxide cleavage reaction proceeded with noticeable epimerization to give **52** as the *trans* diastereomer in a low yield (16%). Loss of product during the attempted methoxide cleavage could have been due to a competitive elimination reaction. During the course of the cleavage reaction, the stereocenter of **52** is likely epimerized at the ester lactone stage as opposed to the imide lactone starting material due to α-substituted tertiary imides being slow to epimerize.\(^{38,39}\)
which do not affect the stereochemistry of the product, for the conversion of imide lactones to compounds for which characterization data is available in the literature would need to be available if this strategy for identification of imide lactone stereochemistry is to be effective.

**Synthesis of Malonyl Diimide 60**

Compound 57 was initially targeted by a previous member of Dr. Zercher's research group. The disconnection strategy involved use of malonyl dichloride. Treatment of malonyl dichloride with the oxazolidinone 58 did not form bis-imide 57. Several modifications were made to this attempted reaction, but the bis-imide 57 (Scheme 19) was not formed. These reaction difficulties, along with the expense and high water sensitivity of malonyl dichloride, led to consideration of alternate routes for the formation of the bisimide 57.

![Scheme 19- Initial attempts of synthesis of 57](image-url)
An alternative synthetic strategy involved a Claisen condensation. This disconnection would require the generation of the carbamoyl chloride 59 and acyl oxazolidinone 45. Both starting materials 59 and 45, were prepared from commercially available 2-oxazolidinone 46 using a method reported by Ashburn and coworkers.\textsuperscript{41} The \textsuperscript{1}H NMR of the crude reaction mixture of the mixed Claisen reaction gave no evidence for the generation of the bis-imide 60. The water sensitivity of 59, as well as the lack of production of 60, led to exploration of alternate approaches.

![Scheme 20 - Retrosynthesis of 60](image)

![Scheme 21 - Attempted Claisen condensation synthesis of 60](image)

Lin reported the preparation of compound 61 by treatment of L-phenylalanine-derived oxazolidinone 58 with trimethylsilylchloride and subsequently Meldrum's acid in
the presence of copper and copper (II) chloride. The production of bis-imide 61 was an unexpected result in an attempt to synthesize carboxylic acid imide 62. Removal of the chlorine atom by zinc metal insertion followed by a protic quench was viewed as an alternate approach for the formation of bis-imide 57. However, zinc insertion into 57 should produce the same zinc enolate intermediate that would be formed in a chain extension reaction. Therefore, treatment of α-chloro malonyl diimide 61 with chain extension conditions was believed to be identical to the treatment of malonyl diimide 57 under identical conditions. Therefore, formation of the α-chloro malonate derivative was viewed as highly desirable. Unfortunately, efforts to reproduce the formation of the α-chloro malonyl diimide were unsuccessful. The attempted formation of α-chloro malonyl diimide 63 gave 45 as a sole product. Compound 45 was believed to be produced by decarboxylation of proposed intermediate 64 (Scheme 23). The original report of the preparation of α-chloro bisimide 61 was supported by complete spectral characterization, including X-ray crystallography. Therefore, the problem in reproducing the work was due to an incomplete understanding of the reaction leading to 61.
Alternate synthetic pathways for the formation of a malonyl diimide were explored, but eventually a very simple preparation of bis-imide carbamates was applied to the oxazolidinone system. This procedure proved to be relatively efficient and inexpensive.\textsuperscript{42,43} The bis-imide was produced by treatment of a melted mixture of oxazolidinone and malonic acid with acetic anhydride. Although the reaction mechanism has not been delineated, the reaction could proceed through ketene intermediates (65 and 66).
Synthesis of Chiral Malonyl Diimide 57

A chiral malonyl diimide 57 could be generated from an (L)-phenylalanine-derived oxazolidinone under similar conditions as used for the achiral analogue 60.\textsuperscript{43} Lithium aluminum hydride reduction of (L)-phenylalanine gave the amino alcohol 67. Treatment of 67 with triphosgene gave the (L)-phenylalanine-derived oxazolidinone 58. Treatment of the (L)-phenylalanine-derived oxazolidinone with acetic anhydride and
malonic acid provided the chiral malonyl diimide 57 in a yield, although moderate, that was sufficient for studying γ-lactone formation utilizing a chiral auxiliary.

Scheme 25- Synthesis of chiral malonyl diimide 57

Chain Extension Chemistry of Malonyl Diimide 60

Initial attempts to apply the standard chain extension-aldol reaction to 60 with two equivalents of carbenoid failed to produce any chain-extended product. Compound 68 was isolated as a single product. Since the chain extension methodology works well with β-keto imides\(^6, 14, 17, 22\) and α-carboxyester imides,\(^22, 33\) the presence of imide functionality was not perceived to be problematic. Therefore, longer reaction times and/or use of five equivalents of carbenoid were investigated to see if chain extension of 60 was possible. Use of five equivalents of carbenoid for the typical reaction time (\textit{ca.} 30 min.) resulted in the formation of the same product (68). However, exposure of 60 to longer reaction times resulted in the appearance of chain extension material 69. Analysis of the crude reaction mixture showed evidence of post chain extension alkylation products 70, as well
as starting material 60 in the NMR spectrum of the crude reaction mixture.\cite{44} The optimal time for aldehyde addition, which is required for the chain extension-aldol reaction, would be at a point in time when the starting material (60) was fully consumed and no post chain extension alkylation (formation of 70) had occurred. The results described above reveal that compound 70 is being produced prior to the complete consumption of starting material; therefore, no ideal time was identified for the addition of the aldehyde. Weimin Lin reported success in introducing the aldehyde before the β-keto carbonyl species in chain extension-aldol reactions,\cite{22} therefore we investigated the early addition of aldehydes to the reaction mixture.

![Scheme 26- Zinc-mediated chain extension of 60.](image)

When benzaldehyde was added to five equivalents of carbenoid immediately prior to addition of the bisimide, benzyl alcohol was noted in the proton NMR spectra of the crude reaction mixture as a major side product. Generation of benzyl alcohol is presumably due to a competitive Meerwein-Ponndorf-Verley type reduction of benzaldehyde as a result of its extended exposure to diethyl zinc. In order to inhibit the reduction pathway the equivalents of carbenoid were reduced to 2.1. The presence of three benzylic proton resonances was observed in the proton NMR of the crude reaction
mixture. The presence of two benzylic protons would be consistent with a mixture of diastereomers of 52, with the third benzylic resonance being due to the possible contribution of an uncyclized aldol product. However, isolation of imide lactones 52 and ester lactone 38 from the reaction mixture indicated that reduction of benzaldehyde was still occurring and excluded presence of an uncyclized aldol product. Production of 38 would be consistent with a transesterification facilitated by the benzyl alkoxide produced from the reduction of benzaldehyde.

Scheme 27- Initial zinc-mediated chain extensions of malonyl diimide 60

Different reaction times of 60 with identical chain extension-aldol conditions with benzaldehyde were investigated. When comparing the proton NMRs of crude reaction mixtures generated after 5h and 80h (Figure 8 and Figure 9 respectively), it appears that the trans diastereomer of 38 was produced predominantly. The minor diastereomer of 52 diminishes over time as the presence of trans 38 increases. The disappearance of minor
Imide lactone 52 with the increase of trans 38 would suggest that the benzyl alkoxide, produced by reduction of benzaldehyde, is selectively reacting with the minor imide lactone 52.

Figure 8- $^1$H NMR spectra of the crude reaction mixture produced from the chain extension-aldol reaction of 60 with benzaldehyde utilizing five equivalents of carbenoid after 5h.

Figure 9- $^1$H NMR spectra of the crude reaction mixture produced from the chain extension-aldol reaction of 60 with benzaldehyde utilizing five equivalents of carbenoid after 80h.
The slow reactivity of 60 in the zinc-mediated chain extension-aldol reaction is not fully understood. The analogous malonyl ester imide 40 and β-keto imide 47 have been reported to react under chain extension conditions with typical reaction times on the order of 30 minutes.\textsuperscript{6,45} The slow chain extension of 60 appears to be due to a slow 3-exo-trig cyclization during the donor-acceptor cyclopropane formation step. This slow cyclization could be caused by the increase of steric bulk adjacent to the homoenolate 71 that is not inherent to the similar cyclizations of 72 and 73.

Synthetic efforts to prepare the imide amide substrate (74) are currently underway to investigate this phenomenon. The intermediate homoenolate 75, which could presumably be generated from substrate 74 under the chain extension conditions, would exist in a similar steric environment as 71, although the Lewis basic site found in the additional carbamate functionality would be absent. If the slow chain extension of 60 is a result of steric effects, 74 would also be predicted to experience a slow chain extension reaction. If the slow chain extension is a result of electronic effects of the additional oxazolidinone functionality, malonyl amide imide 74 should react in a more similar fashion to ester imide 40.
The initial attempt to form 74 was using a disconnection strategy that involved an acylation reaction between 2-oxazolidinone and 3-oxo-3-(pyrrolidin-1-yl)propanoyl chloride. This disconnection appears to be straightforward, however generation of 3-oxo-3-(pyrrolidin-1-yl)propanoyl chloride from 3-oxo-3-(pyrrolidin-1-yl)propanoic acid was not successful using thionyl chloride or oxalyl chloride. The selective reaction occurring with the carboxylic acid over the amide functionality was considered to be the challenge in this strategy. Deprotonation of the 3-oxo-3-(pyrrolidin-1-yl)propanoic acid prior to addition of the thionyl chloride did not facilitate conversion of 3-oxo-3-(pyrrolidin-1-yl)propanoic acid to 3-oxo-3-(pyrrolidin-1-yl)propanoyl chloride. The 3-oxo-3-(pyrrolidin-1-yl)propanoic acid was generated as reported in the literature.46

A mixed Claisen condensation disconnection strategy involving acyl oxazolidinone 45 and pyrrolidine-1-carbonyl chloride was also investigated as a means to generate 74. The pyrrolidine-1-carbonyl chloride was generated in a similar fashion as reported by Takemoto and co-workers.47 The mixed Claisen condensation strategy did not work. It is worth noting that resonances due to the presence of pyrrolidine-1-carbonyl chloride and acyl oxazolidinone 45 were noticed in the proton NMR of the crude reaction mixture after an aqueous workup.
Summary of Tandem Chain Extension-aldol Chemistry of Malonyl Diimides

Four aldehydes and their reaction with achiral malonyl diimides were studied in a chain extension aldol reaction. Two aromatic aldehydes were selected, as well as two aliphatic aldehydes. The aliphatic aldehydes reacted with the enolate to generate the syn aldol product selectively. When the aldol reaction using pivaldehyde was conducted under high dilution, the syn aldol product was formed exclusively, within the detection limits of NMR.

Previous work in the area of tandem chain extension-aldol reactions had shown that the stereoselectivity of the chain extension-aldol reaction is dependent on the concentration. The chain extension-aldol of malonyl diimide 60 was studied to see if a similar concentration dependency would be observed (Table 2). As illustrated in Table 2,
a dependence on concentration in the stereoselectivity of the tandem chain extension-aldol reaction was observed. A dependence on the equivalents of carbenoid used in the reaction was also revealed. As seen in the comparison of entry 1 to entry 4 (Table 2), the only change in reaction conditions was the number of equivalents of carbenoid. An increase in Lewis acid concentration (zinc) could facilitate aldol reaction through an open transition state, with the result of enhancing anti aldol product formation. As revealed in a comparison of entry 3 to entry 5, where the only change is the concentration of the reaction, exclusive formation of one diastereomer is observed when the reaction is run at low concentration. The decrease in concentration would be anticipated to facilitate aldol reaction through a closed transition state, which would lead to more syn aldol product formation. The ratio of aldol products were determined by the $^1$H NMR of the crude reaction mixture.

Concentration also has an effect on the amount of Meerwein-Ponndorf-Verley reduction side products that are formed in the reaction. At high dilution, (Entry 3, Table 2) production of one diastereomer 76 in the absence of the ester lactone 77 was observed. The generation of ester lactone 77 increases as concentration increases. It is unclear whether the high dilution inhibits the reduction of benzaldehyde or the transesterification of 76 with the benzyl alkoxide intermediate formed in the reduction.
Table 2- Stereoselectivity of the chain extension-aldol reaction of 60 with pivaldehyde as affected by concentration and carbenoid equivalents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbenoid Equiv</th>
<th>Substrate Concentration</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>20mM</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>6mM</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4mM</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>20mM</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>40mM</td>
<td>75</td>
</tr>
</tbody>
</table>

When the malonyl diimide substrate 60 was subjected to the tandem chain extension-aldol conditions with various aldehydes, syn aldol selectivity was generally observed in product formation of the β-carboxy imide γ-lactones (76), as well as the β-carboxy ester γ-lactones formed from the transesterification. Pivaldehyde gave the highest stereoselectivity, although benzaldehyde actually favored formation of the anti isomers. The syn selectivity is a bit unexpected, since both the chiral and achiral β-keto imide starting material provided products with high anti diastereoselectivity in the tandem chain extension-aldol reaction. A contributor to the moderate syn aldol selectivity in the reaction of the di-imide could be the increased dilution and the use of fewer equivalents of carbenoid when compared to the β-keto imide substrates. The increase in syn aldol selectivity would be consistent with higher dilution, which would facilitate the aldol reaction occurring through a closed transition state. A decrease in
carbenoid equivalents would also be anticipated to increase the syn selectivity by facilitating a closed transition state.

The reaction of benzaldehyde with the generated imide enolate (Entry 3) (Table 3) produced predominantly anti aldol product. The anti aldol product formation would be consistent with an open transition state;\textsuperscript{6,17} however, the disparity between the stereoselectivities of the aldol reaction involving the anisaldehyde and that involving benzaldehyde is not fully understood. The reaction of 60 with an aromatic aldehyde, which is substituted with an electron-withdrawing group, in a chain extension aldol reaction could shed light on whether the stereoselectivity difference with the aromatic aldehydes is due to an electronic effect.

![Chemical structure diagram](image)

\[ R = \text{trans, syn} \]
\[ b = \text{cis, anti} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Eq.</th>
<th>[M]</th>
<th>Ratio Imide Lactone</th>
<th>Ratio Ester Lactone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( t )-Bu</td>
<td>2</td>
<td>6mM</td>
<td>a: 88 b: --</td>
<td>a: 12 b: --</td>
<td>29a</td>
</tr>
<tr>
<td>2</td>
<td>( C_6H_{11} )</td>
<td>2</td>
<td>4mM</td>
<td>a: 75 b: 25</td>
<td>a: -- b: --</td>
<td>18a, 36ab</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>2</td>
<td>4mM</td>
<td>a: 33 b: 67</td>
<td>a: -- b: --</td>
<td>48ab</td>
</tr>
<tr>
<td>4</td>
<td>( p )-OMeC( _6 )H( _4 )</td>
<td>2</td>
<td>4mM</td>
<td>a: 56 b: 22</td>
<td>a: 11 b: 11</td>
<td>25ab</td>
</tr>
</tbody>
</table>

Table 3- Stereoselectivity of the tandem chain extension-aldol of diimide 60
Identification of Stereoisomers

The zinc-mediated tandem chain extension-aldol reaction, when applied to the malonyl diimide substrate with pivaldehyde, produced both an imide lactone 76 and an ester lactone 77. Compound 76 was converted to the ester lactone 78 using a two-step reaction sequence involving cleavage of the imide and alkylation of the resultant carboxylic acid. The imide cleavage was facilitated by lithium peroxide, which has been shown previously to be tolerant of α-stereocenters.22,48 The alkylation of the resultant carboxylic acid was performed using triethyloxonium tetrafluoroborate. Both diastereomers of 78 had previously been made from malonyl imide ester 40 and the major diastereomer was tentatively assigned as the trans-lactone based on analogy to aldol selectivity of the ester enolates under chain extension conditions.25,45 The ester lactone 78, generated from the major diastereomer of imide lactone 76, possessed identical spectral properties to the major diastereomer ester lactone 78 that was generated from the tandem chain extension-aldol of imide ester starting material 40. This would indicate that the stereoselectivity of the chain extension-aldol with the malonyl diimide 60 and malonyl imide ester 40 both favored production of the same aldol stereochemistry (syn or anti) when using pivaldehyde.

\[
\begin{align*}
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{O} & \text{O} & \text{O} & \text{O} & \text{O} & \text{O} \\
\text{Et}_2\text{Zn, CH}_2\text{I}_2 & \text{t-BuCHO} & \text{LiOH, H}_2\text{O}_2 & \text{Et}_3\text{O-BF}_4 \\
\begin{array}{c}
60 \\
76 \\
78
\end{array}
\end{align*}
\]

Scheme 29- Production of imide lactone 76 and conversion to ester lactone 78
An attempt was made to assign the relative stereochemistry of the major stereoisomer of 78 through a variety of 1-D NOE experiments. When irradiating the t-butyl protons and observing the β-methyne resonance or visa versa, similar NOE enhancements were observed for both diastereomers. When examining the conformers available for both diastereomers and taking into account the flexibility of 5-membered heterocycles, the observation of similar NOE enhancements (Figure 11) for both diastereomers appear reasonable. Both cis and trans isomers are able to adopt a conformation in which the t-butyl protons and the methyne proton of interest are within similar distances from each other, therefore observation of similar 1-D NOE behavior is not surprising.
An alternative strategy in an attempt to determine the stereochemical assignment of the major isomer involved consideration of a Lewis Acid-mediated allylation, which has been shown to add more stereoselectively to cis-substituted cyclic hemiacetals than the trans isomers (Scheme 31). If both stereoisomers of 78 could be converted to hemiacetals and then reacted with allyltrimethylsilane and boron trifluoride etherate, the cis isomer would be expected to give higher stereoselectivity in the allylation reaction, which would allow stereochemical assignments to be made on the basis of the reaction stereoselectivity. Unfortunately, both stereoisomers of 78 are not readily available and attempted conversion of trans-lactone 78 to hemiacetal 79, by treatment with DIBAL, provided an unidentified mixture of products.
Slow crystal growth was able to provide a crystal suitable for X-ray crystallographic analysis, which revealed \textit{trans} stereochemistry in the major imide lactone 76 (Figure 12).\textsuperscript{49} Since the imide had been converted to ester 78, which was identical to the major isomer observed in the reaction of the imide-ester 40, this result solidified the previous tentative stereochemical assignment of ester lactone 78.
The structure of ester lactone 77 was assigned by use of a mild transesterification protocol shown in the literature to tolerate α-stereocenters. As expected, the transesterification of 77 provided 78 with no evidence of epimerization; unfortunately, the reaction did not go to completion. Since the trans-stereochemistry of ester 78 had been assigned through conversion from 76, the stereochemistry of 77 was established as the trans isomer.
When the zinc-mediated tandem chain extension-aldol reaction conditions were applied to the malonyl diimide substrate 60 using hexanal as the aldehyde, a mixture of diasteromeric imide lactones 80 was observed. Slow crystal growth of the major diastereomer from diethyl ether was able to provide a crystal suitable for X-ray crystallographic analysis, which revealed trans stereochemistry in the major imide lactone isomer 80 (Figure 13). A mixture of diastereomers of 80 (6.6:1 respectively) was also transformed to their respective carboxylic acids using a lithium peroxide-mediated cleavage reaction. No epimerization during this cleavage process was observed as evidenced by an identical diasteromeric ratio observed in the carboxylic acid products (6.6:1). The trans-lactone carboxylic acid 81 is known in the literature. Comparison of the literature’s spectroscopic data to that of the major carboxylic acid reinforced the stereochemical assignment made by crystal structure.
Scheme 33- Zinc-mediated chain extension-aldol of 60 with hexanal

Figure 13- Structure of 80 provided by X-ray Crystallographic Analysis

Scheme 34- Lithium peroxide mediated cleavage of 80
When malonyl diimide 60 was treated under the zinc-mediated tandem chain extension-aldol reaction conditions in the presence of anisaldehyde, a mixture of diastereomeric imide lactones 82 was produced, as well as a mixture of diastereomers of the ester lactones 83. A side product with NMR spectral properties consistent with succinate derivative 84 was isolated in trace amounts when this reaction was carried out under concentrated conditions (20 mM). Isolation of the major diastereomer in the absence of the minor diastereomer of 82 was not successfully accomplished. The structure of the major diastereomer (82) was assigned by conversion of a diastereomeric mixture of trans and cis lactones 82 (6:1 respectively) to the trans and cis carboxylic acids 85 (9:1 respectively) through lithium peroxide-mediated imide cleavage. The cleavage proceeded with a slight modification of stereochemistry as indicated by non-identical diasteromeric ratios of the carboxylic acids 85 when compared to the lactones 82. The NMR data of the major carboxylic acid 85 diastereomer matches the data reported for the trans-paraconic acid 85 reported in the literature.29

![Scheme 35- Synthesis of imide lactones 82 and ester lactones 83](image)
The relative stereochemistry of imide lactone 82 can also be assigned by an observed magnetic anisotropy effect involving one of the oxazolidinone protons. The resonances for which the unusual chemical shift was observed was assigned as an oxazolidinone on the basis of a COSY study and correlated to the minor diastereomer. An upfield shift of one oxazolidinone proton is observed in the minor diastereomer, which most likely is due to a cis relationship between the phenyl group and the oxazolidinone. This hypothesis was supported by a conformer distribution search at the MMFF level of theory followed by a single-point energy and NMR calculation at the HF/321g(*) level of theory. Taking into account the NMR shifts and the respective
Boltzmann distribution at room temperature in the absence of solvation, the NMR shifts can be calculated.

As a general trend in the calculated proton NMR shifts (Table 4), it was noticed that the cis isomer of 82 was the only isomer in which one of the oxazolidinone protons (H1) was calculated to give rise to a resonance that was shifted upfield to where the resonance was observed experimentally. The cis isomer has several low lying energy conformers in which the aromatic ring is placed in an orientation that could give rise to a shielding effect, commonly referred to as the magnetic anisotropy effect, that would cause the proton to resonate further upfield than typically observed for acylated oxazolidinone protons. The low lying conformers of the trans isomer do not assume the orientation required to produce the shielding effect that is seen with the cis isomer.
Table 4- Summary of conformational and \( ^1 \text{H} \) NMR computational analysis of lactones 82

<table>
<thead>
<tr>
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Figure 15. $^1$H NMR of a 2.4:1 (major : minor) diastereomeric mixture of 82

When malonyl diimide 60 and benzaldehyde were treated with the zinc carbenoid-mediated tandem chain extension-aldol reaction conditions, a mixture of diastereomers of imide lactone 52 was produced, as well as a mixture of diastereomers of ester lactone 38. Isolation of the major diastereomer of 52 in the absence of the minor diastereomer was not successful. The stereochemistry of the diastereomer 52 was assigned by observation of a selective upfield shift of a $^1$H NMR resonance due to magnetic anisotropy.
Scheme 37- Chain extension-aldol reaction of 60 with benzaldehyde

In a similar fashion to the anisaldehyde-derived lactone, one isomer gave rise to a
$^1$H resonance that was significantly upfield. The upfield resonance was observed in the
major product and was assigned to an oxazolidinone on the basis of COSY spectra.
Computational methods (Table 5) predicted that the cis isomer of 52 was the only isomer
in which one of the oxazolidinone protons would resonate in the upfield region.

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Table 5- Summary of conformational and $^1$H NMR computational analysis of 52
The stereochemistry of the benzyl ester 38 was identified by treating it with dibutyltin oxide as a Lewis acid, effecting a mild transesterification protocol.\textsuperscript{50} The transesterification reaction provided 86 and 87 as products. Compound 87 was likely the result of Lewis acid catalyzed lactone opening with ethanol. Since ethanol was used as the solvent, hence used in excess, this result was not unanticipated. The ester lactone 86 was compared to the characterization data reported in the literature, which supported the assignment of the ester lactone 38 as the \textit{trans} isomer. The observed $^1$H NMR
resonances for the major succinate derivative in the NMR of the crude reaction mixture is similar, but not identical, to the NMR data for the \((S,R)\) diastereomer reported in the literature.\(^{53}\) The relative stereochemistry of the succinate derivative 87 can therefore be tentatively assigned as arising from the \(\text{trans}\)-lactone ester 86 and a \(\text{syn}\)-aldol product.

![Scheme 38 - Transesterification of 38](image)

The assignment of the \(\text{trans}\) stereochemistry of ester lactone 38 also supports the assignment of relative stereochemistry for imide lactone 52. Since 38 has been shown to arise from the minor imide lactone 52, that was generated in the chain extension aldol reaction of malonyl diimide 60 with benzaldehyde (Figure 8 and Figure 9), the minor imide lactone 52 would likely be \(\text{trans}\) as well.

A diastereomeric mixture of imide lactones 52 (1.3 : 1) was treated with lithium peroxide to give a mixture of carboxylic acids 88 (1 : 1.5). The transformation did not proceed with complete retention of the ratio of diastereomers. The major diastereomer of the carboxylic acid mixture was identified as the \(\text{trans}\) isomer. The lithium peroxide mediated cleavage has been reported as not affecting the stereochemistry \(\alpha\) to the imide. The change of the diastereomeric ratio may be due to selective cleavage of one diastereomer of the imides 52, although other explanations could be offered as well.
When chiral malonyl diimide 57 was treated with five equivalents of carbenoid in the presence of benzaldehyde, four major products were observed in the NMR spectra of the crude reaction mixture (4:1:1:1). The major product, 89a as well as one of the minor products, were successfully isolated in a pure. Both the compounds correspond to diastereomers of 89. Although not isolated in pure form, the other minor products are believed to be diastereomers of either the ester lactones 52 or the remaining diastereomers of imide lactone 89. The major diastereomer 89a has a benzylic proton resonance at 1.48 ppm, which is significantly upfield from the other resonances. The proton assignment was made by use of one and two dimensional $^1\text{H NMR}$ spectroscopy, which indicated that the proton resonance at 1.48 ppm corresponds to one of the benzylic protons on the oxazolidinone. This assignment was based on the 2-D COSY spectra, which showed spin-coupling to the oxazolidinone methine proton. This proton resonance is further upfield than typical benzylic proton resonances are observed. This upfield shift is likely due to magnetic anisotropy due to the other aromatic ring. A conformer search utilizing Spartan ‘04 identified low lying energy conformers of the cis diastereomers 89a-b that places the aromatic ring in an orientation that could induce a magnetic anisotropy.

Scheme 39- Lithium peroxide mediated cleavage of imide lactone 52

Chain extension-aldol chemistry of chiral malonyl diimide 57

![Diagram of chemical reaction]
effect. Similar computational analysis of low lying conformers of the \textit{trans} diastereomers 88c-d reveals that the \textit{trans} isomers do not adopt this type of orientation.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure17.png}
\caption{COSY spectra of 89}
\end{figure}

Proton NMR shift calculations of the possible diastereomers (Table 6) show that \textit{cis} diastereomers are the ones in which upfield shifts for the oxazolidinone benzylic protons are predicted. Diastereomer 88a is predicted to have more of an upfield shift for the oxazolidinone benzylic proton, than the other \textit{cis} diastereomer 88b. The \textit{cis}
diastereomer 88a also possesses the absolute stereochemistry, induced by facial selectivity of the enolate, that would be predicted based on previous studies involving chain extension-aldol reactions involving chiral oxazolidinone auxiliaries. The cis stereochemistry of 88a would also be consistent with the anti aldol selectivity that was previously observed with chiral β-keto imides, and rationalized with an open transition state.\textsuperscript{6,17}

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Table 6- Summary of conformational and \textsuperscript{1}H NMR computational analysis of 89 and experimentally observed proton shifts.
The change of the diastereomeric ratio may be due to selective cleavage of one diastereomer of the imides 52, although other explanations could be offered as well.

\[
\begin{align*}
\text{Ph} \quad \text{Ph} \\
\text{O} \quad \text{H} \\
\text{O} \quad \text{H} \\
\text{Ph} \\
\end{align*}
\]

Scheme 39- Lithium peroxide mediated cleavage of imide lactone 52

Chain extension-aldol chemistry of chiral malonyl diimide 57

When chiral malonyl diimide 57 was treated with five equivalents of carbenoid in the presence of benzaldehyde, four major products were observed in the NMR spectra of the crude reaction mixture (4:1:1:1). The major product, 89a as well as one of the minor products, were successfully isolated in a pure. Both the compounds correspond to diastereomers of 89. Although not isolated in pure form, the other minor products are believed to be diastereomers of either the ester lactones 52 or the remaining diastereomers of imide lactone 89. The major diastereomer 89a has a benzylic proton resonance at 1.48 ppm, which is significantly upfield from the other resonances. The proton assignment was made by use of one and two dimensional $^1$H NMR spectroscopy, which indicated that the proton resonance at 1.48 ppm corresponds to one of the benzylic protons on the oxazolidinone. This assignment was based on the 2-D COSY spectra, which showed spin-coupling to the oxazolidinone methine proton. This proton resonance is further upfield than typical benzylic proton resonances are observed. This upfield shift
The scope of the zinc-mediated tandem chain extension-aldol reaction was expanded to include γ-methoxy β-keto imides. The chain extension-aldol reaction of the γ-methoxy β-keto imides favored production of syn aldol products, although low selectivity is observed in the aldol reaction at standard concentration. Aldol products from the γ-methoxy β-keto imide were able to be converted to the γ-lactones via CAN oxidative cleavage of hemiacetals. Imide cleavage of the γ lactones with sodium methoxide provided results consistent with epimerization of the ester lactone.

The scope of the tandem chain extension aldol reaction was also expanded to include malonyl diimides. The chain extension reaction of malonyl diimides is slow. Aldehyde was added into the reaction mixture before malonyl diimide in order to avoid formation of post chain extension-methylation product. Reduction of the aldehyde in the reaction mixture was observed when extended reaction times were used. Reaction conditions were developed to reduce the amount of side products that were formed due to the aldehyde reduction. The reaction conditions used to minimize aldehyde reduction made use of high dilution, as well as a lowered number of equivalents of diethylzinc.

The chain extension-aldol reactions of malonyl diimides were more selective when compared to the corresponding reactions of the γ-methoxy β-keto imide starting material. The chain extension-aldol reaction of malonyl diimides with aliphatic aldehydes, as well as anisaldehyde, favored formation of syn aldol products. The chain extension aldol reaction of chiral and achiral malonyl diimides with benzaldehyde favored anti aldol product formation.
An observed magnetic anisotropy effect was used to identify the relative stereoselectivity of the chain extension aldol reaction of malonyl diimides with aromatic aldehydes. Computational modeling of the imide lactones suggest that only the cis diastereomers of the lactones would give rise to the resonances that were shifted upfield due to the magnetic anisotropy effect.
CHAPTER IV

EXPERIMENTAL SECTION
GENERAL EXPERIMENTAL

Solvents

Anhydrous solvents (methylene chloride, tetrahydrofuran, toluene, methanol, diethyl ether, and acetonitrile) were obtained from an Innovative Technology Inc. Solvent Delivery System prior to use. Solvent removal (in vacuo) was accomplished by use of a rotary evaporator (typically 25 °C, 25 mmHg) and a vacuum pump line (typically <5 mTorr).

Reagents

Unless noted otherwise, all reagents were obtained from commercial sources and were used as received. Aldehydes and amines were dried and distilled prior to their use. Diethylzinc (neat) was purchased from Aldrich.

Chromatography

Column chromatography was accomplished through use of Silia-P Flash Silica Gel with 40-63 μm particle size. Mobile phases were prepared as described in the detailed experimental. TLC analysis was conducted on glass-backed TLC plates and visualized under UV light or through use of anisaldehyde stain. TLC solvent systems were identical to the mobile phase used for column chromatography, unless otherwise noted.
Spectroscopy

NMR spectroscopy was conducted using a Varian *Mercury* 400 MHz $^1$H, 101 MHz $^{13}$C or a Varian *INOVA* 500 MHz $^1$H, 126 MHz $^{13}$C NMR spectrometer. Carbon spectra were decoupled. All shifts are reported downfield relative to TMS (δ ppm). When TMS was not used as an internal standard, the NMR spectrum was referenced by the residual solvent peak. IR spectroscopy was conducted using a Thermo Nicolet iS10 FTIR using the diamond ATR probe.

**DETAILED EXPERIMENTAL SECTION**

*trans*-Benzyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate (38)

A dry 100-mL round-bottomed flask was equipped with a stirbar, septum, and constant flow of nitrogen through the septa. The flask was charged with DCM (35 mL), cooled to 0 °C using an ice bath, and stirring was initiated. Diethylzinc (0.2 mL, 2 mmol) and methylene iodide (0.16 mL, 2 mmol) were added in that order using a syringe and carbenoid was allowed to stir for 10 minutes. Benzaldehyde (0.102 mL, 1 mmol) and bisimide (0.242 g, 1 mmol, dissolved in 15 mL DCM) were added by syringe. The reaction mixture was allowed to stir for 5 days and was quenched with saturated ammonium chloride solution (40 mL), extracted with diethylether (3 x 50 mL), washed with brine (2 x 50 mL), dried with anhydrous sodium sulfate, filtered by gravity, and the solvent was removed *in vacuo*. Products were purified by flash column chromatography (5:1 Hexanes: Ethyl acetate) to give 0.048 g (30 %) of 38 as a clear oil. $^1$H NMR (400 MHz...
MHz, CDCl₃) δ 7.40-7.25 (m, 10H), 5.63 (d, J = 7.3 Hz, 1H), 5.25-5.15 (mab, 2H), 3.37 (ddd, J = 7.3, 8.9, 9.4 Hz, 1H), 3.02 (dd, J = 8.9, 17.8 Hz, 1H), 2.91 (dd, J = 17.8, 9.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) ppm 174.2, 170.8, 138.1, 135.2, 129.2, 129.1, 129.0, 128.7, 125.7, 82.4, 77.5, 77.3, 77.0, 67.8, 49.0, 32.5. IR (neat, ATR) 2924.5, 1783.8, 1731.8, 696.5.

4-Methoxy-1-(2-oxooxazolidin-3-yl)butane-1,3-dione (40)

A dry 500-mL round-bottomed flask was equipped with a stir bar, septum, and placed under a nitrogen atmosphere using a constant flow of nitrogen through a needle placed in the septum. The flask was charged with anhydrous THF (200 mL) and was lowered into a dry ice-acetone bath that was maintained at a temperature between -8 °C and -4 °C as monitored by a thermometer in the bath. Stirring was initiated and n-butyl lithium (6.0 mL, 13.3 mmol, 2.2M solution in hexanes) was added to the reaction vessel followed by diisopropylamine (2.2 mL, 15.5 mmol) and LDA was allowed to form for 5 minutes. The reaction solution was cooled to -78 °C using the dry ice acetone bath. 3-Acetyloxazolidin-2-one (1.7 g, 12.9 mmol) dissolved in THF (15 mL) was added to the LDA solution dropwise over the course of 1 h utilizing a syringe pump. After the acetyloxazolidin-2-one addition completed, methoxyacetyl chloride (0.37 mL, 4.0 mmol) was added to the reaction mixture and the reaction mixture was allowed to stir for 1.5 h. The reaction was then quenched using HCl (1M), and extracted using diethyl ether (3 x 125 mL). The combined organic extracts were washed with HCl (1 M), sat. NaHCO₃, and brine. The organic layers were dried over sodium sulfate, which was removed by
gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg). The product was purified by column chromatography (2:1; hexanes : ethyl acetate; R_f = 0.1) to give 0.159 g (20%) of 40 as a clear oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 4.45 (t, J = 8.1 Hz, 2H), 4.11 (s, 2H), 4.06 (t, J = 8.1 Hz, 2H), 4.06 (s, 2H), 3.44 (s, 3H) \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \delta 202.1, 166.6, 153.9, 77.2, 62.5, 59.5, 47.2, 42.2

2-Methoxyacetyl chloride\textsuperscript{54} (43)

A 25-mL round-bottomed flask was equipped with a stir bar, septum and a nitrogen atmosphere using constant nitrogen flow through a needle in the septum. DMF (0.1 mL) was added to the flask followed by methoxyacetic acid (4.6 mL, 60 mmol) and stirring of the solution was initiated. Thionyl chloride (6.6 mL, 90 mmol) was added slowly by syringe to the stirring solution. A reflux condenser was inserted between the septum and the round-bottomed flask and the reaction mixture was heated to reflux using a heating mantle for 2.5h. The reaction mixture was distilled through a vigreux short path distillation head (bp = 108-113 °C) to give 43 as a pale yellow liquid. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 4.37 (s, 2H), 3.49 (s, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \delta 171.8, 77.4, 59.5.

3-Acetyloxazolidin-2-one (45)

A dry 25-mL round-bottomed flask was fitted with a stirbar, reflux condenser, and constant flow of nitrogen through the septa capped reflux condenser. The reaction flask was charged with 2-oxazolidinone (1.7 g, 20 mmol), sodium acetate (0.51 g, 6.1 mmol) and acetic anhydride (11 mL, 117 mmol) in the indicated order. Stirring of the reaction
mixture was initiated followed by heating of the reaction mixture to reflux by heating mantle under nitrogen for 4 h. Heating and stirring were then discontinued and the reaction mixture was allowed to cool to room temperature. The reflux condenser was exchanged for a short-path distillation head and excess acetic anhydride was distilled off under aspirator vacuum. The short-path distillation head was replaced with a reflux condenser and toluene (11 mL) was added to the reaction flask. The solution was heated to reflux and hot filtered by gravity into a heated 125-mL erlenmeyer flask containing a small amount of boiling toluene. This extraction/hot filtration was repeated with an additional amount of toluene (11 mL). The reaction mixture was concentrated using a rotary evaporator (40 °C, 25 mmHg) to a final volume of ca. 20 mL. Diethyl ether (20 mL) was added to the resultant solution to induce crystallization and the solution was placed in the fridge overnight. The 3-acetyloxazolidin-2-one was isolated by vacuum filtration. The mother liquor was retained, concentrated and additional crystallization gave a combined 1.3 g (52 %) of 45 as a white solid, mp = 66.4-67.9. $^1$H NMR (400 MHz, CDCl$_3$) δ 4.42 (t, $J$ = 7.9 Hz, 2H), 4.03 (t, $J$ = 8.1 Hz, 2H), 2.54 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.5, 153.8, 62.0, 42.4, 23.2.

2-(Hydroxy(phenyl)methyl)-5-methoxy-1-(2-oxooxazolidin-3-yl)pentane-1,4-dione (50-51)

A dry 100-mL round-bottomed flask was equipped with a stir bar, septa, and was placed under a nitrogen atmosphere using a constant flow of nitrogen through a needle in the septa. The flask was charged with DCM (50 mL) and was placed in an icebath to
cool the solution to 0 °C and stirring of the solution was initiated. Diethylzinc (0.32 mL, 3.2 mmol) followed by methylene iodide were added to the reaction flask and carbenoid was allowed to stir for 15 minutes. Compound 40 (0.16 g, 0.79 mmol), dissolved in DCM (5 mL), was added to the reaction flask and allowed to stir for 30 min. Benzaldehyde (0.08 mL, 0.79 mmol) was added to the reaction flask and allowed to stir for 1 h. The reaction was quenched with saturated ammonium chloride (25 mL) and the reaction mixture was extracted with diethyl ether (3 x 50). The combined organic extracts were washed with brine and dried over anhydrous sodium sulfate, which was removed by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 0.11 g (48%) of 50-51 as a crude yellow oil, which was carried onto the CAN oxidation unpurified. \( ^1H \) NMR and \( ^{13}C \) NMR spectra of the crude reaction mixture are available in the appendix. The presence of benzylic proton resonances in the \( ^1H \) NMR were consistent with the aldol products 50 and 51. Benzylic protons: \( ^1H \) NMR (400 MHz, CDCl₃) \( \delta 5.67 \ (d, J = 7.5 \ Hz, 1H), 5.64 \ (d, J = 8.9 \ Hz, 1H), 5.46 \ (d, J = 9.5 \ Hz, 1H), 5.42 \ (d, J = 6.9 \ Hz, 1H) \).

3-(5-Oxo-2-phenyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (52) via CAN oxidation

A 20-mL scintillation vial, containing 50-51 (0.11 g, 0.36 mmol), was equipped with a stir bar, septum and a nitrogen atmosphere by constant flow of nitrogen through a needle in the septum. Acetonitrile (6.4 mL) and water (1.6 mL) were added to the reaction vial in the indicated order. Stirring of the solution was initiated. Ceric
ammonium nitrate (0.78 g, 1.4 mmol) was added to the stirring solution. The reaction mixture was allowed to stir for 2 h. Water (5 mL) was then added to the reaction mixture. The product was extracted using diethyl ether (3 x 10 mL). The combined organics were dried over anhydrous sodium sulfate, which was removed by gravity filtration. The solvent was removed by a rotary evaporator (25 °C, 25 mmHg) to give 0.086 g (88%) of 52 as a crude yellow oil, which was carried on unpurified. The spectroscopic data from the crude reaction mixture contains proton resonances that match the spectroscopic data of purified 52 generated from the chain extension-aldol reaction of malonyl diimide 60. Detailed NMR data can be found in the detailed experimental procedure for the formation of 52 via chain extension-aldol reaction. $^1$H NMR spectra of the crude reaction mixture is available in the appendix.

3-(5-Oxo-2-phenyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (52) via chain extension-aldol reaction

A dry 1000-mL round-bottomed flask was equipped with a stir bar, septum and nitrogen atmosphere by constant flow of nitrogen through a needle in the septum. The flask was charged with DCM (500 mL) and stirring was initiated. The reaction flask was lowered into an ice-bath. Diethylzinc (0.42 mL, 4 mmol) followed by methylene iodide (0.32 mL, 4 mmol) were added sequentially via syringe into the stirring solution. Carbenoid was allowed to form for 18 min and presence was confirmed by the appearance of a light grey tint to the reaction solution. Compound 60 (0.48 g, 2 mmol, in 15 mL DCM) was added to the reaction flask, followed quickly by benzaldehyde (0.2
mL, 2 mmol). The reaction solution was allowed to warm to room temperature and to stir for 60 h. The reaction was quenched through addition of saturated ammonium chloride solution (50 mL) and the product was extracted with DCM (4 x 250 mL). The organic phase was washed with brine and dried over saturated sodium sulfate, which was filtered away by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 0.72 g (99%) of a yellow viscous oil containing a mixture of cis and trans diastereomers (2.6:1). The product was purified by column chromatography (5:1, hexanes : ethyl acetate, Rf = 0.07) to give 41.8 mg (7.6 %) of 52 as a mixture of diastereomers (2:1; major : minor), 24 mg (4.4%) of 52 as a mixture of diastereomers, 198 mg (36 %) of 52 as a mixture of diastereomers (1.3:1), and 37 mg (10%) of the ester lactone 52 as a mixture of diastereomers (5:1). **Major cis 52 :** \[^{1}H\text{NMR}\] (500 MHz, CDCl\textsubscript{3}) δ 7.40-7.23 (m, 5H), 5.87 (d, \(J = 8.2\) Hz, 1H), 5.14 (ddd, \(J = 4.4, 8.2, 9.1\) Hz, 1H), 4.20-4.15 (m, 1H), 3.82-3.69 (m, 2H), 3.26 (dd, \(J = 4.4, 17.8\) Hz, 1H), 3.20-3.11 (m, 1H), 2.80 (dd, \(J = 9.1, 17.8\) Hz, 1H). \[^{13}C\text{NMR}\] (126 MHz, CDCl\textsubscript{3}) δ 175.2, 169.8, 152.9, 135.2, 129.1, 128.4, 126.1, 81.3, 62.1, 44.6, 42.4, 30.9. **Minor trans 52 :** \[^{1}H\text{NMR}\] (500 MHz, CDCl\textsubscript{3}) δ 7.40-7.23 (m, 5H), 5.89 (d, \(J = 7.1\) Hz, 1H), 4.50-4.40 (m, 3H), 4.09-4.03 (m, 2H), 3.17 (dd, \(J = 8.8, 10.5\) Hz, 1H), 2.77 (dd, \(J = 8.8, 17.5\), 1H). \[^{13}C\text{NMR}\] (126 MHz, CDCl\textsubscript{3}) δ 173.8, 170.4, 153.0, 137.5, 129.0, 128.9, 125.9, 81.6, 62.4, 47.9, 42.6, 32.9.
1,3-Bis((S)-4-benzyl-2-oxooxazolidin-3-yl)propane-1,3-dione (57)

A 20-mL scintillation vial was equipped with a stir bar and charged with (S)-4-benzyl-2-oxooxazolidin-2-one (0.42 g, 2.3 mmol) and malonic acid (0.12 g, 1.1 mmol). The reaction vial was lowered into an oil bath preheated to 70 °C and stirring of the reaction mixture was initiated. Acetic anhydride (0.23 mL, 2.3 mmol) was added after the mixture of solids was completely melted. The reaction mixture was stirred at 70 °C for 4.5 h. The reaction mixture was cooled to room temperature generating a viscous residue which was dissolved with DCM (3 x 10 mL). The combined organic extracts were washed with saturated sodium bicarbonate (3 x 20 mL). The organic phase was dried over anhydrous sodium sulfate, which was removed by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give the bisimide as a yellow oil. The product was purified by column chromatography (2:1; hexanes : ethyl acetate Rf = 0.25) to give 0.49 g (49 %) of the chiral bisimide 57 as a clear viscous oil. 

\[
\text{H NMR} (500 MHz, CDCl}_3 \delta 7.15-7.25 (m, 10H), 4.69-4.75 (m, 2H), 4.51 (s, 2H), 4.27-4.21 (m, 2H), 4.18 (dd, J = 9.1, 2.9 Hz, 2H), 3.37 (dd, J = 13.6, 3.3 Hz, 2H), 2.82 (dd, J = 13.6, 9.7 Hz, 2H).
\]

\[
\text{C NMR} (126 MHz, CDCl}_3 \delta 166.4, 153.6, 135.3, 129.6, 129.1, 127.5, 66.6, 55.2, 45.3, 37.7.
\]

\[
\text{IR (neat, ATR)} 1709.82, 1693.66, 1389.82, 1184.22
\]

(S)-4-Benzyloxazolidin-2-one (58)

To a dry 100-mL round-bottomed flask fitted with a stirbar, septum, and under a nitrogen atmosphere was added (S)-2-amino-3-phenylpropan-1-ol (67) (2.5 g, 16 mmol) dissolved in DCM (10 mL). The reaction mixture was cooled to 0 °C using an ice bath
and stirring was initiated. Triethylamine (5 mL, 34 mmol) was added to the flask followed by dropwise addition of triphosgene (1.8 g, 6.1 mmol, dissolved in 15 mL DCM) over the course of 1 h using a syringe pump. The reaction mixture was stirred for an additional 2 h at 0 °C and then was warmed to room temperature. The reaction was quenched through addition of water (10 mL) and methanol (6 mL). The reaction mixture was concentrated using a rotary evaporator (25 °C, 25 mmHg) to give an oil residue. The residue was dissolved and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with HCl (1M), saturated sodium bicarbonate and brine. The combined organic extracts were dried with sodium sulfate, filtered by gravity and the solvent was removed in vacuo to give 2.1 g (71 %) of (S)-4-benyloxazolidin-2-one as a white solid.

\[ {^1}H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.10-7.35 \ (m, 5H), \ 6.45 \ (s, 1H), \ 4.31-4.39 \ (m, 1H), \ 4.00-4.15 \ (m, 2H), \ 2.90 \ (dd, J = 13.6, 6.3 \text{ Hz}, 1H), \ 2.80 \ (dd, J = 13.6, 6.6 \text{ Hz}, 1H). \]

\[ {^{13}}C \text{ NMR} \ (126 \text{ MHz, CDCl}_3) \delta 159.7, \ 136.0, \ 129.1, \ 128.8, \ 127.1, \ 69.4, \ 53.7, \ 41.2. \]

1,3-Bis(2-oxooxazolidin-3-yl)propane-1,3-dione (60)

A 50-mL round-bottomed flask fitted with a stir bar was charged with malonic acid (1.9 g, 18 mmol) followed immediately by 2-oxazolidinone (3.4 g, 40 mmol). The reaction flask was lowered into an oil bath preheated to 70 °C, while stirring of the solution was initiated. After the mixture melted, acetic anhydride (3.8 g, 40 mmol) was added. The reaction mixture was allowed to stir for 3 h. The residual solid was dissolved in DCM (400 mL) and washed with sodium bicarbonate (4 x 75 mL) and brine (4 x 75 mL). The combined organic layers were dried over sodium sulfate and filtered by
gravity. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 3.5 g (80 %) of the crude malonyl diimide 60. The product was further purified by recrystallization from boiling acetone. Concentration of the mother liquor gave an oil which was crystallized from acetone to generate additional crystals to give a combined 1.95 g (45%). mp = 164-166 °C. $^1$H NMR (500 MHz, DMSO-d$_6$) δ 4.41 (t, $J=8$ Hz, 4H), 3.90 (t, $J=8$ Hz, 4H), 4.30 (s, 2H). $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ 166.3, 153.7, 62.6, 43.9, 42.1. IR (neat, ATR) 2993.0, 1787.4, 1676.6, 1364.7, 1185.

(S)-2-Amino-3-phenylpropan-1-ol (67)

A dry 500-mL, three-necked round-bottomed flask was equipped with a mechanical stirrer, two glass stoppers and a reflux condenser. The reflux condenser was fit with a septum and nitrogen gas flow through a needle. The round-bottomed flask was charged with THF (250 mL) and cooled to 0 °C using an ice bath while lithium aluminum hydride (5.6g, 150 mmol) was added. The reaction mixture was heated to reflux for 0.5 h after which the reaction flask was removed from heat. L-Phenylalanine was added in portions (3 x 4 g and 1 x 4.5 g), each when aggressive bubbling from the previous addition has subsided. The reaction mixture was heated to reflux for 2 h. Potassium hydroxide (2.8g, 50 mmol) dissolved in water (12 mL) was added dropwise through the reflux condenser. The mixture was heated to reflux for an additional 0.5 h and then filtered hot. The filtrate was dried over magnesium sulfate, filtered and solvent removed in vacuo to give 11.1 g (73 %) of (S)-2-amino-3-phenylpropan-1-ol as a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35-7.15 (m, 5H), 3.61 (dd, $J=10.80$, 3.81 Hz,
1H), 3.38 (dd, J = 10.79, 7.21 Hz, 1H), 3.14-3.05 (m, 1H), 2.78 (dd, J = 13.35, 5.19 Hz, 1H), 2.51 (dd, J = 13.32, 8.72 Hz, 1H), 2.56-1.95 (m, 2H).

13C NMR (126 MHz, CDCl3) δ 138.59, 129.11, 128.48, 126.32, 65.97, 54.11, 40.57.

**trans-3-(2-tert-Butyl-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one (76)**

A dry 1000-mL round-bottomed flask was equipped with a stirbar, septum, and constant flow of nitrogen through the septa. The flask was charged with DCM (500 mL), which was cooled to 0 °C using an ice bath, and stirring of the solution was initiated. Diethylzinc (0.65 mL, 6 mmol) and methylene iodide (0.50 mL, 6 mmol) were added in that order by syringe and carbenoid was allowed to form for 12 min. Compound 60 (0.73 g, 3 mmol, dissolved in 15 mL DCM) and pivaldehyde (0.11 mL, 1 mmol) were added using a syringe. The reaction mixture was allowed to stir for six days and was quenched with saturated aqueous ammonium chloride (50 mL) and the aqueous layer was extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, which was removed by gravity filtration, and the solvent was removed using a rotary evaporator (25 °C, 25 mmHg) to give 0.82 g of light yellow oil. The product was purified by column chromatography (5:1; hexanes : ethyl acetate; Rf= 0.06) to give 0.22 g (29%) of 76 as a white solid. An X-ray grade crystal was obtained by slow evaporation from diethyl ether in the fridge. mp= 95.0-96.5 °C. 1H NMR (500 MHz, CDCl3) δ 4.72 (d, J = 7.1 Hz, 1H), 4.53-4.38 (m, 3H), 4.14-3.99 (m, 2H), 3.02 (dd, J = 17.9, 10.3 Hz, 1H), 2.64 (dd, J = 17.9, 9.5 Hz, 1H), 0.95 (s, 9H). 13C NMR (126 MHz,
trans-Ethyl 2-tert-butyl-5-oxotetrahydrofuran-3-carboxylate (78) via alkylation

A dry 25 mL round-bottomed flask was equipped with a stirbar, septum, and constant flow of nitrogen through the septum. The flask was charged with DCM (12 mL) and 90 (0.065 g, 0.35 mmol) and stirring was initiated. Triethylxonium tetrafluoroborate (1M solution, 1.1 mL, 1.1 mmol) was added followed by triethylamine (0.07 mL, 0.4 mmol), both by syringe. The reaction mixture was allowed to stir overnight. The reaction mixture was extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with HCl (1M solution, 3 x 25 mL), saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate, which was removed by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 0.088 g (79%) of 78 as a light yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.42 (d, $J = 6.4$ Hz, 1H), 4.29-4.14 (m, 2H), 3.14 (ddd, $J = 10.3$, 7.4, 6.4 Hz, 1H), 2.89 (dd, $J = 18.1$, 7.4 Hz, 1H), 2.77 (dd, $J = 18.1$, 10.3 Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 0.99 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.7, 171.4, 88.4, 60.7, 40.0, 33.6, 32.0, 23.8, 13.0.

trans-Ethyl 2-tert-butyl-5-oxotetrahydrofuran-3-carboxylate (78) via transesterification

A dry 10-mL round-bottomed flask was equipped with a stir bar, septum, and a nitrogen atmosphere using a constant flow of nitrogen through a needle in the septum.
Compound 77 (11 mg, 0.04 mmol, in 5 mL ethanol) was added to the reaction flask followed by dibutyltin oxide (2 mg, 0.01 mmol) and stirring was initiated. A reflux condenser was inserted between the septum and reaction flask and the reaction mixture was heated to reflux by heating mantle for 23 h. The reaction mixture was allowed to cool to room temperature and added into saturated sodium bicarbonate solution. The product was extracted with ethyl acetate (4 x 5 mL). The combined organic phase was dried over anhydrous sodium sulfate, which was filtered away by gravity filtration. The solvent was removed by rotary evaporation (45 °C, 25 mmHg) to give 8.5 mg (82%) of a mixture of 78 and starting material 77 (1:1.9 respectively) as a light yellow oil. The 78 generated from transesterification showed identical \(^1\text{H NMR}\) properties to the 78 generated from alkylation in the \(^1\text{H NMR}\) spectra of the crude reaction mixtures. Detailed NMR data can be found in the detailed experimental procedure for the formation of 78 via alkylation. The \(^1\text{H NMR}\) spectra of the crude reaction mixture is available in the appendix.

3-(5-Oxo-2-pentyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (80)

A dry 1000-mL round-bottomed flask was equipped with a stirbar, septum, and constant flow of nitrogen through the septum. The flask was charged with DCM (500 mL), which was cooled to 0 °C using an ice bath, and stirring was initiated. Diethylzinc (0.42 mL, 4 mmol) and methylene iodide (0.32 mL, 4 mmol) were added in that order using a syringe and carbenoid was allowed to stir for 13 min. Bisimide (0.48 g, 2 mmol, dissolved in 15 mL DCM) and pivaldehyde (0.27 mL, 2 mmol) were added using a
syringe. The reaction mixture was allowed to stir for six days and was quenched with saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with diethyl ether (2 x 100 mL) and DCM (2 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, which was removed by gravity filtration. The solvent was removed using a rotary evaporator to give 0.689 g (97% mass recovery based on expected product formation) of 80 producing a mixture of diastereomers (2.6:1) (trans:cis). The product was purified by column chromatography (3:1; Hexanes : Ethyl acetate; Rf= 0.07) to give 96.8 mg (18%) of the major diastereomer, 98.8 mg (18%) of a mixture of the diastereomers (6.6:1), and 97.9 mg (18%) of a mixture of diastereomers (1:2.5). An X-ray grade crystal was obtained by slow evaporation of diethyl ether from a saturated solution of the major diastereomer. **trans-80 diastereomer**: mp = 64.5-65.2 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.76 (dt, J = 8.0, 5.4 Hz, 1H), 4.49 (t, J = 8.3, 2H), 4.21 (ddd, J = 12.7, 7.1, 5.6 Hz, 1H), 4.07 (t, J = 8.3, 2H), 2.94 (dd, J = 17.6, 9.3 Hz, 1H), 2.75 (dd, J = 17.6, 6.8 Hz, 1H), 0.8-1.8 (m, 11H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.4, 171.3, 153.2, 81.8, 62.4, 44.6, 42.7, 35.1, 32.3, 31.4, 29.7, 25.0, 22.4, 14.0. IR (ATR) 1767.6, 1685.8, 1391.0, 1202.7. $^{13}$C NMR resonance at δ 29.7 and $^1$H NMR resonances at δ 0.85-0.93 and 1.10-1.80 were observed due to an impurity in the hexanes used for column chromatography.

**5-Oxo-2-pentyltetrahydrofuran-3-carboxylic acid (81)**

To a dry 20-mL scintillation vial containing 80 (0.082 g, 0.30 mmol, as a trans:cis mixture of diastereomers; 6.5:1) was added THF (6 mL), water (1.5 mL) and a stirbar.
Stirring of the solution was initiated. Hydrogen peroxide (35% in H₂O, 0.08 mL, 0.76 mmol) followed quickly by lithium hydroxide (0.029 g, 0.70 mmol) were added. The reaction mixture was allowed to stir for 3 h. The reaction mixture was washed with diethyl ether (2 x 10 mL) and chloroform (2 x 10 mL). The aqueous layer was retained and acidified using HCl (1M aqueous solution) to a pH of 2 as indicated by pH paper. The carboxylic acid was extracted using ethyl acetate (3 x 10 mL). The combined ethyl acetate extracts were dried over anhydrous sodium sulfate, which was removed by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 48 mg (79%) of the carboxylic acid 81 as a mixture of diastereomers (6.6:1, trans:cis). trans-Isomer 81 ¹H NMR (500 MHz, CHCl₃) δ 4.63 (ddd, J = 7.9, 7.2, 4.7 Hz, 1H), 3.10 (ddd, J = 9.6, 8.4, 7.0 Hz, 1H), 2.95 (dd, J = 17.9, 8.4 Hz, 1H), 2.83 (dd, J = 17.9, 9.6 Hz, 1H), 1.89-1.29 (m, 9H), 0.95-0.84 (m, 3H). ¹³C NMR (126 MHz, CHCl₃) δ 176.1, 174.8, 82.0, 45.4, 35.3, 32.0, 31.3, 24.9, 22.4, 13.9.

3-(2-(4-Methoxyphenyl)-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one 82

A dry 1000-mL round-bottomed flask was equipped with a stir bar, septum, and a nitrogen atmosphere by a constant flow of nitrogen through a needle in the septum. The reaction flask was charged with DCM (500 mL), lowered into an ice bath and stirring was initiated. Diethylzinc (0.42 mL, 4 mmol) and methylene iodide (0.32 mL, 4 mmol) were added to the reaction flask in the indicated order. Carbenoid was allowed to form for 15 min and was confirmed by a light gray tint to the reaction solution. Malonyl diimide 60 (0.49 g, 2 mmol) was added to the stirring solution followed shortly by anisaldehyde
(0.27 mL, 2.2 mmol). The reaction solution was allowed to warm to room temperature at which time the solution was allowed to stir for 96 h. The reaction was quenched with addition of saturated ammonium chloride (50 mL) and extracted with DCM (3x 250 mL). The combined organic phase was dried over anhydrous sodium sulfate, which was filtered away by gravity filtration. The solvent was removed by rotary evaporator (25 °C, 25 mmHg) to give 0.669 g (85%) of a yellow viscous oil containing a mixture of diastereomers of 82 (5:2) and ester lactone diastereomers (1:1). The product was purified by column chromatography (2:1 hexanes : ethyl acetate, Rf = 0.06) to give 38 mg (6.2%) of 82 as a mixture of diastereomers (5:1; major : minor), 45 mg (7.4%) as a mixture of diastereomers (2:1), and 69 mg (11.3%) of a mixture of diastereomers (1:1).

**Trans 82**

\[ ^1H\text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.34-7.30 (m, 2H), 6.92-6.88 (m, 2H), 5.82 (d, J = 7.3 Hz, 1H), 4.52-4.38 (m, 3H), 4.09-3.98 (m, 2H), 3.81 (s, 3H), 3.13 (dd, J = 17.3, 8.9 Hz, 1H), 2.76 (dd, J = 17.3, 8.9 Hz, 1H)\]

\[ ^{13}C \text{NMR} (126 \text{ Hz, CDCl}_3) \delta 173.8, 170.4, 160.2, 153.0, 129.3, 127.6, 114.23, 81.7, 62.4, 47.8, 42.6, 33.1. \]

**cis 82**

\[ ^1H\text{NMR} (500 \text{ MHz, CDCl}_3) \delta 7.19-7.14 (m, 2H), 6.80-6.84 (m, 2H), 5.85 (d, J = 8.3 Hz, 1H), 5.07 (dd, J = 4.9, 8.4, 9.2 Hz, 1H), 4.21 (dt, J = 6.1, 9.1, 1H), 3.88 (dt, J = 7.4, 9.1 Hz, 1H), 3.80 (s, 3H), 3.76 (ddd, J = 7.4, 9.3, 10.9 Hz, 1H), 3.30-3.23 (m, 2H), 2.77 (dd, J = 9.2, 17.9 Hz, 1H).\]

\[ ^{13}C \text{NMR} (126 \text{ Hz, CDCl}_3) \delta 175.2, 169.8, 160.2, 153.0, 127.5, 127.2, 113.7, 81.1, 62.2, 55.4, 44.7, 42.4, 30.8.\]
2-(4-Methoxyphenyl)-5-oxotetrahydrofuran-3-carboxylic acid (85)

A 20-mL scintillation vial containing a stirbar and the imide lactone 82 as a mixture of diastereomers (6:1, trans : cis) (45 mg, 0.15 mmol) was charged with THF (4 mL) and water (1 mL). The solution was allowed to stir and it was cooled to 0 °C using an ice bath. Lithium hydroxide monohydrate (15 mg, 0.38 mmol) was added to the reaction mixture followed shortly by hydrogen peroxide (0.05 mL, 35% aqueous solution, 0.4 mmol). The reaction mixture was allowed to stir for 2 h. Residual starting material and oxazolidinone was extracted from the product mixture with methylee chloride (2 x 4 mL) and diethyl ether (2 x 4 mL). The aqueous layer was retained and acidified to a pH of 2 as indicated by pH paper. The carboxylic acid was extracted from the aqueous layer with ethyl acetate (3 x 4 mL). The combined ethyl acetate extracts were dried over sodium sulfate, which was filtered by gravity. The solvent was removed by a rotary evaporator (25 °C, 25 mmHg) to give 30 mg of 85 (86%) as a mixture of diastereomers (9:1, trans : cis). The spectral properties of the major carboxylic acid is consistent with NMR data in the literature as the trans-isomer.\textsuperscript{29} trans 85 : \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 7.35-7.20 (m, 2H), 6.85-6.95 (m, 2H), 5.62 (d, J = 7.25, 1H), 3.82 (s, 3H), 3.39 (dd, J= 8.7, 16.1 Hz, 1H), 3.02 (dd, J = 8.9, 17.8 Hz, 1H), 2.95 (dd, J = 9.5, 17.9 Hz, 1H).

Ethyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate (86)

A dry 25 mL round-bottomed flask was equipped with a stirbar, septum, and constant flow of nitrogen through a needle in the septum. The flask was charged with trans-38 (0.048 g, 0.16 mmol, in 15 mL absolute ethanol) followed by addition of
dibutyltin oxide (0.015 g, 0.06 mmol). A reflux condenser was inserted between the septum and reaction flask and the reaction mixture was heated to reflux overnight. The reaction mixture was poured into aqueous saturated sodium bicarbonate solution (20 mL), extracted with ethyl acetate (3 x 25 mL). The organic extracts were filtered through celite, dried over aqueous sodium sulfate, which was filtered away by gravity. The solvent was removed by a rotary evaporator to give 0.034 g (85%) of a mixture of trans 86 and 87 (3.2:1 respectively) as a light yellow oil. 86 \(^{1}H\text{NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.32 (m, 5H), 5.66 (d, \(J = 7.2\) Hz, 1H), 4.29-4.18 (m, 2H), 3.32 (ddd, \(J = 7.2, 8.8, 9.4\) Hz, 1H), 3.00 (dd, \(J = 8.7, 17.8\) Hz, 1H), 2.90 (dd, \(J = 9.5, 17.8\) Hz, 1H), 1.28 (t, \(J = 7.14\) Hz, 3H). \(^{13}C\text{NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 174.2, 170.8, 138.1, 127.9, 128.9, 125.4, 82.3, 61.9, 48.7, 32.2, 14.1. 87 \(^{1}H\text{NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.45-7.32 (m, 5H), 5.17 (d, \(J = 4.5\) Hz, 1H), 4.14 (q, 7.2 Hz, 2H), 4.06 (q, \(J = 7.1\) Hz, 2H), 3.19 (td, \(J = 4.5, 9.2\) Hz, 1H), 2.76 (dd, \(J = 9.4, 16.9\) Hz, 1H), 2.50 (dd, \(J = 4.4, 16.9\) Hz, 1H). \(^{13}C\text{NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 173.2, 172.4, 141.1, 128.4, 127.8, 125.9, 73.4, 61.1, 60.7, 48.7, 31.1, 13.7

5-Oxo-2-phenyltetrahydrofuran-3-carboxylic acid 88

To a 20-mL scintillation vial containing a stirbar and the imide lactone 52 as a mixture of diastereomers (1.3:1, cis : trans) (23 mg, 0.08 mmol) and a stirbar was added THF (4 mL) and water (1 mL). The solution was allowed to stir and it was cooled to 0 °C using an ice bath. Lithium hydroxide monohydrate (9 mg, 0.2 mmol) was added to the reaction mixture, followed quickly by hydrogen peroxide (0.02 ml, 35% aqueous
solution, 0.2 mmol). The reaction mixture was allowed to stir for 1 h. Residual starting material and oxazolidinone was extracted from the product mixture with methylene chloride (2 x 4 mL) and diethyl ether (2 x 4 mL). The aqueous layer was retained and acidified to a pH of 2 as indicated by pH paper. The carboxylic acid was extracted from the aqueous layer with ethyl acetate (3 x 4 mL). The combined ethyl acetate extracts were dried over sodium sulfate, which was removed by gravity filtration. The solvent was removed by a rotary evaporator (25 °C, 25 mmHg) to give 15 mg (88%) of 88 as a mixture of diastereomers (1:1.6, cis: trans). The spectral properties of the major carboxylic acid is consistent with NMR data in the literature as the trans isomer.\(^{53}\) \(^1\)H NMR of the crude reaction mixture is available in the appendix. **Major diastereomer** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.28 (m, 5H), 5.69 (d, \(J = 6.9\) Hz, 1H), 3.37 (ddd, \(J = 6.9, 8.3, 9.5\) Hz, 1H), 3.01 (dd, \(J = 8.3, 17.9\) Hz, 1H), 2.93 (dd, \(J = 9.5, 17.9\) Hz, 1H).

**Minor diastereomer** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.28 (m, 5H), 5.79 (d, \(J = 7.8\) Hz, 1H), 3.76 (ddd, \(J = 5.4, 7.9, 8.6\) Hz, 1H), 3.06 (dd, \(J = 5.4, 17.7\) Hz, 1H), 2.83 (dd, \(J = 8.7, 17.7\) Hz, 1H).

**(S)-4-Benzyl-3-((2S,3R)-5-oxo-2-phenyltetrahydrofuran-3-carbonyl)oxazolidin-2-one (89)**

A dry 100-mL round-bottomed flask was equipped with a stir bar, septum, and constant flow of nitrogen through the septum. The flask was charged with DCM (40 mL). The reaction flask was cooled in an ice bath to 0 °C and stirring of the solvent was initiated. Diethylzinc (0.22 mL, 2.1 mmol) was added followed by methylene iodide
(0.17 mL, 2.1 mmol). Carbenoid was allowed to form at 0 °C for ten min and formed a milky white suspension. Benzaldehyde (0.05 mL, 0.5 mmol) was added, followed quickly by compound 57 (0.20 g, 0.5 mmol, in 7.2 mL DCM). The reaction mixture was allowed to warm to room temperature and stir at room temperature for four days. The reaction mixture was quenched with saturated aqueous ammonium chloride (20 mL). The product was extracted with diethyl ether (3 x 50 mL) and washed with brine. The combined organic phases were dried over sodium sulfate, which was filtered away by gravity filtration. The solvent was removed by using a rotary evaporator (25 °C, 25 mmHg) to give 0.26 g of a yellow oil. The product was purified by flash column chromatography on silica (2:1; hexanes : ethyl acetate; Rf= 0.17) to give 12 mg (5 %) of the major diastereomer and 6 mg (2 %) of a minor diastereomer as clear oils.

**Compound 89, Major Diastereomer :** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54-6.89 (m, 10H), 6.05 (d, $J$ = 8.8 Hz, 1H), 5.05 (ddd, $J$ = 9.5, 8.8, 6.4 Hz, 1H), 3.43 (dd, $J$ = 18.1, 6.4 Hz, 1H), 4.40-4.31 (m, 1H), 4.03 (ddd, $J$ = 8.9, 7.7, 1.1 Hz, 1H), 3.94 (dd, $J$ = 9.2, 2.7 Hz, 1H), 2.81 (dd, $J$ = 18.1, 9.5 Hz, 1H), 2.40 (dd, $J$ = 13.5, 3.3 Hz, 1H), 1.48 (dd, $J$ = 13.5, 11.4 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 175.3, 169.3, 153.2, 135.7, 135.4, 129.4, 129.3, 129.2, 128.8, 127.5, 127.0, 81.4, 66.7, 55.4, 44.7, 36.7, 31.1.

**Compound 89, Isolated Minor Diastereomer :** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57-7.07 (m, 10H), 5.92 (d, $J$ = 7.3 Hz, 1H), 4.70 (dddd, $J$ = 9.4, 5.9, 4.3, 3.6 Hz, 1H), 4.40 (td, $J$ = 9.1, 7.3 Hz, 1H), 4.29-4.21 (m, 2H), 3.27 (dd, $J$ = 13.4, 3.4 Hz, 1H), 3.21 (dd, $J$ = 17.4, 9.0 Hz, 1H), 2.87 (dd, $J$ = 13.5, 9.2 Hz, 1H), 2.74 (dd, $J$ = 17.4, 9.0 Hz, 1H).
trans-2-tert-Butyl-5-oxotetrahydrofuran-3-carboxylic acid (90)

A dry 50-mL round-bottomed flask was equipped with a stirbar and charged with THF (22 mL) and water (6 mL). Stirring of the reaction mixture was initiated. Lithium hydroxide (0.041 g, 0.985 mmol) followed by hydrogen peroxide (35% in H2O, 0.11 mL, 1.1 mmol) were added to the stirring solution. Imide lactone 76 (0.126 g, 0.49 mmol) was then added and the reaction mixture was allowed to stir for two hours at room temperature. The reaction mixture was extracted with ether (2 x 50 mL) and the aqueous layer retained and acidified using HCl (1M aqueous solution) to a pH of 2 as monitored by pH paper. The carboxylic acid was extracted using ethyl acetate (3 x 25 mL), dried over anhydrous sodium sulfate, filtered by gravity, and the solvent was removed in vacuo to give 0.065 g (71%) of the carboxylic acid as a white solid. mp = 111.9-113.3 °C. ¹H NMR (400 MHz, CDCl₃) ppm 4.46 (d, J = 5.83 Hz, 1H), 3.19 (ddd, J = 10.38, 6.82, 5.87 Hz, 1H), 2.93 (dd, J = 18.18, 6.85 Hz, 1H), 2.81 (dd, J = 18.18, 10.38 Hz, 1H), 0.99 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 177.6, 175.1, 89.5, 40.9, 35.1, 32.8, 25.0. IR (neat, ATR) 2958.8, 1759.8, 1720.7, 1178.7
Computational analysis of aromatic aldehyde derived imide lactones

Each imide lactone was subjected to a conformer distribution analysis based on the MMFF level of theory using Spartan '04. Each conformer returned from the conformer distribution was then subjected to a single-point NMR and energy calculation at the HF/321g(*) level of theory. Tables of the Boltzmann distributions (both MMFF and HF/321g(*)) as well as the proton NMR shifts for each of the imide lactone conformers can be found in the Appendices. The overall NMR shifts were calculated based on the Boltzmann distributions. The imide lactones derived from the achiral malonyl diimide were also subjected to a geometry optimization at the HF/321g(*) level of theory.
LIST OF REFERENCES


44. Generation of post chain extension alkylation product was indicated by several key proton resonances (500 MHz, CDCl$_3$) δ 3.25 (dd, $J = 18.2$, 9.85 Hz, 1H), 2.95 (dd, $J = 18.2$, 4.5 Hz, 1H), and 1.13 (d, $J = 7.04$, 3H), which is consistent with generation of post chain extension methylation, but was not isolated from the crude reaction mixture.


49. Crystallographic data of the major diastereomer of 3-(2-tert-butyl-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one was provided by Jerry Jasinski and Ray J Butcher at Keene State College in Keene, NH 03435

51. X-Ray crystallographic data for the major diastereomer of 3-(5-oxo-2-pentyltetrahydrofuran-3-carbonyl)oxazolidin-2-one was provided by Jon Briggs at the University of New Hampshire in Durham, NH 03824.


55. 77 was obtained in mg quantities as a side product from the purification of 3-(2-tert-butyl-5-oxotetrahydrofuran-3-carbonyl)oxazolidin-2-one. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.43 (d, \(J = 5.8\) Hz, 1H), 3.84 (s, 2H), 3.17 (ddd, \(J = 5.9, 6.7, 10.3\) Hz, 1H), 2.92 (dd, \(J = 6.8, 18.1\) Hz, 1H), 2.77 (dd, \(J = 10.3, 18.1\) Hz, 1H), 0.98 (s, 9H), 0.96 (s, 9H)
APPENDIX A:

EXPANDED COMPUTATIONAL DATA
Table 7- Computation of $^1\text{H}$ NMR shifts for oxazolidinone resonances of *trans*-82 from MMFF conformer distribution followed by HF/321g(*) single-point energy calculation.
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Table 8- Computation of $^1$H NMR Shifts for oxazolidinone resonances of trans-82 from MMFF conformer distribution followed by HF/321g* optimization calculation.
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Table 9—Computation of ¹H NMR shifts for oxazolidinone resonances of cis-82 from MMFF conformer distribution followed by HF/321g(*) single-point energy calculation.
Table 10-Computation of $^1$H NMR shifts for oxazolidinone resonances of cis-82 from MMFF conformer distribution followed by HF/321g(*) optimization calculation.
Table 11-Computation of $^1$H NMR shifts for oxazolidinone resonances of trans-52 from MMFF conformer distribution followed by HF-321g* single-point energy calculation.

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Table 12-Computation of $^1$H NMR shifts for oxazolidinone resonances of trans-52 from MMFF conformer distribution followed by HF/321g(*) single-point energy calculation.

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<th>HF/321g(*) Boltzmann Dist.</th>
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<th>$\delta H^5$</th>
<th>$\delta H^6$</th>
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<th>( \delta H^4 )</th>
<th>( \delta H^5 )</th>
<th>( \delta H^6 )</th>
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Table 13-Computation of \(^1\)H NMR shifts for oxazolidinone resonances of cis-52 from MMFF conformer distribution followed by HF/321g(*) single-point energy calculation.

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<th>Label</th>
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<th>Boltzmann Dist.</th>
<th>( \delta H^1 )</th>
<th>( \delta H^2 )</th>
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</table>

Table 14-Computation of \(^1\)H NMR shifts for oxazolidinone resonances of cis-52 from MMFF conformer distribution followed by HF/321g(*) optimization.
APPENDIX B:

SPECTRA
$^{1}H$ NMR
$^1$H NMR
52 via CAN Crude $^1$H NMR
$^{13}$C NMR
$^{13}$C NMR
$^1$H NMR
78 Crude $^1$H NMR Via Transesterification
89 Major COSY NMR
$^1H$ NMR
APPENDIX C:

X-RAY STRUCTURES