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I Ceric ammonium nitrate-mediated oxidative cleavages of hemiacetals II Synthesis of beta-proline derivatives through the tandem chain extension-imine capture reaction

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I. CERIC AMMONIUM NITRATE-MEDIATED OXIDATIVE CLEAVAGES OF HEMIACETALS

II. SYNTHESIS OF β-PROLINE DERIVATIVES THROUGH THE TANDEM CHAIN EXTENSION-IMINE CAPTURE REACTION

BY

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DEDICATION

This dissertation is dedicated to my parents, Tony and Vicky Jacobine. My father was always someone I wanted to impress more then anything, either athletically or academically. I hope that my work during the past five years has done just that. My mother was always my love and support through the good times and the bad. Her pep-talks before my seminar, progress report, and research proposal were priceless and I would not have made it through graduate school without her endless encouragement.

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I would like to acknowledge the Zercher research group members during my time. Jenn Mazzone, Ian Taschner, and Tim Henderson have been crucial in my laboratory development and have been outstanding group members for most of my time in the group. Our comfort level with each other could turn any friendly discussion into a serious debate, but I learned a lot from each of you and you made the long hours seem quite a bit shorter. Joe Dunn, Greg Bubnis, Dan Stigers, Matt Young, Aida Ajaz and Nick Bencivenga also played an important role in my life in graduate school.

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LIST OF ABBREVIATIONS

LDA	lithium diisopropyl amide
Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
PG	protecting group
PCC	pyridinium chlorochromate
TFA	trifluoroacetic acid
CDI	carbonyl diimidazole
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBT	1-hydroxybenzotriazole
TMS	trimethylsilyl
Pmb	*p*-methoxybenzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
AIBN	2,2'-azo *bis*(isobutyronitrile)
LAH	lithium aluminum hydride
CAN	ceric ammonium nitrate

ABSTRACT

CERIC AMMONIUM NITRATE-MEDIATED OXIDATIVE CLEAVAGES OF HEMIACETALS

SYNTHESIS OF β-PROLINE DERIVATIVES THROUGH THE TANDEM CHAIN EXTENSION-IMINE CAPTURE REACTION

by

Alexander M. Jacobine

University of New Hampshire, September 2010

A novel ceric ammonium nitrate-mediated oxidative cleavage of hemiacetals generated through the use of the zinc carbenoid-mediated tandem chain extension-aldol reaction was developed. This chemistry has been applied towards the formation of a class of natural products, phaseolinic acids, in two steps from a commercially available β-keto ester, methyl 4-methoxyacetoacetate.

The tandem chain extension-imine capture reaction has also been developed to provide access to β-proline derivatives. Two activated imines were studied and provided access to different diastereomers, making the chemistry versatile. β-Keto esters, β-keto amides, and β-keto imides were subjected to the tandem chain extension-imine capture reaction conditions and proved to be reasonably successful in most cases. β-Keto esters

were efficient in the synthesis of free –NH β-proline derivatives in three steps and β-keto imides were efficient in the synthesis of Boc-protected β-proline derivatives in just two steps.

The zinc carbenoid-mediated chain extension imine capture reaction has developed into a flexible route in obtaining different diastereomers of protected and unprotected β-proline derivatives in minimal steps from commercially available starting materials.

CHAPTER I

INTRODUCTION

Peptide Isosteres

One of the main strategies in drug design focuses around the idea of isosteric replacement. The concept of isosteres was proposed by Langmuir[1] to describe molecules having the same number of atoms and valence electrons. Bioisosteres are isosteres that mimic the biological skeleton and display biological activity. Bioisosteres have the same general structure as the biological molecule and mimic the steric environment, but the bioisosteres can react differently in the body from the parent substance. Isosteres can be grouped into two categories, classical and non-classical.[2, 3]

One example of classical isosteres would be the relationship between peptide **1** and isosteres **2-4**, often referred to as peptide mimics (**Figure 1**). The first peptide mimic **2** contains a ketomethylene isostere in which the carbonyl mimics the amide carbonyl, but the molecule lacks the hydrolyzyable amide bond. A second isosteric replacement used in peptide mimicry is a hydroxyethylene isostere **3**, which has the same basic

structure as the ketomethylene isostere but is presented in a lower oxidation state. The third type is the methyl-substituted hydroxyethylene isostere **4**, similar in structure to the ketomethylene but possessing an additional methyl group and different oxidation state. All three of these isosteres have proven to be effective in the inhibition of aspartic acid protease targets like HIV-1 protease and renin.[4-10]

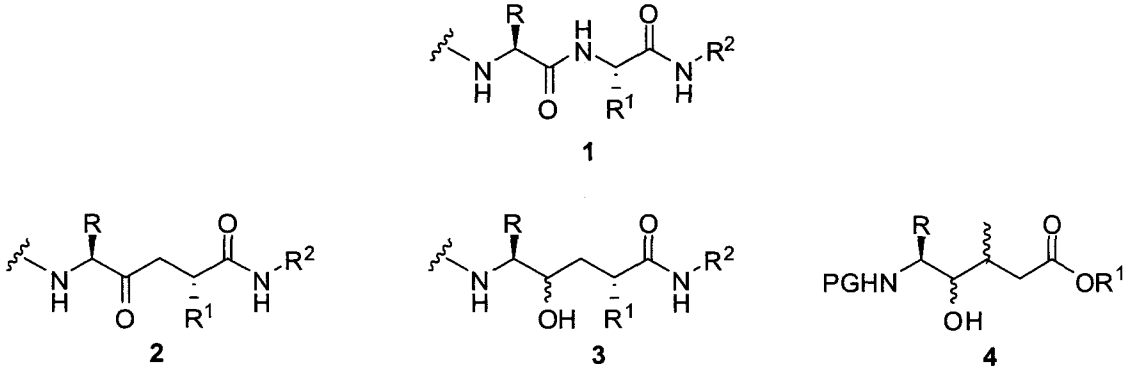
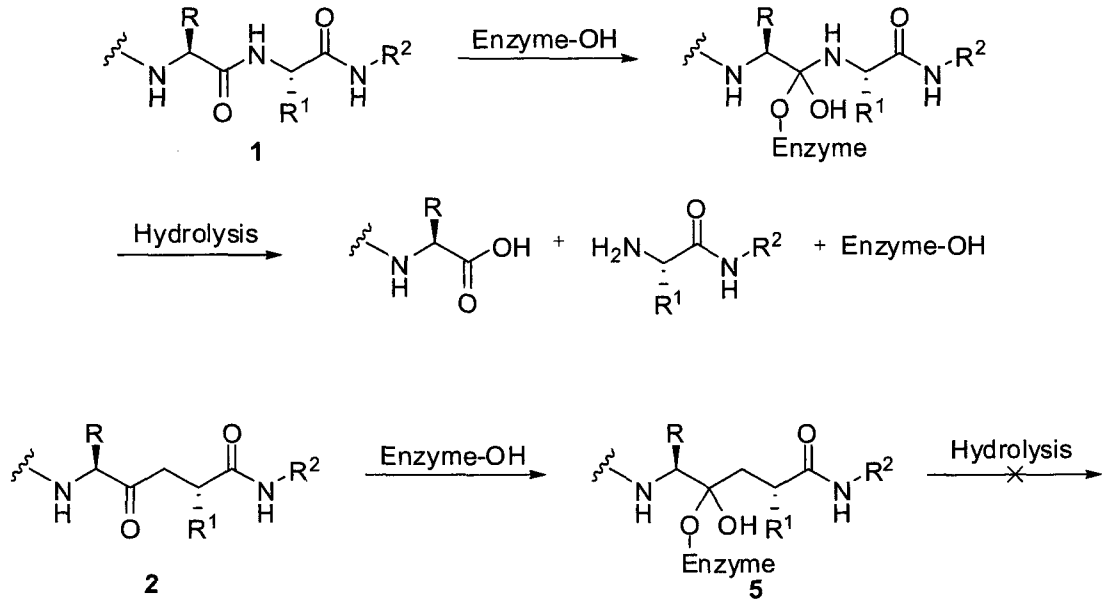


Figure 1. Peptide Backbone and Peptide Isosteres

One of the key features of the ketomethylene isostere is the similar presentation of the ketone to mimic the amide in a naturally occurring peptide. In theory, both the ketomethylene isostere **2** and the peptide **1** can react with nucleophiles in the same way, but the ketomethylene isostere is resistant to hydrolysis, making it a very attractive alternative without drastically altering the structure. When the mimic is recognizable by the active site of the enzyme, but the isosteric unit will not be cleaved by the enzyme (**5**), the key requirement for service as a competitive inhibitor is fulfilled (**Scheme 1**).

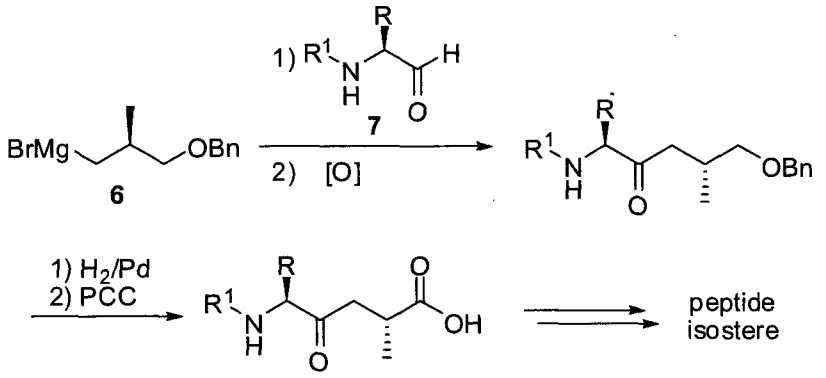


1 2 5

Scheme 1. Hydrolysis of Peptide with Serine Protease and Stability of Ketomethylene Isostere

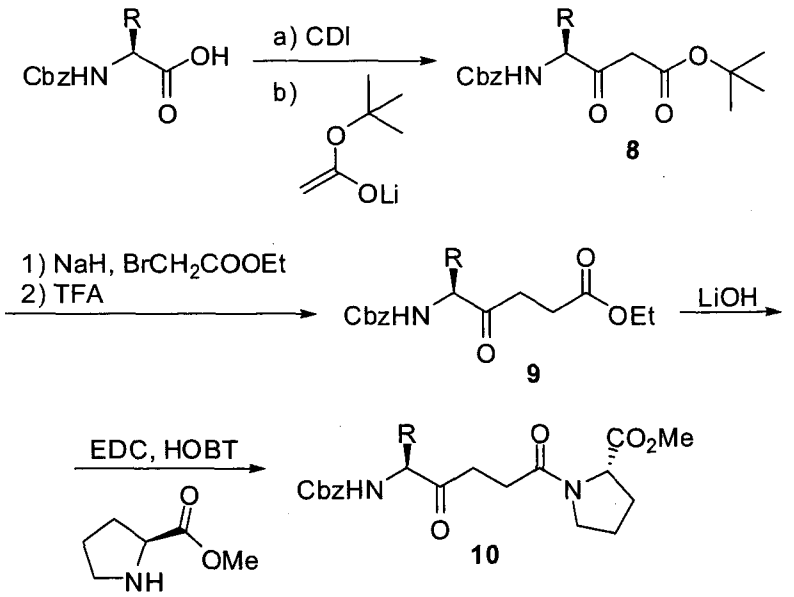
Although these peptide isosteres have proven to be effective when incorporated into peptide mimics, their utility has been limited by their availability. Syntheses of amino acid-derived γ-keto esters are lengthy and inefficient. In order to more fully evaluate the therapeutic potential of these compounds, new and efficient methods need to be developed.

A variety of methods have been reported in the literature for synthesizing these amino acid-derived ketomethylene isosteres. One method used for the generation of the ketomethylene system involved backbone construction by reacting a Grignard reagent **6** with an amino acid-derived aldehyde **7**, followed by subsequent oxidation chemistry (**Scheme 2**). The method is not very direct and suffers from the ease of aldehyde epimerization and limited availability of chiral Grignard precursors.[11]



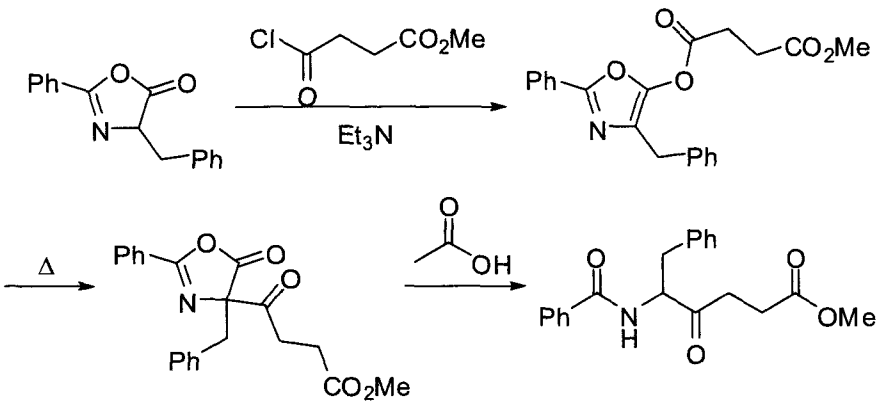
Scheme 2. Peptide Isostere Synthesis via Grignard Reagent

Another approach uses a modified Claisen condensation as a key step to obtain the peptide isosteres. Once the condensation reaction was completed (**8**), subsequent alkylation, deprotection to yield γ-keto ester **9**, hydrolysis and amino acid coupling was necessary to obtain **10**, making this approach, once again, an indirect route to obtain the desired ketomethylene isosteres (**Scheme 3**).[12]



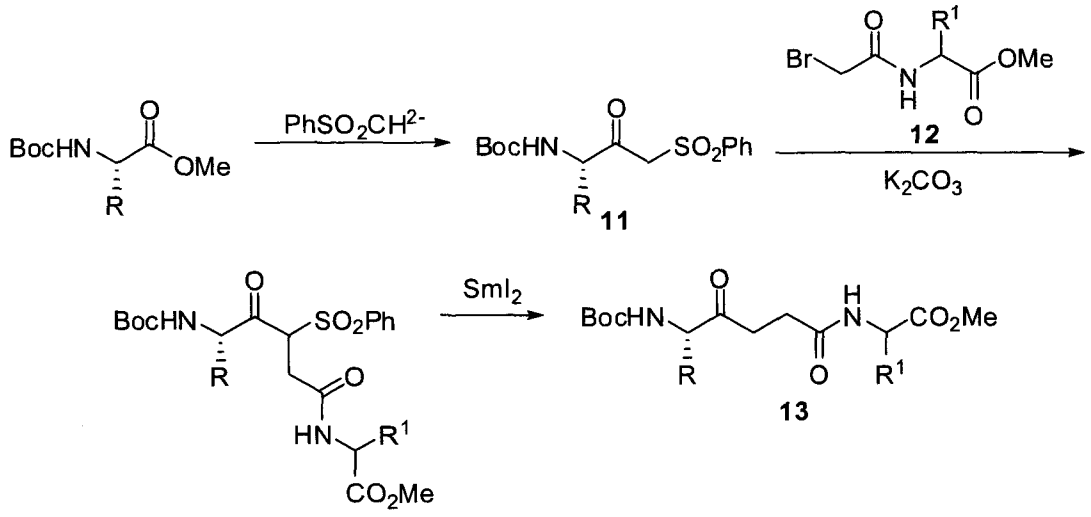
Scheme 3. Peptide Isostere Synthesis via Mixed Claisen Condensation

Using a Dakin-West[13, 14] reaction as a key step to obtain the ketomethylene backbone has also been reported (**Scheme 4**).[15] Although this method was more direct than others, the peptide isostere was synthesized as a racemate.



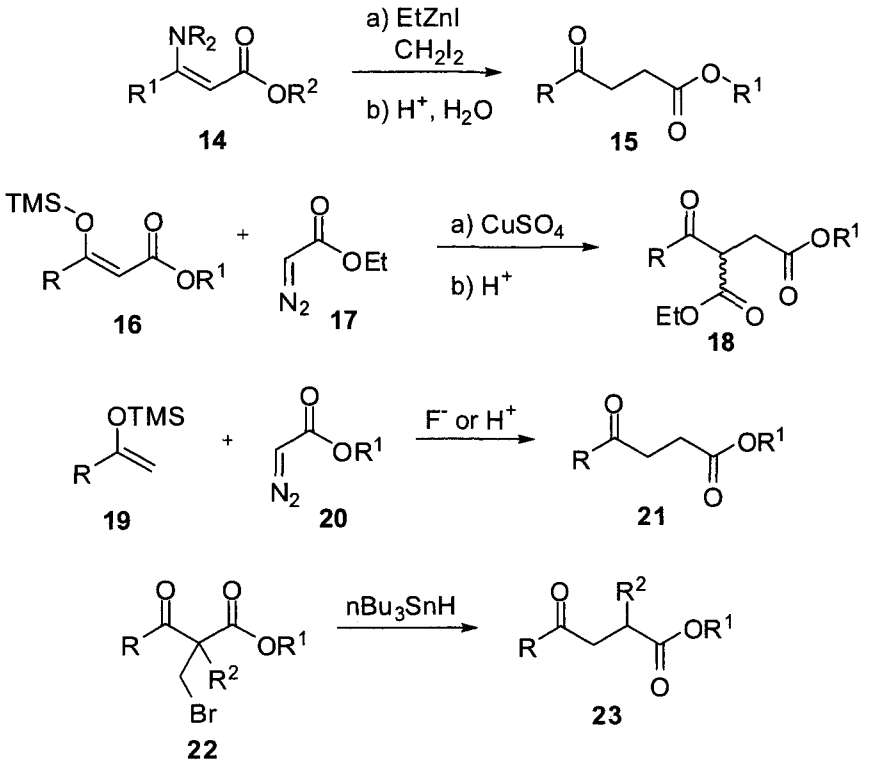
Scheme 4. Modified Dakin-West Approach to Peptide Isosteres

Rudd and co-workers were able to obtain ketomethylene isosteres through alkylation of β-keto sulphones.[16] The intermediate sulphone **11** was reacted with an amino acid-derived system **12** followed by samarium iodide to obtain the peptide isosteres (**Scheme 5**).



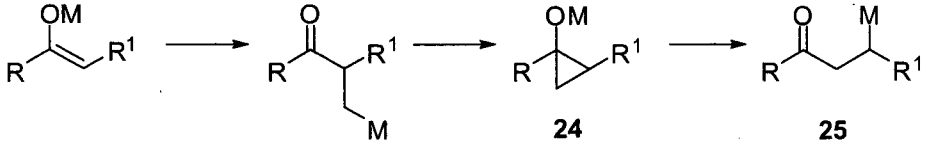
Scheme 5. Peptide Isostere Synthesis via β-Keto Sulphone

Another common method to obtain γ-keto esters is through fragmentation of a donor-acceptor cyclopropane (**Scheme 6**). Bieraugel and co-workers developed a method for this conversion that involves exposure of an enamine (**14**), formed from a secondary amine and a β-keto ester, to a zinc carbenoid.[17] Fragmentation of the cyclopropane and hydrolysis provided the γ-keto ester **15**. Beiraugel's method resulted in low yields of the γ-keto ester, which limited the utility of the chemistry. Saigo and co-workers slightly modified this method and subjected silyl enol ethers (**16**) to copper carbenoids derived from a diazo acetate **17**. Through this approach they were able to obtain γ-keto esters (**18**), although an additional ester functionality was present.[18] Additional studies by Saigo revealed that the reaction of silyl enol ethers with the Simmons-Smith reagent, a zinc carbenoid,[19] was unsuccessful due to uncontrolled multiple additions of the carbenoid.[20] Later, Reissig and co-workers performed similar chemistry by reacting ketone-derived silyl enol ethers (**19**) with methoxycarbonyl-substituted carbenoids (**20**), a slight variation from Beiraugel's and Saigo's methods, although the Reissig method did not involve a conversion from a β-keto ester to a γ-keto ester (**21**).[21-24] The Reissig approach was the most efficient of the carbenoid methods, but required selective formation of a ketone enolate as part of the synthetic scheme. Lastly, Dowd and co-workers developed a radical-mediated process that facilitated the same transformation.[25-28] A major difference between the Dowd method and the previous carbenoid-based approaches was the required utilization of α-substituted β-keto esters (**22**) as starting materials in the radical-based method to form α-substituted γ-keto esters (**23**).



Scheme 6. Bieraugel's, Saigo's, Reissig's, and Dowd's Chain Extension Protocols

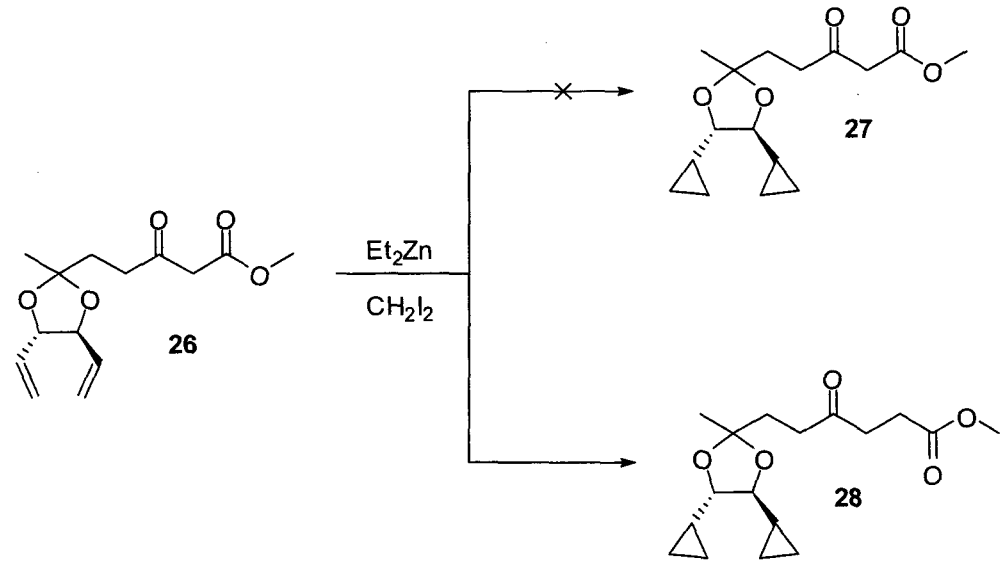
Each of the methods described above is believed to involve formation of a donor-acceptor cyclopropane **24** which fragments due to ring strain to provide the γ-keto ester **25** (**Scheme 7**). All of the donor-acceptor cyclopropane methods discussed above require initial formation of an enol or enamine, which is time consuming and compromises the efficient conversion of the available starting materials to the desired products.



Scheme 7. Formation and Fragmentation of Donor-Acceptor Cyclopropane

Zinc Carbenoid-Mediated Chain Extension Reaction

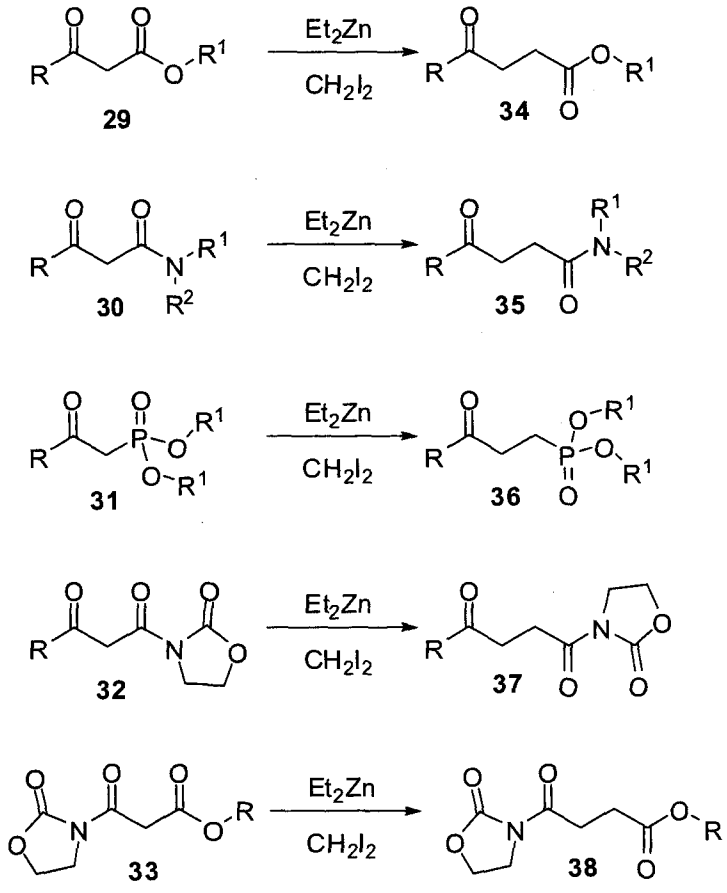
A streamlined variation on the zinc carbenoid-mediated chain extension reaction was first reported by Brogan and Zercher in 1997.[29] This homologation reaction was fortuitously discovered during an attempt to cyclopropanate the olefins of β-keto ester **26** to β-keto ester **27** under standard Furukawa-modified Simmons-Smith cyclopropanation conditions.[30] Analysis of the product by NMR revealed that an additional methylene unit was introduced into the molecule between the two carbonyl groups resulting in the cyclopropanated and homologated γ-keto ester **28** (**Scheme 8**).



Scheme 8. Attempts to Cyclopropanate with Furukawa-modified Reagent and Discovery of Homologation Reaction

This unexpected homologation reaction was studied further and was found to be quite efficient in the conversion of β-keto esters to γ-keto esters. The one-pot homologation reaction efficiently converts β-keto esters (**29**),[29] amides (**30**),[31] phosphonates (**31**),[32] imides (**32**),[33] and α-carboxyester imides (**33**) [34, 35] to their

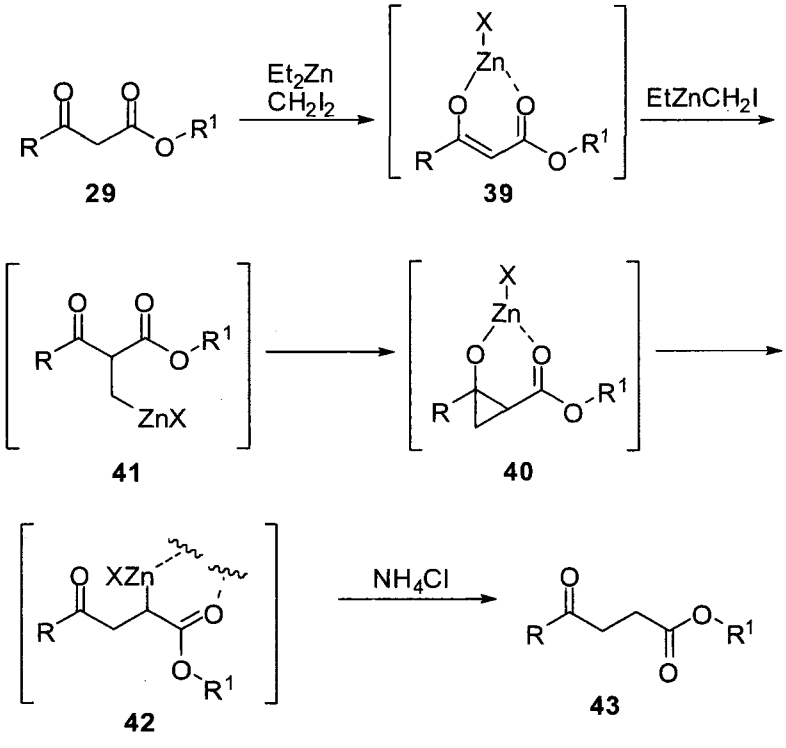
corresponding homologated products **34-38** (**Scheme 9**). β-Diketones also react similarly under the chain extension conditions, but more complex product mixtures are typically seen.[36]



Scheme 9. Substrates Subjected to Chain Extension Conditions

The mechanism of these chain extension reactions has been studied and is believed to proceed through the following sequence of events (as illustrated for a β-keto ester starting material **29**). The reaction between the β-dicarbonyl substrate and the Furukawa-modified Simmons-Smith reagent[30] initially forms an enolate **39,** which leads to the proposed donor-acceptor cyclopropane intermediate **40** through alkylation of the enolate (**41**) and intramolecular cyclization into the ketone. This intermediate undergoes

fragmentation due in part to its ring strain, which results in the regiospecific addition of a methylene unit to the alkyl chain and generation of an intermediate with anion character at the position α- to the ester, amide, phosphonate, or imide. This intermediate (**42**) can be quenched with mild aqueous acid to yield the corresponding γ-keto ester **43** (**Scheme 10**). Intermediates **39** and **42** have been verified by NMR studies, although no direct observation of the existence of a donor-acceptor cyclopropane (**40**) has been made.[37] In fact, recent computational efforts suggest that an alternative low energy path may be available in which the homoenolate **41** is converted to the chain extended intermediate **42** via a concerted [1,2] shift.[38]



Scheme 10. Proposed Mechanism of the Chain Extension Reaction

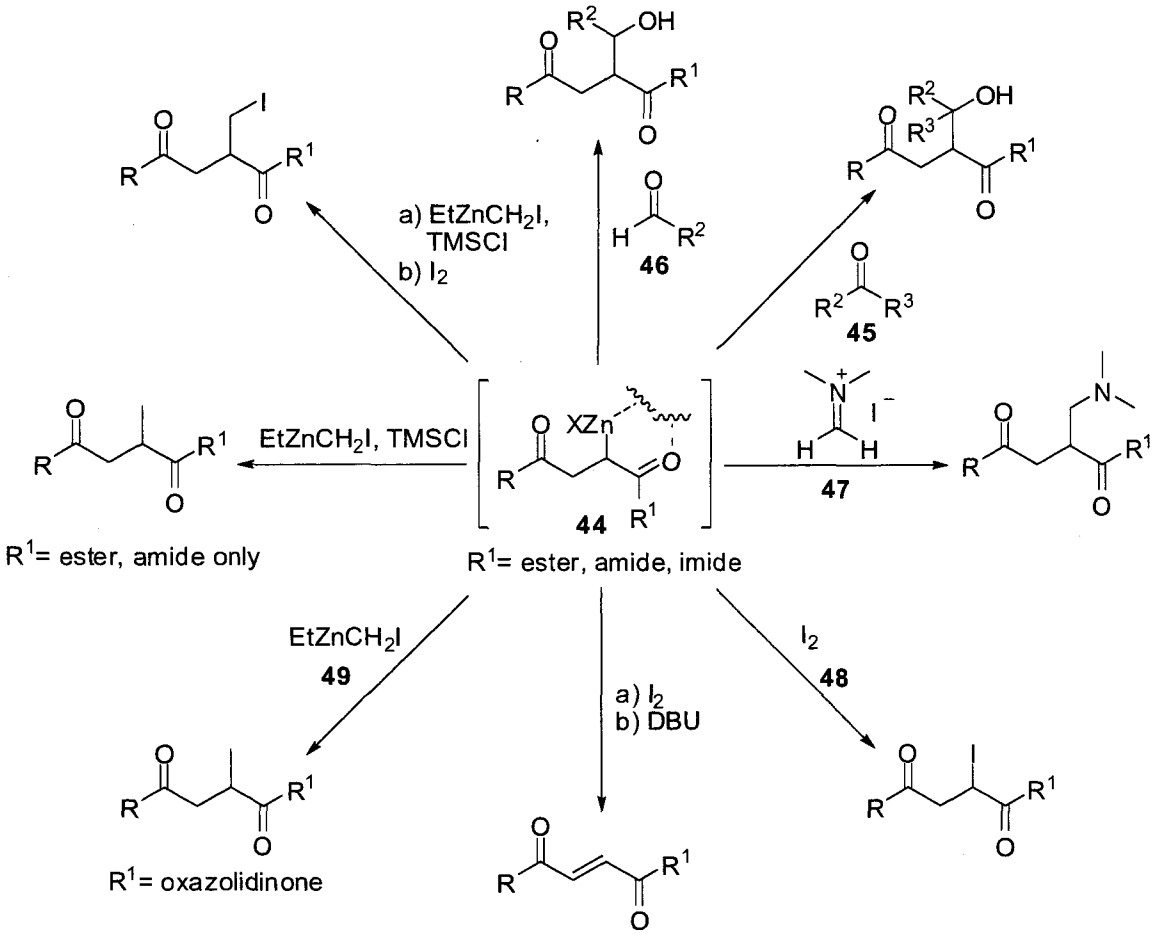
The structure of the intermediate **42** formed in the chain extension reaction appears to be similar to the intermediate generated in the traditional Reformatsky

reaction.[39] The Reformatsky reaction involves the treatment of α-halo esters, usually bromo esters, with zinc metal, usually zinc dust. The zinc inserts into the carbon-halogen bond to produce an ester enolate equivalent, which can be reacted with ketones or aldehydes to create β-hydroxy esters.

The Reformatsky intermediate is known to exist as a dimer both in solution and crystalline form.[40-43] The strong covalent interaction between the zinc and the α-carbon makes the enolate equivalent less reactive then typical enolates. The zinc-mediated chain extension appears to proceed through a similar carbon-bound zinc enolate equivalent based upon NMR studies[37] that also support the presence of an oligomeric intermediate. In analogy to the original Reformatsky reaction intermediate, the chain extension intermediate is proposed to exist as a similar dimeric species.

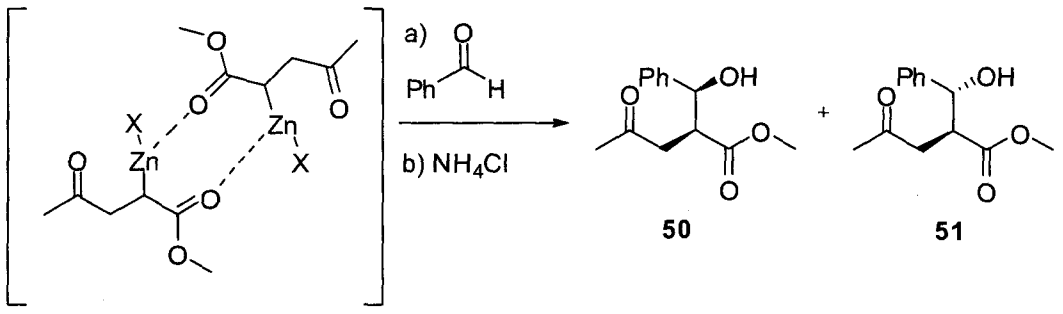
Tandem Zinc Carbenoid-Mediated Chain Extension Reactions

The utilization of the Reformatsky-like organometallic intermediate generated in the chain extension reaction has been studied extensively in the Zercher research group. The development of tandem reaction sequences, in which the latent enolate reacts with various electrophiles, was proposed. Ketones (**45**),[44] aldehydes (**46**),[44] iminium ions (**47**),[44] iodine (**48**),[33, 45, 46] and excess carbenoid (**49**)[47] were all found to be successful electrophiles for reacting with the zinc enolate (**Scheme 11**). Very little research, however, has been devoted to the reaction of the latent enolate generated in the chain extension reaction with imine electrophiles. Generation of β-amino acids, and β-proline derivatives in particular, will be described in detail later in this document.



Scheme 11. Electrophiles Used in the Tandem Process

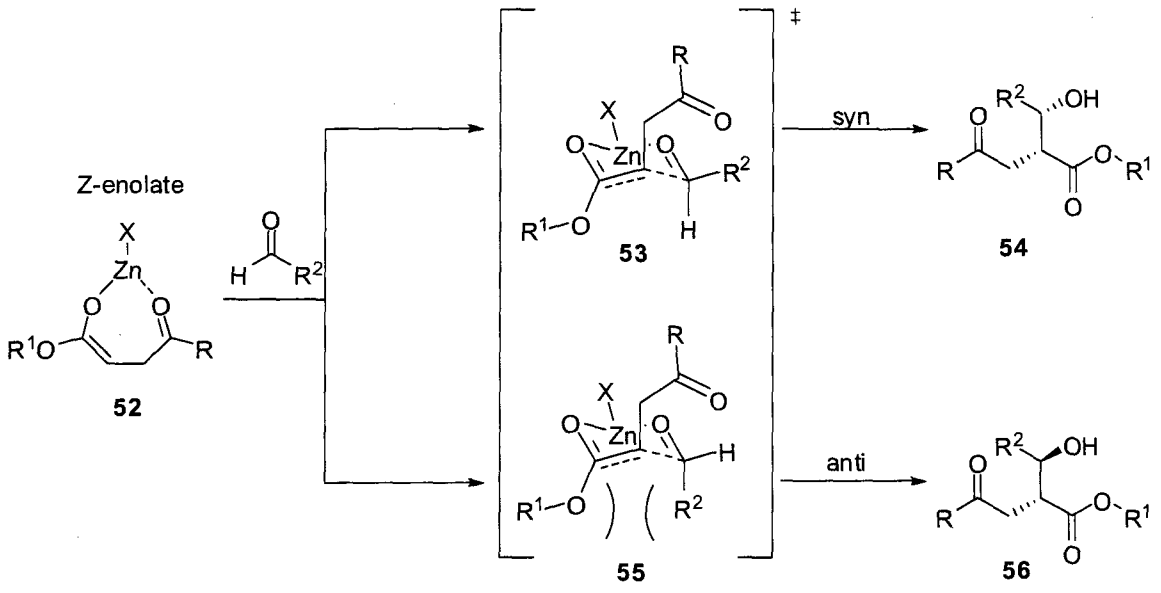
When aldehydes are used as the electrophiles, aldol products are obtained and the *syn*-aldol diastereomer is preferred to the *anti* diastereomer when using most β-ketone-containing starting materials. For example, when benzaldehyde is used as the electrophile and methyl acetoacetate as the β-keto ester, the *syn*-aldol product (**50**) is preferred over the *anti* (**51**) in an approximate ratio of 9:1 (**Scheme 12**).[48] However, tandem chain extension-aldol reactions using β-keto imides appear to favor formation of the *anti* aldol product.[48, 49]



Scheme 12. Ratio of *syn*- and *anti*-Aldol Products

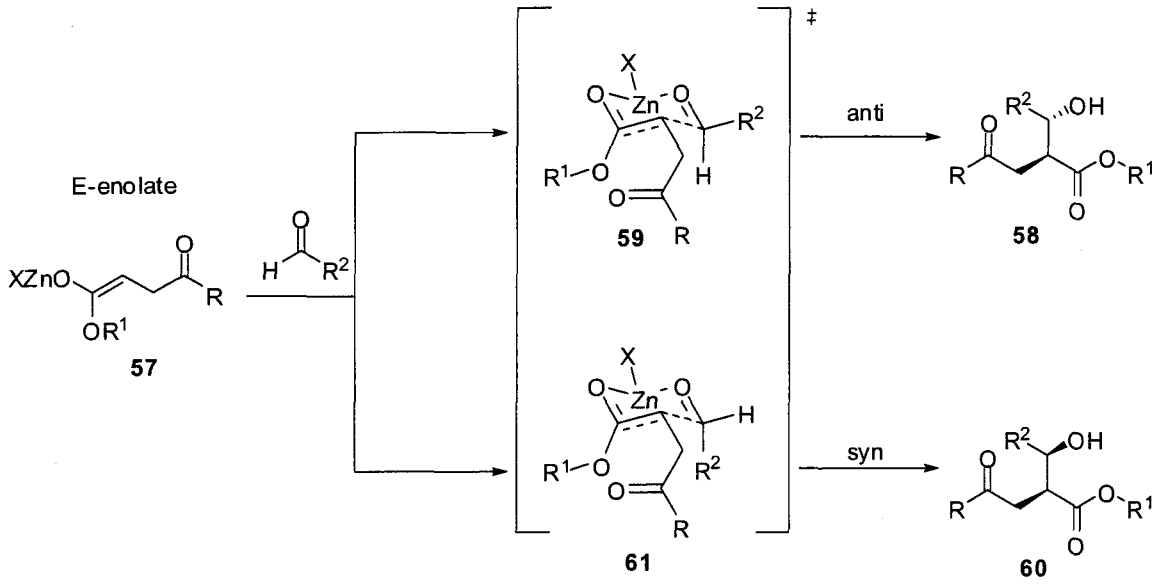
The selectivity of the chain extension aldol reaction can be rationalized from the Zimmerman-Traxler transition state model.[50] This model is applied to analyze the stereoselectivity of aldol reactions proposed to proceed through closed transition states, which is believed to be the case with zinc.[51] Zinc(II) is proposed to stabilize the enolate and activate the electrophile in a closed transition state. Dewar performed calculations on the Reformatsky reaction and proposed that the zinc enolate dimers dissociate upon addition of the electrophile and are converted to the active zinc enolate, which allows the reaction to proceed through a chair-like transition state.[52]

Two possible enolate geometries are available, but the *Z*-enolate **52** is predicted to be favored in the chain extension-aldol reaction due to the chelation involving the zinc and the ketone carbonyl. The stabilized *Z*-enolate can give rise to both the *syn* and the *anti* diastereomers depending on the aldehyde approach to the enolate. When the aldehyde approaches with the R group in the pseudo-equatorial position (**53**), the *syn*-aldol product **54** would be the predicted diastereomer. If the aldehyde approaches with the R group in the pseudo-axial position (**55**), the *anti*-aldol product **56** is obtained (**Scheme 13**).



Scheme 13. Zimmerman-Traxler Closed Transition State of *Z*-Enolate

The *E*-enolate **57** has two similar possibilities for a transition state leading to each of the diastereomers. The *anti*-aldol product **58** would be formed if the aldehyde approaches with the R group of the aldehyde in the pseudo-equatorial position (**59**). The *syn*-aldol product **60** would be formed if the aldehyde R group approaches in the pseudo-axial position (**61**) (**Scheme 14**). Although the *syn* aldol isomer could form from either the *E*- or *Z*-enolate, the formation of the *Z*-enolate through chelation of zinc by the two carbonyl functionalities is proposed. Studies by Aiken have clearly revealed the essential role that the ketone carbonyl plays in the *syn* selective aldol reaction.[37] Formation of the *syn*-aldol product as the major diastereomer is likely due to a bias towards generation of a zinc-chelated *Z*-enolate, but any *anti*-aldol product in the mixture could result from either a change in facial selectivity of the aldehyde or from a reaction involving less favored *E*-enolate.

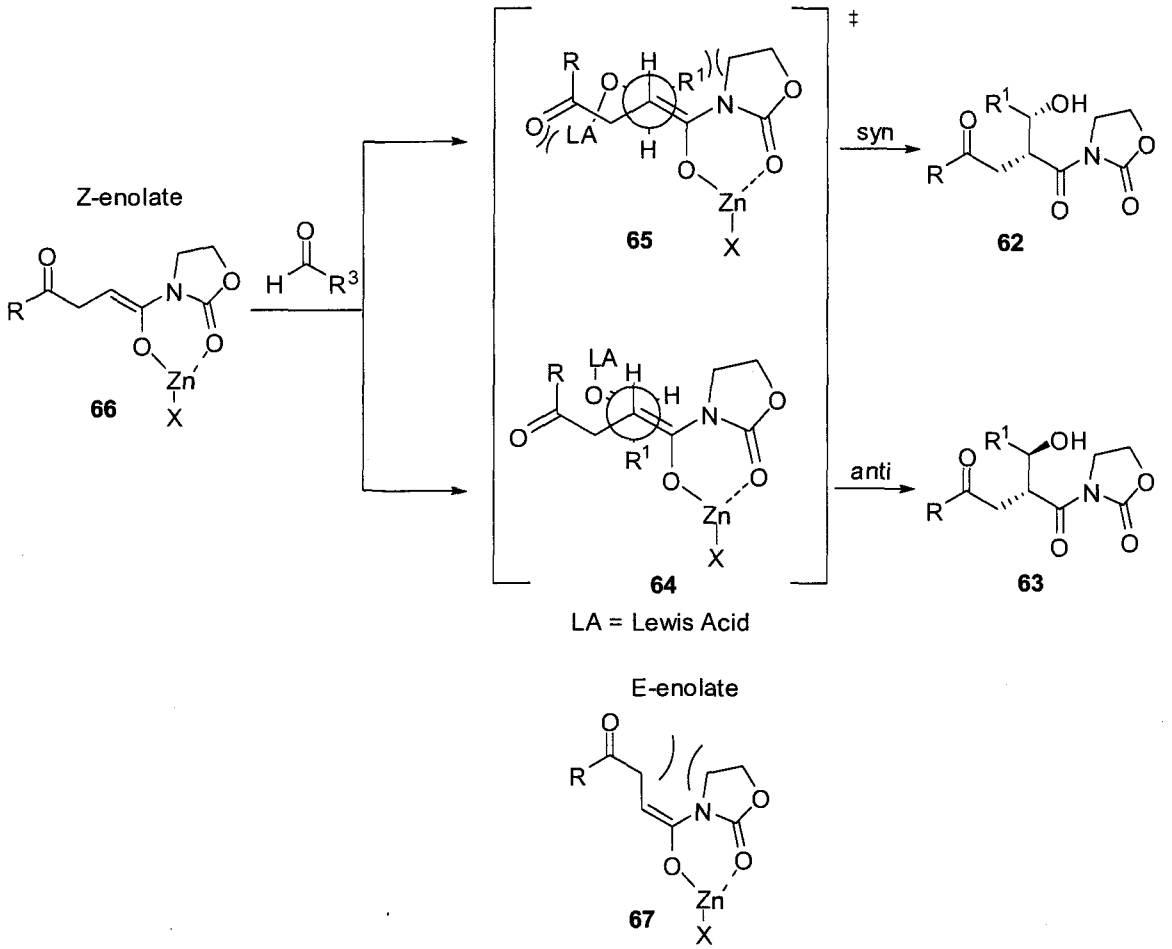


Scheme 14. Zimmerman-Traxler Closed Transition States of *E*-Enolate

As previously mentioned, the *syn*-aldol product is usually the major diastereomer formed during the reaction of β-keto esters and amides, and the results are rationalized through the reaction of the *Z*-enolate in a closed transition state. However, β-keto imides appear to favor formation of the *anti*-aldol product as the major diastereomer in the tandem chain extension aldol reaction. This result is consistent with a transition state model proposed by Heathcock and co-workers, in which the stereoselectivity of an aldol reaction involving an oxazolidinone system was affected by the stoichiometry of Lewis acids.[53] Heathcock found that the use of one equivalent of Lewis acid provided access to the *syn*-aldol product, but two equivalents of Lewis acid favored formation of the *anti*-aldol product. A model was proposed that suggested utilization of excess Lewis acid made the closed transition state unnecessary. The first equivalent would stabilize the enolate and the second equivalent of Lewis acid would activate the aldehyde towards

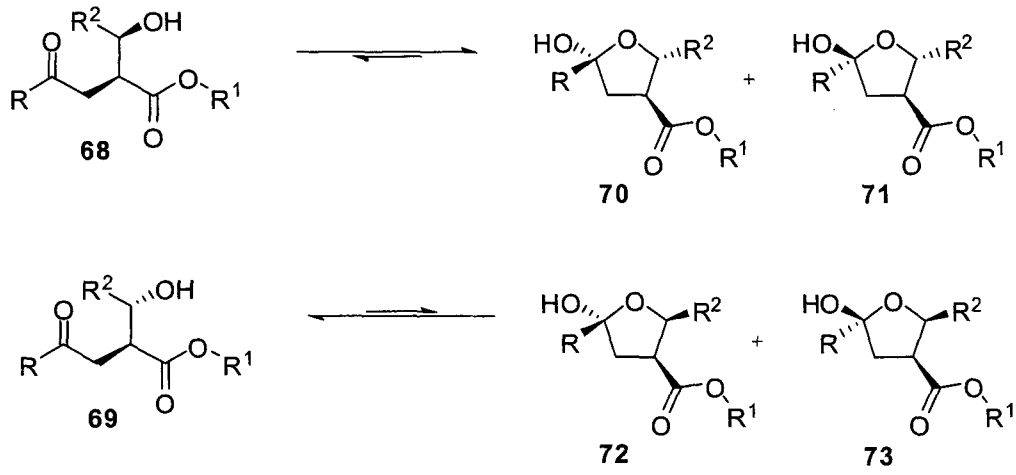
nucleophilic attack. These two Lewis acid-mediated operations are performed simultaneously by a single Lewis acid in a closed transition state.

A similar model can be proposed for the reactivity of the zinc enolates generated through the chain extension of the β-keto imides. An important difference between the imide enolate and the ester and amide enolates is that there is an additional Lewis basic site on the imide carbonyl. This carbonyl is believed to be Lewis basic enough to complex with the zinc, serving to provide the Reformatsky-like organometallic intermediate with more enolate character. This imide enolate may or may not exist in the Reformatsky-like dimeric form and may not need an additional Lewis basic functionality, like the aldehyde or ketone, to induce breakdown of the intermediate proposed by Dewar. It is unclear as to whether the irreversible breakdown of the imide dimer is faster than the esters and amide dimers or whether the equilibrium between the dimer and the enolate is changed due to the presence of the additional Lewis acid site of the β-keto imide. Because of the enhanced reactivity of the β-keto imide enolate and the excess Lewis acid, the enolate could react with the electrophilic carbonyl via an open transition state, leading to the *syn* (**62**) and *anti*-aldol products (**63**). Any avoidance of steric interactions between the imide and the R^1 of the aldehyde in the transition state (**64**) would lead to the *anti*-aldol product **63**. The transition state (**65**) leading to the *syn*-aldol product (**62**) would be disfavored because of these interactions. In the case of the β-keto imide, only the *Z*-enolate **66** needs to be considered because of the steric interactions between the imide and the keto chain in the *E*-enolate **67** (**Scheme 15**).



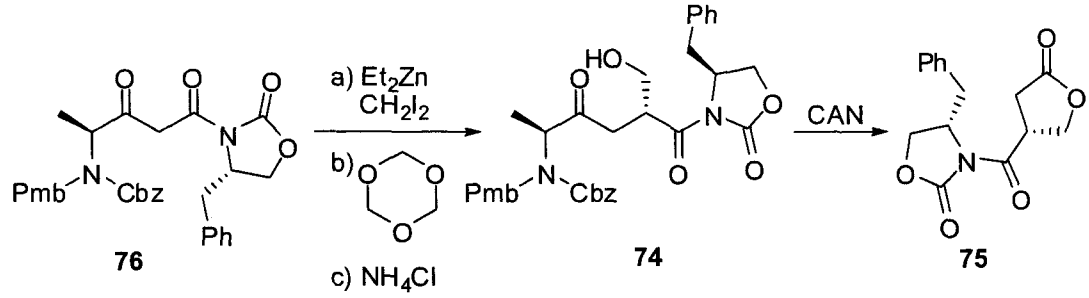
Scheme 15. Open Transition States *Z*- and *E*- Imide Enolates

The analysis of the mixture of *syn* (**68**) and *anti*-aldol (**69**) products is often complicated by the equilibrium that exists between the open and closed (hemiacetal) forms of each diastereomer. Both open and closed forms of both diastereomers are seen by NMR analysis.[48] Therefore, analysis of the aldol products by ^{1}H NMR spectra often reveals the presence of six isomers. Typically, the *syn*-aldol product favors the closed (hemiacetal) form (**70-71**) to a greater extent than the *anti* isomer (**72-73**), which can be rationalized by the *trans* relationship between the ester and R^2 groups in the closed (hemiacetal) form of the *syn*-aldol product (**Scheme 16**).



Scheme 16. Equilibrium Between Open and Closed, Hemiacetal Form

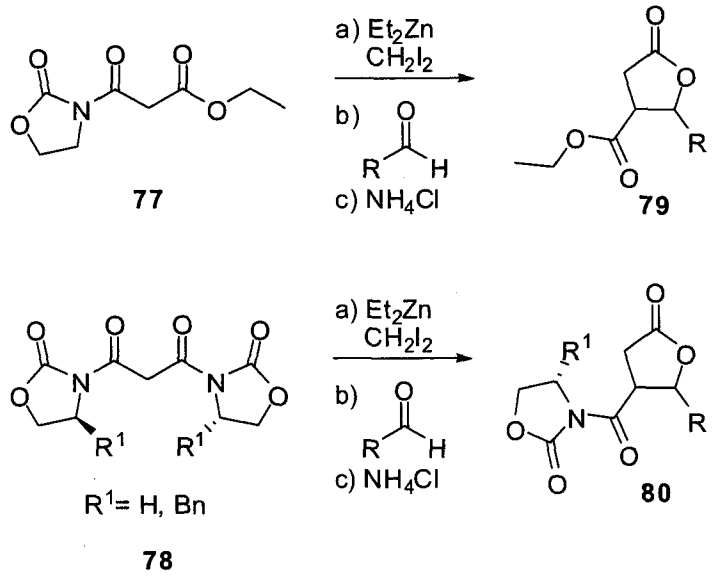
Lin discovered an oxidative cleavage reaction that converted the hemiacetals (**74**) formed in the tandem chain extension-aldol reaction into γ-lactones (**75**) through the use of ceric ammonium nitrate (CAN).[33] His study was focused on amino acid-derived substrates (**76**), which were efficiently converted into the corresponding γ-lactones (**Scheme 17**). Simpler starting materials were not studied. More details of this novel transformation will be described later.



Scheme 17. CAN-mediated Oxidative Cleavage of Chain Extension Aldol Product

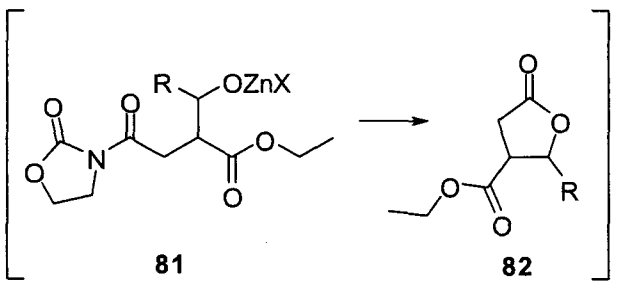
More recently, select non-β-ketone-containing substrates were subjected to the zinc-mediated chain extension reaction conditions. Both α-carboxy ester imides (**77**) and

bis-imides (**78**)[34] were exposed to the tandem chain extension-aldol reaction conditions. Successful homologation and capture of aldehydes were observed (**79-80**) (**Scheme 18**).



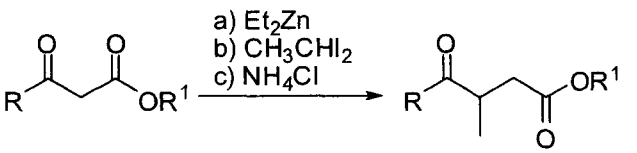
Scheme 18. Formation of γ-Lactones via Chain Extension-Aldol Chemistry

One major difference between these substrates and previous β-ketone containing substrates is the fact that the imide functionality is a good acylating group. The hydroxylate functionality formed in the aldol reaction (**81**) is nucleophilic and will attack the imide to form a 5-membered lactone (**82**) (**Scheme 19**).



Scheme 19. Formation of γ-Lactone with α-Carboxy Ester

In addition to the Furukawa-modified Simmons-Smith reagent generated from diiodomethane, substituted carbenoids have also been used in the chain extension chemistry. Lin, McGinness, and Wilson[54] were able to successfully homologate β-keto esters (**29**) and amides to β-methyl γ-keto esters (**83**) and amides using the carbenoid derived from diethyl zinc and 1,1-diiodoethane (**Scheme 20**). It is important to note, however, that no tandem processes were explored at that time. A study that addresses diastereocontrol in tandem reactions will be described in detail later in this dissertation.

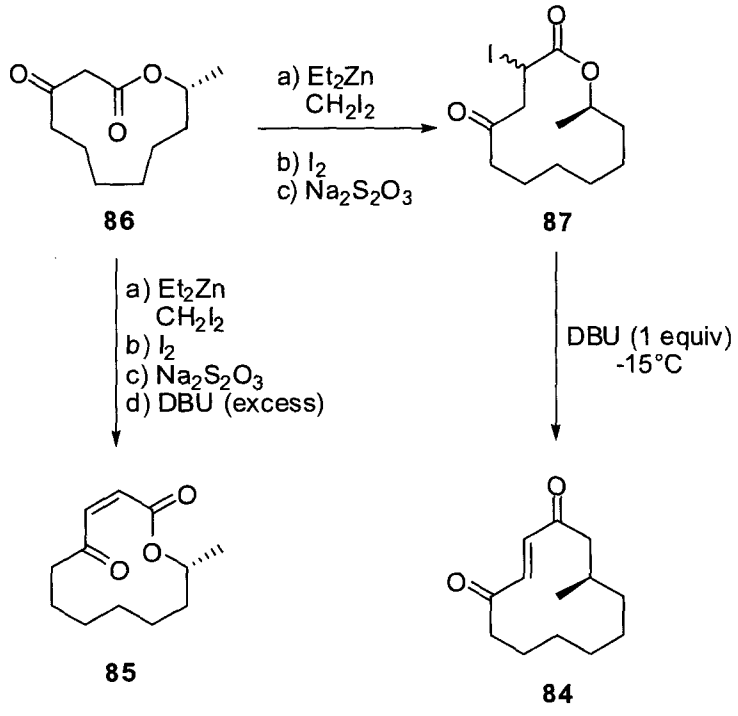


29 **83**

Scheme 20. Chain Extension with Substituted Carbenoid

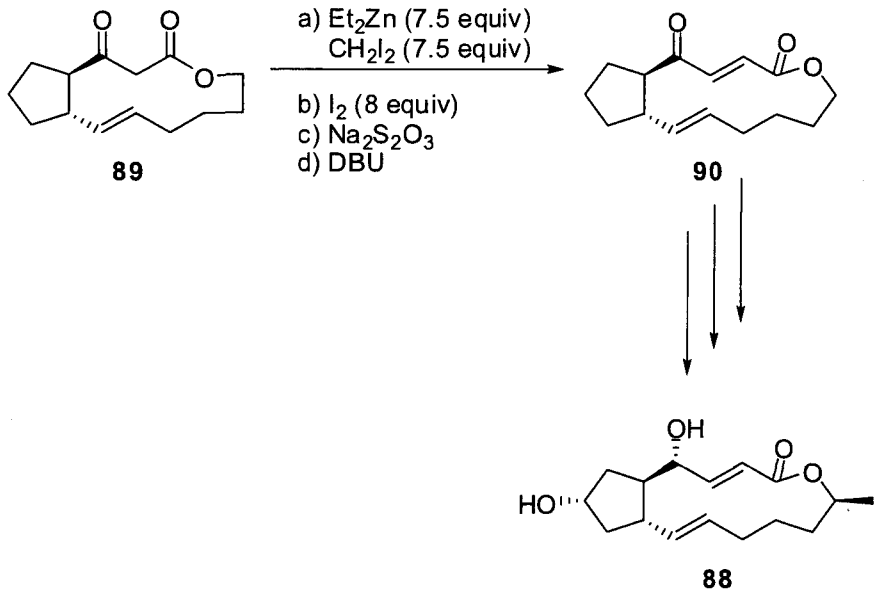
Use of Zinc Carbenoid-Mediated Chain Extension Reaction as Key Step in Synthesis of Complex Systems

The zinc-mediated tandem chain extension reaction has been used as a key step in the synthesis of complex natural products. Ronsheim[55] used the chemistry in key steps in the synthesis of natural products (+)-patulolide A (**84**) and (±)-patulolide B (**85**). By trapping the intermediate produced in the ring expansion reaction of β-keto lactone **86** with iodine (**87**) and inducing elimination by treatment with DBU, Ronsheim was able to convert the advanced intermediate **86** into both of the natural products by careful selection of reaction conditions. Under thermodynamically-controlled elimination conditions, (±)-patulolide B (**85**) was obtained and under kinetically-controlled elimination conditions (+)-patulolide A (**84**) was synthesized (**Scheme 21**).



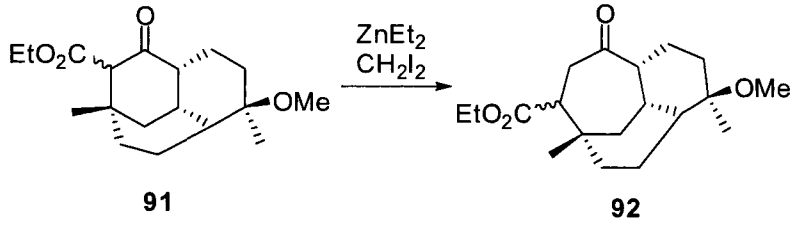
Scheme 21. Synthesis of (+)-Patulolide A and (±)-Pautuloide B

In 2007, Lin used similar chemistry in the formal synthesis of (+)-brefeldin A (**88**).[56] β-Keto lactone **89** was subjected to the Furukawa-modified Simmons-Smith reagent, and then treated sequentially with iodine and base to obtain the homologated macrocyclic lactone with the required *E* alkene stereochemistry (**90**). Conversion of the advanced intermediate to (+)-brefeldin A had been reported previously by Kim through a protocol involving a reduction and deprotection (**Scheme 22**).[57]



Scheme 22. Incorporation of Chain Extension in the Synthesis of (+)-Brefeldin A

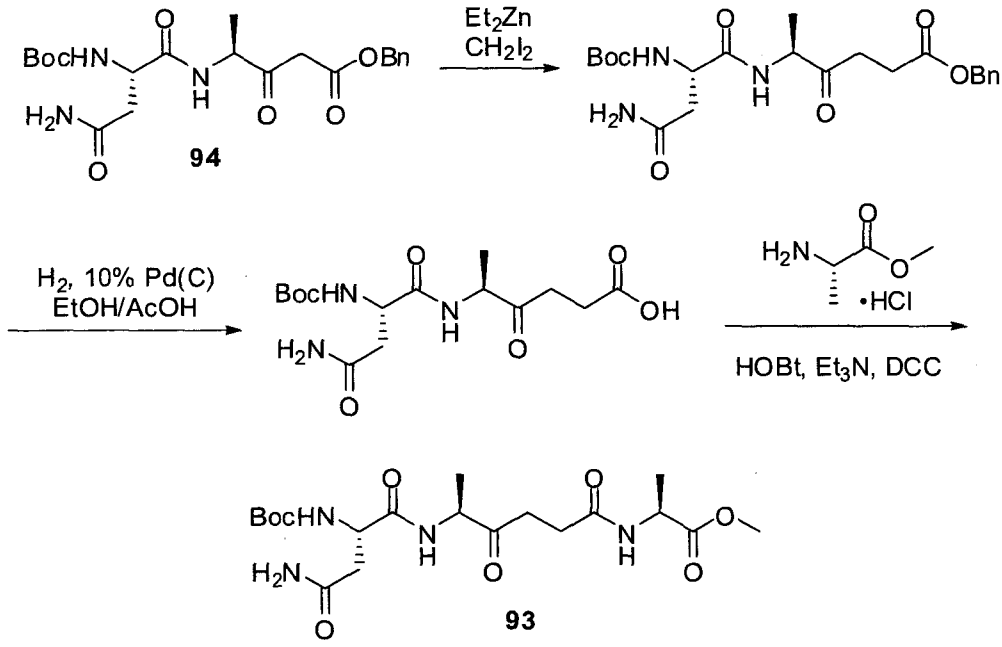
The zinc-mediated chain extension reaction has also been reported in the literature as a key step in the synthesis of vibsane-type diterpenes. Williams and co-workers used the chain extension conditions to convert cyclic β-keto ester **91** to γ-keto ester **92** with reasonable success (**Scheme 23**).[58, 59]



Scheme 23. Utilization of Chain Extension in the Synthesis of Vibsane-type Diterpenes

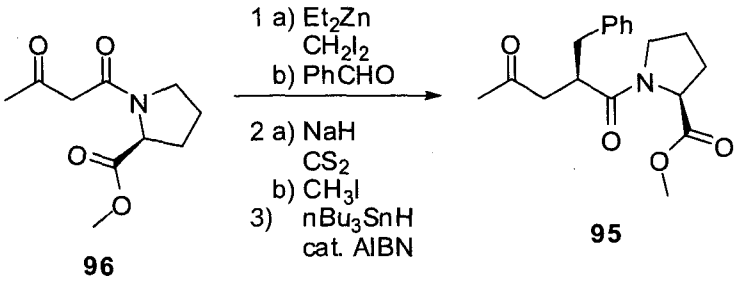
Peptide isosteres have been accessed by using the zinc carbenoid-mediated chemistry as a key step. The backbone of ketomethylene isosteres (**93**) can be formed through the chain extension of an amino acid-derived β-keto carbonyl starting material

(**94**), which can be prepared easily from commercially available starting materials (**Scheme 24**).[60] Lin's work, previously described in **Scheme 17**, was focused on obtaining these types of substrates, as well.



Scheme 24. Formation of Ketomethylene Isostere via Amino Acid Derived β-Keto Ester

Amino acid-derived β-keto amides have also been successfully converted to ketomethylene isosteres using the chain extension chemistry.[61] The tandem aldol reaction provided access to a side chain that mimics the phenylalanine side chain (**95**) through the formation of a xanthate followed by reductive cleavage (**Scheme 25**). Many amino acid-based β-keto amides were subjected to the same reaction conditions and the system that provided the best stereocontrol was the L-proline-derived starting material **96**.



Scheme 25. Formation of Ketomethylene Isostere from β-Keto Amide

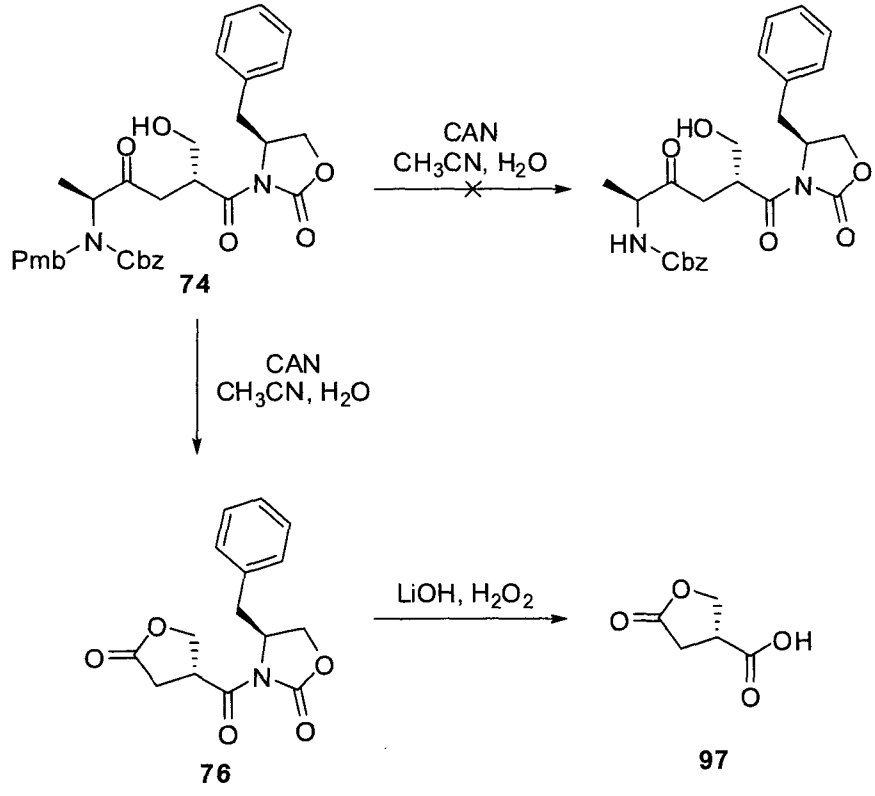
CHAPTER II

CERIC AMMONIUM NITRATE-MEDIATED OXIDATIVE CLEAVAGES OF HEMIACETALS

Introduction of Ceric Ammonium Nitrate Oxidative Cleavage

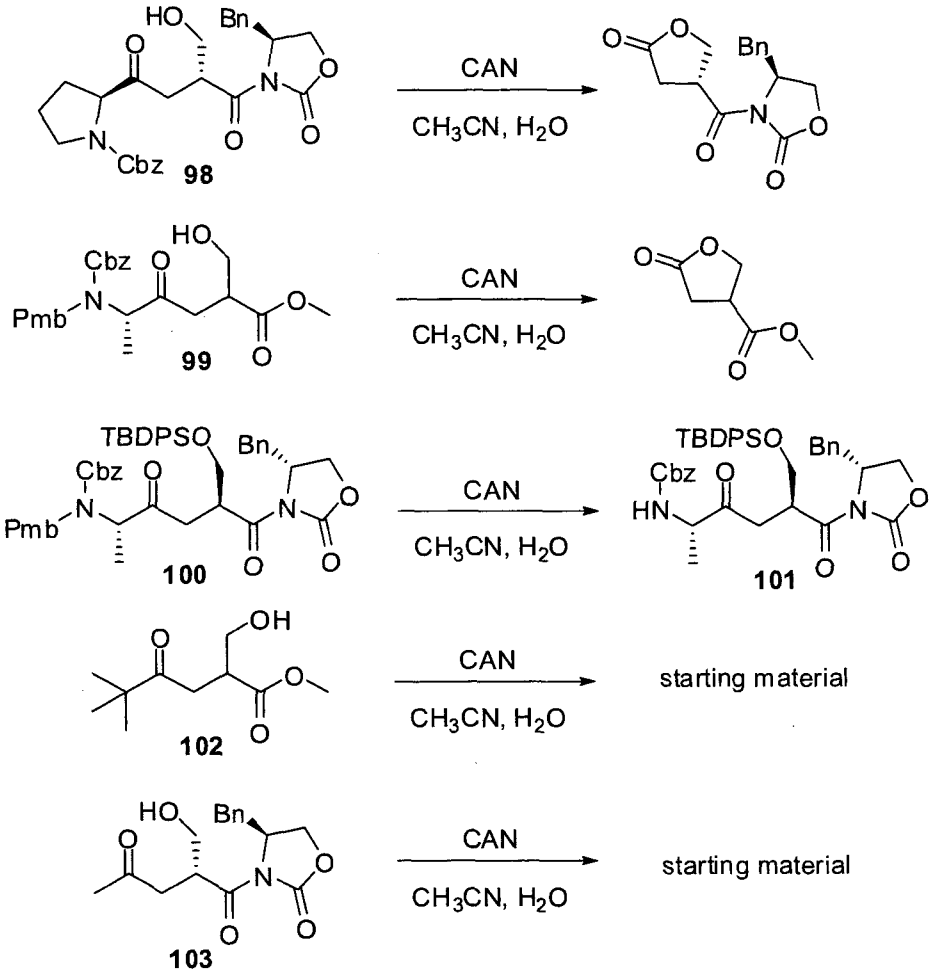
A unique oxidative cleavage reaction was discovered serendipitously by Lin during an attempt to remove a *para*-methoxybenzyl (Pmb) protecting group from an amino acid-derived chain extension aldol product.[33] Instead of simply removing the Pmb group through treatment with ceric ammonium nitrate (CAN),[62] the carbon chain was cleaved and a lactone was formed. Ceric ammonium nitrate can be used to oxidize alkenes, arenes, alcohols, phenols, ethers, carbonyl compounds, nitroalkanes, and organosulfur compounds. The reagent will promote oxidative cleavages of organometallic compounds to generate α-acyl radicals.[63] Ceric ammonium nitrate is a powerful and versatile single electron oxidizing reagent, so the possibility of unanticipated chemistry taking place was not unreasonable, particularly when considering the other functional groups that were present in the molecule.

After cleavage of the imide functionality (**76**) to generate the carboxylic acid **97**, the resultant compound, a member of the paraconic acid family, was compared to literature reports, which verified the correct structure and the absolute stereochemistry that had arisen from the zinc-mediated chain extension aldol reaction (**Scheme 26**).[64] The direct transformation of aldol product **74** to γ-lactone **97** was unprecedented and warranted further exploration in order to determine why the carbon chain had been cleaved, how it was cleaved, the scope of the cleavage reaction, and what potential uses this new reaction possessed.



Scheme 26. Attempted Deprotection of Pmb Group with Ceric Ammonium Nitrate

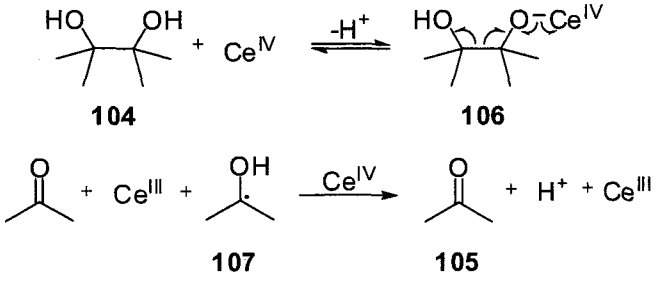
After investigating the reaction, Lin was able to draw two conclusions with regards to this interesting oxidative cleavage. The first conclusion was that it was imperative that the hemiacetal form be present in the reaction mixture. The second necessary feature was the presence of an α-nitrogen with respect to the ketone. Substrates **98** and **99** met both of these prerequisites and the CAN-mediated oxidative cleavage proceeded efficiently with these two substrates. When the hemiacetal form was not available, as in the case of **100** with the hydroxyl group protected, the oxidative cleavage did not take place. In this case the Pmb group was removed (**101**) as originally expected. Substrates **102** and **103** derived from β-keto esters and imides without α-nitrogens, were also subjected to the CAN-mediated oxidation conditions and no reaction took place (**Scheme 27**).



Scheme 27. Substrates Subjected to CAN Oxidation Conditions

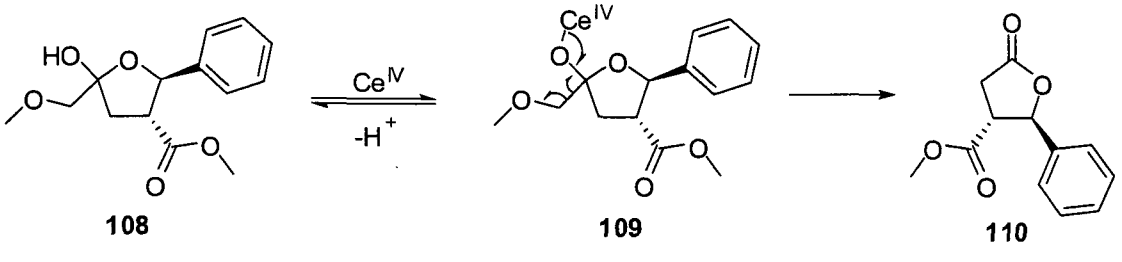
The CAN oxidation reaction is proposed to proceed through the hemiacetal, a prerequisite supported by studies of Lin.[33] A proposed mechanism is based on a literature report in which cerium(IV) was used to convert 1,2-diols (**104**) to their respective ketones (**105**) through a single electron transfer process.[65] The proposed mechanism involved an initial coordination of the cerium to one of the hydroxyl groups (**106**) followed by a single electron transfer to form intermediate radical **107** with accompanying cleavage of the carbon-carbon bond (**Scheme 28**). The mechanism was proposed to involve the coordination to only one of the hydroxyl groups on the basis of

radical trapping experiments. Similar rates of oxidation of the 1,2-diols and their monomethyl ethers were observed.



Scheme 28. Proposed Mechanism by Trahanovsky and co-workers for 1,2-Diols with Cerium^{IV}

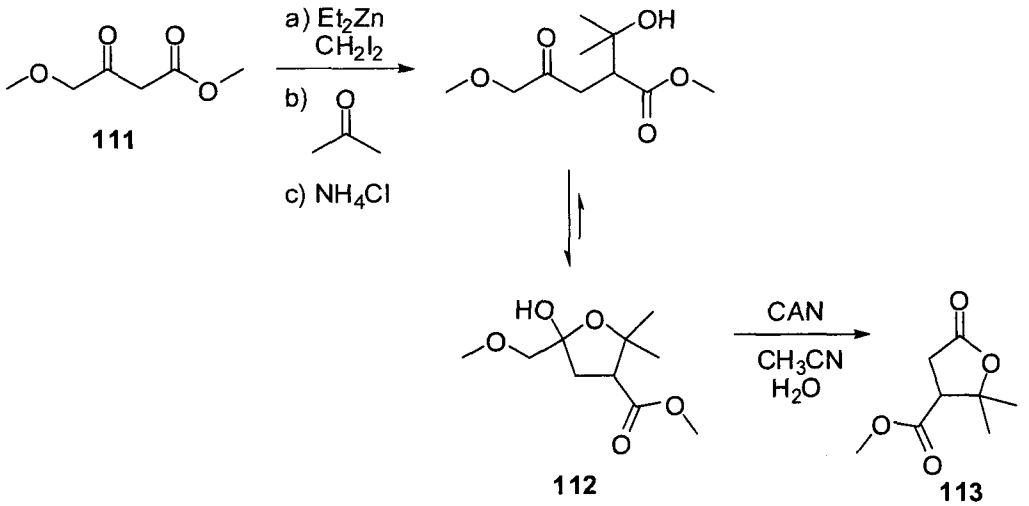
Based on this literature report, a similar mechanism can be proposed to account for Lin's observed results. The hydroxyl group of the hemiacetal **108**, produced in the tandem chain extension-aldol reaction involving a β-keto ester and benzaldehyde, is believed to complex with the cerium, followed by single electron transfer (**109**) to cleave the carbon-carbon bond and create the lactone **110** observed as the product (**Scheme 29**). The stereocenters established in the chain extension-aldol reaction are not involved in the mechanism and, based on the results of Lin, are not epimerized, even under the strongly acidic conditions.



Scheme 29. Proposed Mechanism of the CAN Oxidation

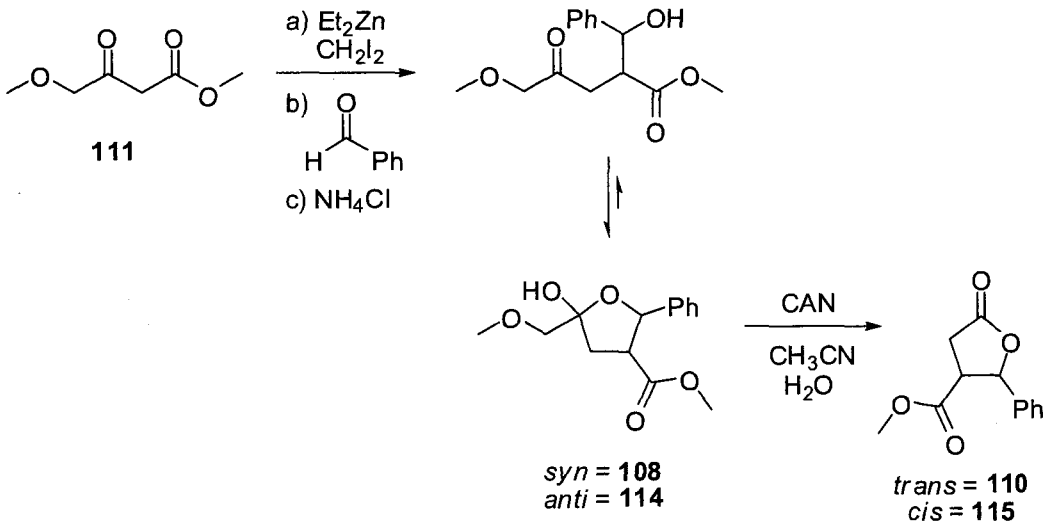
Methodology of Oxidative Cleavage

The substrates with α-heteroatoms studied by Lin were all derived from amino acids. In order to probe versatility of this reaction, we proposed to replace the amino acid-derived β-keto ester (or imide), which required numerous synthetic steps to prepare, with a commercially available substrate, methyl 4-methoxyacetoacetate (**111**). This compound was subjected to the zinc-mediated chain extension reaction conditions and the organometallic intermediate reacted with a number of carbonyl-containing electrophiles. The first electrophile used in the tandem chain extension-aldol reaction was acetone. Since acetone is a symmetric ketone, a single aldol product (**112**) would be produced as opposed to a mixture of diastereomers formed from an aldehyde. The yield of the chain extension-aldol reaction was 63%. The CAN oxidation reaction provided the γ-lactone **113** in 85%, demonstrating that the presence of an α-nitrogen is not required for the oxidative cleavage reaction (**Scheme 30**).



Scheme 30. Formation of Acetone-derived γ-Lactone **113**

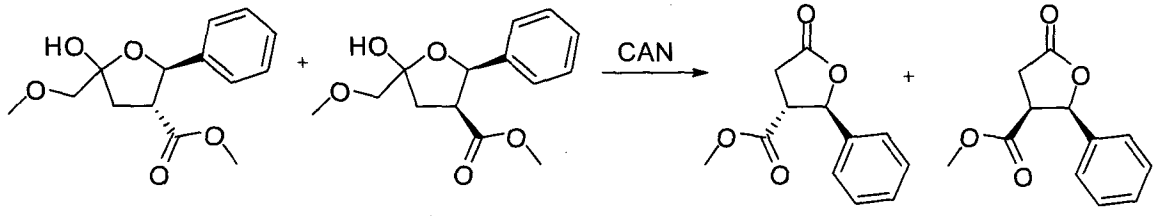
Since the tandem chain extension-aldol reaction involving methyl 4-methoxyacetoacetate and acetone provided access to a single aldol product, the next step in the study was to increase the complexity of the reaction by using an electrophile that would provide access to a mixture of diastereomers. The use of benzaldehyde in a chain extension-aldol reaction with methyl pivaloylacetate was reported[48] to provide access to the *syn* diastereomer as the major product with reasonable stereoselectivity (12:1 *syn:anti*). When methyl 4-methoxyacetoacetate (**111**) was used as the starting material for the chain extension-aldol reaction, the bias favoring formation of the *syn* aldol product was not as strong as observed with substrates like methyl pivaloylacetate. The ^{1}H NMR of the crude reaction mixture suggested a 3:1 ratio of diastereomers were formed in the aldol reaction (**108, 114**), but the major diastereomer was not able to be identified at that time. After optimization of the CAN-mediated oxidative cleavage reaction of the crude reaction mixture, a 3:1 ratio of lactone diastereomers were formed, which suggested that both diastereomers were being converted to the γ-lactones (**Scheme 31**). The major diastereomer formed in the oxidative cleavage was confirmed to be the *trans* γ-lactone **110** through comparison to the literature,[66] although it was unclear at the time which diastereomer was the major product in the chain extension-aldol reaction. The yield of the chain extension-aldol reaction was 68% and the CAN-mediated oxidation reaction provided an 82% yield of the lactones **110** and **115**.[67]



Scheme 31. Formation of Benzaldehyde-derived γ-Lactones **110** and **115**

In order to determine the stereoselectivity of the chain extension aldol reaction and to prove that the stereochemistry was not changed during the CAN-mediated oxidation, separation of one diastereomer was required. Subjection of that pure diastereomer to the CAN-mediated oxidation conditions would produce a lactone that could be compared to characterization data present in the literature. The major aldol product from the chain extension aldol reaction with benzaldehyde was successfully separated via column chromatography and subjected to the CAN-mediated oxidation conditions, which provided access to the *trans* γ-lactone **110**. After identifying that the major aldol product could be converted to the *trans* lactone, the crude reaction mixture of the two diastereomers, present in a 3:1 ratio, was subjected to CAN under the same reaction conditions. An identical 3:1 ratio of lactones was obtained and compared to the literature data. Since the ratio of products remained 3:1, with the major product being the *trans* lactone, it was concluded that no epimerization was taking place during the CAN oxidation (**Scheme 32**). At this point, it was concluded that the major diastereomer of the

chain extension-aldol reaction was the *syn* diastereomer (**108**), which was consistent with previous research results in the group. The *anti* diastereomer from the chain extension-aldol reaction (**114**) was converted to the *cis* lactone (**115**). It is important to note that 3:1 (*syn:anti*) ratio of diastereomeric products indicated that the aldol reaction was much less diastereoselective than previous tandem chain extension-aldol reactions in the group, but this was the first time methyl 4-methoxyacetoacetate was used as the starting β-keto ester.



108 **114** **110** **115**

Scheme 32. CAN Oxidation of Major Diastereomer of the Chain Extension Aldol Reaction and Crude Mixture of Diastereomers

The low diastereoselectivity observed by methyl 4-methoxyacetoacetate compared to other β-keto esters studied by previous group members was unexpected. The major difference was the presence of a Lewis basic functionality that was absent in the earlier studies. The ether functionality present on the chain provides an additional opportunity for the zinc complexation, which could compromise formation of the *Z*-enolate (**52**) proposed to be important in the formation of the *syn*-aldol product. If the zinc is not chelated between the ketone and the ester enolate, as proposed for *Z*-enolate formation, but is chelated with the ether functionality (**116**), a mixture of *E*- and *Z*-enolates would be possible. Intermolecular zinc complexation (**117**), assisted by the methoxy functionality, could also compromise effective *Z*-enolate formation resulting in

a mix of *E*- and *Z*-enolates as well, resulting in the same loss of diastereoselectivity (**Figure 2**). Although it is difficult to completely rationalize this loss in diastereocontrol, the Lewis base interaction between the methoxy group and the zinc and its effect on selective enolate formation are likely involved in the reduced aldol selectivity.

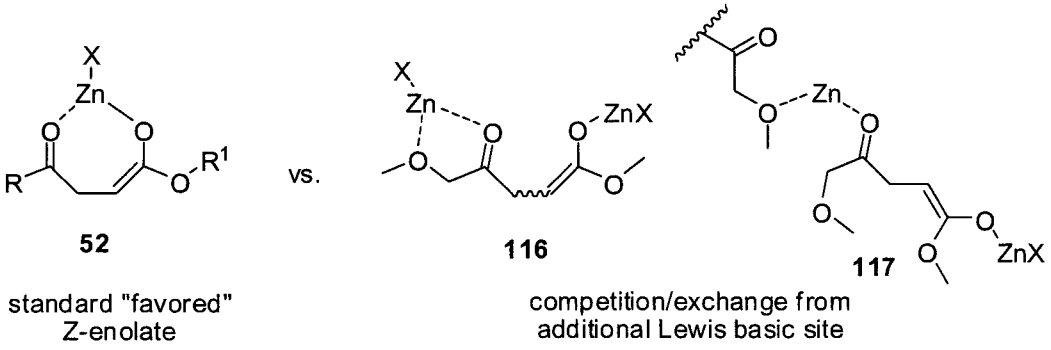
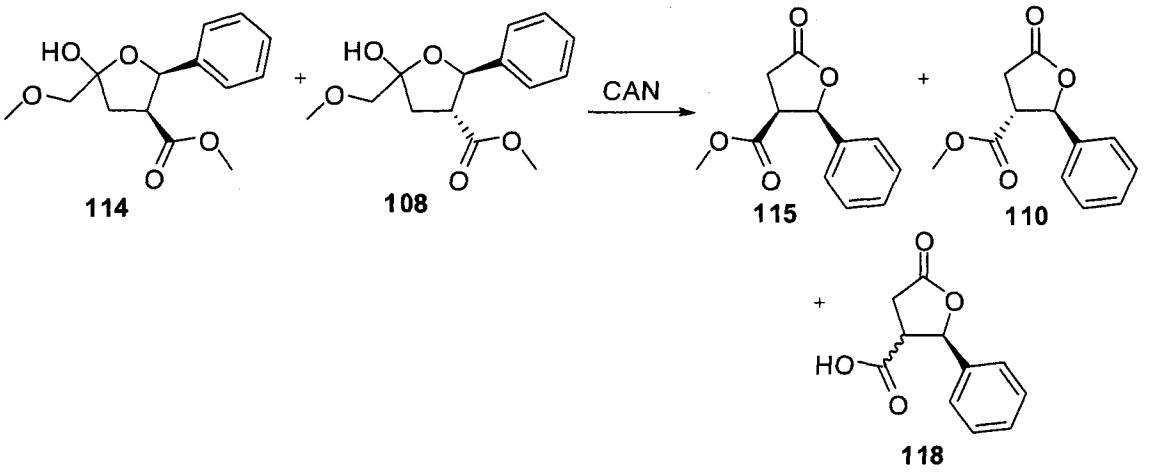


Figure 2. Explanation for Decreased Diastereoselectivity with Methyl 4-Methoxyacetoacetate

One complication that arose during the oxidative formation of the benzaldehyde-derived lactones was hydrolysis of the ester functionality (**118**) during the CAN-mediated oxidation conditions (**Scheme 33**). Since the pH of the CAN-mediated oxidation was approximately 2 and water was present as a co-solvent to aid in the solubility of the CAN, extended reaction times resulted in partial hydrolysis of the esters to form carboxylic acids. The *syn* (**108**) and *anti* (**114**) aldol products hydrolyzed at different rates, but it was unclear, however, which diastereomer was hydrozyling faster. This originally caused some confusion and concern, because NMR analysis suggested that three compounds appeared to be present in the crude reaction mixture and the ratio of these compounds changed from reaction to reaction. One would expect only two products to be present in solution, both the *trans* (**110**) and *cis* (**115**) methyl ester

lactones; however, the difference of a few hours of reaction time dramatically changed the composition of the crude reaction's product mixture.



Scheme 33. Hydrolysis of Ester to Carboxylic Acid

The major, *syn*-aldol product was hydrolyzed to the carboxylic acid faster then the *anti*-aldol product, as determined by the ratio of products in the crude reaction mixtures of the CAN oxidation reaction products. It appeared as if the *cis* lactone, which comes from the *anti*-aldol product, provided consistent ratios of ester to carboxylic acid from reaction to reaction, even with slightly different reaction times. This contrasted to the various ratios of ester: acid observed for the *trans* product when different reaction times were used.

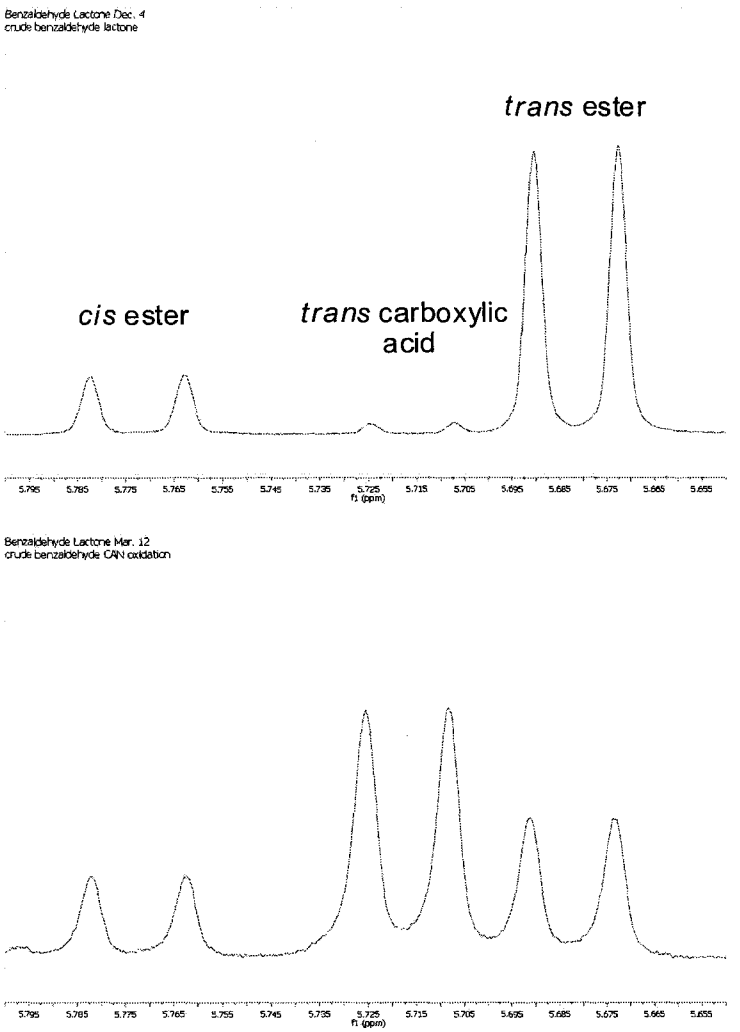
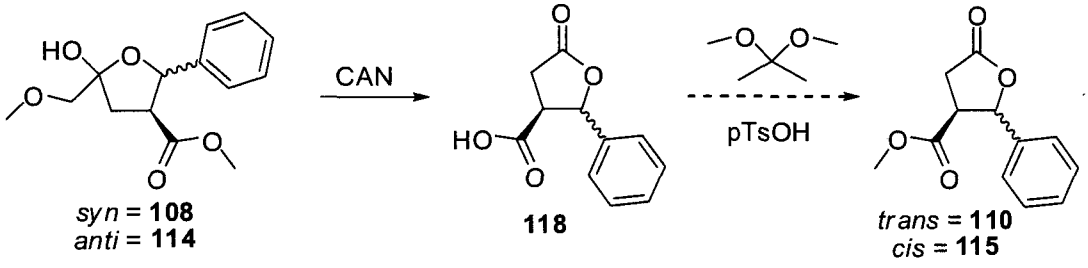


Figure 3. NMR Spectrum of Benzylic Proton of the CAN Oxidation of Benzaldehyde Aldol Product after 1 hour and 2 hours

The reaction time was optimized to 45 minutes by careful monitoring of the reaction by TLC. The optimized reaction conditions allowed for the isolation of the lactone products with the methyl ester intact. An alternative would have been to allow the reaction to proceed for an extended period of time, so that both esters (**110, 115**) would hydrolyze to the carboxylic acids (**118**). This was not preferred, since no literature data that would allow direct determination of the product identity was available for the

carboxylic acids. Furthermore, conversion of the acids to the esters (**110, 115**) would be necessary, which would involve additional chemistry to produce the known compounds (**Scheme 34**). Additional control studies would have been necessary to ensure that the stereochemical issues were understood.



syn = **108**
anti = **114**

118

trans = **110**
cis = **115**

Scheme 34. Potential Chemistry to Convert Carboxylic Acids to Esters

One interesting aspect of the ^{1}H NMR spectrum of the two diastereomers was a significant difference in chemical shifts of the ester's α-protons and the methyl ester protons. This difference can be explained by magnetic anisoptropy, a spectroscopic phenomenon seen with compounds that have π-electrons. When aromatic protons are placed in a magnetic field, the π-electrons are induced to circulate around the ring, creating a ring current.[68] The circulating electrons create a magnetic field which deshields the aromatic protons, causing them to resonate further downfield than expected. However, if a proton in the molecule happens to fall directly above or beneath the aromatic ring, that proton will be shifted upfield, sometimes significantly (**Figure 4**).

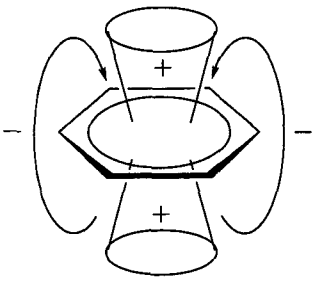


Figure 4. Induced Magnetic Field of Aromatic Ring and Chemical Shift Change

In the case of the benzaldehyde-derived lactones (**110, 115**), a significant change in chemical shifts was caused by this induced magnetic field. The methyl ester of the *trans* lactone (**110**) resonated at 3.78 ppm, about 0.5 ppm further downfield than the methyl ester of the *cis* lactone (**115**), which was observed at 3.29 ppm. The methine proton α to the ester of the *cis* diastereomer resonated at 3.74 ppm, about 0.4 ppm further downfield than the *trans* protons at 3.35 ppm.

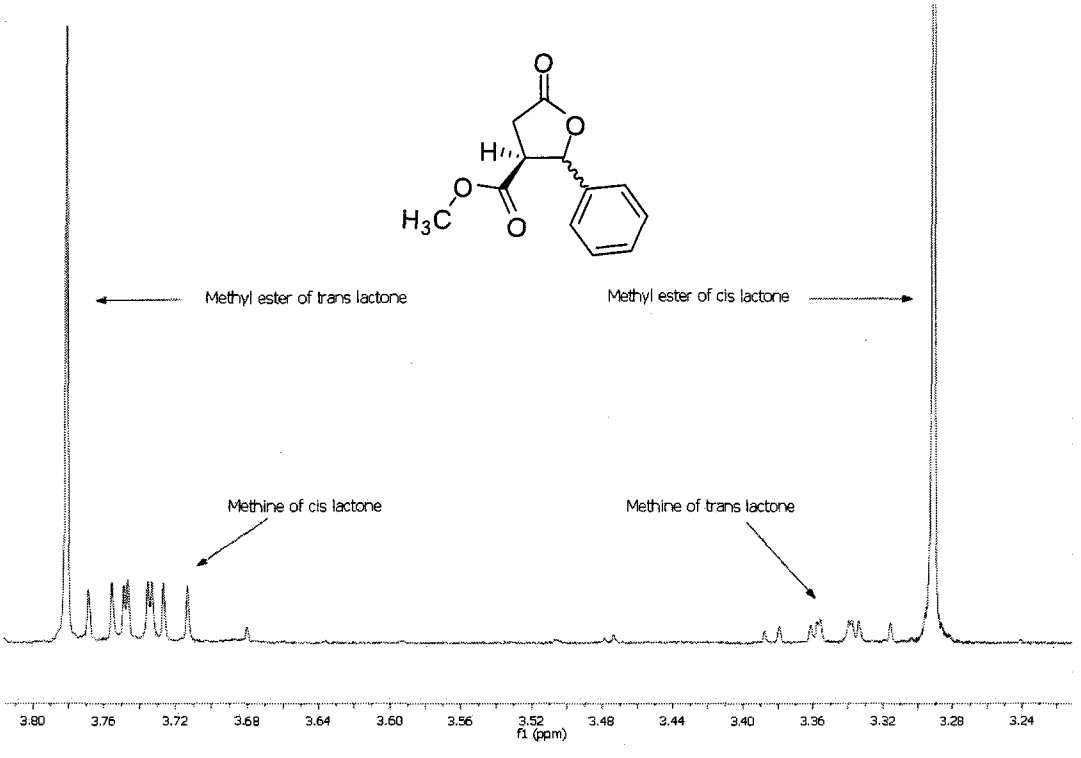


Figure 5. 400 MHz ^{1}H NMR of Purified Mixture of Lactone Diastereomers Displaying Magnetic Anisotropy

Computational modeling of the two diastereomers lends support for this hypothesis. Both the *cis* and *trans* lactones were modeled at the B3LYP 6-311G* level of theory in order to verify that the methyl ester and the methine resided in either of the shift areas created from the aromatic ring. The lowest energy conformations for each diastereomer were calculated and compared, although other conformations of each molecule contribute to the overall chemical shifts. It is apparent that the methyl group in the *cis* lactone falls directly beneath the aromatic ring, which would shift the protons upfield as seen experimentally at 3.29 ppm. A typical methyl ester would resonate in the range of 3.6-3.8 ppm,[69] which is in line with the resonance observed for the *trans* lactone. The methine protons on each lactone have dramatically different ^{1}H NMR chemical

shifts, although a comparison of conformational minima for the two diastereomers does not clearly illustrate the proposed magnetic anisotropic influences affecting these protons. A computational study, which takes into account all of the conformational geometries, would be required to understand the anisotropic impact on these distinct methine proton chemical shifts, but this study was not undertaken.

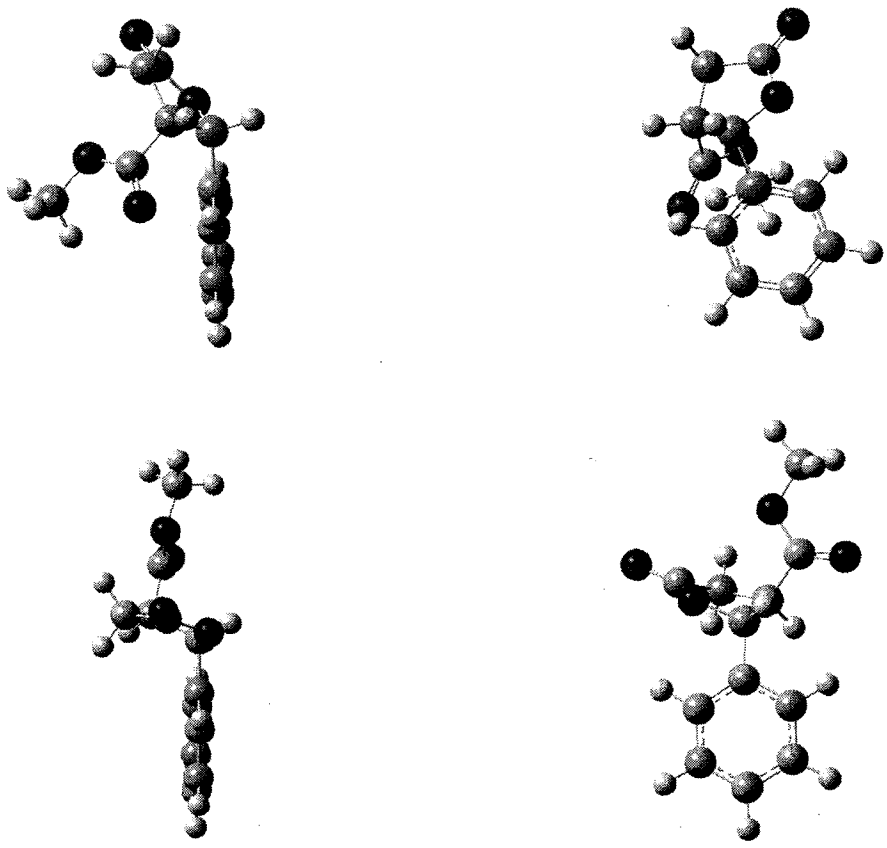
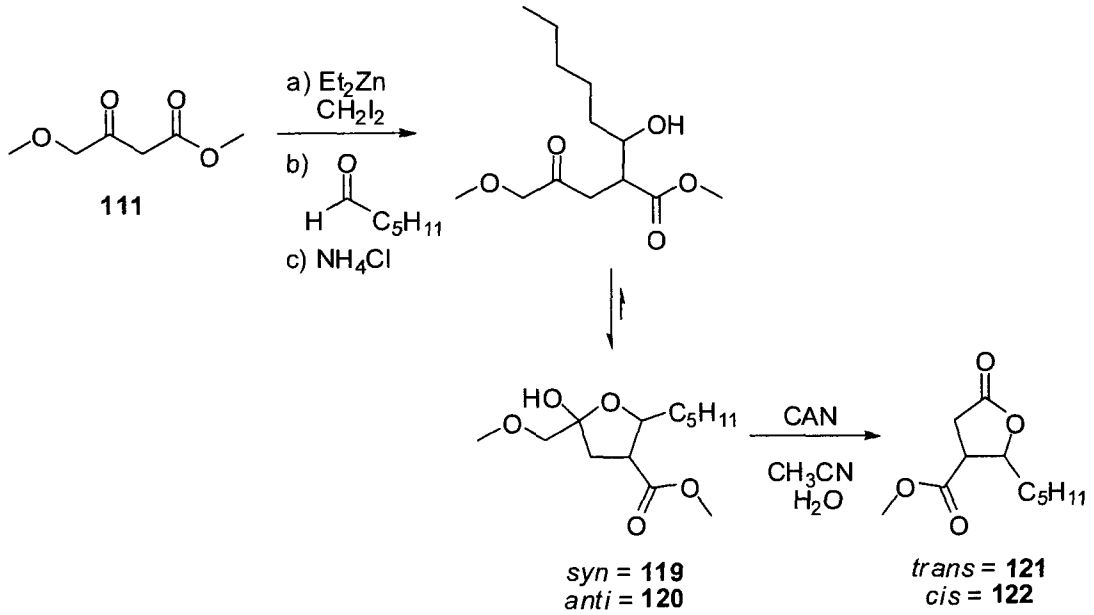


Figure 6. Lowest Energy Conformations of *cis*- and *trans*-Lactones **110** and **115** at B3LYP 6-311G*

In an attempt to broaden the scope of this reaction, and with a synthetic approach to a natural product in mind, hexanal was chosen as another electrophile to use in the

tandem chain extension-aldol process with methyl 4-methoxyacetoacetate (**111**). Hexanal provided access to a similar 3:1 ratio of diastereomers (**119, 120**) as had been observed in the benzaldehyde reaction. Similar yields to the tandem chain extension-aldol reactions with both the acetone and benzaldehyde substrates were observed. The chain extension aldol reaction with hexanal provided a 65% yield of the aldol products, and the CAN oxidation proceeded in 80%, which provided efficient access to **121** and **122 (Scheme 35)**.

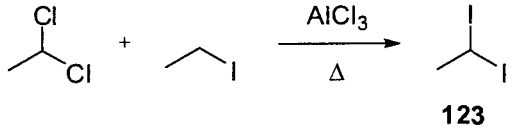


Scheme 35. Formation of Hexanal Derived γ-Lactones **121** and **122**

Studies Using Substituted Carbenoids

Recent studies on the zinc carbenoid-mediated chain extension chemistry have resulted in an expansion of scope to include substituted-carbenoids.[54] By replacing diiodomethane with 1,1-diiodoethane (**123**) as the reagent to form the zinc carbenoid, the product contains a β-methyl substituent rather than the traditional unsubstituted methylene. Unlike diiodomethane, 1,1-diiodoethane is not commercially available and

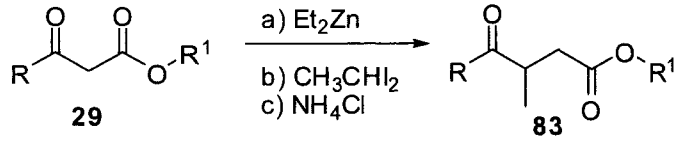
needs to be freshly prepared due to its rapid degradation during storage. The reagent is easy to prepare in a halogen exchange reaction and can be purified by vacuum distillation **(Scheme 36)**.[70]



123

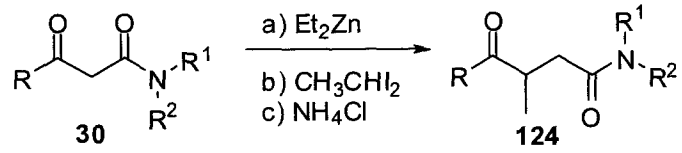
Scheme 36. Formation of 1,1-Diiodoethane

The mechanism of the chain extension reaction using the methyl-substituted carbenoid is believed to be identical to the standard chain extension reaction. The only procedural difference between the reactions using the two different carbenoids is the preformation of the zinc enolate with diethyl zinc, rather then subjecting the β-keto substrate to the preformed substituted carbenoid. Lin, McGinness, and Wilson studied the use of a substituted carbenoid with β-keto esters (**Table 1**) and amides (**Table 2**), which resulted in efficient conversions to the corresponding β-methyl γ-keto products.



R	R^1	Yield
Me	Me	76%
t-Butyl	Me	82%
Ph	Et	84%
Me	Bn	80%
Me	*t*-Butyl	88%

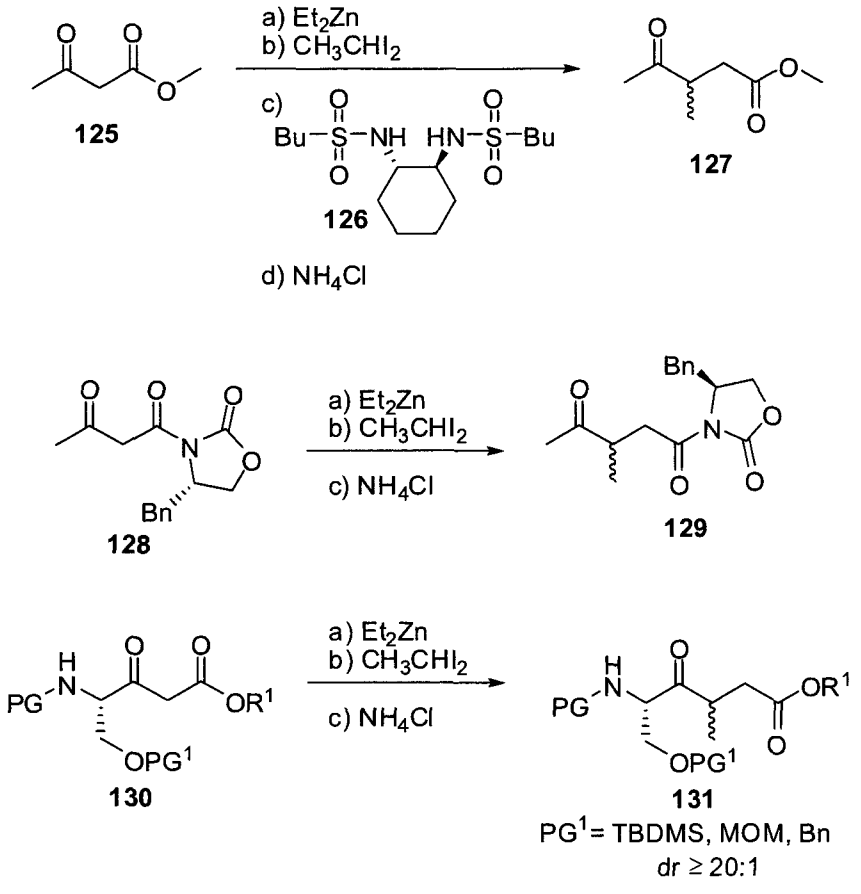
Table 1. β-Keto Esters Subjected to Methyl-Substituted Carbenoid



R	R^1	R^2	Yield
Me	Me	Me	67%
Me	$(CH_2)_4$	----	74%
t-Butyl	Me	Me	Inseparable from SM
i-Propyl	Me	Me	Inseparable from SM

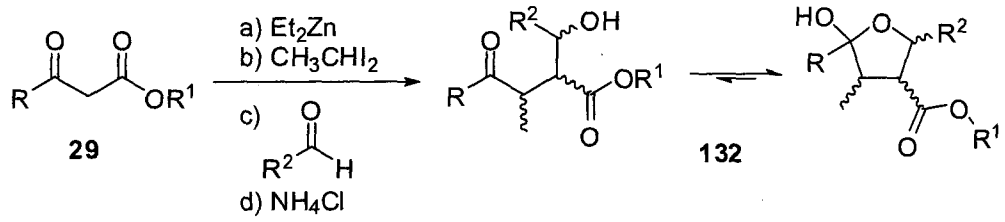
Table 2. β-Keto Amides Subjected to Methyl-Substituted Carbenoid

The homologated products contained a newly formed stereocenter, therefore attempts have been made to control the stereocenters in both enantioselective and diastereoselective processes. Lin attempted to control the enantioselectivity of a β-keto ester system (**125**) by introducing a chiral ligand (**126**), a *N,N*-bis(butanesulfonyl) derivative,[71] but a racemic mixture (**127**) was obtained.[33] Lin also attempted to control the diastereoselectivity by using a β-keto imide derived from phenylalanine (**128**), but a 1:1 mixture of diastereomers was obtained (**129**). More recently, Mazzone has been studying the reactions of amino acid derived β-keto esters (**130**) and has observed significant diastereoselectivity when a serine derivative (**131**) is utilized (**Scheme 37**).[72]



Scheme 37. Attempts at Controlling the Stereochemisty of the Methyl Group

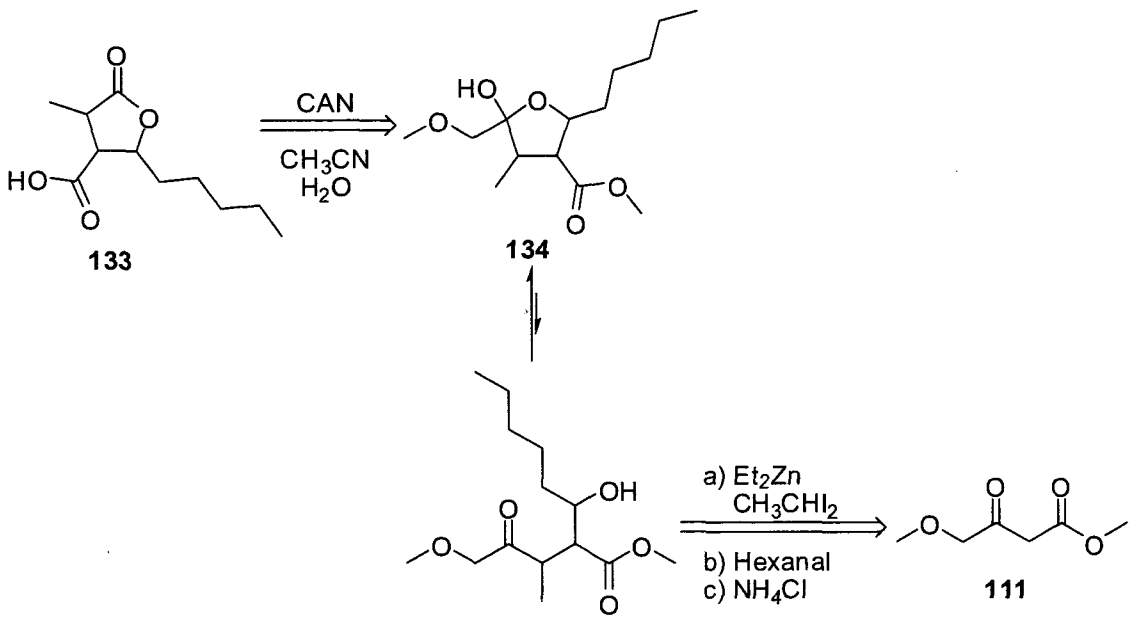
Early studies of the chain extension reaction using the substituted carbenoid focused on simple homologation of the β-dicarbonyl starting materials, but these studies did not include the investigation of any of the tandem reaction variations. Potentially, the same tandem processes that have been used in the standard, Furukawa-modified carbenoid chain extension chemistry could be used with the substituted carbenoid. This would expand the utility and scope of the chain extension chemistry. For example, by reacting the latent enolate, produced by a reaction of the substituted carbenoid and a β-keto ester (**29**), with an aldehyde (**132**), three stereocenters could be created in a one-pot reaction (**Scheme 38**).



Scheme 38. Chain Extension-Aldol Reaction with Methyl-Substituted Carbenoid

Synthesis of Phaseolinic Acid

One motivation for using this substituted carbenoid chemistry in conjunction with the CAN-mediated oxidative cleavage reaction was to access the phaseolinic acid (**133**) family of natural products. Retrosynthetic analysis suggests that the tri-substituted γ-lactone can be obtained through the CAN-mediated oxidative cleavage. The required hemiacetal (**134**) would come from the chain extension aldol reaction that utilizes the substituted carbenoid and hexanal. The study reported above, in which hexanal was used as an electrophile with the Furukawa carbenoid, was performed in anticipation of this approach to the natural product. Since the γ-heteroatom is removed during the CAN oxidative cleavage, the same β-keto ester, methyl 4-methoxyacetoacetate (**111**), was used again.



Scheme 39. Retrosynthetic Analysis of Phaseolinic Acid **133**

Paraconic acids are a family of trisubstituted γ-butyrolactones with a carboxylic acid group in the β-position. Members of the paraconic acid family possess a wide array of biologically significant activities, including antitumor, antibiotic, antifungal, and antibacterial activities.[73] The natural products can be isolated from various species of lichens, mosses, and fungi. Phaseolinic acid is a metabolite of the fungus *Macrophomina phaseolina* and possesses a pentyl side chain at the 5-position and a methyl group at the 3-position (**135-138**) (**Figure 7**). A number of reported syntheses have appeared in the literature, but many of them have been lengthy, ranging from four to ten steps.[73-79] Amador, et al, published the synthesis of all four diastereomeric methyl esters, which were then hydrolyzed to the carboxylic acids.[73] We anticipated that use of the CAN-mediated oxidation chemistry could provide access to this class of natural products in just two steps from commercially available starting materials. One drawback to our approach is that many previous syntheses have been enantioselective and the chain extension-aldol

approach would not offer such control. Even with no absolute sterocontrol, this concise method would be an attractive approach to this family of phaseolinic acids.

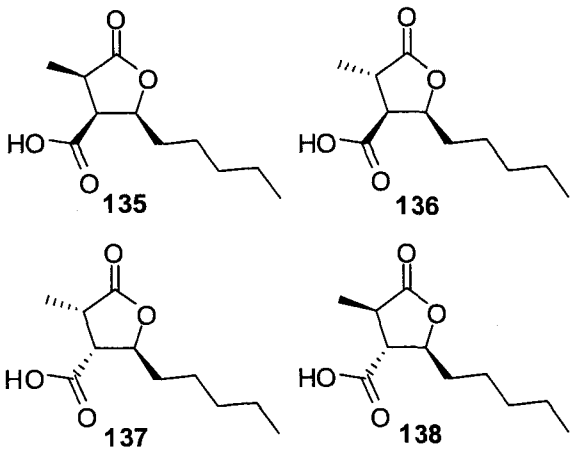
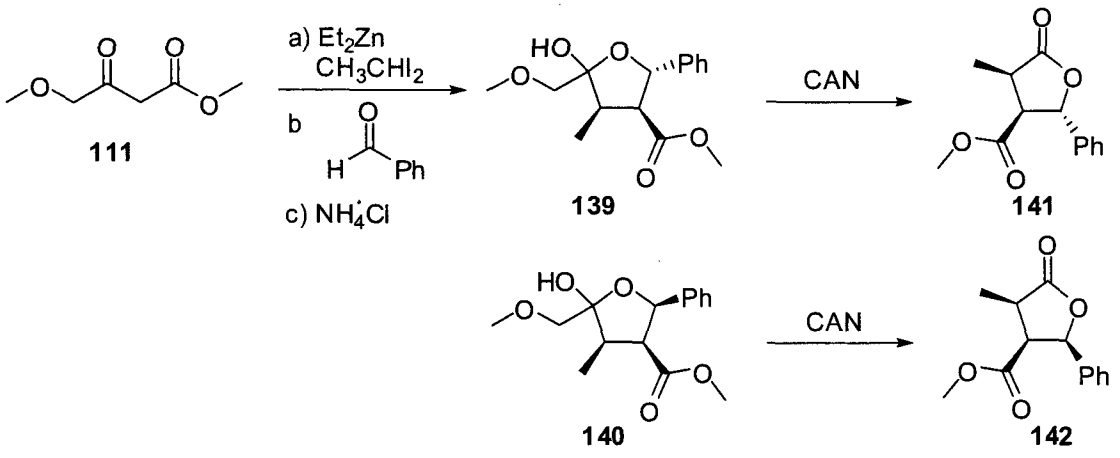


Figure 7. Four Diastereomers of Phaseolinic Acid

Before combining the chain extension-aldol reaction and the CAN-mediated oxidative cleavage reaction in a synthetic approach to the natural product, a model study was proposed. The model study was deemed necessary since the chain extension methodology with the substituted carbenoid was relatively new. The CAN-mediated oxidation chemistry had been optimized with simpler systems, but the same reaction conditions were believed to be suitable for the synthesis of the natural product. However, the tandem chain extension-aldol reaction had never been performed with a substituted carbenoid. Benzaldehyde was selected as a model electrophile due both to its simplicity and successful utility in similar chain extension-aldol reactions. A larger concern was the reactivity of the enolate generated in the chain extension reaction. The chain extension reaction using the substituted carbenoid (derived from 1,1-diiodoethane) was known to be slower than the chain extension reaction using the Furukawa carbenoid. In fact, Lin, McGinness, and Wilson found it necessary to add a second portion of substituted

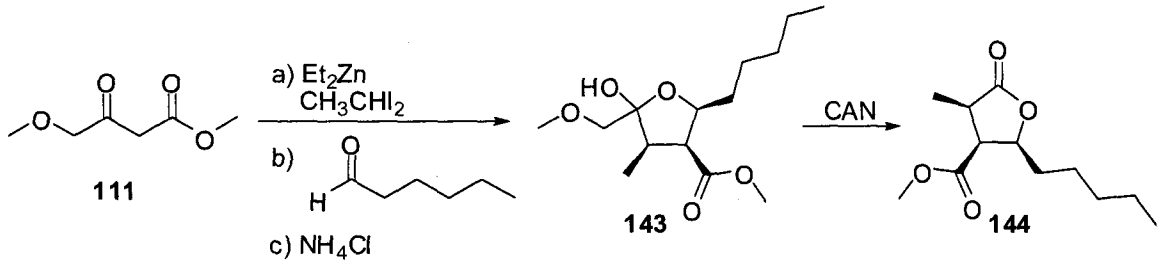
carbenoid to increase the yields during their initial studies. The same approach for the tandem chain extension-aldol reaction was undertaken and a second portion of substituted carbenoid was added before the aldehyde was added. The aldol portion of the reaction was also allowed to proceed for longer periods of time. In the chain extension-aldol reaction involving the Furukawa carbenoid, the aldol reaction is allowed to proceed for approximately an hour, but the aldol reaction that was initiated by the chain extension with the substituted carbenoid was allowed to react between six and fifteen hours, depending on the electrophile. The extended reaction times were determined by monitoring the consumption of the starting materials by TLC and by NMR analysis of the crude reaction mixture when standard reaction times were used.

The mixture of diastereomers were separated via column chromatography and both the major isomer, which was one of the *syn* isomers (**139**) and a minor isomer, one of the *anti*-aldol products (**140**), were oxidized separately to yield their respective γ-lactones (**Scheme 40**). The ratio of diastereomers in the crude reaction mixture of the tandem chain extension-aldol reaction was approximately 1.5:1:1 suggesting there was very little, if any, aldol selectivity. This ratio of products also revealed poor facial selectivity of the enolate. Although the methyl esters **141** and **142** had not been reported in the literature, the ethyl esters had been reported.[80] Comparison of the NMR chemical shift data for the ethyl esters found in the literature to the NMR data for the methyl esters produced via the chain extension-aldol reaction and CAN oxidation allowed the assignment of **139** as the major product in the chain extension-aldol reaction and **140** as one of the minor products.[80] The third diastereomer was never successfully isolated through chromatography.



Scheme 40. Synthesis of Tri-Substituted γ-Lactones **141** and **142** Derived from Benzaldehyde

After proving that the tandem chain extension-aldol process with the substituted carbenoid and benzaldehyde followed by the CAN oxidation provided access to the desired γ-lactones, an attempt was made to synthesize the phaseolinic acids. The chain extension aldol reaction with hexanal was surprisingly selective towards the formation of one diastereomer, something that was not seen with the benzaldehyde reaction. One would predict that the aldol stereochemistry would be *syn* selective based on trends observed in previous studies, but the methyl group's influence on the facial selectivity of the aldehyde was unclear. After oxidation of the purified single aldol product **143** with CAN and comparison to characterization data reported in the literature, it was determined that the *cis, cis* lactone **144** was formed (**Scheme 41**).[73] Interestingly, this lactone could only be synthesized if hemiacetal **143**, resulting from an *anti* selective aldol reaction, was formed.



Scheme 41. Synthesis of *cis, cis*-Phaseolinic Acid Derivative **144**

This stereochemical assignment was unanticipated for a couple of reasons. First, the *syn* aldol product is usually the major product in chain extension-aldol reactions involving β-keto esters, presumably due to the biased formation of a *Z*-enolate and reaction through the closed transition state. In order to rationalize the unanticipated result, a closed transition state involving the *Z*-enolate was considered with both an axial approach of the aldehyde R-group and normally preferred pseudo-equatorial approach (**Figure 8**). When applying the closed transition state model, the aldehyde is proposed to approach the *Z*-enolate with its R-group in the pseudo-equatorial position which leads to the *syn*-aldol product (**145**). But in the proposed chair conformation operative in the chain extension reaction involving the substituted carbenoid, the alkyl chain of the aldehyde appears to interact with the additional steric bulk provided by the methyl group. On the other hand, if facial selectivity of the aldehyde were reversed and the aldehyde approached with the alkyl chain (R-group) in the axial position to avoid steric interactions with the alkyl group, the product would possess the *anti*-aldol stereochemistry (**146**), which was observed in the reaction. The steric interactions between the alkyl chain and the approaching aldehyde are less of an issue with the

Furukawa carbenoid-mediated reaction. Further studies are needed to understand the reversal of the facial selectivity of the electrophile.

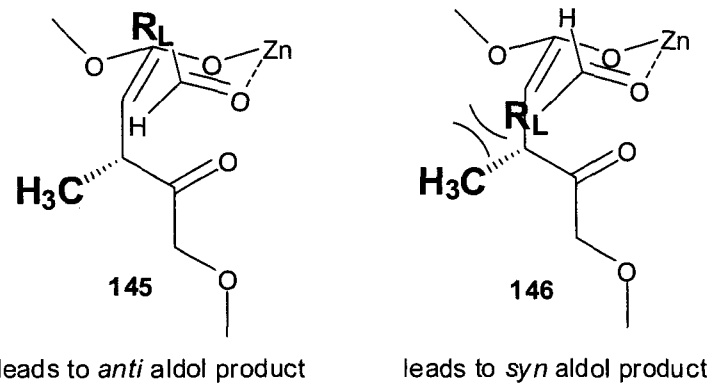


Figure 8. Reversal of Facial Selectivity in Closed Transition State

Based on the experimental results, only one of the two possible *anti*-aldol diastereomers formed in the reaction which led to formation of the *cis, cis*-γ-lactone after treatment with CAN. This suggested the reaction proceeded preferentially on one face of the enolate, presumably with the methyl group away from the aldehyde to avoid steric interactions. If both enolate faces were reacting equally, it would be expected that both of the *anti*-aldol products **143** and **147** would be formed (**Figure 9**). More examples of the tandem chain extension-aldol reaction with the substituted carbenoid would need to be studied to understand more details regarding the facial selectivity of the enolate, but at this point it is apparent that one of the enolate faces is reacting predominantly.

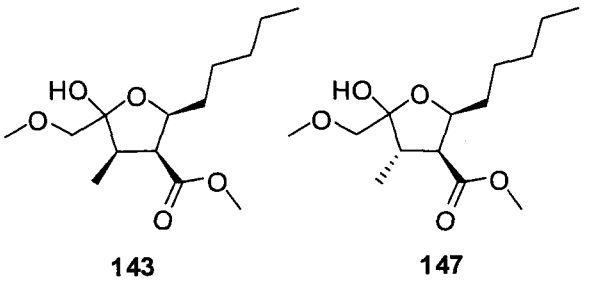
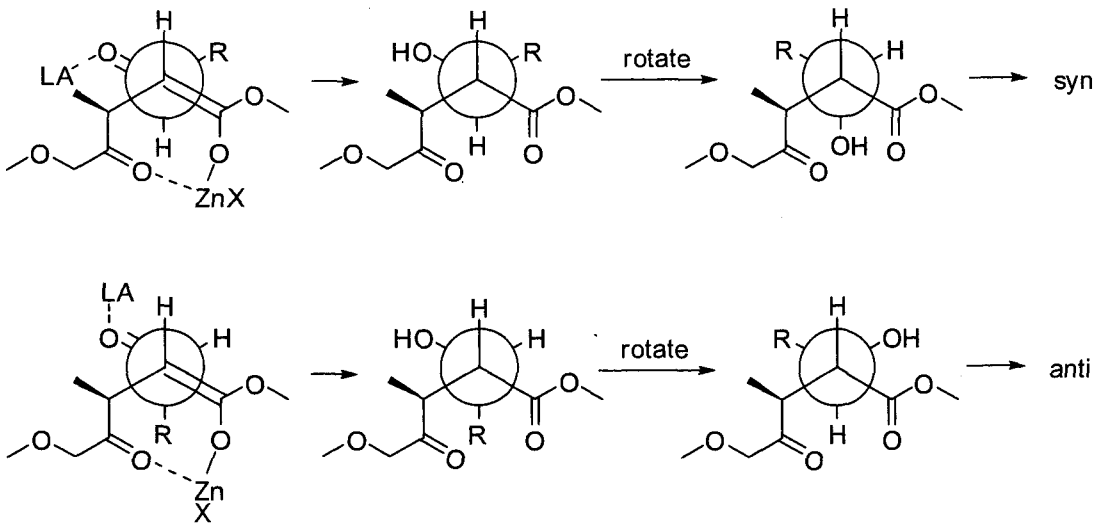


Figure 9. Possible *anti*-Aldol Diastereomers Coming from Facial Selectivity of *Z*-Enolate

Although it is assumed that the tandem chain extension-aldol reaction is proceeding through a closed transition state, there is the possibility that an open transition state is operative. Since the *Z*-enolate would still be the preferred enolate generated in the chain extension of methyl 4-methoxyacetoacetate, steric interactions involving the Lewis acid or aldehyde chain would play a significant role in determining the stereoselectivity of a reaction that proceeds through an open transition state. It is unclear to as which steric interaction is less favored, since both would presumably play a role **(Scheme 42)**.



Scheme 42. Open Transition State of *Z*-Enolate Leading to *syn* and *anti* Products

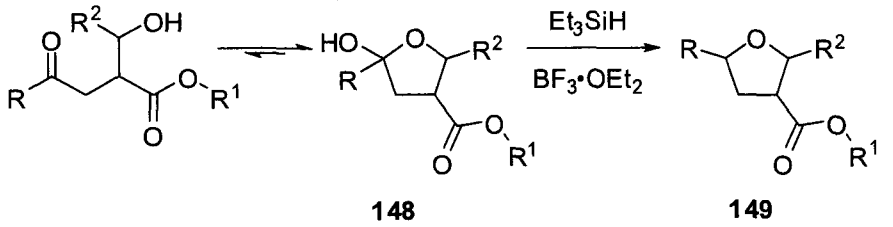
Using this CAN-mediated oxidation chemistry, *cis, cis* phaseolinic acid methyl ester **144** was obtained in just two steps with a 39% yield from commercially available starting material.[67] The chain extension-aldol reaction, followed by the oxidation to the γ-lactone, provides rapid access in reasonable yields to this class of natural products. Also, the zinc-mediated chain extension-aldol reaction, in which a substituted carbenoid is used in the chain extension reaction, has proven to be a powerful reaction, creating three stereocenters in one tandem process. Previous work in the Zercher research group has optimized the conditions of the tandem processes with the Furukawa-modified reagent, but tandem processes using the substituted carbenoid are still being optimized. By control of the stereochemistry of the β-methyl-substituent, either enantioselectively or diastereoselectively, and control of the diastereoselectivity of the aldol reaction, this method could become an attractive and versatile synthetic method.

CHAPTER III

SYNTHESIS OF β-PROLINE DERIVATIVES THROUGH THE TANDEM CHAIN EXTENSION-IMINE CAPTURE REACTION

Incorporation of Carbon-Nitrogen Electrophiles

Much of the previous work in the Zercher research group has centered on using carbon-oxygen π-systems as electrophiles in the tandem chain extension reaction. The diastereoselectivity of the tandem chain extension reaction has been heavily studied with many β-keto systems, and each group on the backbone can be controlled by careful selection of starting materials. When electrophiles such as aldehydes are used, there is an equilibrium between the open and closed form of the α-substituted γ-keto ester, and usually the closed form, a hemiacetal (**148**), is favored. These hemiacetals can be reduced using triethylsilane in the presence of a Lewis acid to provide access to tetrahydrofuran backbones (**149**) with the establishment of an additional stereocenter (**Scheme 43**).[81]



Scheme 43. Synthesis of Tetrahydrofuran Derivatives

Little research has been performed on carbon-nitrogen π-systems as electrophiles in conjunction with the chain extension methodology, even though the backbone obtained through the incorporation of a carbon-nitrogen system followed by reduction would provide access to a β-amino acid, β-proline **150**. If the same tandem chain extension processes can be utilized, the β-proline backbone **151** should be obtainable in a diastereoselective process in only a few steps (**Figure 10**). It is also unclear as to whether or not the carbon-nitrogen π-systems would provide similar diastereocontrol to that observed with carbon-oxygen electrophiles. Furthermore, there are several concerns regarding the use of imines that makes their involvement different from the typical tandem chain extension-aldol chemistry. These concerns will be discussed below.

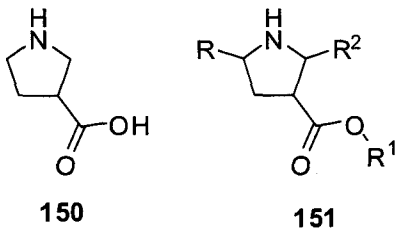
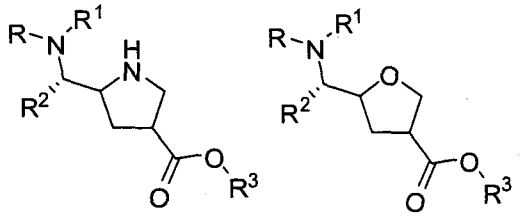


Figure 10. β-Proline and β-Proline Derivative Obtained Through Tandem Chain Extension Chemistry and Reduction

β-Amino acids have recently received a lot of attention due to their service as the fundamental building blocks of β-peptides. Only one naturally occurring β-amino acid, β-alanine, has been identified, which is why β-peptide-based antibiotics are being pursued as ways of evading antibiotic resistance.[82, 83] β-Amino acid derivatives have been used as building blocks for the synthesis of many pharmaceuticals.[84]

Even though many peptides utilize proline residues to control the conformation of peptides, β-proline is not used for this purpose. β-Proline has the potential to control the structure of β-peptides.[85-88] Additionally, β-proline has found use in the synthesis of receptor ligands,[89-91] in compounds of medicinal interest,[92, 93] and in fluorescent agents.[94, 95] One major challenge to the use of β-proline and derivatives is that few efficient synthetic approaches have been described.[96-98]

β-Proline peptide mimics (**152**) are important because they are non-hydrolyzable and linear, which results in a conformationally rigid backbone, similar to the embedded tetrahydrofuran isosteres (**153**) (**Figure 11**).[99] The backbone appears to mimic the peptide backbone so that the carbonyl terminus and the amine terminus of the dipeptides align in a traditional staggered peptide conformation. Finally, the carbonyl and the amine terminus are easily functionalizable for longer peptide chains and molecules.[100]

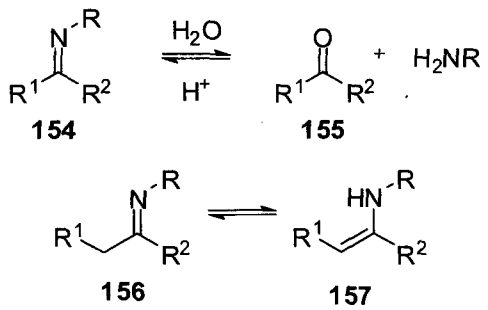


152 **153**

Figure 11. β-Proline Dipeptide Mimic **152** and Embedded Tetrahydrofuran Isostere **153**

Activated Imines

In order to obtain these β-amino acid backbones, the electrophile in a tandem zinc-mediated chain extension reaction could be an iminium ion, which was previously studied in the group,[44] or an imine. The use of imines in the tandem reaction sequence presents many challenges. Imines (**154**) are not as electrophilic as ketones and aldehydes; furthermore, imines are often prone to decomposition by hydrolysis to their aldehyde derivative **155**. Many imines (**156**) exist in equilibrium with an enamine tautomeric form (**157**), and the enamine is often favored (**Scheme 44**). The enamine presents a problem, because their chemistry is drastically different from an imine. Each of these concerns needs to be addressed when using imines as electrophiles.



Scheme 44. Imine Hydrolysis and Enamine Tautomerization

One approach to address these concerns is through the use of activated imines. Activated imines are more resistant to enamine tautomerization and more electrophilic than unactivated imines, because the activating groups inductively withdraw electron density from the carbon of the π-system. Some very common activated imines are *N*-acylimines (**158**),[101] *N*-acyliminium ions (**159**),[102] *N*-sulfonylimines (**160**),[103] *N*-sulfinimines (**161**),[104] and *N*-phosphinoylimines (**162**) (**Figure 12**).[105]

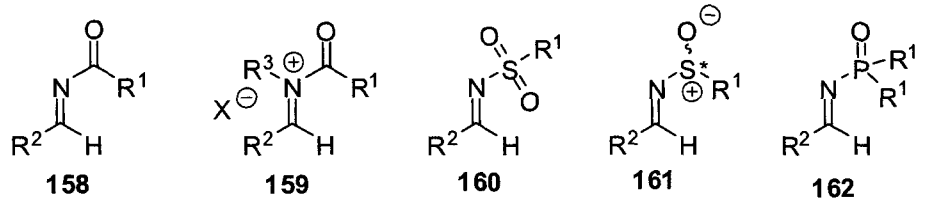
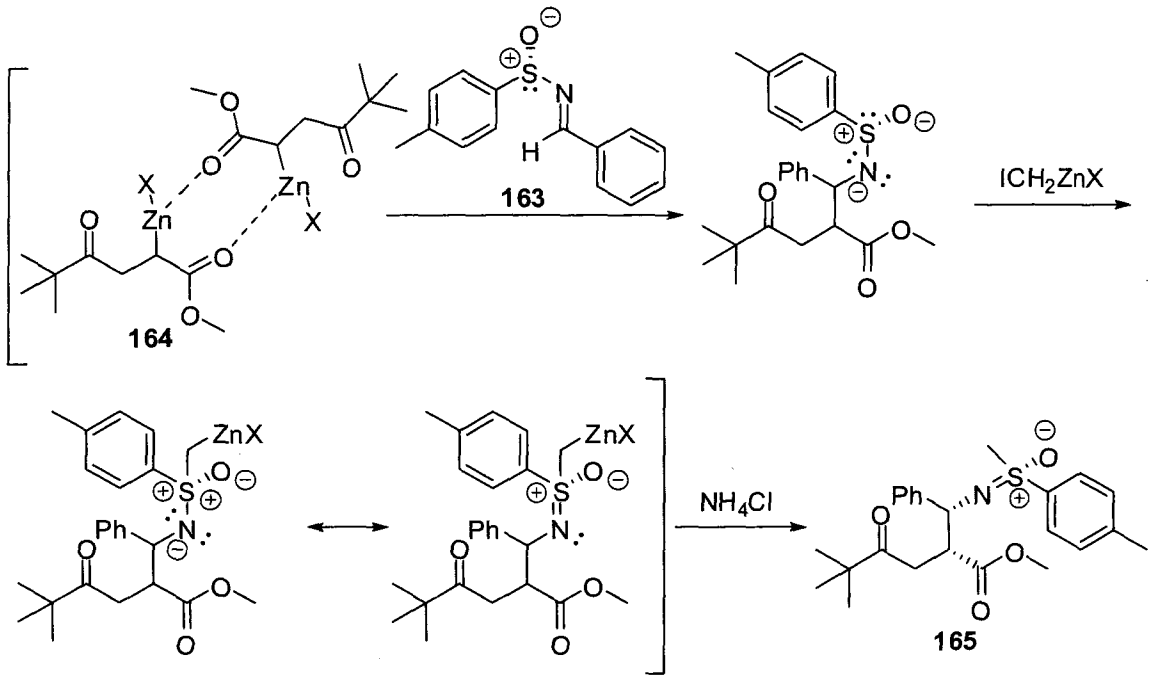


Figure 12. Classes of Activated Imines in the Literature

N-Acylimines (**158**) and *N*-acylimium ions (**159**) are typically unstable due to rapid hydrolysis, polymerization, or tautomerization to the enamine and are rarely isolated and characterized. *N*-Sulfonylimines (**160**) are less reactive then the *N*-acyl and *N*-acyliminium ions and can be isolated and characterized. However, the sulfonamides arising from nucleophilic attack at the imine carbon are very stable and deprotection through cleavage of the nitrogen-sulfur bond is difficult. *N*-Sulfinimines (**161**) have found utility in organic synthesis because they can be synthesized in an enantiomerically pure form and used in enantioselective syntheses. Sulfinimines are also easily deprotected under acidic conditions.

Sulfinimine **163** was previously studied in a tandem chain extension reaction by Puchlopek.[100] Enantiomerically pure sulfinimine[106] was synthesized and added to the enolate generated in the zinc-mediated chain extension reaction (**164**) (**Scheme 45**). After purification and analysis, the desired product was not formed. Analysis by x-ray crystallography confirmed the product contained an additional methyl group attached to the sulfur (**165**), coming presumably from excess zinc carbenoid. The resulting sulfoximine was difficult to deprotect, which would be required for formation of a β-proline derivative. It was apparent that the sulfinimine would react with the excess

carbenoid used in the chain extension; therefore this mandated that another activated imine be identified for the tandem chain extension reaction.



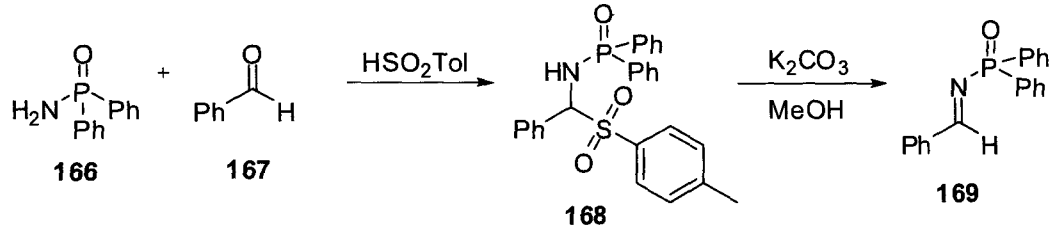
Scheme 45. Sulfinimine **163** and the Product Obtained from Chain Extension

N-Phosphinoylimines

A review published in 2005 focused on *N*-phosphinoylimines (**162**) and their versatility in organic synthesis.[105] *N*-Phosphinoylimines are attractive activating groups for imines for a number of reasons. First, they are usually more stable than *N*-acyl or *N*-sulfonylimines and can often be isolated and purified. Second, the moderate reactivity of *N*-phosphinoylimines is often useful in promoting asymmetric reactions. Lastly, the phosphinamide products can be deprotected easily under acidic conditions. One major drawback for these types of activated imines, and most others, is that while aromatic imines have been well studied, little work has been reported on the preparation of aliphatic systems. This is because of the previously discussed enamine tautomerization;

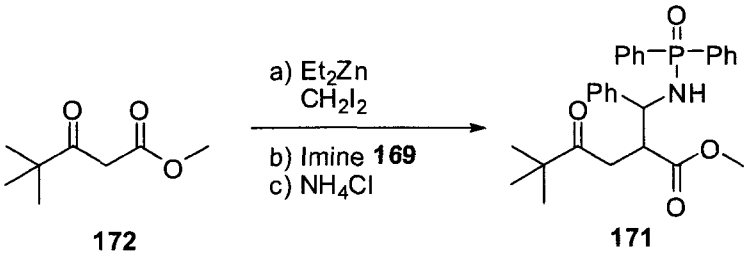
aromatic imines do not have an α-proton, so tautomerization is not a concern. The synthesis of aromatic *N*-phosphinoylimines has been described in the literature.[107]

The initial attempts to synthesize β-proline derivatives via the chain extension-imine capture reaction were initiated using these *N*-phosphinoylimines as the electrophiles. Commercially available *N*-phosphinamide **166** was reacted with benzaldehyde (**167**) to yield sulphone **168**. This isolated intermediate **168** was then reacted with base to form the elimination product, *N*-phosphinoylimine **169**. The two step sequence provided access to the desired imine in reasonable yields (52% overall) (**Scheme 46**).



Scheme 46. Synthesis of *N*-Phosphinoylimine **169**

Imine **169** was used in the tandem chain extension-imine capture reaction with methyl pivaloylacetate **170**, but very little α-substituted γ-keto ester **171** was formed (**Scheme 47**). The major product in the crude reaction mixture was the chain extended compound, a γ-keto ester. Only trace amounts of product were observed by ^{1}H NMR, most likely because of the decreased reactivity of the electrophile. In order to determine whether these imines were suitable for reacting with the zinc enolate generated in the chain extension reaction, control studies were performed.

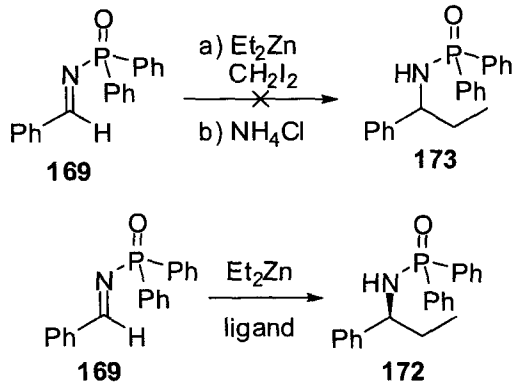


172 **171**

Scheme 47. Chain Extension-Imine Capture Reaction with *N*-Phosphinoylimine **169**

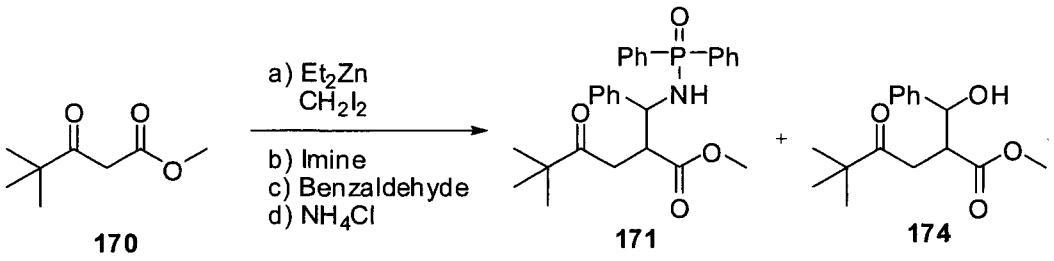
The major product characterized by ^1H NMR was the γ-keto ester resulting from the chain extension of methyl pivaloylacetate. Formation of this product suggested that the latent enolate produced during the chain extension reaction could have been quenched before it had the chance to react with the imine. Another possibility was that the imine was reacting with the enolate too slowly. Additionally, there was the possibility of zinc carbenoid reacting with the imine, causing it to decompose, leaving the latent enolate unreacted until the acidic quench. Each of these hypotheses were tested.

The Furukawa carbenoid was formed, added to the *N*-phosphinoylimine (**169**), and allowed to stir for 16 hours. No reaction between the two reagents was observed (**172**), which suggested that excess carbenoid was not responsible for decomposing the imine. It is important to note that the original paper[107] reported the addition of diethyl zinc in the presence of a chiral ligand into a *N*-phosphinoylimine (**173**). Even though the zinc carbenoid is electrophilic, the opportunity for an ethyl ligand bound to the zinc to add to the imine appeared possible; however, no evidence of this type of reaction was observed in this control study (**Scheme 48**).



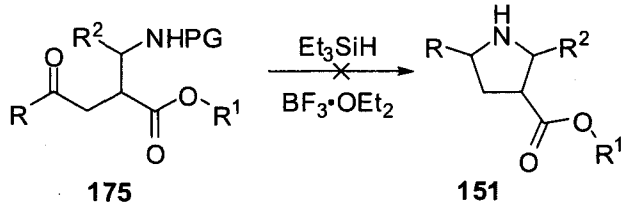
Scheme 48. Reported Addition of Diethyl Zinc to Imine and Control Study with Zinc Carbenoid

It was also determined that active enolate was still present after 2 hours of reaction time. This was revealed by the addition of benzaldehyde to a chain extension reaction that had been exposed to the *N*-phosphinoylimine for 2 hours (**Scheme 49**). The aldol product (**174**) was determined to be the major product by ^{1}H NMR analysis. This result suggested the imine was not being captured by the enolate (**171**), because the imine was not sufficiently electrophilic. The time period for the reaction of enolate with the imine was extended from a few hours, standard for aldehydes and ketones, to 3-5 days. After 3-5 days of reaction time, the yields were still very low and the γ-keto ester was still the major product. Nevertheless, formation of the imine capture product was occurring and studies on the isolation, characterization, and further transformation of the product were undertaken.



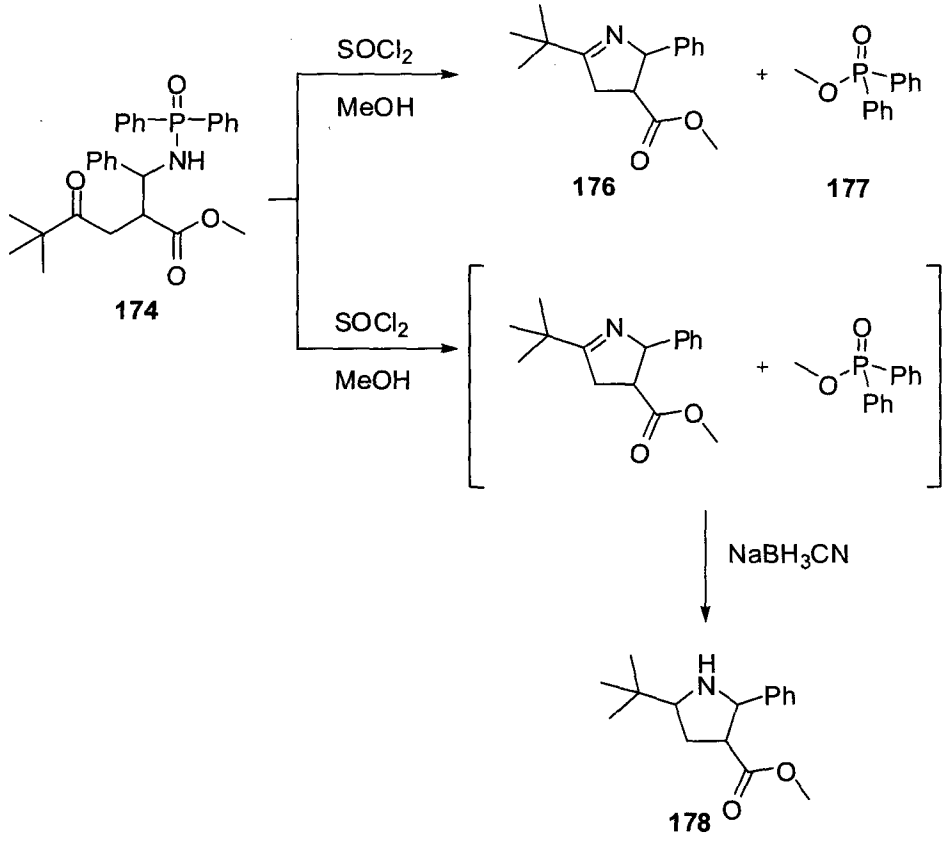
Scheme 49. Verification of Active Enolate in Solution

One major difference between the tandem chain extension-aldol reaction and the tandem chain extension-imine capture reaction involving methyl pivaloylacetate is that the product exists exclusively in the open form when imines are used as electrophiles. Typically with aldehydes, the hemiacetal form is the more stable form of the product. No ketone is observed by ^{13}C NMR, and resonances for a hemiacetals are usually observed. When activated imines are used, the open form appears to be favored (**175**). This determination is supported by the presence of a ketone resonance in the ^{13}C NMR and no evidence of a hemiaminal resonance. This observation suggested that use of the triethylsilane reduction of the hemiaminal in an effort to form the β-proline (**151**) may be inefficient (**Scheme 50**). An alternative approach to synthesize the desired target was required.



Scheme 50. Open Form of Imine Capture Product

In an effort to convert the β-amino acids to the desired β-proline derivatives, alternative deprotection and reduction reactions were attempted. Separation of the deprotected cyclic imine **176** from the methyl diphenylphosphinate byproduct **177** of the reaction was difficult to perform by extraction or column chromatography. Since the deprotection of the phosphinamide **174** was done under acidic conditions and the sodium cyanoborohydride reduction of the cyclic imine **176** was to be performed under acidic conditions, a one-pot protocol to facilitate the formation of the product (**178**) and its separation from byproduct **177** was proposed (**Scheme 51**).

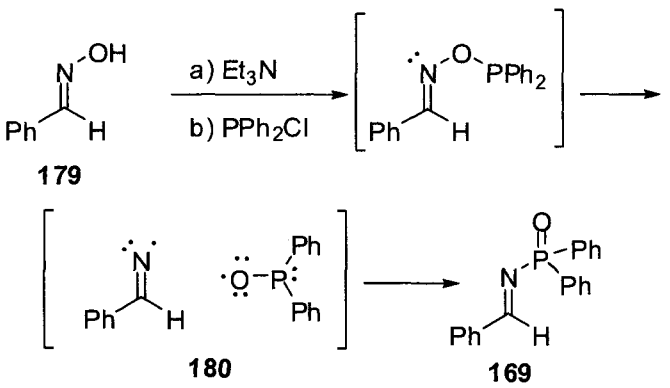


Scheme 51. One-Pot Deprotection and Reduction

Through application of a one-pot deprotection-reduction protocol, β-proline derivative **178** was obtained in just two steps from the *N*-phosphinoylimine. Studies by

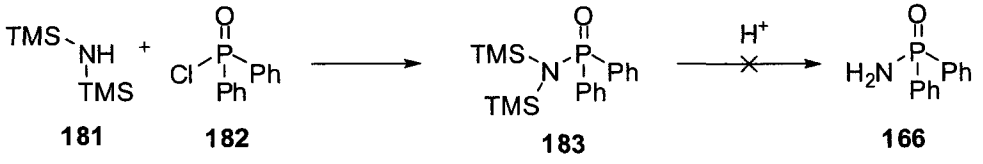
NMR revealed the presence of three diastereomers in a 1:4:7 ratio. This ratio was determined by comparing the integrations of the benzylic protons of the products and the identification of the major isomer will be described later.

The starting materials for synthesizing the *N*-phosphinoylimine were quite expensive, so alternative routes were attempted. The long reaction times for *N*-phosphinoylimine formation were also undesired, but no alternatives were described in the literature. Two attempts were made to develop alternative syntheses of the *N*-phosphinoylimine **169**. A radical rearrangement that was used for the synthesis of the same *N*-phosphinoylimine has been reported.[108] This reaction was attractive because the starting materials, oximes, were inexpensive and easy to synthesize. Benzaldehyde was reacted with hydroxylamine hydrochloride to obtain benzaldehyde oxime **179**. This oxime was reacted with triethylamine and chlorodiphenylphosphine at -78 °C and the solution was allowed to warm to room temperature, during which a radical rearrangement (**180**) occurred to afford **169** in low yields with many unidentifiable by-products (**Scheme 52**).



Scheme 52. Radical Rearrangement to Synthesize *N*-Phosphinoylimine **169**

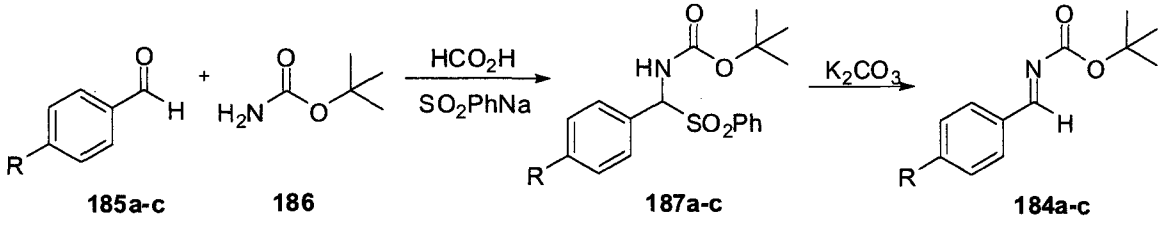
An attempt was made to prepare **166** by reacting 1,1,1,3,3,3-hexamethylsilazane **181** with diphenylphosphinic chloride **182**. Analysis by NMR suggested the presence of **183**, but the removal of the trimethylsilyl groups to obtain **166** proved to be unsuccessful under acidic conditions; however, this reaction was not studied in detail (**Scheme 53**).



Scheme 53. Attempted Synthesis of *N*-Phosphonamide **166**

N-Boc Imines

The chain extension-imine capture reaction that utilized *N*-phosphinoylimines was expensive, low yielding, and required long reaction times. All of these issues rendered the chemistry undesirable. A new protocol in the literature reported the utilization of *N*-Boc imines[109] as electrophiles for a very similar reaction as had been reported for the *N*-phoshinoylimines. The synthesis of *N*-Boc imines (**184a-c**) involves a two-step sequence starting from an aromatic aldehyde **185** and commercially available *tert*-butyl carbamate **186**. The intermediate sulphone (**187**) is reacted with base to afford *N*-Boc imine (**184a-c**) in modest yields (43-55%) (**Scheme 54**).

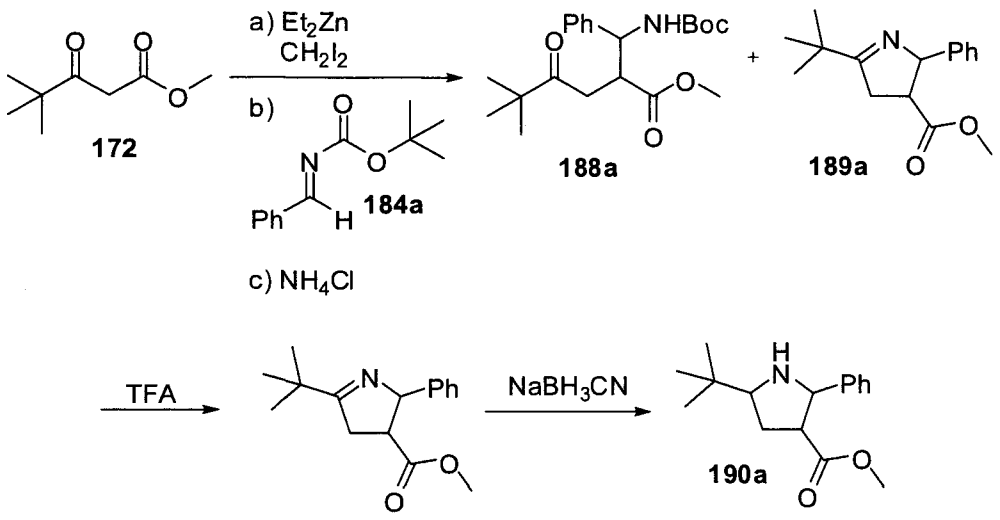


a) R = H
b) R = OCH_3
c) R = CH_3

Scheme 54. Synthesis of *N*-Boc Imines **184a-c**

The newly formed benzaldehyde-derived imine **184a** was subjected to the enolate produced in a chain extension reaction using same Furukawa-modified Simmons-Smith reagent. The *N*-Boc imine was found to be more reactive then the previously studied *N*-phosphinoylimine. After carefully monitoring the reaction by thin layer chromatography, the reaction appeared to have gone to completion in just 12 hours, compared to a reaction time of 3-5 days when using the *N*-phosphinoylimines. The yield of the reaction was also notably higher. Approximately 75-85% of the anticipated mass was recovered rather then 30-40% mass recovery with the *N*-phosphinoylimines.

It was observed by ^{1}H and ^{13}C NMR that the crude reaction mixture contained an approximate 1:1 ratio of the desired α-substituted γ-keto ester **188a** and the deprotected cyclic imine **189a**. The Boc protecting group, not surprisingly, appears to be labile under the Lewis acidic conditions. This side reaction was not viewed as a major concern, since the next step of the synthetic sequence would involve deprotection of the Boc group under acidic conditions. The crude reaction mixture product in the chain extension-imine capture reaction was subjected to trifluoroacetic acid (TFA), which is a method of choice for removal of a Boc group,[110] rendering cyclic imine **189a**. Cyclic imine **189a** was then subjected to sodium cyanoborohydride in acidic methanol,[111] which resulted in formation of β-proline derivatives (**190a**).



Scheme 55. Synthesis of β-Proline Derivative **190a** with *N*-Boc Imine **184a**

The ^{1}H NMR spectra of the crude reaction mixtures of the β-proline derivatives had some interesting differences when comparing the products synthesized from the *N*-phosphinoylimine and the *N*-Boc imine. The doublets associated with the benzylic protons in the β-proline derivatives revealed that the ratio of diastereomers formed in the two reactions was notably different. The ratio obtained in the reaction of the *N*-Boc imine was approximately 9:1:2, which was not only more selective than the reduction of the cyclic imine derived from the *N*-phospinoylimine, but the major diastereomer formed in the reaction sequence was different.

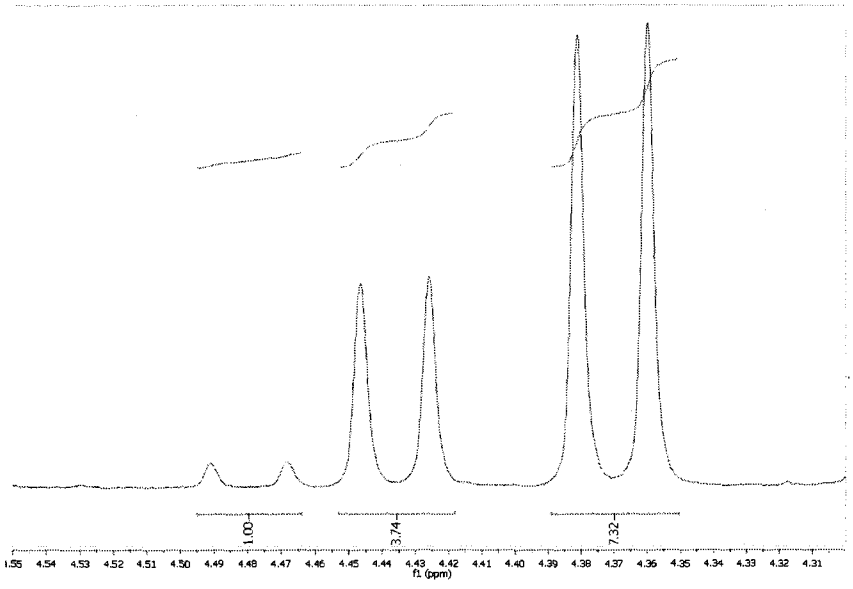


Figure 13. Benzylic Protons from Crude Reaction Mixture of Chain Extension-Imine Capture with *N*-Phosphinoylimine

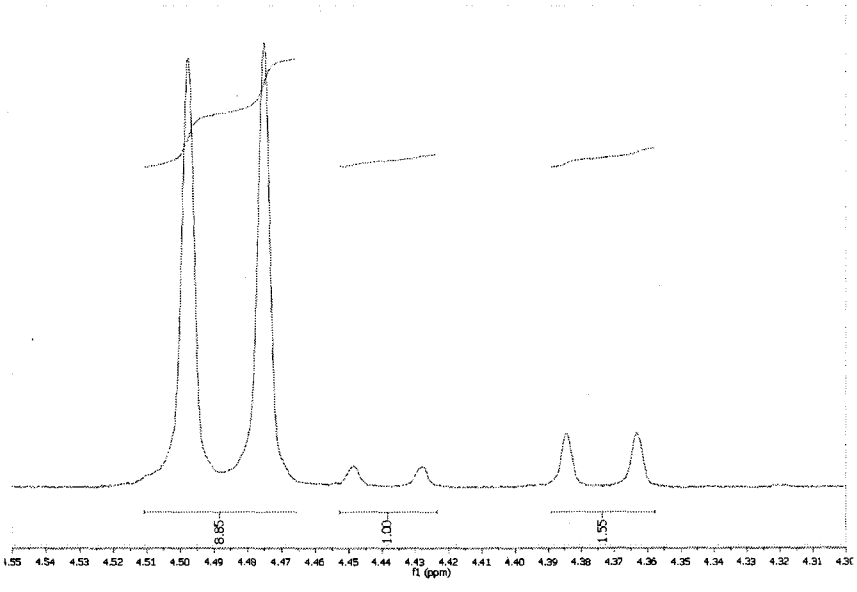
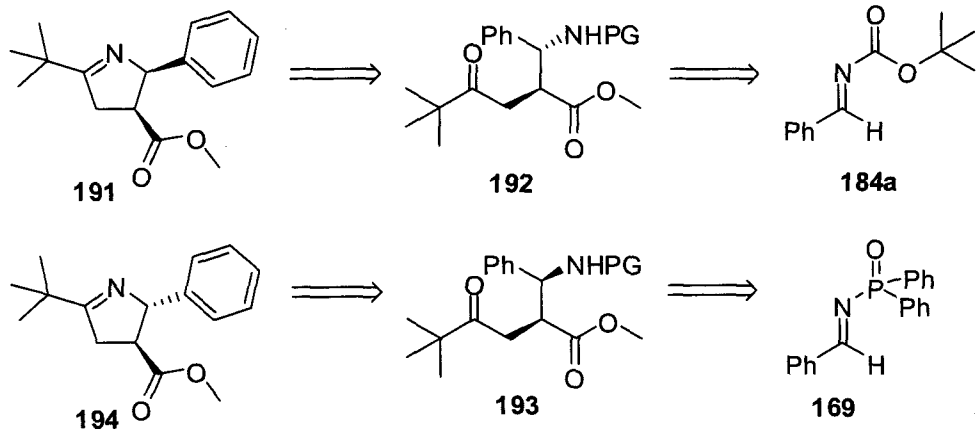


Figure 14. Benzylic Protons from Crude Reaction Mixture of Chain Extension-Imine Capture with *N*-Boc Imine

The zinc-mediated chain extension-imine capture reaction seemed to be a determining factor in the diastereocontrol, since two of the three stereocenters are set in that reaction. As previously mentioned, both the *syn* and *anti*-aldol products are present in open and closed (hemiacetal) forms. The *syn*-aldol product leads to a *trans* relationship between the substituents in the hemiacetal form and the *anti*-aldol leads to the *cis*-substituted hemiacetal. One major difference between the imine capture chemistry and the aldol chemistry is that no open chain-hemiacetal equilibrium exists with the imine capture products. However, a cyclic imine is generated only after the deprotection of the activating group, and the imine contains a carbon-nitrogen π-bond, which is sp^2 hybridized and planar. One would expect greater selectivity in the reduction of the cyclic imine if both of the substituents were on the same face of the molecule, providing an open face for hydride attack with minimal steric interactions. In order for both substituents to exist in the *cis* relationship on the cyclic imine (**191**), the imine capture product would have to have been formed with the *anti* relationship (**192**) (aldol terminology). If the *syn* products (**193**) (aldol terminology) were formed in the imine capture reaction, the cyclic imine would have its substituents in the *trans* relationship (**194**). Little bias in the attack of the hydride on **194** would be anticipated, since both sides of the molecule possess some steric bulk. A *cis* disubstituted cyclic imine (**191**) would be expected to provide bias for a diastereoselective hydride addition. Decreased steroselectivity was observed when the *N*-phosphinoylimine (**169**) was used in the tandem reaction process, which presumably favored the *syn* imine capture product. Much better selectivity was observed in reduction of the cyclic imines derived from the *N*-Boc

imine (**184a**), presumably due to formation of the *anti* diastereomer in the imine capture reaction (**Scheme 56**).



Scheme 56. Cyclic Imine Diastereomers Coming from Each Imine

This hypothesis proved to be correct when an x-ray grade crystal of the major product formed in the chain extension imine capture reaction using benzaldehyde-derived *N*-Boc imine **184a** was analyzed. The stereochemical relationship was, in fact, *anti*, which provided access to the cyclic imine with the *cis* relationship of the two substituents (**Figure 15**). An X-ray grade crystal of the major product derived from *p*-tolualdehyde was also analyzed. The same *anti* relationship for the imine capture reaction was confirmed.

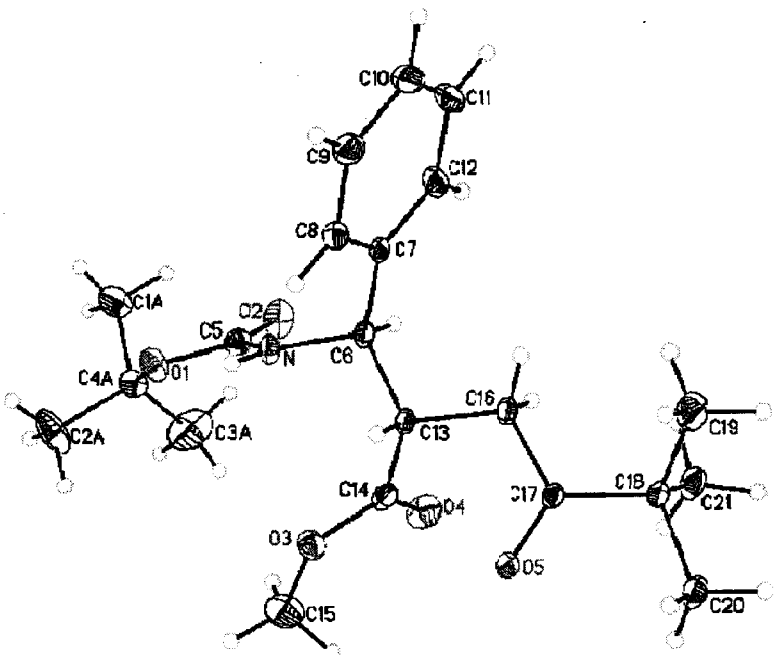


Figure 15. X-Ray Crystal Structure of Chain Extension-Imine Capture Product with Methyl Pivaloylacetate (**172**) and Benzaldehyde-derived *N*-Boc Imine **184a**

Rationalization of Diastereoselectivity

Attempts were made to understand the diastereoselectivity differences between the two different activated imines. The first hypothesis dealt with an *E* to *Z* isomerization of the imine (**Scheme 57**). If one of the imines reacted via the *E* geometry (**195**) and the other were reacting via the *Z* geometry (**196**), one would expect different diastereoselectivity to be observed. Although the aldehyde-derived *N*-phospinoylimines are believed to be predominantly in the *E* geometry based on NMR studies,[112] it is known that ketone-derived *N*-phosphinoylimines exist as a rapidly interconverting mixture of *E* and *Z* isomers.[113] The isomerization of either of the activated imines is a possibility.

195 196

Scheme 57. *E* to *Z* Isomerization of the Activated Imines

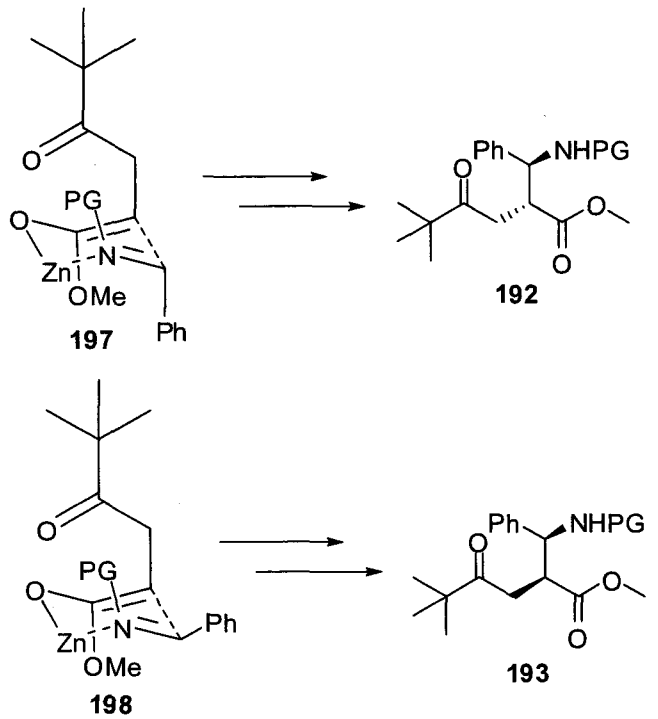
In order to investigate this hypothesis, some simple computational experiments were performed. The energies of the *E* and *Z* isomers of each imine were calculated at the HF 3-21G* level of theory (**Table 3**). Very little difference in energy was observed between the *E* and *Z* *N*-phosphinoylimines. A much larger energy difference exists for the *N*-Boc substituted imines. The barrier of inversion was slightly lower for the *N*-phosphinoylimine than the *N*-Boc imines. The transition state for the interconversion of the two isomers involves nitrogen inversion, as opposed to π-bond rotation.

Imine	***E* (kcal/mol)**	**T.S. (kcal/mol)**	***Z* (kcal/mol)**
N-Phosphinoyl	0	+11.45	+1.82
N-Boc	0	+13.89	+5.56

Table 3. Calculations of *E* to *Z* Isomerization at HF 3-21G*

If the isomerization of imine was taking place and if the imine capture was proceeding through a closed transition state, the imine reacting in the *E*-conformation (**197**) would provide access to the *anti* imine capture product (**192**). If the imine was reacting in the *Z*-isomer, the product formed would be the *syn* imine capture product. The computational results reveal that the *N*-phosphinoylimine has a lower isomerization energy barrier and also possesses a lower energy difference between the two isomers. Since the observed diastereoselectivity of the *N*-phosphinoylimines is predominantly *syn*

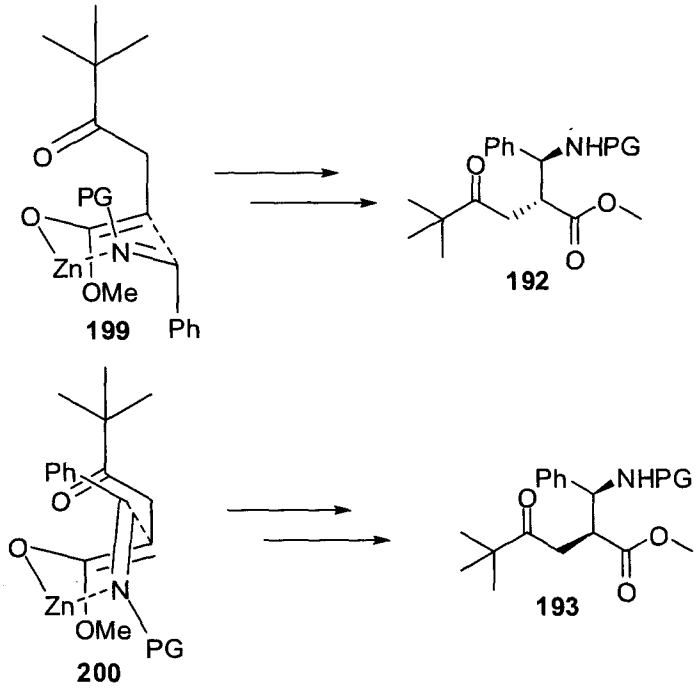
(**193**), a hypothesis can be proposed in which the *N*-phosphinoylimine isomerizes to the *Z*-imine and reacts through a closed transition state (**198**) to give the *syn* product (**Scheme 58**). However, the energy barrier for interconversion of the *E* and *Z* isomers is easily surmountable at the reaction temperature. Diastereoselectivity must be evaluated at the aldol transition state.



Scheme 58. *E* and *Z* isomers of Activated Imines Leading to *syn* and *anti* Products

Previous research on chain extension-aldol reactions and literature precedence[114-116] for the activated imines has resulted in a proposal that the aldol reactions are proceeding through chair-like transition state using a *Z*-enolate. The analogous electronic structure of the imines suggests the possibility of a similar transition state operating in the chain extension-imine capture reaction. This would likely be the case because the imines would need to be Lewis acid activated by the zinc enolate. The A-values of each of the

activating groups are drastically different. A $P(O)Ph_2$ group has an A-value of 2.46[117] and a Boc group is close to 1.2. The A-value of a Boc group was not found, but a reasonable comparison to an isopropyl ester was made.[118] By considering the chair transition state (**199**) of each reaction involving the *E*-imine, unfavorable steric interactions between the activating group and the keto chain would increase with increasing size of the activating group. A significant amount of 1,3-diaxial strain would appear regardless of the size of the group, but a very large group would presumably make the chair transition state even more disfavored. In order to relieve this strain and avoid the steric interactions, the reaction could react through a twist-boat conformation (**200**) (**Scheme 59**).



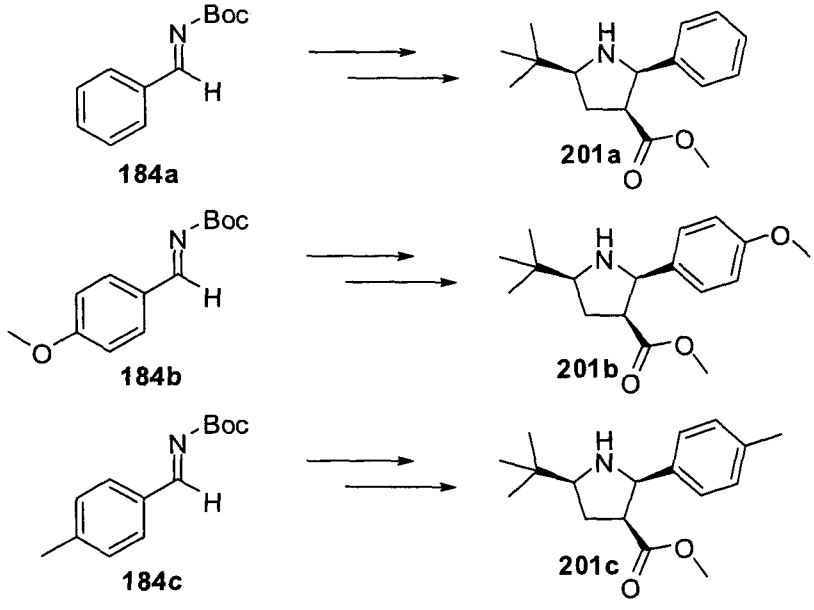
Scheme 59. Chair and Twist-Boat Conformations

Since the twist-boat conformation is typically higher in energy than the chair conformation, there would have to be a significant energetic reasons for the imine to react

in that fashion. If the activating group is reasonably small, such as the Boc group, the chair is most likely the conformation in which the reaction will take place. A large activating group, like the $P(O)Ph_2$ group, may induce a conformational change in the transition state, and the result would be formation of the *syn*-aldol product.

Although the chain extension-imine capture reaction is believed to proceed through a closed transition state, it is possible that the reaction proceeds through an open transition state. If both of the imines reacted in different orientations in an open transition state, they would lead to different diastereomers.

Even without a definitive rationale for the dramatic change in diastereoselectivity caused by the two imines, a goal was established to understand the scope of the *N*-Boc imine capture chemistry. Benzaldehyde, *p*-methoxybenzaldehyde, and *p*-tolualdehyde imines (**184a-c**) were all synthesized[119] and successfully used as electrophiles in the chain extension imine capture reaction with methyl pivaloylacetate. Three different β-proline derivatives (**201a-c**) were produced (**Scheme 60**).



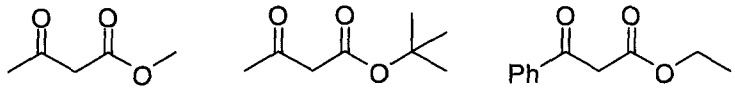
Scheme 60. Major Diastereomers of β-Proline Derivatives from Methyl Pivaloylacetate

The stereochemistry of the major products produced with benzaldehyde and *p*-tolualdehyde derived imines were both verified by x-ray crystallography. Similar diastereocontrol in the preparation of β-proline derivatives suggests that the *p*-methoxybenzaldehyde-derived imine reacted to produce an *anti* aldol-like stereoisomer in the chain extension-imine capture reaction.

It is important to note that the purification of these β-proline derivatives and the intermediates were very difficult and often not completely successful. The products often streaked down the chromatography column and product was invariably lost during flash chromatography on both silica and alumina; therefore, the yields of purified intermediates were reduced during each chromatographic purification. Mass recovery of the crude reaction mixture was often good, with the presence of only minor amounts of impurities observable by NMR analysis, but the yields of purified products were much lower than desired. Obtaining completely clean product was very challenging; however, with few alternatives, flash chromatography was still the best way to purify these oils.

Expansion of Methodology

Different β-keto esters, methyl acetoacetate **202**, *tert*-butyl acetoacetate **203**, and ethyl benzoylacetate **204**, were subjected to the chain extension imine capture conditions, but the results were mixed (**Figure 16**). None of these β-keto esters (**202-204**) provided the desired imine capture product and many unidentified by-products were formed in the reaction.

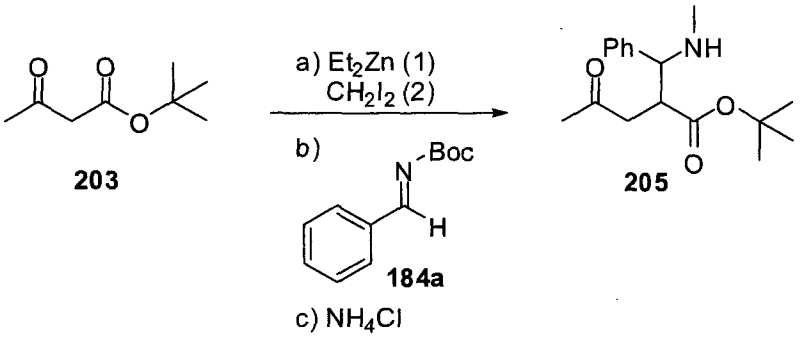


202 203 204

Figure 16. Other β-Keto Esters Subjected to the Chain Extension-Imine Capture Reaction

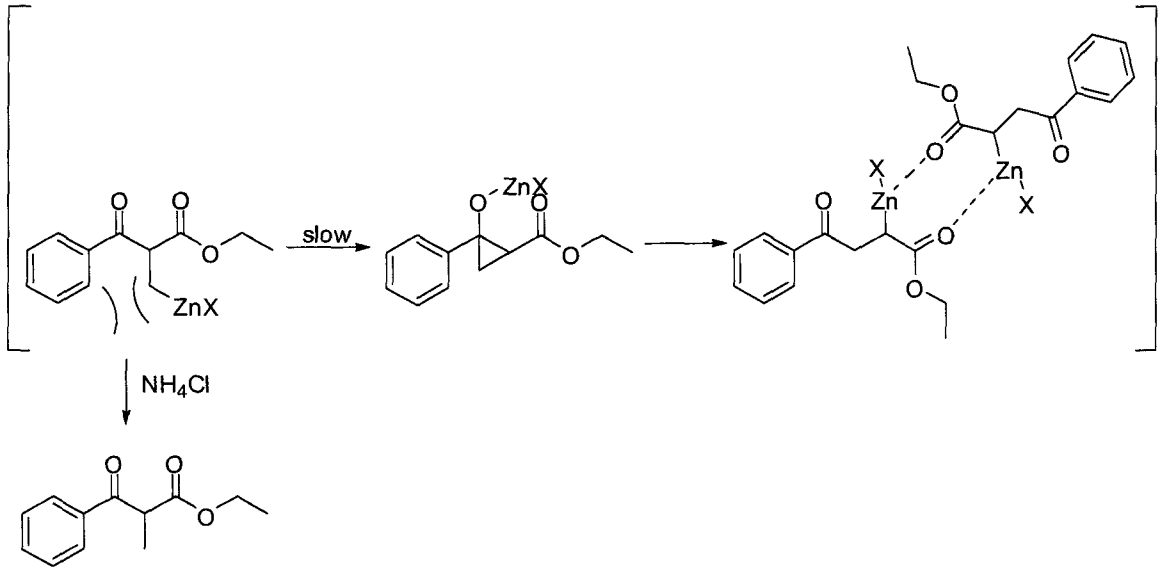
In the case of methyl acetoacetate (**202**), the lack of steric bulk at either the ketone or ester end of the starting material may have contributed to self-aldol chemistry. Unfortunately, the *N*-Boc imines are slow to react with the latent enolate, leaving the opportunity for the enolate to react with other electrophiles in solution. The ketone of methyl acetoacetate, or of the chain-extended γ-keto ester, is certainly a competent electrophile.

The same concern was present with *tert*-butyl acetoacetate **203**, but interestingly, the ^{1}H and ^{13}C NMR revealed that the major product formed in the chain extension-imine capture reaction was the methylated and deprotected product **205** (**Scheme 61**). This product was formed when a *bis*-carbenoid (ICH_2ZnCH_2I),[120, 121] a more reactive carbenoid that can serve as a replacement for the typical Furukawa-modified reagent, was used. The Furukawa-modified carbenoid ($EtZnCH_2I$) did not provide access to the desired product or the methylated and deprotected product **205**.



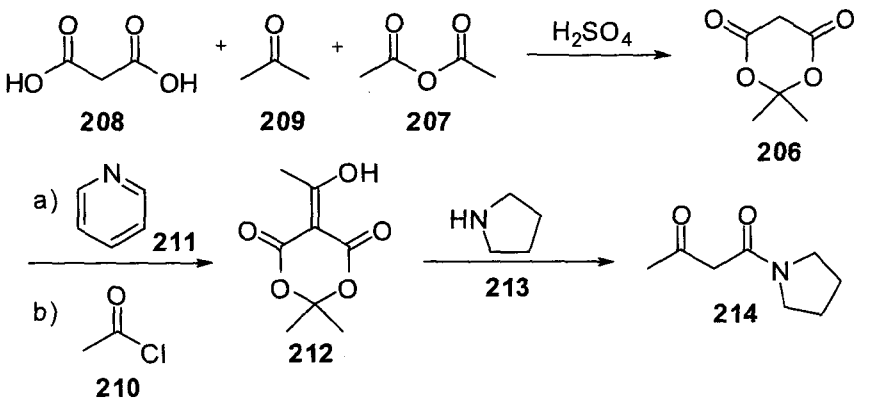
Scheme 61. Chain Extension Imine Capture with *tert*-Butyl Acetoacetate (**203**)

Ethyl benzoylacetate (**204**) was also subjected to the chain extension imine capture conditions, however this β-keto ester was already known to undergo the chain extension very slowly, which resulted in inefficient conversion to the γ-keto ester (**Figure 62**).[122] When the crude reaction mixture was analyzed by ^{1}H and ^{13}C NMR, some desired product appeared to have been formed, but the major components were starting material and methylated β-keto ester. Methyl pivaloylacetate was the only β-keto ester that cleanly and efficiently provided the desired products in the chain extension-imine capture reaction.



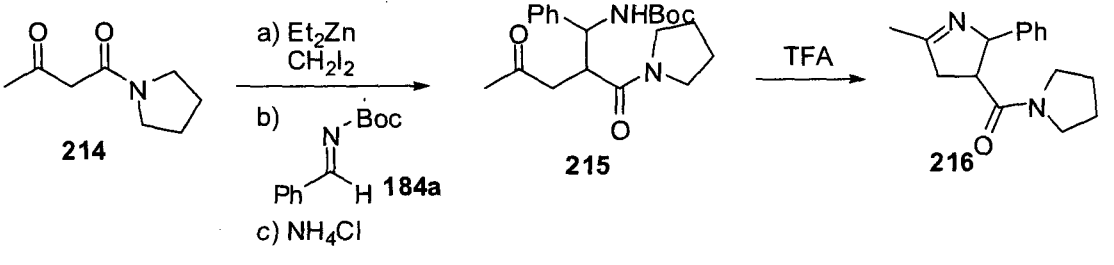
Scheme 62. Slow Homoenolate Attack to Form Donor-Acceptor Cyclopropane and Formation of Methylated β-Keto Ester Byproduct

The next substrates that were subjected to the chain extension imine capture reaction were β-keto amides. β-Keto amides are not nearly as accessible from commercial sources as β-keto esters, so the amides were synthesized from commercially available materials. Synthesis of the β-keto amides was achieved through three steps and could be scaled up to obtain grams of the desired product. The first step involved formation of Meldrum's acid **206** from acetic anhydride **207**, malonic acid **208**, sulfuric acid, and acetone **209**.[123] This crystalline solid can be acylated with acetyl chloride **210** in the presence of pyridine **211**, and the acylated Meldrum's acid adduct **212** can be opened with a nucleophile.[124] Pyrrolidine **213** was used to provide access to the β-keto amide **214** (**Scheme 63**).



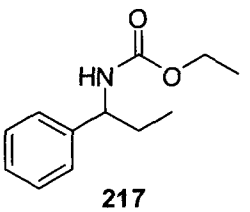
Scheme 63. Synthesis of Pyrrolidine Derived β-Keto Amide **214**

The β-keto amide (**214**) was subjected to the chain extension conditions using both the Furukawa carbenoid and *bis*-carbenoid. Although both of the chain extension conditions provided access to product, the *bis*-carbenoid provided a cleaner crude reaction mixture. A mixture that contained both the α-substituted γ-keto ester (**215**) and the deprotected cyclic imine (**216**) were produced. Formation of this mixture seems to be unavoidable, since the *N*-Boc imines require approximately 16 hours of reaction time to produce optimal yields of β-amino acids. Lewis acid induced deprotection of the Boc-group will occur during this long reaction time. The crude reaction mixture was carried on without further purification and was subjected to TFA in an effort to increase the amount of the cyclic imine formed in the mixture (**Scheme 64**).



Scheme 64. Synthesis of β-Keto Amide Derived Cyclic Imine **216**

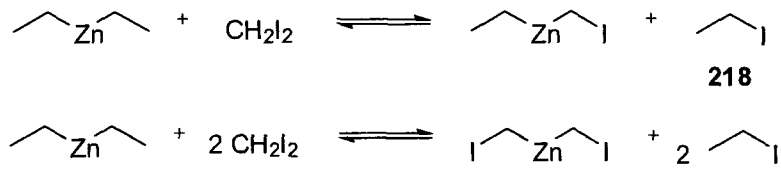
During the purification of the cyclic imine via column chromatography, a very interesting compound was obtained. The ^{1}H NMR of the crude reaction mixture of the imine capture reaction revealed am approximate 1:1:1 mixture of the desired imine capture product, the cyclic imine, and a byproduct. Since the crude reaction mixture of the imine capture reaction was not purified, this byproduct was carried through the reaction with TFA and then isolated by chromatography, which revealed that compound **217** was generated during the chain extension imine capture reaction (**Figure 17**).



217

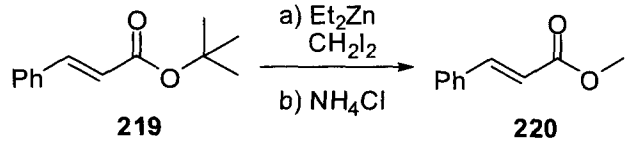
Figure 17. Byproduct **217** from Chain Extension-Imine Capture Reaction

The preparation of this byproduct under chain extension imine capture conditions is interesting. Ethyl addition into the imine can be explained by the nucleophilic behavior of diethyl zinc that is used in the reaction. The trans-esterification of the Boc protecting groups to generate an ethyl carbamate is not easily understood. Nucleophilic addition of an ethyoxy group to the carbamate with lost of *tert*-butyl alcohol would not be expected to occur easily. The alternative explanation is the action of an electrophilic ethyl source on the carbamate. During the formation of the Furukawa and *bis*-carbenoid, there is at least one equivalent of ethyl iodide (**218**), an electrophilic ethyl source, generated (**Scheme 65**). The participation of ethyl iodide in any chain extension reaction is unprecedented.



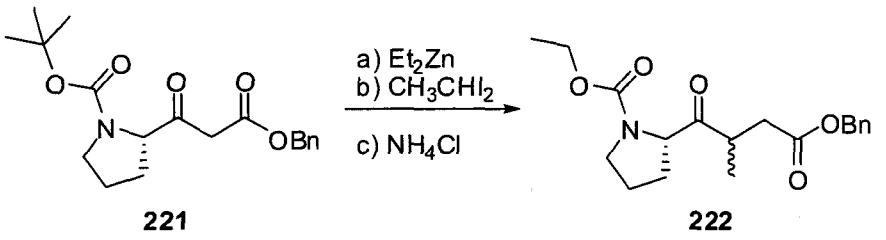
Scheme 65. Generation of Furukawa-modified and *bis*-Carbenoid

Transesterification of esters and interconversion of carbamates through the action of carbenoid conditions has been observed in the Zercher group on several occasions. For instance, Verbicky observed the conversion of *tert*-butyl ester **219** to methyl ester **220** in the presence of the carbenoid derived from diiodomethane (**Scheme 66**).[125]



Scheme 66. Transesterification with Furukawa-modified Carbenoid

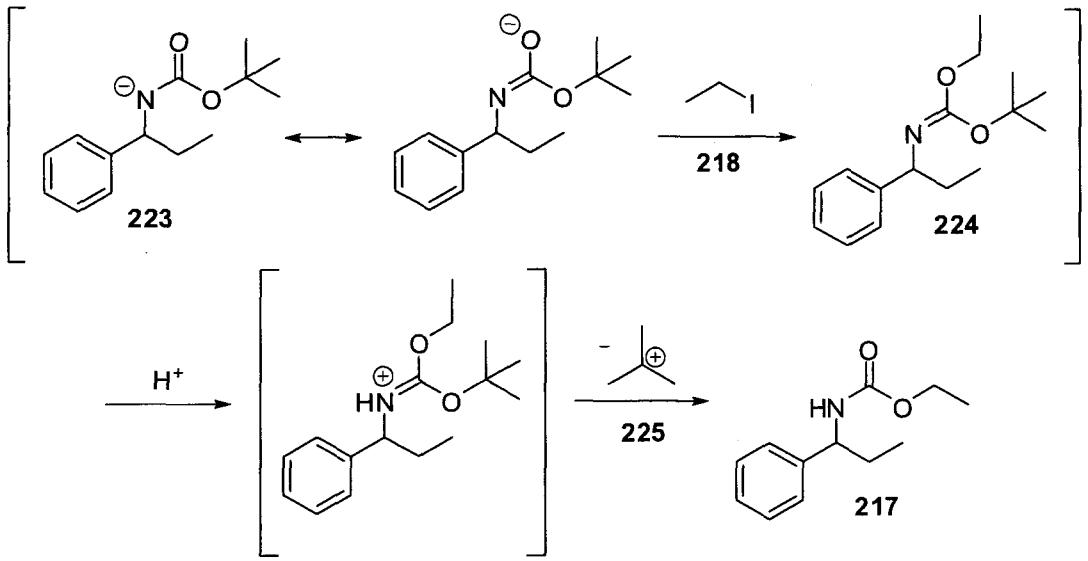
Mazzone has also seen the conversion of a *N*-Boc carbamate (**221**) to an ethyl carbamate (**222**) while using the substituted carbenoid derived from 1,1-diiodoethane (**Scheme 67**).[72] Both of these observations can be rationalized by the Lewis acidity of the zinc carbenoid and the stability of the *tert*-butyl carbocation lost during the transformation. It is important to note that both of these cases involved the substitution of the same number of carbons as the generated carbenoid (the Furukawa carbenoid appeared to convert the Boc group to a methyl ester and the methyl-substituted Furukawa carbenoid converted the Boc to an ethyl ester). The conversion of a Boc-group to an ethyl carbamate through treatment with the Furukawa carbenoid was unprecedented.



Scheme 67. Transesterification with Methyl-Substituted Carbenoid

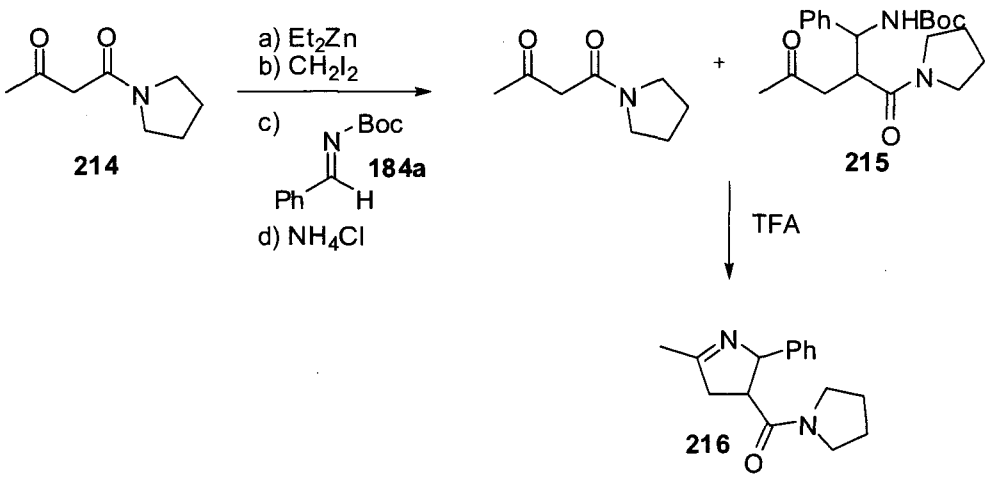
In order to determine whether the *N*-Boc imines were reacting with the zinc-carbenoid, control studies were performed. Both the Furukawa-modified carbenoid and *bis*-carbenoid were generated and an equivalent of *N*-Boc imine was added to each, separately. The reactions were allowed to stir for 16 hr, which is the typical reaction time for the chain extension-imine capture reaction. In both cases the identical by-product X was observed, which clearly illustrated that the imine was reacting when exposed to the carbenoid. A mechanism to explain the formation of the byproduct was proposed.

An ethyl group, either from diethyl zinc or the ethyl(iodomethyl)zinc, is likely to add to the imine, which generates a resonance stabilized carbamate anion (**223**). This intermediate can react with ethyl iodide (**218**) to render **224**, which after an acidic work-up could lose a *tert*-butyl cation (**225**) to generate the observed product **217** (**Scheme 68**). Other plausible mechanisms could be proposed, but further studies would be needed in order to elucidate all the mechanistic details. It is likely that the conversion of the *N*-Boc imine to this product has happened in earlier studies, but it was not observed.



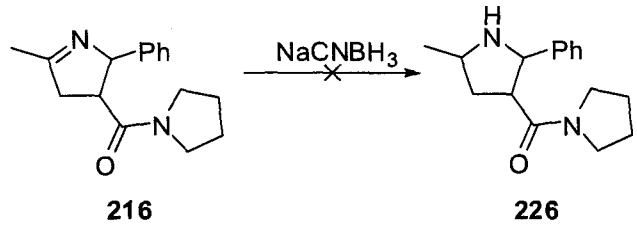
Scheme 68. Proposed Mechanism for the Formation of the Observed Byproduct **217**

In order to limit the formation of this undesired by-product, the β-keto amide (**214**) was reacted with carbenoid in a 1:1:1:1 ratio (β-keto amide: Et_2Zn: CH_2I_2: *N*-Boc imine) of all reactants and reagents. Additionally, the zinc enolate was generated by exposure of the β-keto amide to Et_2Zn. The enolate was subjected to diiodomethane to initiate carbenoid formation. This approach differs from the standard preformation of carbenoid followed by addition of the β-keto substrate. The stoichiometry was used to ensure that a minimal amount of ethyl iodide was generated during the formation of the carbenoid in solution. Although starting material was still present in the reaction mixture, no byproduct **217** was observable by ^1H NMR analysis of the crude reaction mixture even after a reaction time of 16 hours. The crude mixture, which consisted of starting material and the chain extension imine capture product (**215**), was carried along without purification and subjected to the deprotection conditions (**Scheme 69**).



Scheme 69. Synthesis of Cyclic Imine **216** from β-Keto Amide **214**

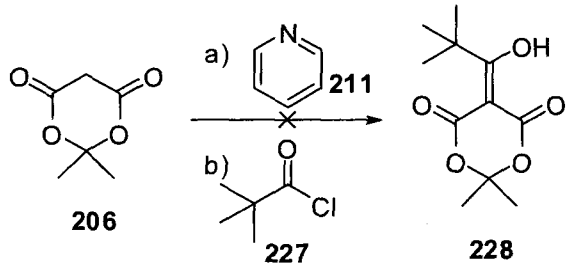
Unfortunately the reduction of the cyclic imine **216** using the standard sodium cyanoborohydride conditions was unsuccessful, even after many attempts were made. The sodium cyanoborohydride reaction was efficient and reproducible with the methyl pivaloylacetate-derived substrates, but this reagent never seemed to provide access to the desired β-proline derivative **226**. Longer reactions times, increased amounts of sodium cyanoborohydride, and even the use of sodium triacetoxyborohydride were all attempted, but none yielded anything other than starting material. Although NMR analysis suggested that the chain extension-imine capture reaction and subsequent deprotection step appeared to work well, it was likely that the cyclic imine may not have actually been prepared, since the reduction did not work after multiple attempts (**Scheme 70**).



216 **226**

Scheme 70. Unsuccessful Reduction of β-Keto Amide-Derived Cyclic Imine **216**

When considering different β-keto amides as substrates for the tandem chain extension-imine capture reaction, it was proposed that a pivaloylacetamide should react similarly to methyl pivaloylacetate, a β-keto ester that gave excellent results. The problem was that this β-keto amide is not commercially available, and its preparation proved to be a challenge. Acylation of Meldrum's acid (**206**) with pivaloyl chloride (**227**) in the presence of pyridine (**211**), followed by attack with an amine was proposed as a route to **228**, yet even after extended reaction times, the pivaloylated compound **228** was never obtained (**Scheme 71**).



Scheme 71. Failed Attempts at the Pivaloylation of Meldrum's Acid

A different approach to the synthesis of **229** was taken that involved reacting amide enolates with pivaloyl chloride **227** in an effort to obtain the desired product. The generation of the amide enolate followed by introduction to the acid chloride was attempted, but only starting materials were returned. It seemed apparent that the acid

chloride's carbonyl was sterically hindered and would not react efficiently with nucleophiles. In order to investigate the formation of a β-keto amide **229**, commercially available *N,N*-dimethylacetamide **230** was used as the amide since that part of the molecule not expected to be important for the chain extension reaction. Finally, after many attempts, the desired β-keto amide was synthesized, purified, and used in the chain extension imine capture reaction.

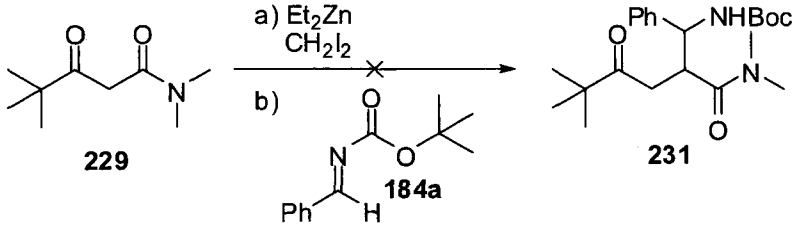
230 **227** **229**

Attempt	Reagents	Solvent	Temperature	Time	Yield
1	NaH	THF	r.t	12 h	0%
2	NaH	THF	reflux	18 h	0%
3	NaH	1,4-dioxane	reflux	18 h	0%
4	NaH	1,4-dioxane	reflux	4 d	0%
5	LDA	THF	-78 °C - r.t.	3 h	67%

Table 4. Attempted Syntheses of Pivaloyl Acetamide (**229**)

After finally obtaining the pivaloyl acetamide **229** and using it in the chain extension imine capture reaction, the results were unexpected. After a few attempts it appeared that the chain extension reaction itself was slow and was never able to efficiently convert the β-keto amide to the homologated enolate (**Scheme 72**). The standard chain extension reaction protocol for a β-keto amide was followed, in which three equivalents of carbenoid are used; however, mainly starting material was observed

by NMR. After increasing the reaction time for the chain extension reaction from 30 minutes to 2 hours, the same results were observed. The equivalents of carbenoid were also increased to help promote the reaction, but no improvements were observed. Therefore, studies on this substrate were abandoned.



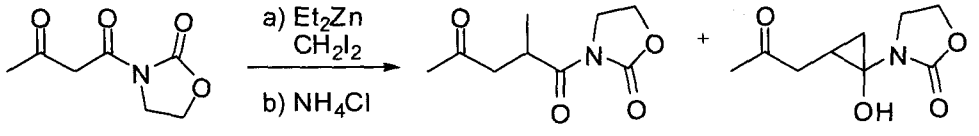
Scheme 72. Unsuccessful Chain Extension-Imine Capture Reaction of β-Keto Amide **229**

McGinness had subjected the same β-keto amide to the methyl-substituted carbenoid and reported very little success in a chain extension reaction, as well.[126] McGinness increased the time of the reaction, increased the equivalents of carbenoid, changed the order of addition, and still observed predominantly starting material. McGinness did not explore a tandem process, but his studies suggested that adding a time-demanding imine capture step would only prolong the lengthy and inefficient reaction with this β-keto amide.

β-Keto Imides

In an effort to explore different substrates as starting materials for the chain extension imine capture chemistry, achiral β-keto imides were explored. β-Keto imides (**232**) have been chain-extended in the zinc carbenoid reaction; however, these studies have revealed several new obstacles to overcome with these substrates. For example, initial efforts to effectively chain extend β-keto imines revealed the formation of the α-

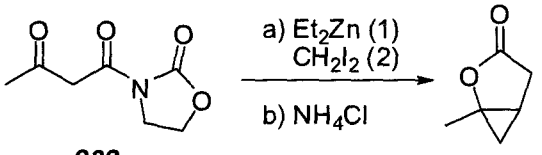
methylated product **233** or cyclopropyl product **234** as side products (**Scheme 73**).[33, 45, 49] These compounds are believed to arise from the reaction of the imide's latent enolate with excess carbenoid. To avoid the formation of these side products in the chain extension-aldol reaction, shorter reaction times are used by introducing the aldehyde or ketone sooner. However, since the activated imines are not nearly as reactive as aldehydes and ketones, the study of the chain extension-imine capture of β-keto imides was attempted with some reservations.



232 **233** **234**

Scheme 73. α-Methylated and Cyclopropanated Products from β-Keto Imide **232**

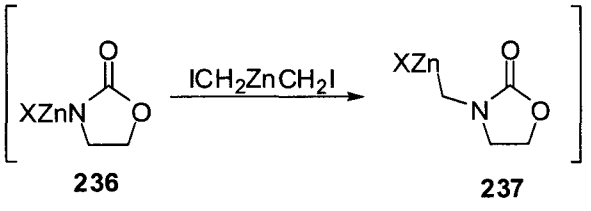
Another complication with the chain extension reaction of β-keto imides is that the oxazolidinone is a very good leaving group. Current investigations by Taschner involve utilization of long reactions times and increased amounts of carbenoid in an effort to favor cyclopropanation. Under these reaction conditions an unprecedented rearrangement and intramolecular acylation provides access to cyclopropyl γ-lactones (**235**) (**Scheme 74**).[127]



232 **235**

Scheme 74. Synthesis of Cyclopropyl γ-Lactones

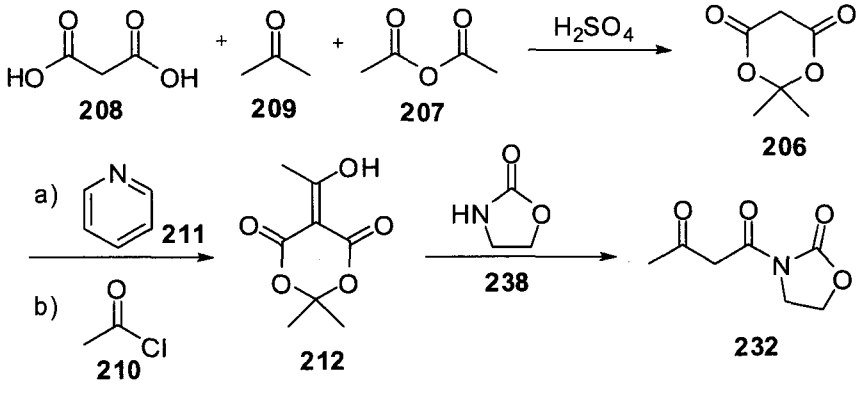
Taschner has also discovered that 2-oxazolidinone anion **236** formed in the acylation reaction can react with carbenoid (**237**) (**Scheme 75**). If the formation of the cyclopropyl γ-lactones happens quickly, an equivalent of oxazolidinone anion would be released and decomposition of the carbenoid would occur.



236 **237**

Scheme 75. Reaction of Carbenoid with 2-Oxazolidinone Anion

The synthesis of the achiral β-keto imide (**232**) was achieved through three steps and could easily be scaled up to obtain grams of the desired product. Meldrum's acid **206** was synthesized and acylated with acetyl chloride (**210**) in the presence of pyridine (**211**). This product (**212**) can be opened by an oxazolidinone (**238**) to provide access to **232**.



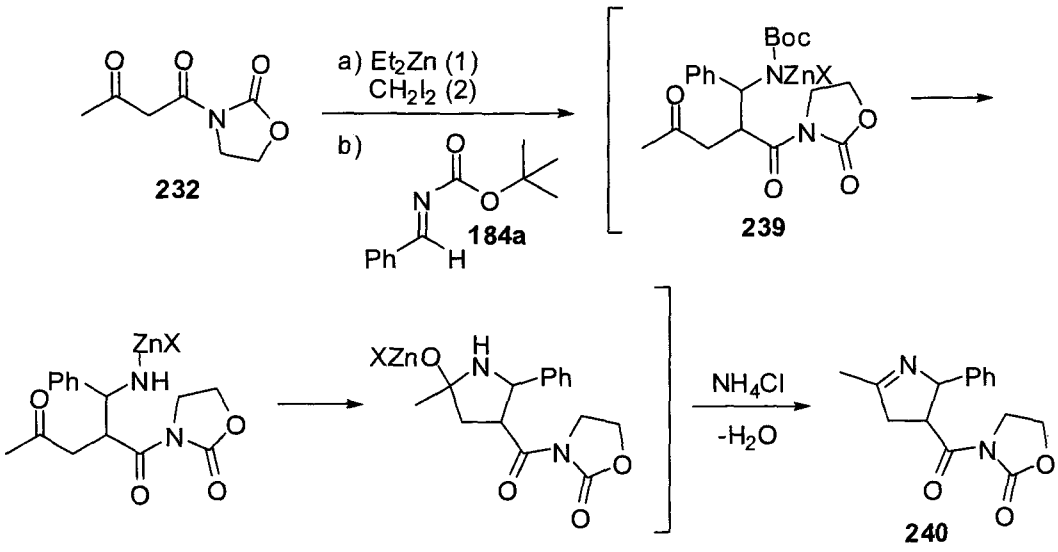
208 **209** **207** **206**

210 **212** **232**

Scheme 76. Synthesis of β-Keto Imide **232** via Meldrum's Acid

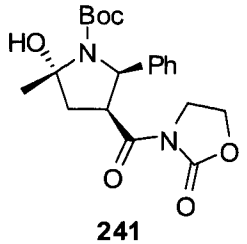
Once synthesized, the achiral β-keto imide **232** was subjected to the chain extension imine capture conditions with both the Furukawa-modified carbenoid and the *bis*-carbenoid. Interestingly, the *bis*-carbenoid was the superior reagent of the two. The main by-product seen by ^{1}H NMR analysis of the crude reaction mixture was the previously mentioned lactone. This lactone and the desired imine capture product were present in almost a 1:1 mixture. However, one very interesting feature of the chain extension reaction of β-keto imide **232** was that the ^{13}C NMR of the crude reaction mixture showed no evidence of a ketone. A strong resonance around 90 ppm suggested the presence of an aminal. In addition, the ^{1}H NMR spectrum suggested that the *tert*-butyl from the Boc group was shifted upfield from where it has typically been observed. This upfield shift could be due to a magnetic anisotropic effect caused by the aromatic ring.

In order for there to be no ketone in the reaction mixture the imine capture product (**239**) must have underwent an unanticipated further reaction. Based on previous results, the removal of the Boc group in the presence of the *bis*-carbenoid was considered a possibility which would provide the free amine. If the free amine were present in solution, imine formation (**240**) was likely to occur rather than generation of a hemiaminal (**Scheme 77**); however, the ^{13}C NMR resonance at 90 ppm strongly suggested the presence of a hemiaminal.



Scheme 77. Deprotection of Boc Group and Dehydration to form Cyclic Imine **240**

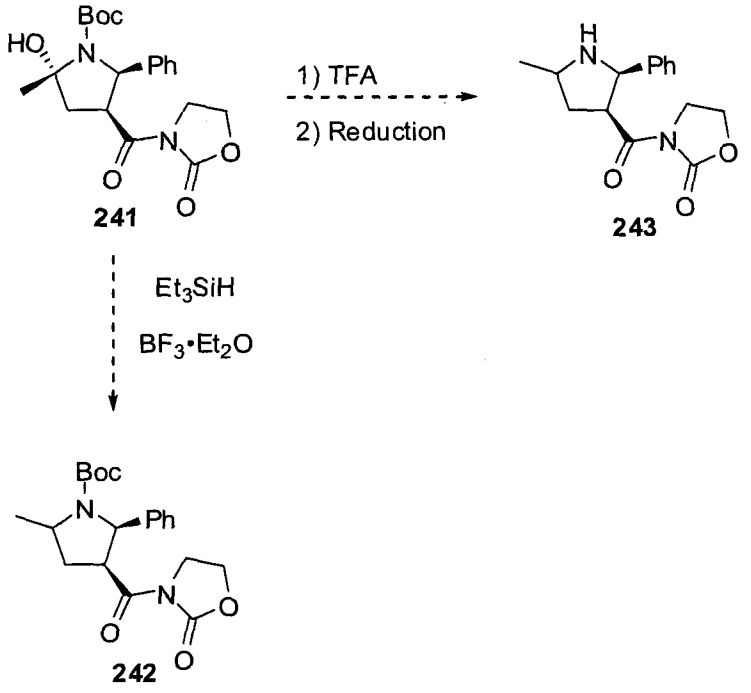
The unknown product was purified via column chromatography and an x-ray grade crystal was grown from hexanes and ethyl acetate (1:1). The results of the x-ray crystallography not only demonstrated the presence of a hemiaminal in the product (**241**), but it also displayed the stereochemistry of the chain extension imine capture reaction with the β-keto imide (**Figure 18**). The *anti*-aldol diastereoselectivity in the formation of the product was not surprising. β-Keto imides have been shown to favor the formation of *anti*-aldol products in the tandem chain extension-aldol reaction and the *N*-Boc imines were also *anti* selective when reacted with the chain extension intermediate formed from β-keto esters. The structure, a Boc-protected hemiaminal **241**, was an interesting product that offered potential versatility to the synthesis of the β-proline derivatives.



241

Figure 18. Structure of Hemiaminal **241**

The isolation of a hemiaminal with the Boc protecting group still intact provides the opportunity for other synthetic transformations. Removal of the hydroxyl functionality while keeping the Boc-protecting group intact appeared possible through application of a literature protocol[128] that utilized a triethylsilane reduction (**242**). This method would provide access to a β-proline derivative in one fewer step than the previous three-step method used with methyl pivaloylacetate. Furthermore, the Boc-protecting group would still be present, which could provide advantages for future application of the β-proline product. Alternatively, removal of the Boc group from the hemiaminal should provide access to a cyclic imine (**243**), which could be reduced with sodium cyanoborohydride to give a β-proline derivative that possesses a free –NH (**Scheme 78**).

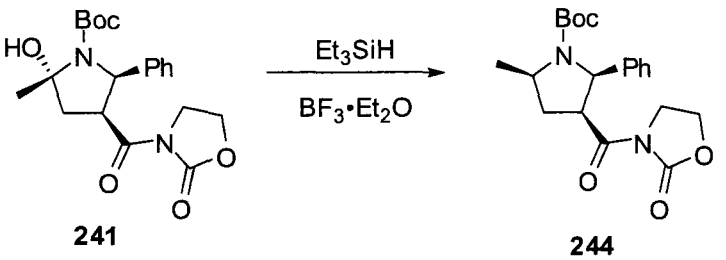


Scheme 78. Possible Routes of Obtaining β-Proline Derivatives from Hemiaminal **241**

As mentioned earlier, the cyclopropyl γ-lactone **235** was a major product of the reaction of β-keto imide **232**. The hemiaminal (**241**) and the lactone were present in an approximate 1:1 ratio, as determined by comparing the integration of the lactone to the hemiaminal resonances in the ^{1}H NMR of the crude reaction mixture. The imine capture product was easily separated from the γ-lactone by recrystallization from hexanes to afford a 55% yield of the hemiaminal. The yield was surprisingly high when taking into account the efficient formation of the γ-lactone that has been reported.[127]

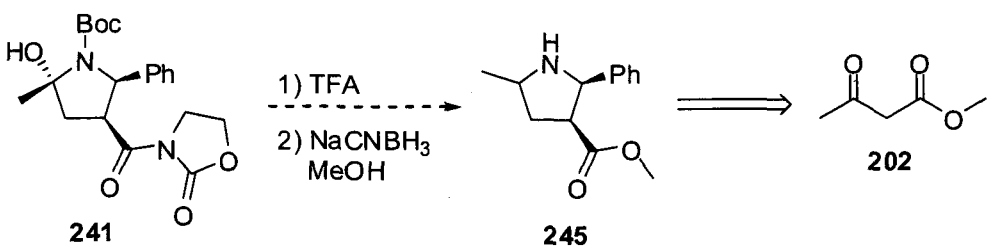
Since the Boc-protected β-proline appeared to be available through reduction of the hemiaminal (**241**), the triethylsilane reduction was the main focus of the research effort (**Scheme 79**). After optimization of the reaction conditions, the reduction did proceed efficiently and the desired Boc-protected β-proline derivative was synthesized and purified. Unfortunately, the C5 stereochemistry of the desired product was not able

to be rigorously determined, but the selectivity in the reduction of the methyl pivaloylacetate substrates suggests that a *cis, cis,* relationship of the three substituents would be favored as the reduction product of **244**.



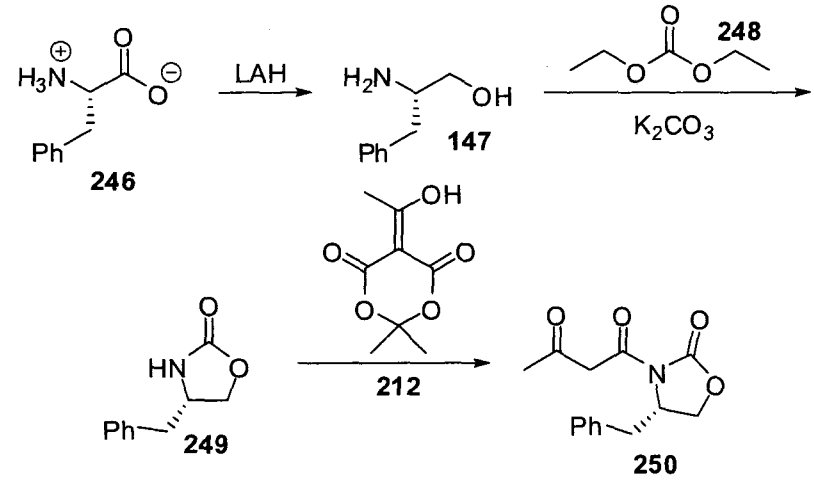
Scheme 79. Reduction of Hemiaminal **241** to Boc-Protected β-Proline Derivative **244**

The sodium cyanoborohydride reduction conditions utilize methanol and anhydrous hydrochloric acid, which could cleave the imide functionality and provide access to methyl ester **245** (**Scheme 80**). This methyl ester is identical to the product that would be formed when using methyl acetoacetate (**202**), which was a starting material for the chain extension-imine capture reaction that was studied with little success. Application of the sodium cyanoborohydride reaction would also add an additional step to the preparation of the β-proline. Furthermore, the triethylsilane method also provided direct access to a Boc-protected β-proline derivative, which was a nice feature since the NH proton would most likely need to be protected for further applications.



Scheme 80. Potential Route to β-Proline Derivative **245**

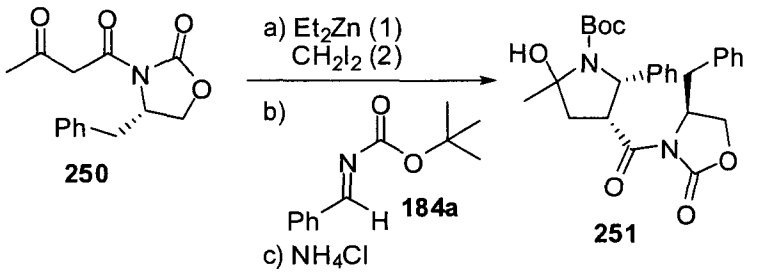
Chiral β-keto imides have also been studied as a means to control the absolute stereochemistry of the tandem chain extension processes.[49] Chiral β-keto imides, which are acylated oxazolidinones, were synthesized from commercially available amino acids in three steps. L-Phenylalanine (**246**) was reduced using lithium aluminum hydride (LAH) and the resultant amino alcohol was converted to the oxazolidinone with diethyl carbonate (**248**) and potassium carbonate.[129] Chiral oxazolidinone **249** was reacted with acylated Meldrum's acid **212** at elevated temperatures to yield the desired chiral β-keto imide **250** (**Scheme 81**).



Scheme 81. Synthesis of L-Phenylalanine-derived β-Keto Imide **250**

This amino acid-derived β-keto imide was subjected to the chain extension-imine capture reaction conditions and the results were similar to the achiral system. The product (**251**) was once again a solid, which offered crystallization as a means for purification (**Scheme 82**). The reaction's major byproduct, observed by NMR analysis of the crude reaction mixture, was the lactone (**235**), which was separated through recrystallization from hexanes. Unfortunately the recrystallization was not as successful

as the achiral β-keto imide (**232**), for it appeared that some chiral β-keto imide starting material (**250**) was carried along in the recrystallized product mixture. The β-keto imide did not affect the triethysilane reduction but it was still present as an impurity in the final β-proline derivative.

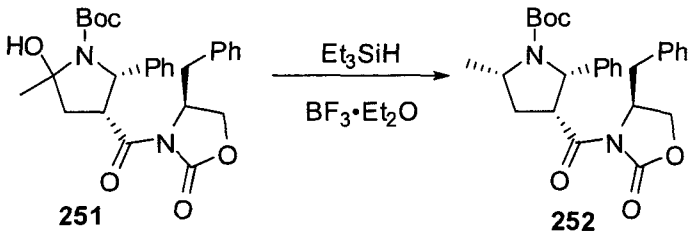


Scheme 82. Hemiaminal **251** from Chain Extension-Imine Capture Reaction of β-Keto Imide **250**

Although an X-ray crystal structure was not obtained, the *anti*-aldol directing ability of the imide system and the *anti* directing ability of the *N*-Boc imine suggested a strong bias for the *anti*-aldol-like selectivity. The absolute stereochemistry of the product would be established through facial selectivity of the enolate. Lai[49] and Lin[33] rigorously established facial selectivity in the tandem chain extension-aldol reaction when using oxazolidinone-directing groups and this information was used to predict the selectivity in the imine capture reaction.

Hemiaminal **251** was next subjected to the triethylsilane reduction conditions and this reaction resulted in the formation of a Boc-protected β-proline derivative **252**. Only one diastereomer was observable in the ^{1}H NMR spectrum of the crude reaction mixture, which suggested high diastereocontrol in the reduction. The *cis* relationship of the C2 and C3 substituents would be expected to favor formation of the *cis*, *cis* products.

Unfortunately the purified material contained minor resonances for a ketone-containing molecule, presumably from the β-keto imide starting material (**250**) which was never fully removed from the reaction mixture.

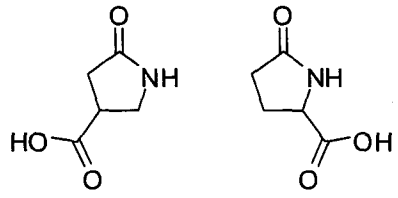


Scheme 83. β-Proline Derivative **252** from L-Phenylalanine β-Keto Imide **250**

Ceric Ammonium Nitrate Oxidative Cleavage of Hemiaminals

After successfully synthesizing the hemiaminals from both the achiral and chiral β-keto imides, the combination of this chemistry with the CAN-mediated oxidation cleavage reaction, which utilized a hemiacetal generated from the tandem chain extension-aldol reaction was considered. The hemiaminal generated from the capture of an imine could provide access to γ-lactams in cases where an α-heteroatom was present on the starting β-ketone system.

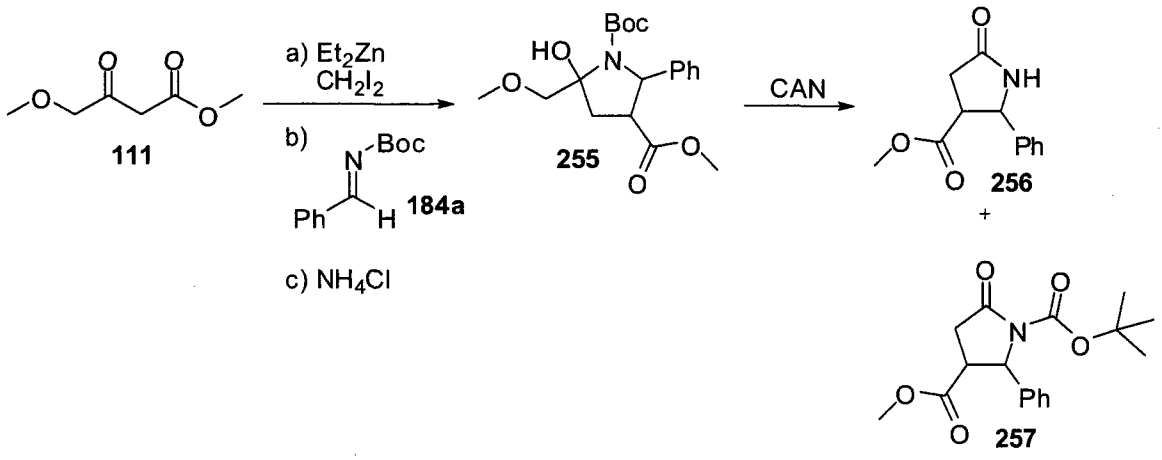
γ-Lactams exhibit interesting biological and pharmacological activities. They can be used as psychotropic[130] and anti-hypertensive agents,[131] inhibitors of proteolytic catalysis,[132] and antimuscarinic agents.[133] They can also be used as intermediates en route to more complicated biologically active compounds.[134-136] The backbone of the γ-lactams formed through a tandem chain extension-imine capture CAN-oxidation sequence would be β-pyroglutamic acid (**253**), an isomer of the amino acid derivative, pyroglutamic acid (**254**) (**Figure 19**). The methyl ester of β-pyroglutamic acid has been reported to be converted to methyl β-proline, as well.[137]



253 **254**

Figure 19. β-Pyroglutamic Acid and Pyroglutamic Acid

The proposed starting material for preparation of enantiomerically pure β-pyroglutamic acid would be an α-methoxy-β-keto imide, which would take several steps to prepare. In an effort to understand the opportunity for accessing a γ-lactam through this approach, commercially available methyl 4-methoxyacetoacetate (**111**) was subjected to the chain extension-imine capture reaction conditions. The major product, which could be isolated by chromatographic purification, was the desired hemiaminal **255**. This hemiaminal was subjected to the CAN-oxidative cleavage reaction conditions and a mixture of γ-lactams was observed by ^{1}H and ^{13}C NMR analysis (**Scheme 84**). Based on a number of benzylic doublets, four compounds appeared to be present in the reaction mixture. It appeared that the original four compounds in the mixture were likely the *cis* and *trans* isomers of each of the Boc-protected (**257**) and free –NH lactams (**256**). It is possible, however, that the rotomeric forms of the Boc-protected lactam were contributing to the presence of the four doublets. The presence of a *tert*-butyl resonance of a Boc-group was surprising, because the acidic CAN oxidation conditions would be anticipated to cleave the Boc-group.

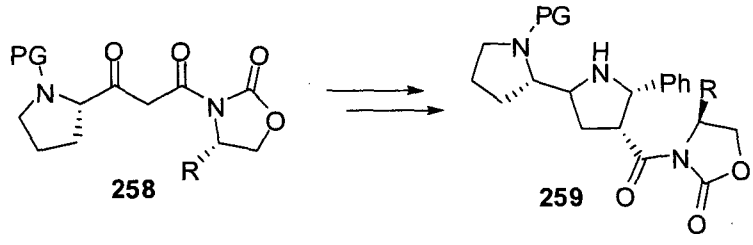


Scheme 84. Chain Extension-Imine Capture and CAN Oxidative Cleavage

Column chromatography was used to isolate two products, which appeared to be the *cis* and the *trans* isomers of the deprotected γ-lactams. The assignment of the products was largely based on comparison to the previously synthesized γ-lactones. Although the stereochemistry of the substituents could not be assigened definitively, it was apparent that both the *syn* and the *anti* imine capture products were made with little selectivity during the imine capture reaction. This poor diastereocontrol is consistent with the poor selectivity observed in aldol reaction of methyl 4-methoxyacetoacetate. Unfortunately, no Boc-protected γ-lactam was successfully separated and characterized, for the Boc group appeared to be lost during the purification on the silica gel. Nonetheless, this study illustrates the potential for formation of γ-lactams through sequential application of the chain extension-imine capture reaction and the CAN-mediated oxidative cleavage. Although the chemistry has been proven to work, further studies are necessary to fully understand the scope and limitations of the chemistry.

Amino Acid-Derived β-Keto Imide

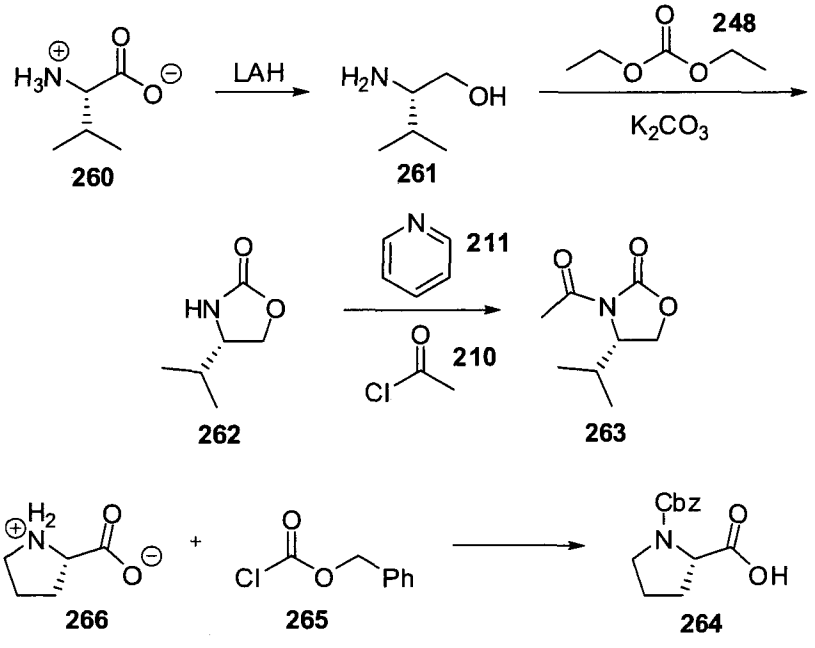
The final and potentially most interesting substrate for this chain extension imine capture chemistry would be an amino-acid derived, chiral β-keto imide. Since *N*-Boc imines provide almost exclusive access to the *anti* aldol products and the β-keto imides are reported to provide similar *anti*-selectivity, incorporation of a chiral directing group on the imide would be expected to control the absolute stereochemistry of the reaction. If an amino acid-derived ketone were used as the starting material (**258**), access to an interesting backbone containing both an α- and β-proline in the same molecule (**259**) should be possible (**Scheme 85**). Use of this molecule as a peptidomimetic or as a chiral diamine could be envisioned.



Scheme 85. Synthesis of Enantiomerically Enriched α-β-Proline Derivative **259**

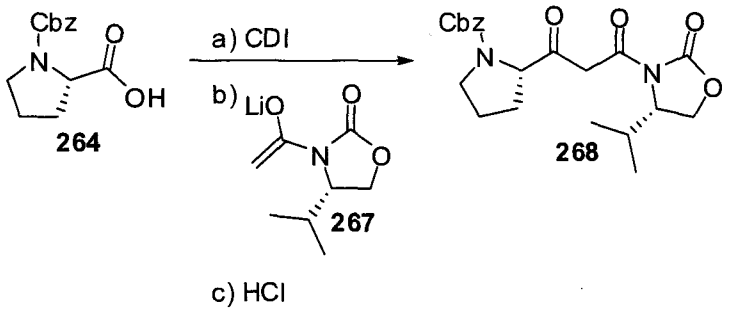
In order to synthesize the amino acid-derived β-keto imide, two substrates had to be synthesized and eventually combined. The first piece to be synthesized was the acylated, chiral oxazolidinone. L-Valine (**260**) was reduced using LAH and the resultant amino alcohol (**261**) was cyclized to the oxazolidinone (**262**) with diethylcarbonate (**248**) and potassium carbonate. This product was acylated using acetyl chloride (**210**) in the presence of pyridine (**211**) to provide the *N*-acyl oxazolidinone **263**.[15] The other segment required for the convergent approach was *N*-Cbz (L)-proline (**264**). Even though this material is commercially available, the material was synthesized by reacting

benzylchloroformate (**265**) with L-proline (**266**) (**Scheme 86**).[138] The next step required that the two substrates be joined through a variation on a mixed Claisen reaction,[139] which would provide the desired, amino acid-derived β-keto imide.



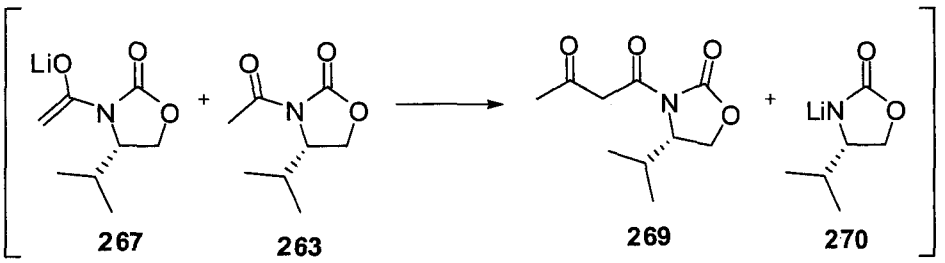
Scheme 86. Synthesis of Each Component in the Convergent Synthesis

A mixed Claisen reaction is typically conducted with an enolate and an ester without α-protons or an acid chloride. The modified Claisen reaction used for the production of the β-keto imide was carried out by first activating the amino acid using *N,N*-carbonyl diimidazole (CDI), followed by addition of the enolate (**267**) that had been formed with LDA (**Scheme 87**).[33] The mixed Claisen reaction provided approximately 50-60% of product **268** and required an excess of the acylated chiral oxazoldinone, which was the most time consuming reagent to synthesize. However, studies by Lin[33] have revealed that this method does not epimerize the amino acid's α-stereocenter, which is crucial for this application.



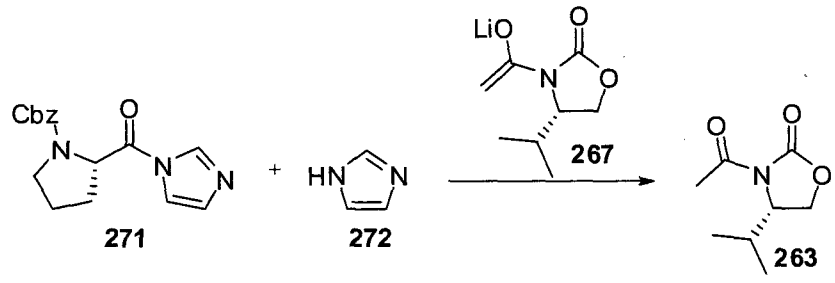
Scheme 87. Modified Mixed Claisen Reaction

As mentioned earlier the Claisen reaction usually provides the desired product in modest yields and requires excess enolate. One of the reasons for this is the possibility of a self-Claisen reaction involving two equivalents of the acylated oxazolidinone (**263**) to form the undesired chiral β-keto imide **269**. Since the oxazolidinone is such a good leaving group, similar to an acid chloride or anhydride, this competitive pathway is always a concern (**Scheme 88**). In order to help avoid the self Claisen reaction and promote the formation of the desired product (**268**), the acylated oxazolidinone (**263**) is added slowly to a dilute solution of LDA. This inverse addition is required to limit the opportunity for the enolate to react with the acylated product to form the self Claisen product.



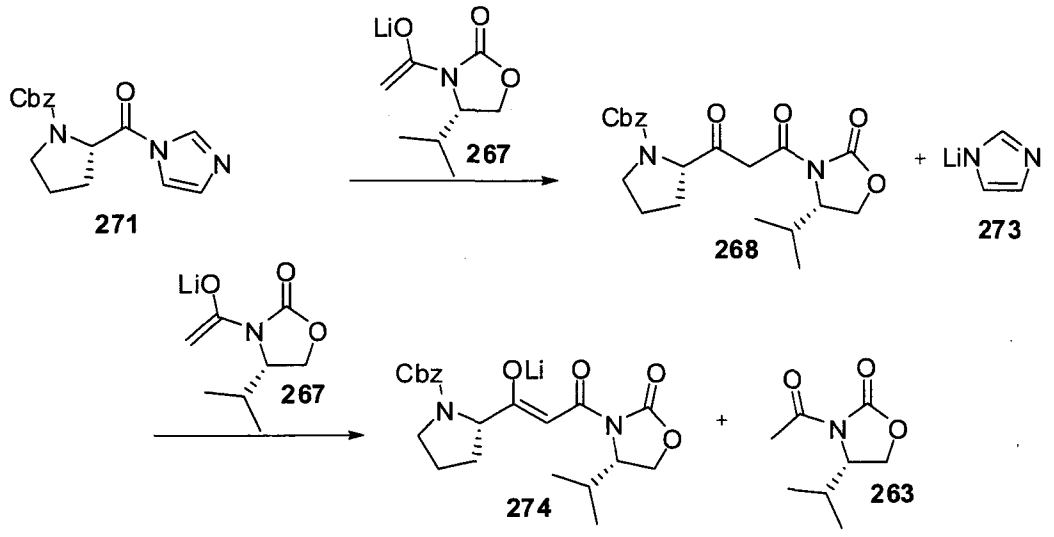
Scheme 88. Self Claisen Reaction to Form Chiral β-Keto Imide **269**

Another factor that contributes to the lower yield is the equivalent of imidazole that is generated during the activation of the amino acid with CDI (**271**). Once the acyl imidazole is added to the enolate of the acylated oxazolidinone (**267**), one equivalent of the enolate is quenched by the imidazole (**272**) proton (pKa ~18).[140] This creates an equivalent of the acylated oxazolidinone (**263**) (pKa ~23) that can undergo a self Claisen reaction, as mentioned above (**Scheme 89**). All of these factors contribute to the modest yields in this reaction.



Scheme 89. Initial Imidazole Quench of Enolate **267**

Once all of the imidazole has reacted, the enolate will react with the activated amino acid (**271**) to generate the β-dicarbonyl (**268**) and another equivalent of imidazole anion (**273**). This β-keto imide (**274**) contains an acidic proton (pKa ~14) and could quench an equivalent of the enolate (**Scheme 90**). In order to optimize the formation of the β-keto imide, four equivalents of enolate are used. Technically only three are necessary, but Lin found that four equivalents provided the highest yields of the reaction.

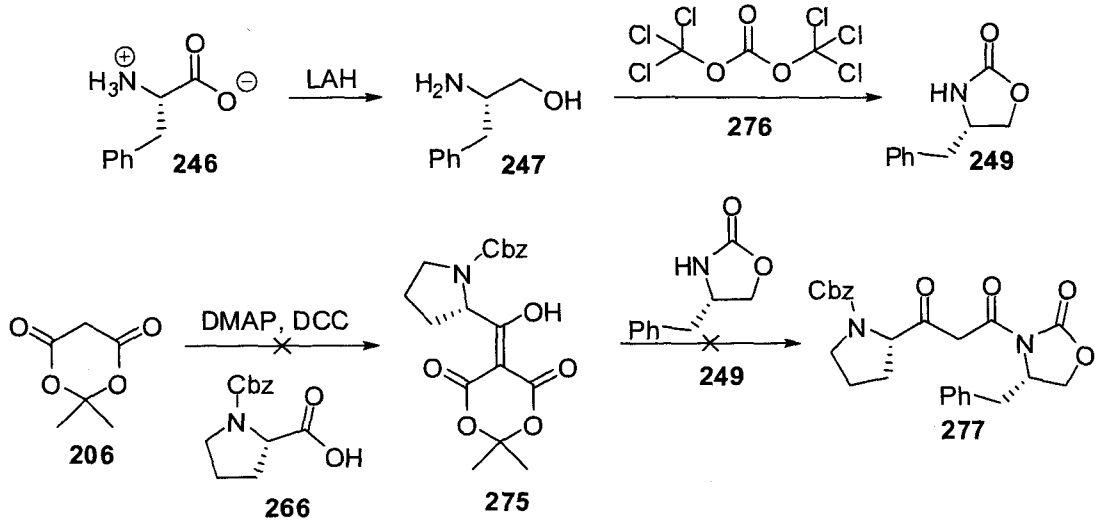


Scheme 90. Quench of Enolate with Generated β-Keto Imide **268**

An alternative approach to obtain the amino acid-derived β-keto imide involved the use of a Meldrum's acid adduct (**275**), but this method was less successful than the modified mixed Claisen. The coupling of Meldrum's acid with an amino acid is reported in the literature, which indicates that the α-stereocenter is unaffected.[141] The reaction conditions use dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) to couple the amino acid to Meldrum's acid.

Once this Meldrum's acid adduct is made, the previously described opening of the Meldrum's acid adduct with a chiral oxazolidinone should provide access to the amino acid-derived β-dicarbonyl. The acylation of Meldrum's acid (**206**) with Cbz-(L)-proline (**266**) was unsuccessful. The product's NMR spectra suggested that some of the desired product may have been formed, so it was exposed to the chiral oxazolidinone (**249**). The formation of the chiral oxazolidinone had been performed using triphosgene (**276**) to cyclize the amino alcohol.[142] This method provided higher yields of the oxazolidinone than the diethyl carbonate and potassium carbonate protocol, but the use of a more

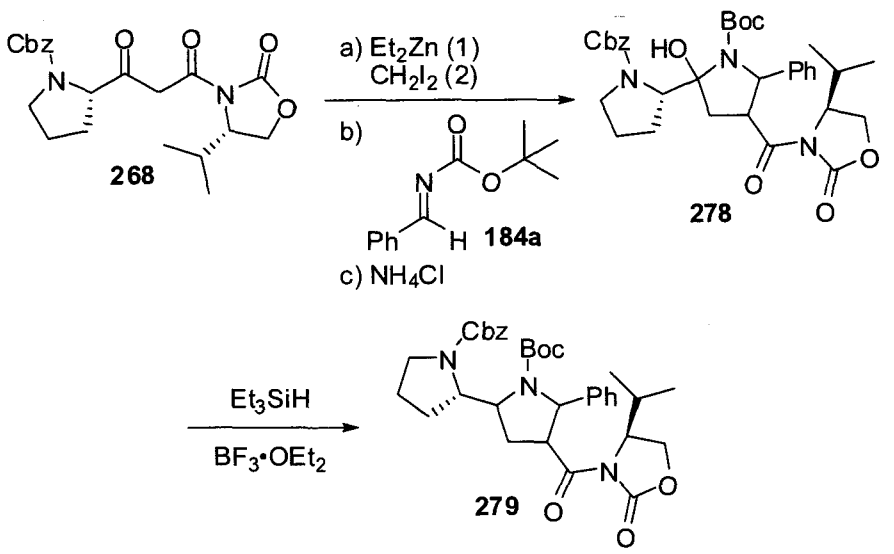
expensive reagent (triphosgene) was required. After attempting to form the amino acid-derived β-dicarbonyl through coupling of Meldrum's acid (**206**) followed by the opening of Meldrum's acid adduct (**275**) with chiral oxazolidinone (**249**) an unidentified mixture was obtained (**Scheme 91**). This route to the β-keto imide was abandoned.



Scheme 91. Unsuccessful Alternative Approach to Amino Acid Derived β-Keto Imide **277**

After obtaining the amino acid derived β-keto imide **268** through the modified mixed Claisen reaction, it was subjected to the chain extension-imine capture reaction using the *bis*-carbenoid and the *N*-Boc imine. As predicted, the reaction provided access to hemiaminal **278**, which was subjected to the triethylsilane reduction conditions. It appeared both by NMR analysis and TLC analysis that a single product was formed but there were two ketone resonances in the ^{13}C NMR that were suspected to be from byproducts of the reaction. After column chromatography the resonances were still present suggesting that the ketones could be part of the product formed. The disappearance of the hemiaminal resonances suggested that the starting material was

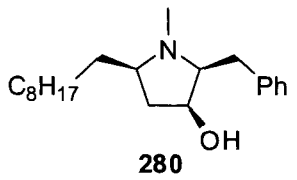
consumed, but it is still unclear as to whether or not this reduction was successful in the conversion of the hemiaminal (**278**) to the β-proline derivative **279** (**Scheme 92**). Efforts towards the determination of the synthesized product are currently ongoing.



Scheme 92. Chain Extension-Imine Capture Reaction and Reduction of Amino Acid-derived β-Keto Imide **268**

Non-Aromatic and Alternative Activated Imines

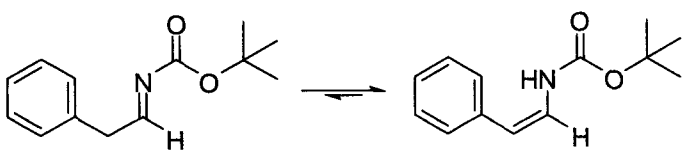
Preussin (**280**),[143] a natural product containing a five-membered heterocycle, was proposed as a target using the chain extension-imine capture methodology (**Figure 20**). As previously mentioned, the application of activated imines to synthesis is often limited to those imines derived from aromatic aldehyde precursors, because of tautomerization between the imine and enamine forms. An approach to this natural product would require the use of an imine prepared from phenylacetaldehyde.



280

Figure 20. (+)-Preussin

In order to gain access to the necessary stereochemistry of the natural product, the use of an *N*-Boc imine was proposed because the desired *anti*-aldol stereochemistry was required. The *N*-Boc imine derived from phenylacetaldehyde (**281**) was prepared using the same protocol for the other imines. The natural product synthesis was aborted after the ^{1}H NMR analysis revealed strong evidence supporting that the enamine form (**282**) was favored at equilibrium (**Scheme 93**). The enamine was useless for the chain extension-imine capture reaction, since there was an acidic -NH proton and no electrophilic carbon.

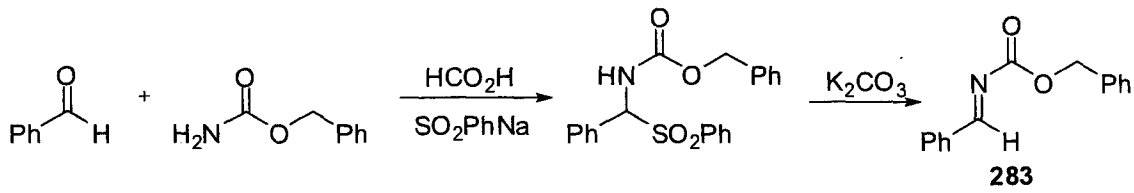


281 **282**

Scheme 93. Enamine Tautomerization of Phenylacetaldehyde-derived Imine

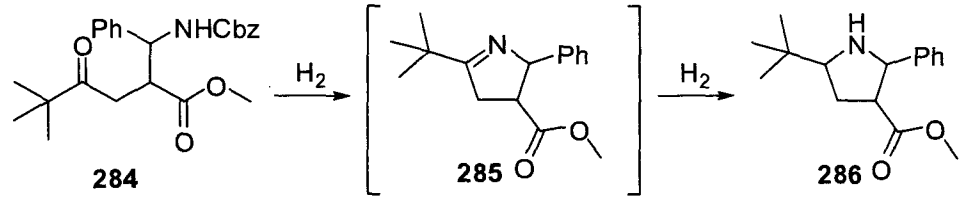
A variation on the carbamate class of activated imines was also studied briefly. A recent report in the literature described the synthesis of *N*-Cbz imines in a very similar fashion to that used for the formation of the *N*-Boc imine.[144] The synthesis of the *N*-Cbz imine was attempted, but product (**283**) was obtained only after many attempts (**Scheme 94**). Interestingly, quantitative yields were reported in the literature, but this approach

afforded low yields of the desired materials in our hands. The spectroscopic data reported in the literature did not match the experimental data we obtained, but our synthetic material did contain NMR resonances reminiscent to the *N*-Boc imine.



Scheme 94. Synthesis of *N*-Cbz Imine **283**

An attractive feature of the *N*-Cbz imines would be the opportunity for an alternative deprotection approach for the formation of β-proline derivatives. Products derived from nucleophilic addition into the *N*-phosphinoylimines and *N*-Boc imines are deprotected under acidic conditions, which could be limiting if acid sensitive functionality were present in the molecule. The chain extension-imine capture product (**284**) with the Cbz group could be deprotected through hydrogenolysis. The potential for a one-pot deprotection (**285**) and reduction (**286**) process could streamline the formation of β-proline derivatives (**Scheme 95**).



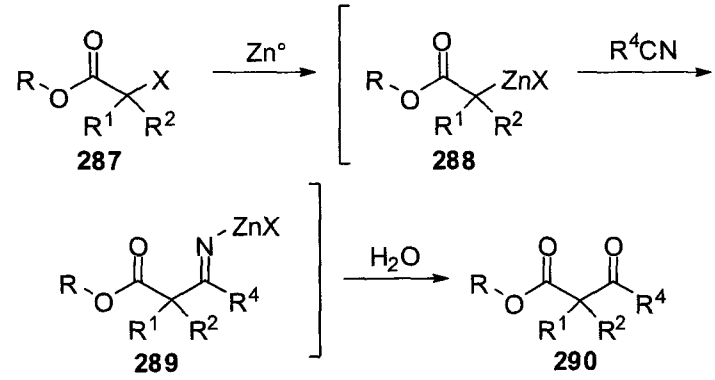
Scheme 95. Potential Access to β-Proline Derivatives via *N*-Cbz Imines

The *N*-Cbz imine (**283**) generated from benzaldehyde was subjected to the chain extension-imine capture reaction. By NMR analysis of the crude reaction mixture, it

appeared as if the imine capture product was obtained in very low yields. After attempting the deprotection of the crude reaction mixture through a transfer hydrogenation with ammonium formate and palladium on carbon, it was proposed that the initial imine capture reaction, in fact, did not take place. It is still unclear as to what happened during the reaction. It is important to note, however, that *N*-Cbz imines have been reported to react with nucleophiles,[144, 145] so the potential of the *N*-Cbz imine reacting in the chain extension imine capture reaction still exists.

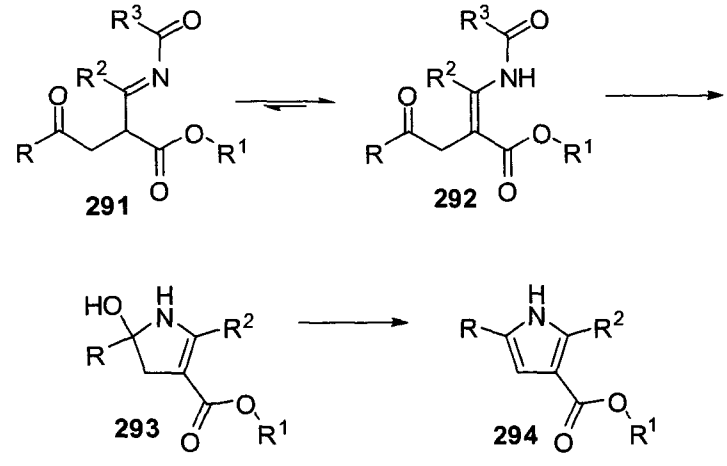
Use of Nitriles and Anhydrides as Electrophiles

In a final attempt to explore the methodology of the tandem chain extension reaction with carbon-nitrogen π-systems, nitriles were studied. One concern involved the formation of an imine anion, which would form upon nucleophilic attack into the nitrile. If this imine anion was allowed to react with aqueous acid, presumably during the quench of the reaction, the imine would be protonated and then hydrolyzed. A β-keto ester would be generated. The Blaise Reaction is a variation on the Reformatsky reaction and utilizes a nitrile as an acyl equivalent to produce a β-keto ester. The Blaise reaction involves the reaction of an α-halo ester (**287**) with zinc to generate an organometallic intermediate (**288**), which reacts with a nitrile (**289**) to provide a β-keto ester (**290**), after hydrolysis (**Scheme 96**).[146]



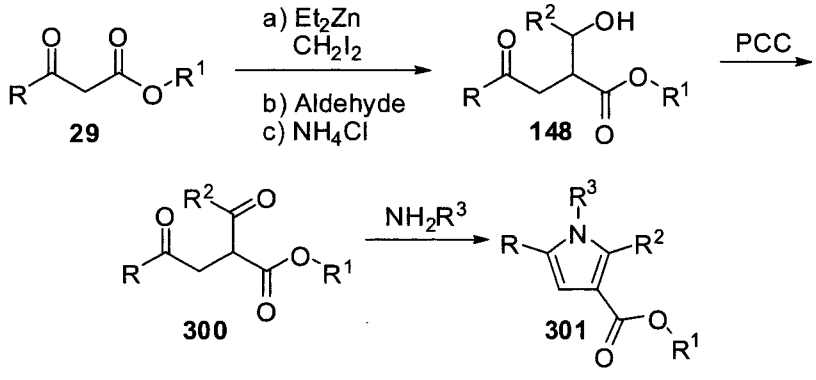
Scheme 96. Blaise Reaction

If the capture of the imine anion by an electrophile other then a proton were successful, the resulting intermediate (**291**) would most likely exist as the conjugated enamine **292**. Anhydrides or acid chlorides were viewed as reasonable reagents to use in trapping the intermediate as an enamine. If this hemiaminal (**293**) formation was not observed, groups that could be easily removed such as Boc anhydride could be used to trap the resultant imine anion which could eventually provide access to the pyrrole derivatives (**294**) through an additional step.



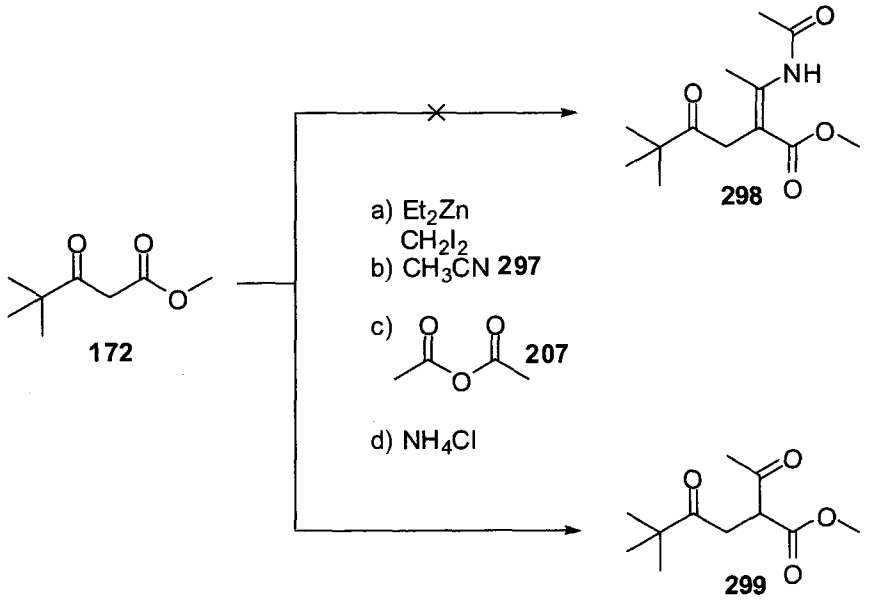
Scheme 97. Potential Pyrrole Derivates via Tandem Chain Extension Chemistry

The synthesis of pyrrole derivatives (**296**) through the use of a zinc-carbenoid chain extension reaction has been reported.[147] Taddei and co-workers synthesized the backbone through sequential application of tandem chain extension-aldol (**148**), oxidation (**295**), and condensation reactions (**296**) (**Scheme 98**). Use of a nitrile as the electrophile could allow access to the same class of molecules in fewer steps. If the dehydration reaction could be coupled with the chain extension reaction, the pyrrole backbone (**296**) could be formed in two steps from the starting β-keto ester (**29**).



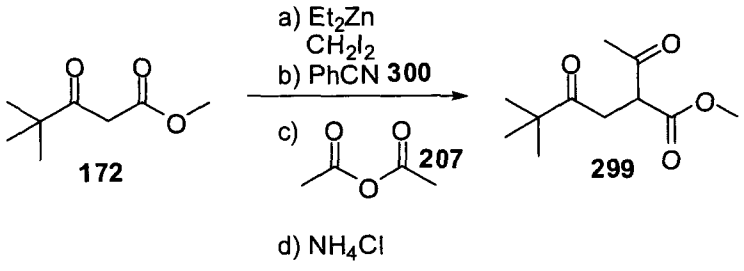
Scheme 98. Reported Three-Step Approach to Pyrrole Derivatives

Methyl pivaloylacetate (**172**) was subjected to the chain extension reaction conditions followed by the addition of acetonitrile (**297**) and acetic anhydride (**207**). The reaction was surprisingly clean. Unfortunately, the NMR of the product did not resemble the desired enamine **298**. Instead, it appeared as if a methyl ketone (**299**) was synthesized (**Scheme 99**). Since both acetonitrile and acetic anhydride were used, it was unclear as to whether the methyl came from a Blaise-like process or if the the enolate reacted directly with the acetic anhydride.



Scheme 99. Attempted Trapping of *N*-Acyl Imine Anion

In order to determine whether the acyl group was coming from a Blaise-type reaction or from the enolate reacting with the acetic anhydride (**207**), benzonitrile (**300**) was used (**Scheme 100**). The results of this reaction suggested that the nitrile was not reacting with the enolate generated through the chain extension reaction. In order to understand this chemistry further studies are necessary. Both of the nitriles used in the exploration of the Blaise-like chemistry are not very electrophilic. It is possible that more electrophilic nitriles could react with the zinc-enolate generated during the chain extension reaction.



Scheme 100. Determination of Source of Acyl Group

Even though the synthesis of pyrrole-derivatives was not successful through the use of nitriles, the results were exciting because a tandem chain extension reaction that used anhydrides as electrophiles had not been reported previously. Acetic anhydride is a simple anhydride and the ^{1}H and ^{13}C NMR of the crude reaction mixture showed very clean conversion and purification of the product was not necessary. The potential for the use of other anhydrides in a tandem process is strong.

CHAPTER IV

EXPERIMENTAL SECTION

Solvents

Anhydrous solvents were obtained from an Innovative Technology Inc. Solvent Delivery System prior to use by passing through a column of molecular sieves.

Reagents

Unless otherwise noted, all reagents were obtained from commercial sources and were used as received. Aldehydes and amines were dried and distilled prior to use.

Chromatography

Column chromatography was accomplished through use of Silica-P Flash Silica Gel with 40-63 μm particle size. Mobile phases were prepared as described in the detailed experimentals. TLC analysis was conducted on glass-backed TLC plates and visualized under UV light and through the use of phosphomolybdic acid stain. TLC solvent systems

were identical to the mobile phase use for column chromatography, unless otherwise noted.

Spectroscopy

NMR spectroscopy was conducted using a Varian *Mercury* spectrometer, which operated at 400 MHz for ^{1}H and at 100 MHz for ^{13}C analysis. All carbon spectra were proton decoupled. All shifts are reported downfield relative to TMS which was assigned 0.0 ppm in both ^{1}H and ^{13}C NMR analysis. IR Spectroscopy was conducted using a Thermo Nicolet iS10 FTIR using the diamond ATR probe.

DETAILED EXPERIMENTAL SECTION

Methyl 5-hydroxy-5-(methoxymethyl)-2,2-dimethyltetrahydrofuran-3-carboxylate (112)

An oven-dried, one-necked, 100-mL round-bottomed flask, equipped with a magnetic stir bar and rubber septum, was charged with dichloromethane (20 mL) via syringe and flushed with nitrogen. The flask was placed in an ice bath and diethylzinc (1 M solution in hexanes) (3.00 mmol, 3.00 mL, 3.00 equiv) was added via syringe followed by slow addition of diiodomethane (3.30 mmol, 0.26 mL, 3.10 equiv) via syringe over 5 min. The resulting solution was allowed to stir for approximately 10 min. Methyl 4-methoxyacetoacetate (1.00 mmol, 0.13 mL, 1.00 equiv) was added via syringe over 5 min and was allowed to stir for an additional 30 min. Acetone (2.00 mmol, 0.15 mL, 2.00 equiv) was added via syringe over 1 min and the reaction mixture was monitored by TLC

(15:2, hexanes: ethyl acetate) until starting material was almost completely gone. The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg) to afford a yellowish liquid. The crude reaction product was purified by flash chromatography (15:2, hexanes: ethyl acetate, R_f=0.13) to afford 0.14 g (0.63 mmol, 63% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 3.71 (s, 3H), 3.51-3.49 (m, 2H), 3.47 (s, 1H), 3.46-3.44 (m, 3H), 3.43 (s, 1H), 3.29 (dd, J=11.8, 7.2Hz, 1H), 2.93 (dd, J=8.5, 4.2 Hz, 1H), 2.52 (dd, J=14.0, 8.5 Hz, 1H), 2.32 (m, 1H), 2.12 (dd, J=12.9, 7.2Hz, 1H), 1.54 (s, 3H), 1.35 (m, 3H), 1.32 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.5, 172.4, 105.2, 103.4, 84.3, 83.9, 77.6, 76.8, 59.8, 53.4, 52.4, 52.1, 52.0, 51.9, 37.6, 37.4, 30.7, 29.6, 25.5, 24.7. IR (neat) ν 3437, 2979, 2829, 2250, 1721, 1445, 1366, 1105, 978, 916, 818, 732, 647, 533 cm^{-1}.

Methyl 2,2-dimethyl-5-oxotetrahydrofuran-3-carboxylate (113)

An oven-dried, one-necked, 25-mL round-bottomed flask was equipped with a magnetic stir bar, was charged with acetonitrile (8 mL) and water (2 mL), and acetone aldol product **112** (0.84 mmol, 0.18 g, 1.00 equiv). Ceric ammonium nitrate (CAN) (3.37 mmol, 1.85 g, 4.00 equiv) was added and allowed to stir. The reaction progress was monitored by TLC (5:1, hexanes: ethyl acetate) until starting material was almost completely gone (about 1 h). Water (5 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40

mmHg) to afford 0.12 g (0.70 mmol, 83% yield) of the product as a slightly colored oil which required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.78 (s, 3H), 3.26 (dd, J=9.3, 8.7 Hz, 1H), 3.15 (dd, J=18.0, 9.3 Hz, 1H), 2.80 (dd, 1H, J=18.0, 8.6 Hz, 1H), 1.62 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.6, 170.6, 86.3, 52.9, 50.5, 32.3, 28.5, 23.4. IR (neat) ν 3110, 2939, 2677, 1741, 1671, 1576, 1427, 1371, 1293, 1124, 997, 937, 844, 773 cm^{-1}.

Methyl 5-hydroxy-5-(methoxymethyl)-2-phenyltetrahydrofuran-3-carboxylate (108, 114)

An oven-dried, one-necked, 100-mL round-bottomed flask, equipped with a magnetic stir bar and rubber septum, was charged with dichloromethane (20 mL) via syringe and flushed with nitrogen. The flask was placed in an ice bath and diethylzinc (1 M solution in hexanes) (3.00 mmol, 3.00 mL, 3.00 equiv) was added via syringe, followed by slow addition of diiodomethane (3.30 mmol, 0.26 mL, 3.30 equiv) via syringe over 5 min. The resulting solution was allowed to stir for approximately 10 min. Methyl 4-methoxyacetoacetate (1.00 mmol, 0.13 mL, 1.00 equiv) was added via syringe over 5 min and was allowed to stir for an additional 30 min. Benzaldehyde (2.00 mmol, 0.20 mL, 2.00 equiv) was added via syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes: ethyl acetate) until starting material was almost completely gone (about 1 hr). The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg) to afford a yellowish liquid. The crude reaction product

was purified by flash chromatography (15:2, hexanes: ethyl acetate, R*f*=0.11) to afford 0.18 g (0.68 mmol, 68% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.43 (m, 5H), 5.55 (d, *J*=8.4 Hz, 1H), 5.44 (d, *J*=6.4 Hz, 1H), 5.34 (d, *J*=6.5 Hz, 1H), 5.22 (d, *J*=9.4 Hz, 1H), 3.55 (m, 1H), 3.17 (s, 1H), 3.13 (s, 1H), 2.36 (m, 1H), 2.06 (m, 1H), 2.04 (m, 1H), 1.39 (s, 1H), 1.26 (t, *J*=7.1 Hz, 1H), 0.93 (t, *J*=7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.9, 174.5, 173.0 172.9, 141.2, 140.9, 138.1, 128.6, 128.5, 128.2, 128.1, 128.0, 126.8, 126.2, 106.2, 105.4, 105.1, 104.8, 84.9, 84.4, 82.5, 81.6, 76.8, 76.4, 76.3, 76.0, 60.0, 59.9, 59.8, 52.6, 52.3, 51.8, 51.4, 51.3, 40.1, 38.2, 38.0, 37.2, 31.1, 21.2. IR (neat) ν 3437, 3061, 3031, 2991, 2948, 2829, 1732, 1493, 1445, 1371, 1199, 1020, 955, 831, 738, 702 cm^{-1}. *Representative ^{1}H Resonances for the Major Diastereomer* (**108**) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42-7.45 (m, 2H), 7.27-7.40 (m, 3H), 5.43 (d, *J*=6.4 Hz, 1H), 5.22 (d, *J*=9.4 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 3.62 (d, *J*=6.5 Hz, 1H), 3.57 (d, *J*=7.1 Hz, 1H) 3.50 (s, 3H), 3.48 (s, 3H), 3.41 (ddd, *J*=12.0, 9.3, 7.3 Hz, 1H), 3.07 (ddd, *J*=9.5, 6.2, 5.5 Hz, 1H), 2.37-2.43 (m, 2H)

Methyl 5-oxo-2-phenyltetrahydrofuran-3-carboxylate (110)[66]

An oven-dried, one-necked, 50-mL round-bottomed flask was equipped with a magnetic stir bar, was charged with acetonitrile (8 mL), water (2 mL), and benzaldehyde aldol product **108** (0.45 mmol, 0.12 g, 1.00 equiv). Ceric ammonium nitrate (CAN) (1.78 mmol, 0.98 g, 4.00 equiv) was added and allowed to stir. The reaction progress was monitored by TLC (5:1, hexanes: ethyl acetate) until starting material was almost completely gone (about 1 hr.). Water (4 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous

sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to give a slightly colored liquid. The crude reaction was purified by flash chromatography (1:1, hexanes: ethyl acetate, R*f*=0.23) to afford 0.08 g (0.36 mmol, 83% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34-7.43 (m, 5H), 5.66 (d, *J*=7.2 Hz, 1H), 3.78 (s, 3H), 3.37 (ddd, *J*=9.4, 8.7, 7.3 Hz, 1H), 2.96 (qd, *J*=17.8, 9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 171.5, 138.2, 129.2, 125.6, 82.4, 53.1, 48.8, 32.5. IR ν 3457, 3034, 2951, 1733, 1495, 1444, 1178, 1001, 760, 700 cm^{-1}.

Methyl 5-hydroxy-5-(methoxymethyl)-2-pentyltetrahydrofuran-3-carboxylate (119, 120)

An oven-dried, one-necked, 100-mL round-bottomed flask, equipped with a magnetic stir bar and rubber septum, was charged with dichloromethane (20 mL) via syringe and flushed with nitrogen. The flask was placed in an ice bath and diethylzinc (1 M solution in hexanes) (3.00 mmol, 3.00 mL, 3.00 equiv) was added via syringe followed by slow addition of diiodomethane (3.30 mmol, 0.26 mL, 3.30 equiv) via syringe over 5 min. The resulting solution was allowed to stir for approximately 10 min. Methyl 4-methoxyacetoacetate (1.00 mmol, 0.13 mL, 1.00 equiv) was added via syringe over 5 min and was allowed to stir for an additional 30 min. Hexanal (2.00 mmol, 0.25 mL, 2.00 equiv) was added via syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes: ethyl acetate) until starting material was almost completely gone (about 1 hr). The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried

over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg) to afford a yellowish liquid. The crude reaction product was purified by flash chromatography (15:2, hexanes: ethyl acetate, R*f*=0.16) to afford 0.16 g (0.59 mmol, 59% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.35 (dd, *J*=12.6, 5.9 Hz, 1H), 4.18 (dd, *J*=14.5, 6.4 Hz, 1H), 3.77-3.73 (m, 3H), 3.71 (s, 2H), 3.69 (d, *J*=4.4 Hz, 1H), 3.52 (dd, *J*=8.7, 1.1 Hz, 1H), 3.49 (d, *J*=0.7 Hz, 1H), 3.47 (s, 1H), 3.46-3.45 (m, 3H), 3.45 (s, 2H), 3.43 (d, *J*=3.4 Hz, 1H), 3.25 (s, 1H), 3.09 (dt, *J*=10.9, 8.0 Hz, 1H), 2.78 (dt, *J*=8.5, 5.7 Hz, 1H), 2.26 (d, *J*=3.9 Hz, 1H), 2.24 (d, *J*=2.9 Hz, 1H), 2.23-2.20 (m, 1H), 2.17 (dd, *J*=8.7, 4.1 Hz, 1H), 1.75-1.51 (m, 5H), 1.50-1.20 (m, 13H), 0.88 (td, *J*=6.9, 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.9, 173.8, 105.0, 104.5, 83.6, 81.9, 59.9, 52.7, 52.3, 48.3, 48.2, 39.3, 37.8, 36.9, 35.5, 31.9, 25.6, 25.3, 22.8, 14.2. IR (neat) ν 3432, 2937, 2351, 1730, 1447, 1370, 1268, 1197, 1107, 944 cm^{-1}.

Methyl 5-oxo-2-pentyltetrahydrofuran-3-carboxylate (121, 122)

An oven-dried, one-necked, 25-mL round-bottomed flask was equipped with a magnetic stir bar, was charged with acetonitrile (2 mL), water (0.5 mL), and hexanal aldol products **119** and **120** (0.07 mmol, 0.02 g, 1.00 equiv). Ceric ammonium nitrate (CAN) (0.28 mmol, 0.15 g, 4.00 equiv) was added and allowed to stir. The reaction progress was monitored by TLC (4:1, hexanes: ethyl acetate) until starting material was almost completely gone (about 5 hrs.). Water (2 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to afford the product 0.01 g (0.06 mmol, 81% yield) as a slightly colored oil

which required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.58 (td, J=7.5, 4.8 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.47-3.41 (m, 1H), 3.09-3.00 (m, 1H), 2.91 (dt, J=17.6, 7.3 Hz, 1H), 2.79 (dt, J=17.7, 6.2 Hz, 1H), 2.67 (dd, J=17.6, 8.7 Hz, 1H), 1.75 (dtt, J=12.3, 9.8, 5.1 Hz, 1H), 1.60-1.46 (m, 2H), 1.45-1.24 (m, 5H), 0.93-0.81 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.1, 174.6, 171,7, 170.9, 131.1, 129.0, 82.1, 52.9, 45.8, 45.3, 44.5, 35.5, 32.5, 32.2, 31.9, 31.6, 29.9, 29.6, 25.7, 25.1, 22.6, 14.1. IR (neat) ν 2952, 2865, 1781, 1737, 1441, 1368, 1269, 1204, 1118, 1003, 950, 862 cm^{-1}.

Methyl 5-hydroxy-5-(methoxymethyl)-4-methyl-2-phenyltetrahydrofuran-3-carboxylate (139, 140)

An oven-dried, one-necked, 100-mL round-bottomed flask, equipped with a magnetic stir bar and rubber septum, was charged with dichloromethane (20 mL) via syringe and flushed with nitrogen. The flask was placed in an ice bath and methyl 4-methoxyacetoacetate (1.00 mmol, 0.13 mL, 1.00 equiv) was added via syringe followed by the slow addition of diethylzinc (1 M solution in hexanes) (3.00 mmol, 3.00 mL, 3.00 equiv) via syringe and allowed to stir for 10 min. 1, 1-diiodoethane (3.16 mmol, 0.28 mL, 3.16 equiv) was added via syringe over 5 min. The resulting solution was allowed to stir for approximately 2 hrs. Benzaldehyde (2.00 mmol, 0.20 mL, 2.00 equiv) was added via syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes: ethyl acetate) until starting material was almost completely gone (about 30 min). The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35

°C, 30 mmHg) to afford a pale-yellowish liquid. The crude reaction product was purified by flash chromatography (5:1, hexanes: ethyl acetate) to afford 0.16 g (0.57 mmol, 57% yield) of the product as a mixture of diastereomers as a colorless oil. *Representative ^1H Resonances for Single Diastereomer* (**139**) (R*f*=0.14) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.19 (m, 5H), 5.97 (s, 1H), 5.27 (d, *J*=6.2 Hz, 1H), 3.58-3.53 (m, 2H), 3.45 (s, 3H), 3.43-3.35 (m, 1H), 3.20 (s, 3H), 2.96 (p, *J*=7.0 Hz), 1.13 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 105.3, 80.7, 74.4 59.9, 52.7, 52.3, 40.3, 32.5, 32.0, 26.1, 22.7, 14.2, 10.3. IR (neat) ν 3402, 2932, 2882, 2826, 1708, 1623, 1494, 1452, 1438, 1391, 1373, 1338, 1259, 1214, 1196, 1122, 1096, 1067, 999, 977, 965, 937, 914, 886, 831 cm^{-1}. *Representative ^1H Resonances for the Mixture of Other Diastereomers* (**140**) *(1.5:1,* R*f*=0.11*)* ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55-7.45 (m, 2H), 7.42-7.20 (m, 8H), 5.49-5.46 (m, 1H), 5.39 (d, *J*=4.1 Hz, 1H), 4.92 (d, *J*=9.7 Hz, 1H), 3.88 (s, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.59-3.56 (m, 2H), 3.48-3.47 (m, 6H), 3.13 (dd, *J*=9.7, 4.1 Hz, 1H), 2.86-2.75 (m, 1H), 2.70 (dq, *J*=14.4, 7.2 Hz, 1H), 1.08-1.03 (m, 3H), 0.99 (d, *J*=7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 171.6, 142.1, 141.7, 128.7, 128.5, 128.0, 127.9, 127.2, 125.9, 106.6, 106.0, 81.7, 81.3, 74.9, 74.3, 59.9, 56.5, 55.6, 52.8, 52.0, 45.5, 39.8, 10.7, 10.1. IR (neat) ν 3429, 3064, 3031, 2931, 2826, 2089, 1734, 1710, 1604, 1495, 1454, 1437, 1377, 1356, 1330, 1281, 1232, 1195, 1174, 1107, 1089, 1016, 975, 941, 925, 848, 792 cm^{-1}.

(2*R*,3*S*,4*R*)-Methyl 4-methyl-5-oxo-2-phenyltetrahydrofuran-3-carboxylate (141)[80]

An oven-dried, one-necked, 25-mL round-bottomed flask was equipped with a magnetic stir bar, was charged with acetonitrile (4 mL), water (1 mL), and the major diastereomer

benzaldehyde aldol product (**140**) (0.05 mmol, 0.02 g, 1.00 equiv). Ceric ammonium nitrate (CAN) (0.18 mmol, 0.10 g, 4.00 equiv) was added and allowed to stir. The reaction progress was monitored by TLC (4:1, hexanes: ethyl acetate) until starting material was almost completely gone (about 6 hr). Water (2 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to provide 0.01 g (0.04 mmol, 72% yield) of the product as a colorless oil which required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44-7.32 (m, 5H), 5.78 (d, J=6.6 Hz, 1H), 3.77 (s, 3H), 3.48-3.38 (m, 2H), 3.13-3.03 (m, 1H) 1.29 (d, J=7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.5, 170.4, 137.9, 121.1, 129.0, 125.6, 80.0, 53.3, 52.6, 37.3, 12.1. IR (neat) 3408, 2931, 1784, 1733, 1593, 1447, 1371, 1280, 1203, 1114, 1040, 1003 cm^{-1}.

(2*S*,3*S*,4*R*)-Methyl-5-hydroxy-5-(methoxymethyl)-4-methyl-2-pentyltetrahydrofuran-3-carboxylate (143)

An oven-dried, one-necked, 100-mL round-bottomed flask, equipped with a magnetic stir bar and rubber septum, was charged with dichloromethane (20 mL) via syringe and flushed with nitrogen. The flask was placed in an ice bath and methyl 4-methoxyacetoacetate (1.00 mmol, 0.13 mL, 1.00 equiv) was added via syringe followed by the slow addition of diethylzinc (1 M solution in hexanes) (5.00 mmol, 5.00 mL, 5.00 equiv) via syringe and allowed to stir for 10 min. 1, 1-diiodoethane (5.00 mmol, 0.39 mL, 5.00 equiv) was added via syringe over 5 min. The resulting solution was allowed to stir for approximately 2 hrs. Hexanal (2.00 mmol, 0.25 mL, 2.00 equiv) was added via

syringe over 1 min and the reaction mixture was monitored by TLC (15:2, hexanes: ethyl acetate) until starting material was almost completely gone (about 2 h). The reaction mixture was quenched with saturated ammonium chloride (10 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 30 mmHg). The crude reaction product was purified by flash chromatography (15:2, hexanes: ethyl acetate, R*f*=0.14) to afford 0.14 g (0.51 mmol, 51% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (s, 1H), 4.02 (dt, *J*=7.3, 5.9 Hz, 1H), 3.75 (s, 3H), 3.42 (m, 7H), 3.08 (dd, *J*=6.8, 6.8 Hz, 1H), 2.76 (pentet, *J*=7.1 Hz, 1H), 1.61 (m, 2H), 1.43 (m, 3H) 1.29 (m, 9H), 1.06 (d, *J*=7.2 Hz, 3H), 0.89 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.2, 105.3, 80.7, 74.4 59.9, 52.7, 52.3, 40.3, 32.5, 32.0, 26.1, 22.7, 14.2, 10.3. IR (neat) ν 3434, 2937, 2353, 1714, 1449, 1386, 1200, 1124, 1006 cm^{-1}.

(2*S*,3*S*,4*R*)-Methyl 4-methyl-5-oxo-2-pentyltetrahydrofuran-3-carboxylate (144)[73]

An oven-dried, one-necked, 25-mL round-bottomed flask was equipped with a magnetic stir bar, was charged with acetonitrile (4 mL), water (1 mL), and hexanal aldol product **143** (0.19 mmol, 0.05 g, 1.00 equiv). Ceric ammonium nitrate (CAN) (0.77 mmol, 0.42 g, 4.00 equiv) was added and allowed to stir. The reaction progress was monitored by TLC (4:1, hexanes: ethyl acetate) until starting material was almost completely gone (about 6 hrs.). Water (2 mL) was added and the solution was extracted with diethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, gravity filtered, and concentrated on a rotary evaporator (35 °C, 40 mmHg) to afford 0.03

g (0.14 mmol, 77% yield) of the product as a slightly colored oil which required no further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.41 (dt, *J*=8.5, 5.1 Hz, 1H), 3.74 (s, 3H), 3.33 (dd, *J*=7.5, 5.1 Hz, 1H), 2.92 (pentet, *J*=7.2 Hz, 1H), 1.80-1.69 (m, 1H), 1.62-1.46 (m, 2H), 1.45-1.27 (m, 6H), 1.24 (d, *J*=7.1 Hz, 3H), 0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.7, 170.3, 79.4, 52.0, 50.9, 39.4, 31.6, 31.1, 25.7, 22.6, 14.1, 10.6. IR (neat) ν 2951, 2867, 1779, 1736, 1634, 1559, 1444, 1378, 1345, 1275, 1180, 1131, 995, 876, 797, 769, 631, 594, 475, 453, 434 cm^{-1}.

Methyl 2-((diphenylphosphorylamino)(phenyl)methyl)-5,5-dimethyl-4-oxohexanoate (171)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (5.00 mmol, 0.50 mL, 5.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (5.00 mmol, 0.38 mL, 5.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Methyl pivaloylacetate (1.00 mmol, 0.14 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. *N*-Phosphinoylimine **169** (0.50 mmol, 0.15 g, 0.50 equiv) was mixed with dichloromethane (5 mL) and dried with 4Å molecular sieves. The solution was added to the round-bottomed flask via syringe and the solution was allowed to stir for 48 h. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (2 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C,

25 mmHg). The crude reaction mixture was purified via column chromatography (15:2, hexanes: ethyl acetate, R*f*=0.22) to afford 0.13 g (0.27 mmol, 27% yield) of the product as a white solid (M.P. = 168-172 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80-7.73 (m, 2H), 7.68-7.61 (m, 2H), 7.50-7.36 (m, 5H), 7.31-7.36 (m, 4H), 7.14-7.08 (m, 2H), 4.37 (dt, *J*=12.3, 6.2 Hz, 1H), 4.09 (br t, *J*= 10.6 Hz, 1H), 3.46-3.35 (m, 4H), 3.05 (dd, *J*=6.5, 3.3 Hz, 2H), 1.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.7, 173.4, 141.4 (d, $J_{C\text{-}P}$=3.7 Hz), 132.9 (d, $J_{C\text{-}P}$=9.8 Hz), 132.1 (d, $J_{C\text{-}P}$=12.0 Hz), 131.8 (d, $J_{C\text{-}P}$=9.6 Hz), 128.7 (d, $J_{C\text{-}P}$=15.2 Hz), 128.5 (d, $J_{C\text{-}P}$=12.8 Hz), 127.8, 126.9, 57.2, 51.9, 48.5 (d, $J_{C\text{-}P}$=3.7 Hz), 44.2, 36.9, 26.7. IR (neat) ν 3250, 3059, 2950, 2904, 1771, 1741, 1725, 1698, 1474, 1434, 1366, 1304, 1184, 1106 cm $^{-1}$.

(2*R*, 3*R*)-Methyl 5-*tert*-butyl-2-phenylpyrrolidine-3-carboxylate (178)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum. The flask was charged with methanol (50 mL) via syringe, and flushed with nitrogen through a needle in a rubber septum. Thionyl chloride (0.5-1.0 mL) was added via syringe and the solution became strongly acidic (pH ~1-2). α-Substituted γ-keto ester **171** (0.27 mmol, 0.13 g, 1.00 equiv) was added as a solution in methanol (1-2 mL) and allowed to stir for 12 h. Sodium cyanoborohydride (0.05 g, 0.81 mmol, 3.0 equiv) was added in one portion and the solution was allowed to stir for 16 h. The reaction mixture was diluted with water (15 mL) and basified (pH ~12-13) with sodium hydroxide (20%). The basic mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was

purified via column chromatography (5:1, hexanes: ethyl acetate, R*f*=0.17) to afford 0.04 g (0.15 mmol, 56% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.42 (m, 2H), 7.34-7.28 (m, 2H), 7.24 (m, 1H), 4.38 (d, *J*=8.5 Hz, 1H), 3.63 (s, 3H), 3.13 (t, *J*=7.9 Hz, 1H), 2.73 (dd, *J*=18.0, 7.9 Hz, 1H), 2.10-1.93 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.4, 143.3, 128.5, 127.6, 127.1, 66.8, 65.8, 52.1, 51.9, 33.7, 31.4, 26.4. IR (neat) ν 2952, 2867, 1733, 1636, 1493, 1453 1435, 1392, 1361, 1243, 1165, 898 cm $^{-1}$.

tert-Butyl phenyl(phenylsulfonyl)methylcarbamate (187a)[109]

A 50-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar and flushed with nitrogen through a needle in a rubber septum. The flask was charged with *tert*-butyl carbamate (0.59 g, 5.00 mmol, 1.00 equiv) and tetrahydrofuran (1.5 mL). Water (3.5 mL), sodium benzenesulfinate (0.82 g, 5.00 mmol, 1.00 equiv), freshly distilled benzaldehyde, measured volumetrically by syringe (0.51 mL, 5.10 mmol, 1.02 equiv), and formic acid (97%, 1 mL) were added and stirred for 18 h at room temperature under nitrogen, during which time the desired product slowly precipitates. The resulting white solid was collected by use of a Büchner funnel and was washed with distilled water (15 mL). The washed solid was transferred to a 100-mL, one-necked, round-bottomed flask and was stirred in a mixture of hexane/dichloromethane (75/7.5 mL). The mixture was stirred for 2 h at room temperature. The solid was collected by use of a Büchner funnel and was washed with hexane/dichloromethane (45/4.5 mL). The solid was dried at room temperature under reduced pressure (0.5 mmHg) for 6 h to afford 1.11 g (3.19 mmol, 64% yield) of the product as white solid (M.P. = 148.0-149.5 °C, Lit. M.P. = 153-154 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, *J*=7.4 Hz, 2H), 7.64 (t, *J*=7.4 Hz, 1H),

7.53 (t, J=7.7 Hz, 2H), 7.40-7.46 (m, 5H), 5.94 (d, J=10.7 Hz, 1H), 5.81 (d, J=10.5 Hz, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7, 137.2, 134.1, 130.1, 130.0, 129.7, 129.3, 129.1, 128.9, 81.4, 74.1, 28.2. IR (neat) ν 3362, 3000, 2975, 2844, 1713, 1694, 1588, 1462, 1444, 1311, 1146, 1008, 930 cm^{-1}.

(*E*)-*tert*-Butyl benzylidenecarbamate (184a)[109]

A 100-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar, reflux condensor and flushed with nitrogen through a needle in a rubber septum. The flask was charged with anhydrous tetrahydrofuran (80 mL), flame-dried potassium carbonate (4.54 g, 32.9 mmol, 6.00 equiv), and *N*-Boc sulphone **187a** (1.91 g, 5.49 mmol, 1.00 equiv). The reaction mixture was stirred and refluxed under nitrogen for 16 h, filtered through a Büchner funnel with two alternating layers of sodium sulfate and celite, and washed with anhydrous tetrahydrofuran (30 mL). The filtrate was concentrated at 30 °C (water bath temperature) by rotary evaporation (25 mmHg) and dried under vacuum (0.5 mmHg) to afford 0.89 g (4.34 mmol, 79% yield) of the product as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.80 (s, 1H), 7.84 (d, J=7.1 Hz, 2H), 7.48 (m, 1H), 7.39 (t, J=7.5 Hz, 2H) 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 162.8, 134.3, 133.6, 130.3, 129.0, 82.3, 28.1. IR (neat) ν 3368, 3063, 2979, 2933, 2245, 1964, 1716, 1635, 1580, 1476, 1453, 1391, 1368, 1314, 1254, 1215, 1152, 1074 cm^{-1}.

(*S*)-Methyl 2-((*R*)-(*tert*-butoxycarbonylamino)(phenyl)methyl)-5,5-dimethyl-4-oxohexanoate (188a)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (3.00 mmol, 0.24 mL, 3.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Methyl pivaloylacetate (1.00 mmol, 0.24 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184a** (1.00 mmol, 0.21 mL, 1.00 equiv) was added as a solution in 3.00 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 h, during which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL) and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromotograpy on alumina (5:1, hexanes: ethyl acetate, R*f*=0.27) to afford 0.20 g (0.52 mmol, 52% yield) of the product as a colorless oil. The crude reaction mixture was a mixture of the desired product and the deprotected cyclic imine. The mixture could be used for further chemistry without purification as well. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.30 (m, 2H), 7.27-7.23 (m, 3H), 5.76 (d, *J*=8.4 Hz, 1H), 4.86 (d, *J*=7.1 Hz, 1H), 3.54 (s, 3H), 3.33 (s, 1H), 2.93 (dd, *J*=18.2, 8.9 Hz, 1H), 2.80 (m, 1H), 1.42 (s, 9H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.4, 174.5,

155.4, 140.7, 128.7, 127.7, 126.3, 79.8, 55.1, 52.1, 46.2, 44.2, 37.4, 28.5, 26.5. IR (neat) ν 3380, 3062, 3030, 2974, 2907, 2875, 1707, 1498, 1455, 1436, 1391, 1366, 1283, 1168, 737 cm^{-1}.

(2*R*, 3*S*)-Methyl 5-*tert*-butyl-2-phenyl-3,4-dihydro-2H-pyrrole-3-carboxylate (191a)

A 20-mL scintillation vial was charged with α-substituted γ-keto ester **188a** (0.38 g, 1.00 mmol, 1.00 equiv), dichloromethane (10 mL) and a magnetic stir bar. The vial was place in an ice-water bath and trifluoroacetic acid (1.5 mL) was added dropwise over a 5 min period. The ice-water bath was removed and the reaction was allowed to stir for 8 h. The mixture was diluted with dichloromethane (10 mL), extracted with water (2 x 15 mL), washed with saturated sodium bicarbonate (3 x 15 mL), dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography (5:1 hexanes: ethyl acetate, R*f*=0.15) to afford 0.23 g of the product (0.89 mmol, 89% mass recovered based on a mixture of **188a** and **191a** as starting materials). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.17 (m, 3H), 7.09-7.04 (m, 2H), 5.51 (d, *J*=9.3 Hz, 1H), 3.53 (td, *J*=9.3, 6.5 Hz, 1H), 3.20 (ddd, *J*=17.3, 6.5, 1.9 Hz, 1H), 3.12 (s, 3H), 2.76 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.8, 172.9, 138.9, 128.1, 127.7. 127.5, 77.8, 51.4, 48.6, 36.8, 36.4 28.5. IR (neat) ν 3062, 3029, 2962, 2926, 2868, 1737, 1638, 1493, 1454, 1435, 1363, 1268, 1202, 1174, 1104, 1076, 1033, 1006, 913, 734 cm^{-1}.

(2*R*, 3*S*, 5*S*)-Methyl 5-*tert*-butyl-2-phenylpyrrolidine-3-carboxylate (190a)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar and rubber septum. The flask was charged with methanol (50 mL) via syringe, and flushed with nitrogen through a needle in a rubber septum. Thionyl chloride (0.5-1 mL) was added via syringe and the solution became strongly acidic (pH ~1-2). Cyclic imine **189a** (0.08 g, 0.27 mmol, 1.00 equiv) was added as a solution in methanol (1-2 mL) and allowed to stir for 5 min. Sodium cyanoborohydride (0.05 g, 0.81 mmol, 3.00 equiv) was added in one portion and the solution was allowed to stir for 16 h. The reaction mixture was diluted with water (15 mL) and basified (pH ~12-13) with sodium hydroxide (20%). The basic mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg) to afford 0.05 g (0.21 mmol, 79% yield) of the product as a colorless oil. The crude reaction mixture required no further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.25 (m, 4H), 7.23-7.17 (m, 1H) 4.49 (d, J=9.0 Hz, 1H), 3.30 (dt, J=8.7, 7.5 Hz, 1H), 3.12 (s, 3H), 2.99 (dd, J=10.2, 6.7 Hz, 1H), 2.29 (s, 1H), 2.00 (ddq, J=12.8, 9.4, 7.1 Hz, 1H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 140.8, 128.1, 127.4, 127.3, 68.7, 65.1, 51.2, 49.9, 33.1, 30.5, 26.9. IR (neat) ν 3350, 3062, 3030, 2955, 2927, 2867, 1960, 1899, 1737, 1623, 1577, 1493, 1450, 1436, 1364, 1299, 1206, 1174, 1106, 696 cm^{-1}.

***tert*-Butyl (4-methoxyphenyl)(phenylsulfonyl)methylcarbamate (187b)[119]**

A 50-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar and flushed with nitrogen through a needle in a rubber septum. The flask was charged

with *tert*-butyl carbamate (0.59 g, 5.00 mmol, 1.00 equiv) and tetrahydrofuran (1.50 mL). Water (3.5 mL), sodium benzenesulfinate (0.82 g, 5.00 mmol, 1.00 equiv), freshly distilled 4-methoxybenzaldehyde, measured volumetrically by syringe (0.62 mL, 5.10 mmol, 1.02 equiv), and formic acid (97%, 1 mL) were added and stirred for 18 h at room temperature under nitrogen, during which time the desired product slowly precipitates. The resulting white solid was collected by use of a Büchner funnel and was washed with distilled water (15 mL). The washed solid was transferred to a 100-mL, one-necked, round-bottomed flask and was stirred in a mixture of hexane/dichloromethane (75/7.5 mL). The mixture was stirred for 2 h at room temperature. The solid was collected by use of a Büchner funnel and was washed with hexane/dichloromethane (45/4.5 mL). The solid was dried at room temperature under reduced pressure (0.5 mmHg) for 6 h to afford 1.36 g (3.60 mmol, 72% yield) of the product as an off-white solid (M.P. = 142.5-144.5 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, J=7.5 Hz, 2H), 7.63 (t, J=7.4 Hz, 1H), 7.53 (t, J=7.7 Hz, 2H), 7.37 (d, J=8.6 Hz, 2H) 6.93 (m, 2H), 5.87 (d, J=10.7 Hz, 1H), 5.71 (d, J=10.6 Hz, 1H), 3.82 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 153.6, 137.3, 134.1, 130.4, 129.7, 129.2, 121.9, 114.5, 81.4, 73.7, 55.6, 28.2. IR (neat) ν 3363, 3004, 2963, 2839, 1696, 1609, 1585, 1506, 1463, 1426, 1307, 1240, 1140, 1082, 934, 839 cm^{-1}.

(*E*)-*tert*-Butyl 4-methoxybenzylidenecarbamate (184b)[119]

A 100-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar, reflux condensor and flushed with nitrogen through a needle in a rubber septum. The flask was charged with anhydrous tetrahydrofuran (80 mL), flame-dried potassium

carbonate (4.54 g, 32.9 mmol, 6.00 equiv), and *N*-Boc sulphone **187b** (1.91 g, 5.49 mmol, 1.00 equiv). The reaction mixture was stirred and refluxed under nitrogen for 16 h, filtered through a Büchner funnel with two alternating layers of sodium sulfate and celite, and washed with anhydrous tetrahydrofuran (30 mL). The filtrate was concentrated at 30 °C (water bath temperature) by rotary evaporation (25 mmHg) and dried under vacuum (0.5 mmHg) to afford 0.99 g (4.22 mmol, 77% yield) of the product as mixture of isomers as a yellow solid (M.P. = 57-60 °C) which is reported in the literature as an oil.[119] ^{1}H-NMR (400 MHz, $CDCl_3$) *Major Isomer* δ: 9.85 (s, 1H), 8.85 (s, 1H), 7.86 (d, *J*=8.9 Hz, 2H), 6.93 (d, *J*=8.9 Hz, 2H), 3.84 (s, 3H), 1.55 (s, 9H). *Minor Isomer* δ: 9.85 (s, 1H), 7.81 (d, *J*=8.9 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 3.85 (s, 3H), 1.42 (s, 9H) ^{13}C NMR (100 MHz, $CDCl_3$) δ: 190.9, 169.9, 164.4, 163.1, 132.7, 132.2, 127.1, 114.6, 82.0, 55.7, 28.1. IR (neat) ν 3963, 3865, 3733, 3671, 3647, 3330, 3068, 2931, 2741, 2638, 2421, 2319, 2132, 2040, 1927, 1696, 1576, 1457, 1256 1024 cm^{-1}.

Methyl 2-((*tert*-butoxycarbonylamino)(4-methoxyphenyl)methyl)-5,5-dimethyl-4-oxohexanoate (188b)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (3.00 mmol, 0.24 mL, 3.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Methyl pivaloylacetate (1.00 mmol, 0.24 mL, 1.00 equiv) was

added via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184b** (1.00 mmol, 0.24 mL, 1.00 equiv) was added as a solution in 3 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 hr in which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromotograpy on alumina (5:1, hexanes: ethyl acetate, R*f*=0.24) to afford 0.21 g (0.57 mmol, 57% yield) of the product as a colorless oil. The crude reaction mixture was a mixture of the desired product and the deprotected cyclic imine. The mixture could be used for further chemistry without purification as well. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, *J*=8.6 Hz, 2H), 6.88-6.80 (m, 2H), 5.67 (m, 1H), 4.80 (m, 1H), 3.78 (s, 3H), 3.60-3.52 (m, 3H), 2.92 (dd, *J*=18.2, 8.2 Hz, 1H), 2.17 (d, *J*=2.8 Hz, 1H), 1.39 (s, 9H), 1.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.5, 174.6, 159.1, 155.4, 127.5, 114.1, 55.5, 54.6, 54.0, 46.3, 44.2, 37.4, 29.5, 28.5, 26.5. IR (neat) ν 3386, 2970, 1706, 1610, 1512, 1366, 1292, 1247, 1168, 1030, 888, 835 cm^{-1}.

Methyl 5-*tert*-butyl-2-(4-methoxyphenyl)-3,4-dihydro-2H-pyrrole-3-carboxylate (189b)

A 20-mL scintillation vial was charged with α-substituted γ-keto ester **188b** (0.41 g, 1.00 mmol, 1.00 equiv), dichloromethane (10 mL) and a magnetic stir bar. The vial was place in an ice-water bath and trifluoroacetic acid (1.5 mL) was added dropwise over a 5 min period. The ice-water bath was removed and the reaction was allowed to stir for 8 h. The

mixture was diluted with dichloromethane (10 mL), extracted with water (2 x 15 mL), washed with saturated sodium bicarbonate (3 x 15 mL), dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography (5:1 hexanes: ethyl acetate, R*f*=0.13) to afford 0.27 g of the product as a colorless oil (0.92 mmol, 92% mass recovered based on a mixture of **188b** and **189b** as starting materials). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.02-6.97 (m, 2H), 6.83-6.76 (m, 2H), 5.47 (d, *J*=9.2 Hz, 1H), 3.76 (s, 3H), 3.51 (td, *J*=9.4, 6.8 Hz, 1H), 3.23-3.17 (m, 4H), 2.76 (ddd, *J*=17.3, 9.4, 0.7 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.3, 172.9, 159.1, 130.9, 128.6, 113.5, 77.3, 55.4, 51.5, 48.5, 36.6, 36.3, 28.5. IR (neat) ν 2962, 2869, 2838, 1735, 1637, 1612, 1585, 1512, 1461, 1438, 1363, 1248, 1176, 1036, 833, 732 cm^{-1}.

Methyl 5-*tert*-butyl-2-(4-methoxyphenyl)pyrrolidine-3-carboxylate (190b)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum. The flask was charged with methanol (50 mL) via syringe, and flushed with nitrogen through a needle in a rubber septum. Thionyl chloride (0.5-1 mL) was added via syringe and the solution became strongly acidic (pH ~1-2). Cyclic imine **189b** (0.08 mL, 0.27 mmol, 1.00 equiv) was added as a solution in methanol (1-2 mL) and allowed to stir for 5 min. Sodium cyanoborohydride (0.05 g, 0.81 mmol, 3.00 equiv) was added in one portion and the solution was allowed to stir for 16 h. The reaction mixture was diluted with water (15 mL) and basified (pH ~12-13) with sodium hydroxide (20%). The basic mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a

rotary evaporator (35 °C, 25 mmHg) to afford 0.06 g (0.22 mmol, 82% yield) of the product as a colorless oil. The crude reaction mixture required no further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25-7.22 (m, 2H), 6.83-6.79 (m, 2H), 4.45 (d, J=9.1 Hz, 1H), 3.78 (s, 3H), 3.25 (m, 1H), 3.17 (s, 3H), 2.96 (dd, J=10.2, 6.5 Hz, 1H), 2.04 (ddd, J=12.7, 10.4, 7.7 Hz, 1H), 1.99-1.87 (m, 2H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 158.9, 133.2, 128.5, 113.4, 68.7, 64.5, 55.4, 51.2, 49.9, 33.1, 30.4, 26.9. IR (neat) v 2954, 2929, 2869, 1734, 1637, 1610, 1584, 1511, 1462, 1394, 1301, 1244, 1173, 1033, 933, 828 cm^{-1}.

tert-Butyl phenylsulfonyl(_p_-tolyl)methylcarbamate (187c)[119]

A 50-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar and flushed with nitrogen through a needle in a rubber septum. The flask was charged with *tert*-butyl carbamate (0.59 g, 5.00 mmol, 1.00 equiv) and tetrahydrofuran (1.5 mL). Water (3.5 mL), sodium benzenesulfinate (0.82 g, 5.00 mmol, 1.00 equiv), freshly distilled *p*-tolualdehyde, measured volumetrically by syringe (0.60 mL, 5.10 mmol, 1.02 equiv), and formic acid (97%, 1.00 mL) were added and stirred for 18 h at room temperature under nitrogen, during which time the desired product slowly precipitates. The resulting white solid was collected by use of a Büchner funnel and was washed with distilled water (15 mL). The washed solid was transferred to a 100-mL, one-necked, round-bottomed flask and was stirred in a mixture of hexane/dichloromethane (75/7.5 mL). The mixture was stirred for 2 h at room temperature. The solid was collected by use of a Büchner funnel and was washed with hexane/dichloromethane (45/4.5 mL). The solid was dried at room temperature under reduced pressure (0.5 mmHg) for 6 h to afford

1.21 g (3.35 mmol, 67% yield) of the product as white solid (M.P. = 158.0-160.5 °C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, *J*=7.5 Hz, 2H), 7.64 (t, *J*=7.2 Hz, 1H), 7.54 (t, *J*=7.7 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 5.88 (d, *J*=11.0 Hz, 1H), 5.70 (d, *J*=10.7 Hz, 1H), 2.38 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.7, 140.2, 137.2, 134.1, 129.7, 129.2, 129.0, 126.9, 81.4, 73.9, 28.2, 21.6. IR (neat) ν 3363, 2990, 2974, 2957, 1704, 1615, 1585, 1507, 1394, 1335, 1308, 1139, 1084, 933, 882, 852 cm^{-1}.

(*E*)-*tert*-Butyl 4-methylbenzylidenecarbamate (184c)[119]

A 100-mL, one-necked, round-bottomed flask was equipped with a magnetic stirring bar, reflux condensor and flushed with nitrogen through a needle in a rubber septum. The flask was charged with anhydrous tetrahydrofuran (80 mL), flame-dried potassium carbonate (4.54 g, 32.9 mmol, 6.00 equiv), and *N*-Boc sulphone **187c** (1.91 g, 5.49 mmol, 1.00 equiv). The reaction mixture was stirred and refluxed under nitrogen for 16 h, filtered through a Büchner funnel with two alternating layers of sodium sulfate and celite, and washed with anhydrous tetrahydrofuran (30 mL). The filtrate was concentrated at 30 °C (water bath temperature) by rotary evaporation (25 mmHg) and dried under vacuum (0.5 mmHg) to afford 0.95 g (4.33 mmol, 79% yield) of the product as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.84 (s, 1H) 7.79 (d, *J*=8.0 Hz, 2H) 7.24 (d, *J*=8.0 Hz, 2H) 2.39 (s, 3H) 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.1, 162.9, 144.7, 131.7, 130.5, 129.8, 82.2, 28.1, 22.0. IR (neat) ν 3360, 3061, 2980, 2977, 1960, 1701, 1666, 1507, 1310, 1142, 913, 982 cm^{-1}.

Methyl 2-((*tert*-butoxycarbonylamino)(*p*-tolyl)methyl)-5,5-dimethyl-4-oxohexanoate (188c)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (3.00 mmol, 0.24 mL, 3.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Methyl pivaloylacetate (1.00 mmol, 0.24 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184c** (1.00 mmol, 0.22 mL, 1.00 equiv) was added as a solution in 3.00 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 h, during which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromotograpy on alumina (5:1, hexanes: ethyl acetate, R*f*=0.23) to afford 0.19 g (0.55 mmol, 55% yield) of the product as a colorless oil. The crude reaction mixture was a mixture of the desired product and the deprotected cyclic imine. The mixture could be used for further chemistry without purification as well. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.13-7.11 (m, 4H), 5.69 (m, 1H), 4.81 (m, 1H), 3.55 (d, *J*=2.2 Hz, 1H), 3.30 (s, 3H), 2.92 (dd, *J*=18.2, 8.1 Hz, 1H), 2.75 (d, *J*=14.1 Hz, 1H), 2.32, (d, *J*=2.7 Hz, 3H), 2.16 (s, 3H), 1.41 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.5, 174.5, 163.1, 155.4,

137.3, 129.4, 126.5, 126.2, 79.7, 54.9, 54.0, 52.0, 46.2, 44.2, 37.4, 36.3, 31.1, 29.9, 28.5, 26.6, 26.5, 21.2. IR (neat) ν 3330, 3131, 3094, 3050, 2968, 2874, 2733, 1902, 1698, 1651, 1556, 1455, 1366, 1285, 1044, 880 cm^{-1}.

Methyl 5-*tert*-butyl-2-*p*-tolyl-3,4-dihydro-2H-pyrrole-3-carboxylate (189c)

A 20-mL scintillation vial was charged with α-substituted γ-keto ester **188c** (0.27 g, 1.00 mmol, 1.00 equiv), dichloromethane (10.0 mL) and a magnetic stir bar. The vial was place in an ice-water bath and trifluoroacetic acid (1.5 mL) was added dropwise over a 5 min period. The ice-water bath was removed and the reaction was allowed to stir for 8 h. The mixture was diluted with dichloromethane (10 mL), extracted with water (2 x 15 mL), washed with saturated sodium bicarbonate (3 x 15 mL), dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromotographay (5:1, hexanes: ethyl acetate, R*f*=0.20) to afford 0.25 g of the product as a colorless oil (0.90 mmol, 90% mass recovered based on a mixture of **188c** and **189c** as starting materials). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, *J*=7.8 Hz, 2H), 6.95 (d, *J*=8.0 Hz, 2H), 5.48 (d, *J*=9.2 Hz, 1H), 3.53 (ddt, *J*=8.4, 7.0, 1.4 Hz, 1H), 3.18 (s, 4H), 2.76 (ddd, *J*=17.3, 9.4, 0.8 Hz, 1H), 2.29 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.4, 172.9, 137.1, 135.7, 128.8, 127.4, 77.6, 51.4, 48.5, 36.7, 36.3, 28.5, 21.3. IR (neat) ν 3350, 3131, 3094, 3050, 2968, 2874, 2733, 1902, 1698, 1651, 1556, 1455, 1366, 1285, 1079, 1044, 1019 cm^{-1}.

Methyl 5-*tert*-butyl-2-*p*-tolylpyrrolidine-3-carboxylate (190c)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum. The flask was charged with methanol (50 mL) via syringe, and flushed with nitrogen through a needle in a rubber septum. Thionyl chloride (0.5-1 mL) was added via syringe and the solution became strongly acidic (pH ~1-2). Cyclic imine **189c** (0.08 mL, 0.27 mmol, 1.0 equiv) was added as a solution in methanol (1-2 mL) and allowed to stir for 5 min. Sodium cyanoborohydride (0.05 g, 0.81 mmol, 3.00 equiv) was added in one portion and the solution was allowed to stir for 16 h. The reaction mixture was diluted with water (15 mL) and basified (pH ~12-13) with sodium hydroxide (20%). The basic mixture was extracted with dichloromethane (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg) to afford 0.06 g (0.21 mmol, 80% yield) of the product as a colorless oil. The crude reaction mixture required no further purification. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, *J*=8.0 Hz, 2H), 7.07 (d, *J*=7.9 Hz, 2H), 4.45 (d, *J*=9.0 Hz, 1H), 3.27 (dt, *J*=8.7, 7.6 Hz, 1H), 3.15 (s, 3H), 2.97 (dd, *J*=10.2, 6.6 Hz, 1H), 2.30 (s, 3H), 2.10-1.98 (m, 2H), 1.93 (ddd, *J*=12.8, 8.5, 6.6 Hz, 1H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 137.9, 136.9, 128.7, 127.3, 68.7, 64.9, 51.2, 49.9, 33.1, 30.6, 27.0, 21.3. IR (neat) ν 3346, 2952, 2926, 2859, 1738, 1513, 1435, 1366, 1201, 1165, 1108, 1042, 934, 820, 718 cm^{-1}.

***tert*-Butyl 2-((methylamino)(phenyl)methyl)-4-oxopentanoate (205)**

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water

bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (6.00 mmol, 0.24 mL, 6.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. *Tert*-butyl acetoacetate (1.00 mmol, 0.17 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184a** (1.00 mmol, 0.21 g, 1.00 equiv) was added as a solution in 3 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 hr in which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography on alumina (15:2 hexanes: ethyl acetate, R*f*=0.58) to afford 0.17 g (0.58 mmol, 58% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.32 (m, 2H), 7.32-7.25 (m, 3H), 4.50 (d, *J*=6.0 Hz, 1H), 3.23 (s, 3H), 3.13 (m, 1H), 2.96 (dd, *J*=17.5, 10.4 Hz, 1H), 2.52-2.43 (m, 2H), 2.11 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.4, 171.9, 139.2, 128.6, 128.1, 127.2, 83.9, 80.9, 57.5, 49.2, 40.6, 30.3, 28.0. IR (neat) ν 2977, 2931, 2824, 1717, 1494, 1454, 1392, 1365, 1314, 1253, 1149, 1090, 973 cm $^{-1}$.

1-(Pyrrolidin-1-yl)butane-1,3-dione (214)

A 250-mL round-bottomed flask was equipped with a magnetic stir bar and a reflux condenser. The flask was charged with acylated Meldrum's acid (**212**)[124] (7.00 g, 37.0 mmol, 1.25 equiv), pyrolidine (2.40 mL, 29.6 mmol, 1.00 equiv), and toluene (80 mL) and was flushed with nitrogen through a needle in a septum. The solution was allowed to

reflux for 15 h and the solution was concentrated under reduced pressure (30 °C, 25 mmHg). The crude reaction mixture was purified via column chromatography (1:1, hexanes: ethyl acetate, R*f*=0.53) to afford 2.98 g (25.9 mmol, 65% yield) of the product as a dark oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.51-3.46 (m, 5H), 3.44-3.40 (m, 3H), (2.29 (s, 3H), 2.01-1.93 (m, 4H). *Enol form resonance* δ: 4.99 (s, 1H), 1.91-1.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.6, 174.1, 170.4, 165.1, 88.9, 80.9, 51.3, 47.3, 46.2, 45.9, 45.0, 30.5, 26.1, 25.8, 24.5, 21.8. IR (neat) ν 3543, 2973, 2876, 2239, 1720, 1640, 1592, 1482, 1441, 1360, 1226, 1194, 1162 cm^{-1}.

tert-Butyl 4-oxo-1-phenyl-2-(pyrrolidine-1-carbonyl)pentylcarbamate (215)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (1.00 mmol, 0.10 mL, 1.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (1.00 mmol, 0.08 mL, 1.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Freshly prepared β-keto amide **214** (1.00 mmol, 0.15 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184a** (1.00 mmol, 0.21 mL, 1.00 equiv) was added as a solution in 3 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 h, during which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and

concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromatography on alumina (5:1 hexanes: ethyl acetate, R*f*=0.19) to afford 0.17 g (0.44 mmol, 44% yield) of the product as a dark oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.17 (m, 6H), 6.82 (d, *J*=8.4 Hz, 1H), 4.76 (dd, *J*=8.5, 2.8 Hz, 1H), 3.38 (dd, *J*=16.3, 6.9 Hz, 1H), 3.34-3.24 (m, 3H), 3.21-3.12 (m, 1H), 2.85-2.73 (m, 1H), 2.17 (s, 3H), 2.14-2.03 (m, 1H), 1.74-1.58 (m, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.2, 171.2, 155.8, 141.9, 128.8, 128.5, 127.6, 126.0, 79.5, 56.6, 46.5, 45.6, 45.5, 43.2, 30.2, 28.6, 25.8, 24.3. IR (neat) ν 3027, 2923, 2871, 1712, 1629, 1493, 1340, 1257, 1226, 1190, 1114, 1027 cm^{-1}.

(5-Methyl-2-phenyl-3,4-dihydro-2H-pyrrol-3-yl)(pyrrolidin-1-yl)methanone (216)

A 20-mL scintillation vial was charged with α-substituted γ-keto amide **215** (0.37 g, 1.00 mmol, 1.00 equiv), dichloromethane (10 mL) and a magnetic stir bar. The vial was place in an ice-water bath and trifluoroacetic acid (1.5 mL) was added dropwise over a 5 min period. The ice-water bath was removed and the reaction was allowed to stir for 8 h. The mixture was diluted with dichloromethane (10 mL), extracted with water (2 x 15 mL), washed with saturated sodium bicarbonate (3 x 15 mL), dried over sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromatography (5:1, hexanes: ethyl acetate, R*f*=0.23) to afford 0.23 g of the product as a colorless oil (0.89 mmol, 89% mass recovered based on a mixture of **215** and **216** as starting materials). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.24 (m, 1H), 7.08 (m, 1H), 5.51 (d, *J*=9.3 Hz, 1H), 3.74 (s, 1H), 3.55 (dt, 1H, *J*=9.3, 6.5 Hz), 3.24 (ddd, *J*=6.5, 1.9, 0.5 Hz, 1H), 3.19 (ddd, *J*=6.5, 1.9, 0.4 Hz, 1H), 2.78 (dd, *J*=17.3,

9.4 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.7, 172.9, 138.9, 128.1, 127.7. 127.5, 77.8, 51.4, 48.6, 36.8, 29.9, 28.5. IR (neat) ν 3062, 3029, 2962, 2926, 2868, 1737, 1638, 1493, 1454, 1435, 1363, 1268, 1202, 1174, 1104, 1076, 1033, 1006, 913, 734 cm^{-1}.

Ethyl 1-phenylpropylcarbamate (217)

This product was isolated from the chain extension-imine capture reaction with β-keto amide **214** and was verified to be the reaction of *N*-Boc imine **184a** and carbenoid through control studies. The mixture was purified via column chromatography on alumina (5:1 hexanes: ethyl acetate, R*f*=0.73) to afford 0.09 g (0.43 mmol, 43% yield) of the product as a colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.29 (m, 2H), 7.29-7.21 (m, 3H), 4.96 (m, 1H), 4.58 (m, 1H), 4.19-4.01 (m, 2H), 1.85-1.76 (m, 2H), 1.25-1.18 (m, 3H), 0.89 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.3, 142.8, 128.8, 127.4, 126.6, 60.9, 56.9, 29.9, 14.8, 10.9. IR (neat) ν 3318, 3030, 2966, 2933, 2875, 1687, 1529, 1454, 1378, 1332, 1281, 1171, 1083, 1042, 903, 836 cm^{-1}.

***N,N*,4,4-Tetramethyl-3-oxopentanamide (229)**

An oven-dried, one-necked, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with tetrahydrofuran (20 mL) via syringe, and flushed with nitrogen through a needle in a septum and was placed in an ice-water bath and was cooled to 0 °C. Freshly distilled diisopropylamine (10.0 mmol, 1.40 mL, 1.00 equiv) and *n*-butyllithium (2.5M in hexanes, 10.0 mmol, 4.00 mL, 1.00 equiv) were added via syringe and allowed to stir for 10 m. The flask was placed in dry ice-acetone

bath and was cooled to -78 °C. Freshly distilled *N,N*-dimethylacetamide (10.0 mmol, 0.92 mL, 1.00 equiv) was added and stirred for 30 min at -78 °C. Pivaloyl chloride (10.0 mmol, 1.22 mL, 1.00 equiv) was added and allowed to stir for 1 h while slowly warming to room temperature. After the reaction was complete it was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography (5:1 hexanes: ethyl acetate, R*f*=0.21) to afford 1.15 g (6.67 mmol, 67% yield) of the product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (s, 2H), 3.06-2.91 (m, 6H), 1.25-1.12 (m, 9H). *Enol form resonance* δ: 5.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.6, 185.0, 172.6, 167.6, 82.2, 44.7, 43.6, 37.9, 36.8, 35.3, 27.7, 26.3. IR (neat) ν 2964, 2872, 1706, 1640, 1619, 1597, 1500, 1479, 1464, 1392, 1368, 1350, 1270, 1218, 1166, 1061, 1014 cm^{-1}.

1-(2-Oxo-oxazolidin-3-yl)butane-1,3-dione (232)

A 250-mL round-bottomed flask was equipped with a magnetic stir bar and a reflux condenser. The flask was charged with acylated Meldrum's acid (**212**)[124] (11.76 g, 62.2 mmol, 1.25 equiv), oxazolidine (4.33 g, 49.8 mmol, 1.00 equiv), and toluene (100 mL) and was flushed with nitrogen through a needle in a septum. The solution was allowed to reflux for 8 h and the solution was concentrated under reduced pressure (30 °C, 25 mmHg). The crude reaction mixture was recrystallized from ethanol (2 x 95%) to afford 6.90 g (40.3 mmol, 81% yield) of the product as a dark brown solid (M.P. = 54.0-57.0 °C, Lit. M.P.[148] = 61-63 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (t, *J*=8.2 Hz, 2H), 4.09-

4.05 (m, 4H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1, 166.7, 153.9, 62.5, 51.2, 42.3, 30.3. IR (neat) ν 2985, 2904, 2853, 1768, 1724, 1701, 1526, 1477, 1420, 1396, 1362, 1334, 1256, 1188, 1047, 1014, 962, 880 cm^{-1}.

(2*R*,4*S*,5*S*)-tert-butyl 2-hydroxy-2-methyl-4-(2-oxooxazolidine-3-carbonyl)-5-phenylpyrrolidine-1-carboxylate (241)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (6.00 mmol, 0.48 mL, 6.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Freshly prepared β-keto imide **232** (1.00 mmol, 0.17 g, 1.00 equiv) was added as a solution in 3 mL of dichloromethane via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184a** (1.00 mmol, 0.21 mL, 1.00 equiv) was added as a solution in 3 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 h, during which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was recrystallized from hexanes to afford 0.23 g (0.59 mmol 59% yield) of the product as a crystalline solid as a mixture of hemiaminal isomers. *Mixture of Diastereomers* ^1H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.19 (m, 5H), 5.76 (d, *J*=9.5 Hz,

1H), 5.33 (d, *J*=8.7 Hz, 1H), 5.19 (s, 1H), 4.87-4.77 (m, 1H), 4.71 (m, 1H), 4.47-4.20 (m, 4H), 4.05-3.93 (m, 2H), 3.89-3.73 (m, 1H), 3.38-3.25 (m, 1H), 3.11 (dd, *J*=18.1, 11.1 Hz, 2H), 3.01-2.89 (m, 1H), 2.15-1.98 (m, 2H), 1.76 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 154.1, 153.5, 140.6, 128.3, 127.8, 126.8, 89.9, 80.7, 62.8, 62.5, 60.6, 45.2, 43.1, 42.7, 39.1, 28.5, 28.1, 27.2, 21.2, 14.4. IR (neat) ν 2977, 1779, 1693, 1672, 1478, 1455, 1363, 1310, 1272, 1221, 1166, 1105, 1037, 909, 843 cm^{-1}. *Representative ^{1}H Resonances for the Major Diastereomer* ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.19 (m, 5H), 5.33 (d, *J*=8.7 Hz, 1H), 5.19 (s, 1H), 4.45-4.20 (m, 4H), 3.87-3.71 (m, 1H), 3.37-3.28 (m, 1H), 3.01-2.87 (m, 1H), 2.15-1.99 (m, 2H), 1.76 (s, 3H), 1.08 (s, 9H).

(2*R*,3*S*)-*tert*-Butyl 5-methyl-3-(2-oxo-oxazolidine-3-carbonyl)-2-phenylpyrrolidine-1-carboxylate (242)

An oven-dried, one-necked, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (15 mL) via syringe, *N*-Boc hemiaminal **241** (0.72 mmol, 0.28 g, 1.00 equiv) and flushed with nitrogen through a needle in a septum. The flask was placed in dry ice-acetone bath and was cooled to -78 °C. Boron trifluoride etherate (0.78 mmol, 0.10 mL, 1.10 equiv) was added via syringe in one portion and allowed to stir for 10 min. Triethy silane (0.72 mmol, 0.12 mL, 1.00 equiv) was added via syringe in one portion and allowed to stir for 2 h. The solution was quenched with saturated sodium bicarbonate (5 mL) and was extracted with dichloromethane (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was

purified via flash column chromatography (4:1 hexanes: ethyl acetate, R*f*=0.19) to afford 0.20 g (0.53 mmol, 74% yield) of product as a sticky white solid. *Mixture of Diastereomers* ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31-7.18 (m, 3H), 7.14 (d, *J*=7.1 Hz, 2H), 5.41 (d, *J*=9.3 Hz, 1H) 5.32 (d, *J*=9.0 Hz, 1H), 4.40 (ddd, *J*=11.9, 9.3, 7.1 Hz, 1H), 4.29 (m, 1H), 4.20 (dt, *J*=16.2, 8.2 Hz, 1H), 3.93 (dt, *J*=17.2, 6.1, Hz, 1H), 3.78 (ddd, *J*=16.5, 9.5, 7.1 Hz, 1H), 3.26 (ddd, *J*=10.8, 9.3, 6.6 Hz, 1H), 2.48-2.35 (m, 1H), 2.16 (dt, *J*=13.4, 6.8 Hz, 1H), 1.61 (d, *J*=6.0 Hz, 3H), 1.38-1.18 (br s, 9H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 154.9, 153.4, 141.1, 128.2, 127.7, 126.9, 79.8, 64.2, 62.4, 53.8, 47.3, 42.7, 34.2, 28.4, 21.3 IR (neat) ν 2972, 2929, 1774, 1686, 1601, 1478, 1455, 1363, 1341, 1299, 1268, 1220, 1125, 1036, 1004, 977, 882 cm^{-1}. *Representative ^{1}H Resonances for the Major Diastereomer* ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 3H), 7.16-7.13 (m, 2H), 5.41 (d, *J*=9.3 Hz, 1H), 4.40 (ddd, *J*=11.9, 9.3, 7.1 Hz, 1H), 4.29 (tt, *J*=11.0, 5.5 Hz, 1H), 4.20 (dt, *J*=16.2, 8.2 Hz, 1H), 3.94 (tt, *J*=12.2, 6.2 Hz, 1H), 3.78 (ddd, *J*=16.5, 9.5, 7.1 Hz, 1H), 3.26 (ddd, *J*=10.8, 9.3, 6.6 Hz, 1H), 2.48-2.34 (m, 1H), 2.16 (dt, *J*=13.4, 6.8 Hz, 1H), 1.61 (d, *J*=6.0 Hz, 3H), 1.27 (s, 9H).

(*S*)-1-(4-Benzyl-2-oxooxazolidin-3-yl)butane-1,3-dione (250)

A 250-mL round-bottomed flask was equipped with a magnetic stir bar and a reflux condenser. The flask was charged with acylated Meldrum's acid (**212**)[124] (11.76 g, 62.2 mmol, 1.25 equiv), phenylalanine derived oxazolidine (8.80 g, 49.8 mmol, 1.00 equiv), and toluene (100 mL) and was flushed with nitrogen through a needle in a septum. The solution was allowed to reflux for 8 h and the solution was concentrated under reduced pressure (30 °C, 25 mmHg). The crude reaction mixture was recrystallized from ether to

afford 9.88 g (37.8 mmol, 76% yield) of the product as an orange solid (M.P. = 87-91 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.31 (m, 2H), 7.30-7.20 (m, 3H), 4.78-4.66 (m, 1H), 4.27-4.13 (m, 2H), 4.07 (s, 2H), 3.41-3.32 (m, 1H), 2.82 (dt, *J*=13.5, 8.5 Hz, 1H), 2.29 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.2, 180.5, 170.5, 166.6, 153.9, 135.5, 135.3, 129.7, 129.2, 127.6, 90.1, 66.6, 66.3, 55.2, 54.9, 51.6, 38.3, 37.9, 30.4, 22.4. IR (neat) ν 3069, 3026, 2998, 2930, 2865, 2122, 1780, 1740, 1716, 1686, 1602, 1581, 1491, 1408, 1216, 1176, 1077, 994, 862 cm^{-1}.

(*S*)-4-Benzyloxazolidin-2-one (249)

A 500-mL, one-necked, round-bottomed flask was equipped with a magnetic stir bar, a 125-mL pressure equalizing addition funnel, and was flushed with nitrogen through a needle in a rubber septum. The flask was charged with phenyl alanine amino alcohol (8.20 g, 54.25 mmol, 2.5 equiv) and dichloromethane (300 mL) and was placed in an ice water bath and cooled to 0 °C. Triethyl amine (18.78 mL, 113.92 mmol, 5.25 equiv) was added dropwise followed by slow addition of triphosgene (6.45 g, 21.7 mmol, 1 equiv) dissolved in dichloromethane (120 mL) over 2 h. The solution was allowed to stir for 16 h and was quenched with methanol/water (6/10 mL), stirred for 1 h and concentrated on a rotary evaporator (35 °C, 25 mmHg) to a residue. Ethyl acetate (100 mL) was added to the residue and was washed with 1M hydrochloric acid (2 x 50 mL), saturated sodium bicarbonate (2 x 50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). Diethyl ether (50 mL) was added to the concentrated solution and the solid product crashed out of the solution. The product was collected by use of a Büchner funnel to

afford 2.11 g (11.9 mmol, 55% yield) of the product as a yellow solid (M.P. = 79-81 °C, Lit. M.P.[149] = 87-88.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (t, *J*=7.6 Hz, 2H), 7.26 (t, *J*=6.7 Hz, 1H), 7.18 (d, 7.7 Hz, 2H), 6.18 (s, 1H), 4.41 (t, *J*=7.7 Hz, 1H), 4.11 (m, 2H), 2.88 (dq, *J*=13.6, 6.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.9, 136.1, 129.3, 129.1, 127.4, 69.7, 54.0, 41.6. IR (neat) ν 3261, 3060, 3031, 2999, 2968, 2940, 2921, 1738, 1699, 1603, 1548, 1496, 1406, 1365, 1282, 1247, 1196, 1095, 997, 935 cm^{-1}.

(*S*)-4-Isopropyloxazolidin-2-one (262)

A 250-mL, one-necked, round-bottomed flask was equipped with a magnetic stir bar, a reflux condenser, and was flushed with nitrogen through a needle in a rubber septum. The flask was charged with L-valine amino alcohol (9.95 g, 96.5 mmol, 1.00 equiv), diethyl carbonate (117 mL, 965 mmol, 10.0 equiv), and potassium carbonate (1.04 equiv) and was refluxed for 12 h. The reflux condenser was removed and the flask was equipped with a short distillation head and distilled (75 mL of diethyl carbonate). The concentrated mixture was washed with 1M sodium hydroxide (2 x 50 mL) and brine (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude mixture was recrystallized in diethyl ether to afford 3.24 g (25.1 mmol, 26% yield) of the product as a white solid (M.P. = 56-58 °C, Lit. M.P.[150] = 74-75 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.68 (s, 1H), 4.45 (t, *J*=8.7 Hz, 1H), 4.10 (dd, *J*=8.7, 6.3 Hz, 1H), 3.61 (dd, *J*=15.2, 6.7 Hz, 1H), 1.73 (qd, *J*=13.5, 6.8 Hz, 1H), 0.97 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 68.8, 58.6, 32.9, 18.2, 17.9. IR (neat) ν 3262,

3162, 2973, 2961, 2913, 2874, 1739, 1721, 1479, 1444, 1403, 1385, 1289, 1242, 1088, 1007, 961 cm^{-1}.

(*S*)-3-Acetyl4-isopropyloxazolidin-2-one (263)

A 25-mL, one-necked, round-bottomed flask was equipped with a magnetic stir bar, a reflux condenser, and was flushed with nitrogen through a needle in a rubber septum. The flask was charged with acetyl chloride (1.65 mL, 23.1 mmol, 3.00 equiv), pyridine (0.62 mL, 7.70 mmol, 1.00 equiv), and the flask was placed in an ice water bath and cooled to 0 °C. Chiral oxazolidinone **262** was added slowly and the thick solution was reluxed for 16 h. The solution was cooled to room temperature and was washed with 5% hydrochloric acid (2 x 5 mL), saturated sodium bicarbonate (2 x 5 mL), water (5 mL), and brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg) to afford 1.20 g (7.01 mmol, 91% yield) of the product as a dark oil. ^{1}H NMR (400 MHz, CDCl3) δ: 4.44 (m, 1H), 4.30 (t, *J*=8.7 Hz, 1H), 4.23 (dd, *J*=9.1, 3.0 Hz, 1H), 2.52 (s, 3H), 2.38 (m, 1H), 0.93 (d, *J*=7.1 Hz, 3H), 0.88 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.3, 154.4, 63.5, 58.4, 28.5, 23.9, 18.1, 14.7. IR (neat) ν 3543, 3388, 2965, 2877, 1783, 1703, 1486, 1466, 1376, 1305, 1209, 1151, 1120, 1063, 1040 cm^{-1}

(*S*)-Benzyl-2-(3-((*S*)-4-isopropyl-2-oxooxazolidin3-yl)-3-oxopropanyl)pyrrolidine-1-carboxylate (268)

A 25-mL, one necked round-bottomed flask was flushed with nitrogen through a needle in a septum and was charged with anhydrous tetrahydrofuran (10 mL), Cbz-protected L-

proline (**264**) (0.49 g, 2.00 mmol, 1.00 equiv), and 1,1-dicarbonyl imidazole (0.35 g, 2.20 mmol, 1.10 equiv). This mixture was manually swirled periodically for 15 m. In a separate 100-mL, one-necked round-bottomed flask was equipped with a stir bar and flushed with nitrogen through a needle in a septum. The flask was charged with anhydrous tetrahydrofuran (40 mL) and diisopropyl amine (1.12 mL, 8.00 mmol, 4.00 equiv) and placed in an ice-water bath and was cooled to 0 °C. After the solution was cooled, *n*-BuLi (2.5 M, 3.20 mL, 8.00 mmol, 4.00 equiv) was added and the solution was allowed to stir for 10 min. After 10 min, the solution was placed in a dry ice-acetone bath and was cooled to -78 °C and acylated oxazolidinone **268** (1.37 g, 8.00 mmol, 4.00 equiv, in 3 mL of anhydrous tetrahydrofuran) was added over 40 min via syringe pump. The acyl imidazole solution was transferred to the enolate solution via cannula and the mixture was allowed to stir at -78 °C for 3 h. After 3 h, the reaction was quenched by slow addition of 1M HCl (5 mL). The solution was extracted with diethyl ether (3 x 20 mL) and the combined organic layers were washed with brine (25 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromatography (hexanes: ethyl acetate 5:1, R*f*=0.21) to afford 0.50 g of the product (1.24 mmol, 62% yield) as a colorless oil as a mix of rotomeric forms. $[\alpha]^{24}_{D}$ -21.4°. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.26 (m, 5H), 5.22-5.03 (m, 2H), 4.51-4.35 (m, 2H), 4.33-4.16 (m, 3H), 4.08 (m, 1H), 3.64-3.43 (m, 2H), 2.47-2.35 (m, 1H), 2.33-1.78 (m, 4H), 1.00-0.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.5, 203.4, 166.7, 166.4, 155.5, 154.6, 154.5, 154.4, 136.8, 136.5, 128.7, 128.4, 128.3, 128.1, 67.6, 67.4, 65.6, 65.3, 63.8, 58.7, 48.5, 47.9, 47.5, 29.8,

28.6, 24.6, 23.7, 18.1, 14.8. IR (neat) ν 3385, 3033, 2963, 2879, 1776, 1696, 1631, 1485, 1413, 1359, 1266, 1210, 1115 cm^{-1}

(2'*S*)-1'-Benzyl 1-*tert*-butyl 2-hydroxy-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)-5-phenyl-2,2'-bipyrrolidine-1,1'-dicarboxylate (278)

An oven-dried, one-necked, 50-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (10 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (0.12 ml, 1.20 mmol, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (0.18 ml, 2.40 mmol, 6.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Freshly prepared amino acid-derived β-keto imide **268** (0.15 g, 0.41 mmol, 1.00 equiv) was added as a solution in 2 mL of dichloromethane via syringe and the solution was allowed to stir for 30 min. Freshly prepared *N*-Boc imine **184a** (0.09 g, 0.41 mmol, 1.00 equiv) was added as a solution in 2 mL of dichloromethane in one portion via syringe and the solution was allowed to stir for 15 h, during which the reaction slowly warmed to room temperature. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography (hexanes: ethyl acetate 8:1, R*f*=0.12) to afford 0.12 g (0.19 mmol, 47% yield) of the product as a sticky white solid. $[\alpha]^{24}_{D}$ +36.1°. ^{1}H-NMR (400 MHz, C_6D_6, 60 °C) δ: 7.82-7.65 (m, 3H), 7.43-7.37 (m, 1H), 7.32-7.15 (m, 6H), 6.77 (s, 1H), 6.04 (s, 1H), 5.46

(d, *J*=10.1 Hz, 1H), 5.30 (s, 1H), 4.57 (s, 1H), 3.97-3.92 (m, 1H), 3.78-3.46 (m, 6H), 2.44-2.38 (m, 1H), 1.85-1.78 (m, 2H), 1.70-1.52 (m, 6H), 1.31 (s, 9H), 0.87 (d, *J*=6.8 Hz, 1H), 0.75-0.61 (m, 3H), 0.59 (d, *J*=6.9 Hz, 3H), 0.47 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ: 168.6, 153.8, 141.3, 128.5, 128.2, 127.2, 94.6, 80.0, 67.2, 66.9, 64.4, 64.2, 63.4, 58.8, 47.6, 45.5, 38.1, 28.7, 28.2, 27.9, 27.7, 24.1, 17.7, 17.4, 15.1. IR (neat) ν 3334, 2968, 2509, 2161, 2026, 1978, 1774, 1695, 1586, 1496, 1410, 1303, 1204, 1039 cm^{-1}.

(2'*S*)-1'-Benzyl 1-*tert*-butyl 4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)-5-phenyl-2,2'-bipyrrolidine-1,1'-dicarboxylate (279)

An oven-dried, one-necked, 10-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (5 mL) via syringe, *N*-Boc hemiaminal **278** (0.09 mmol, 0.06 g, 1.00 equiv) and flushed with nitrogen through a needle in a septum. The flask was placed in dry ice-acetone bath and was cooled to -78 °C. Boron trifluoride etherate (0.10 mmol, 0.01 mL, 1.10 equiv) was added via syringe in one portion and allowed to stir for 10 min. Triethysilane (0.09 mmol, 0.02 mL, 1.00 equiv) was added via syringe in one portion and allowed to stir for 2 h. The solution was quenched with saturated sodium bicarbonate (5 mL) and was extracted with dichloromethane (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via flash column chromatography (5:1 hexanes: ethyl acetate, R*f*=0.11) to afford 0.04 g (0.06 mmol, 67% yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46-7.15 (m, 24H), 6.17 (d, *J*=9.6 Hz, 1H), 6.10 (d, *J*=9.6 Hz, 1H) 5.27-4.95

(m, 6H), 4.87-4.66 (m, 5H), 4.66-4.54 (m, 2H), 4.53-4.05 (m, 14H), 3.66-3.36 (m, 7H), 3.19-2.91 (m, 3H), 2.53-2.31 (m, 4H), 2.29-2.14 (m, 3H), 2.13-1.94 (m, 5H), 1.89-1.67 (9H), 1.49-1.18 (m, 26H), 1.02-0.81 (m, 13H), 0.77 (d, *J*=6.0 Hz, 3H), 0.70 (d, *J*=6.8 Hz, 3H), 0.68-0.53 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.6, 208.1, 174.3, 174.1, 155.3, 155.2, 155.1, 155.0, 154.4, 140.7, 140.6, 136.5, 129.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.2, 127.9, 127.1, 79.8, 79.7, 67.3, 67.2, 65.3, 64.7, 64.2, 64.1, 59.5, 57.0, 47.4, 46.9, 42.2, 40.9, 30.10, 29.9, 29.4, 29.3, 28.8, 28.5, 24.5, 23.8, 18.1, 15.3, 15.2. IR (neat) ν 2922, 2852, 1764, 1703, 1494, 1453, 1354, 1301, 1165, 1021 cm^{-1}.

Methyl 2-acetyl-5,5-dimethyl-4-oxohexanoate (299)

An oven-dried, one-necked, 100-mL round-bottomed flask was equipped with a magnetic stir bar, rubber septum, was charged with dichloromethane (20 mL) via syringe, and flushed with nitrogen through a needle in a septum. The flask was placed in an ice water bath, cooled to 0 °C, and neat diethylzinc (3.00 mmol, 0.30 mL, 3.00 equiv) was added via syringe in one portion followed by slow addition, over 30 sec, of diiodomethane (3.00 mmol, 0.24 mL, 3.00 equiv) via syringe. The resulting solution was allowed to stir for approximately 10 min. Methyl pivaloylacetate (1.00 mmol, 0.14 mL, 1.00 equiv) was added via syringe and the solution was allowed to stir for 30 min. Acetic anhdryide (1.00 mmol, 0.10 mL, 1.00 equiv) was added and allowed to stir for 2 h. The solution was quenched with saturated ammonium chloride (2 mL), extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator (35 °C, 25 mmHg). The crude reaction mixture was purified via column chromatography (10:1 hexanes: ethyl acetate, R*f*= 0.22) to afford 0.13 g (0.77 mmol, 77%

yield) of the product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (dd, J=8.4, 5.6 Hz, 1H), 3.74 (s, 3H), 3.24 (dd, J=18.4, 8.4 Hz, 1H), 3.02 (dd, J=18.5, 5.6 Hz, 1H), 2.37 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.6, 202.6, 169.7, 53.7, 52.8, 44.1, 36.1, 30.5, 26.7. IR (neat) ν 2958, 2873, 1743, 1702, 1479, 1462, 1435, 1362, 1269, 1203, 1062, 1036, 1001 cm^{-1}.

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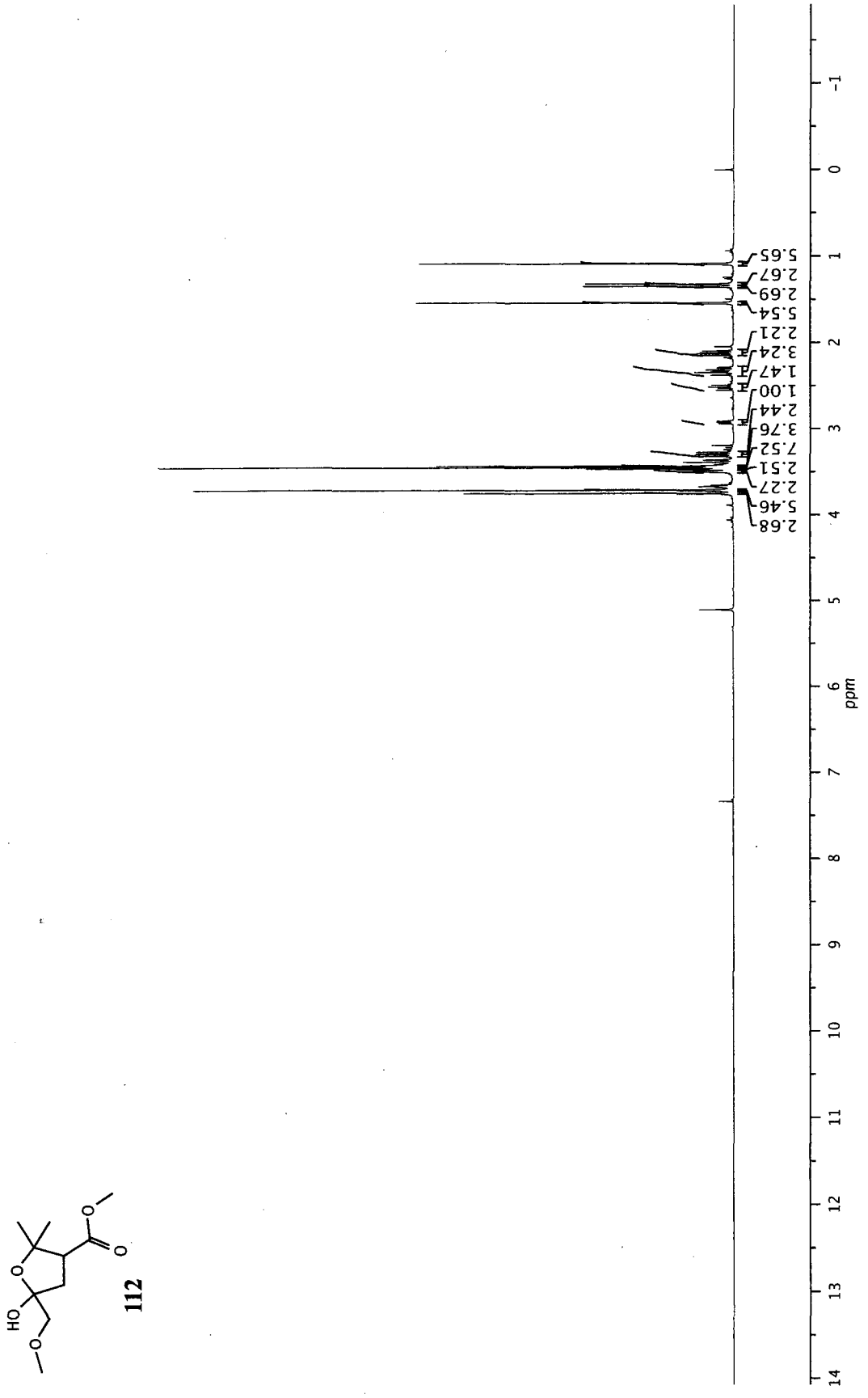
APPENDIX A

SPECTRA



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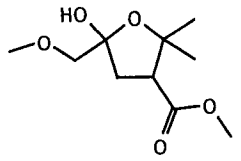

112

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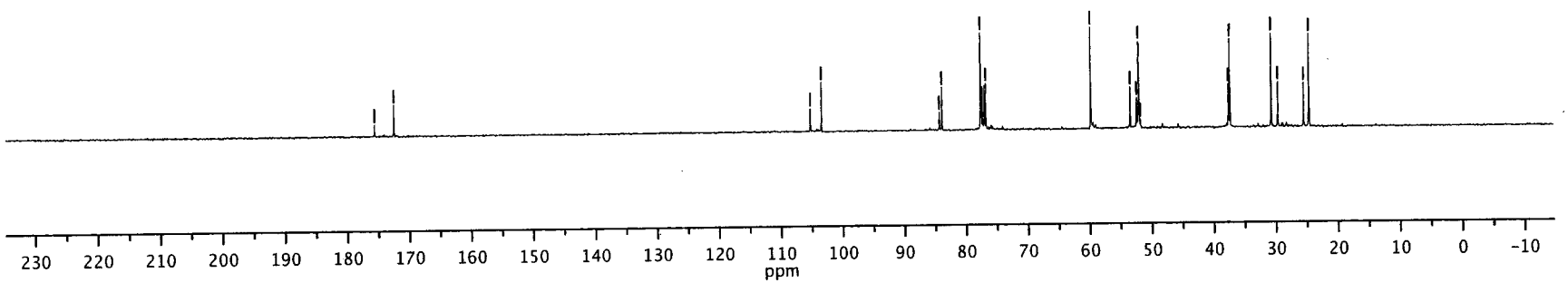

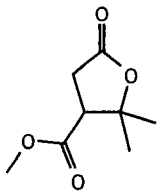

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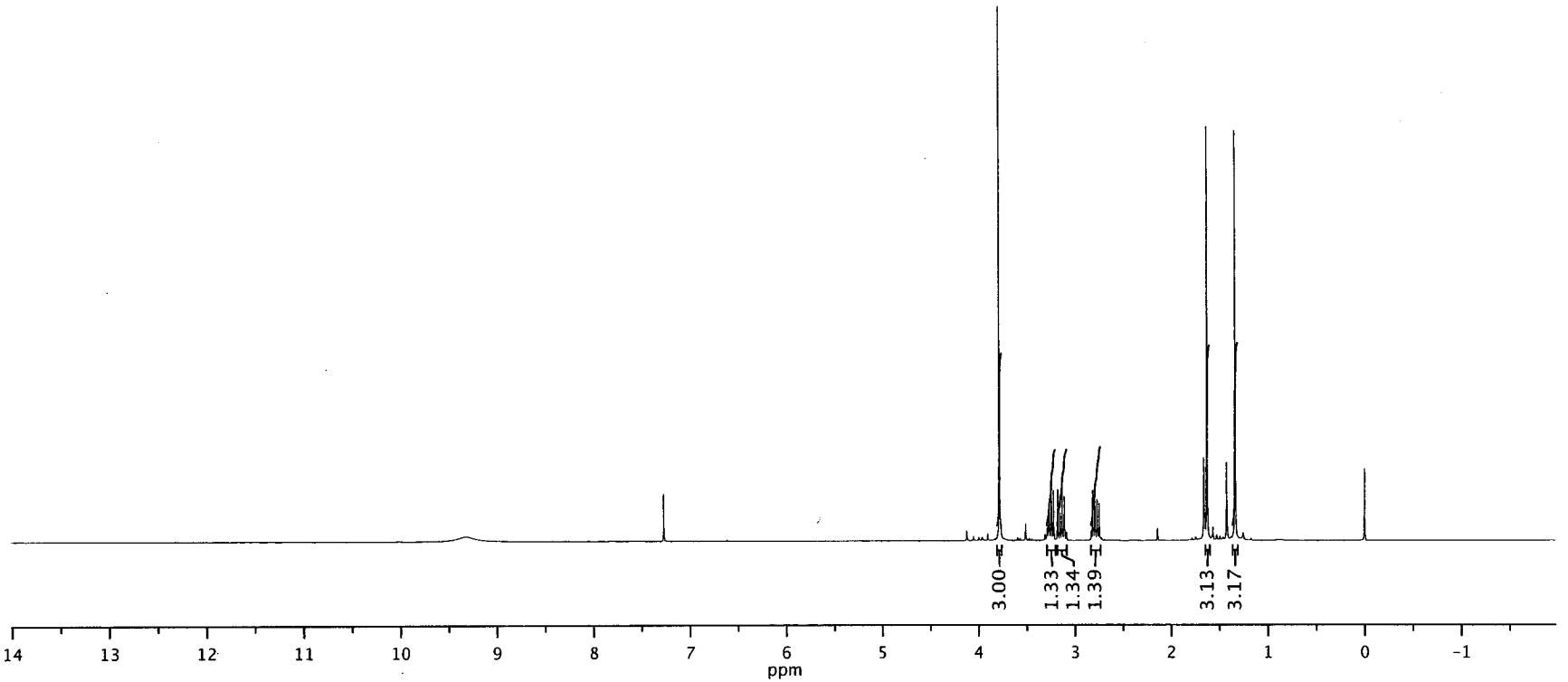

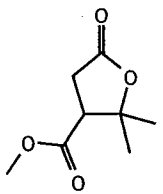

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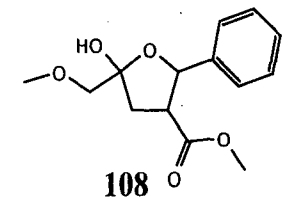
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O
O

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10.06
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1.83
3.13
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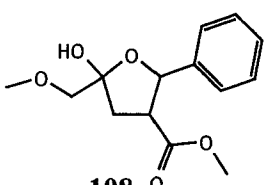

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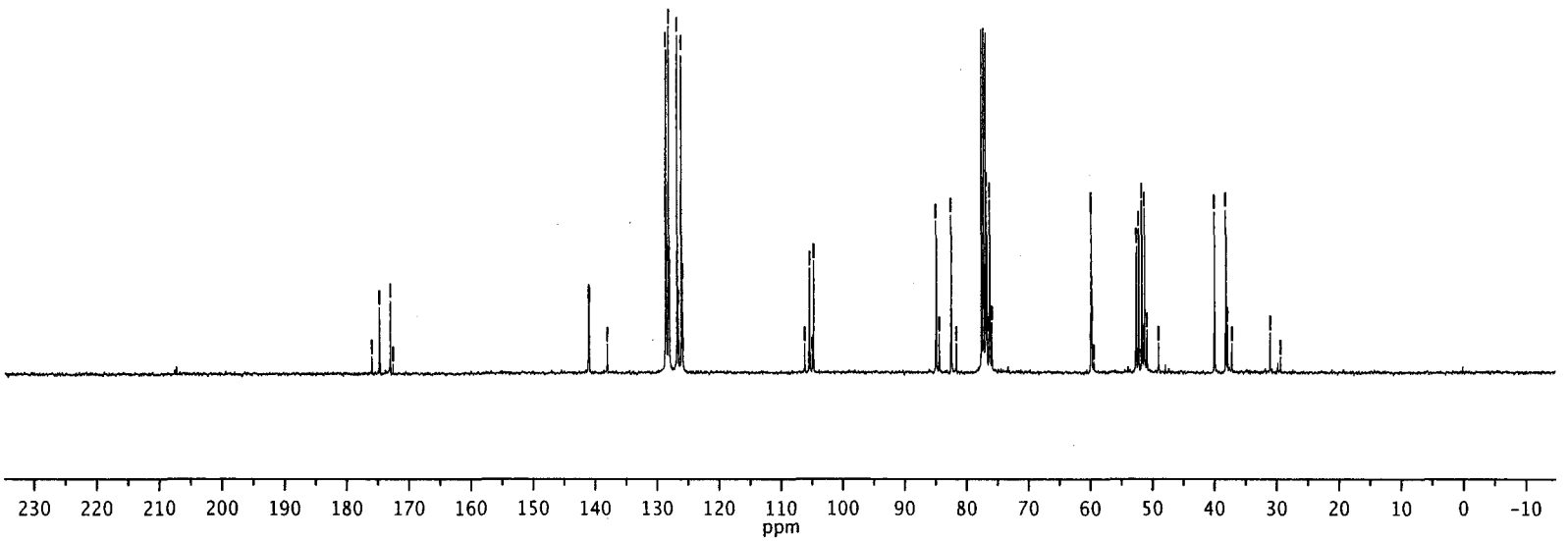

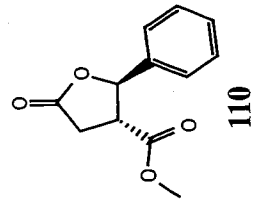

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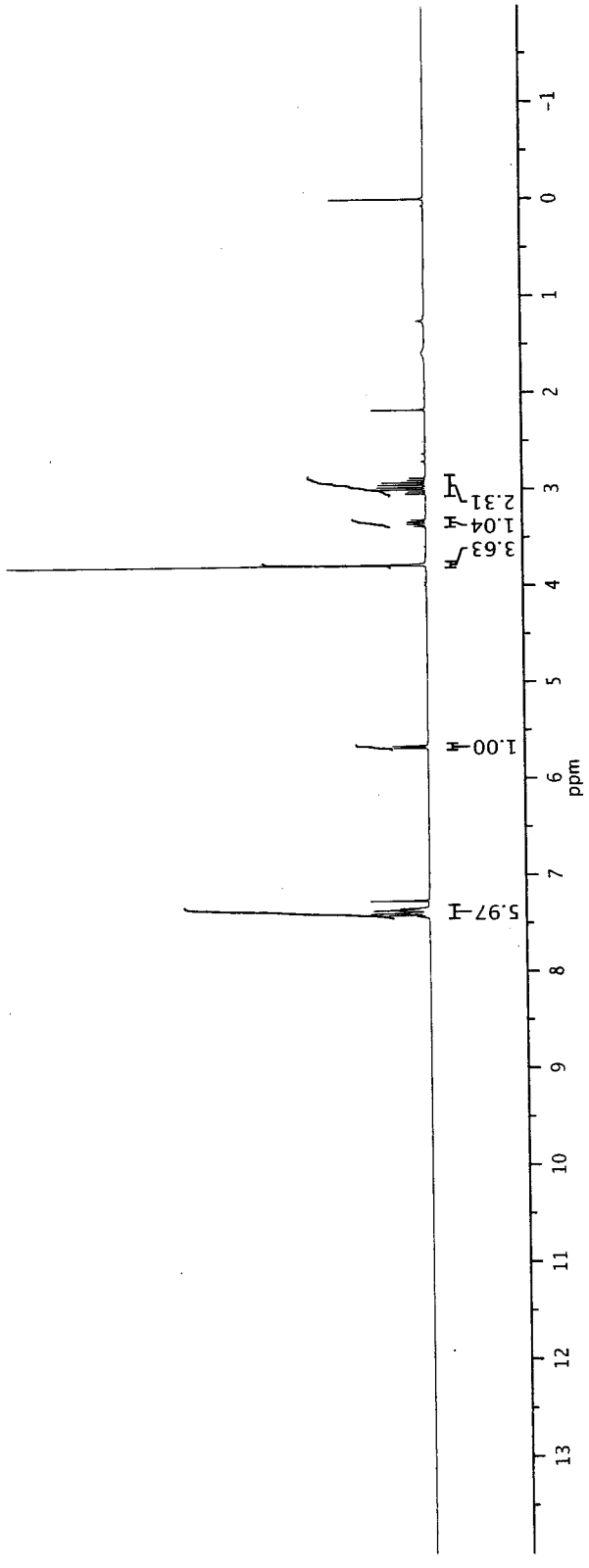

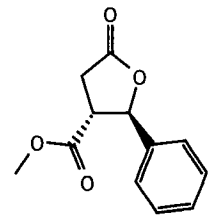

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32.50
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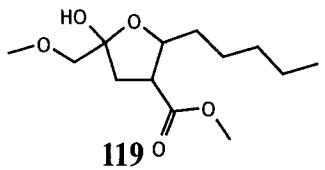
ppm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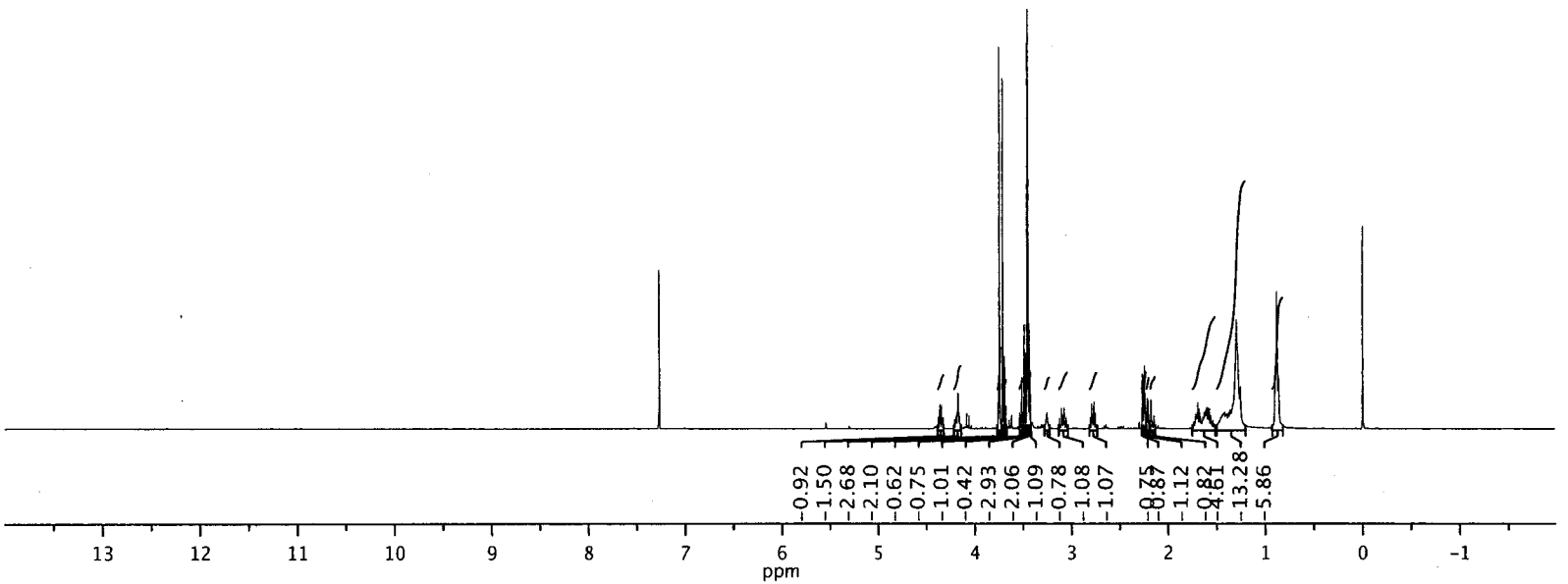
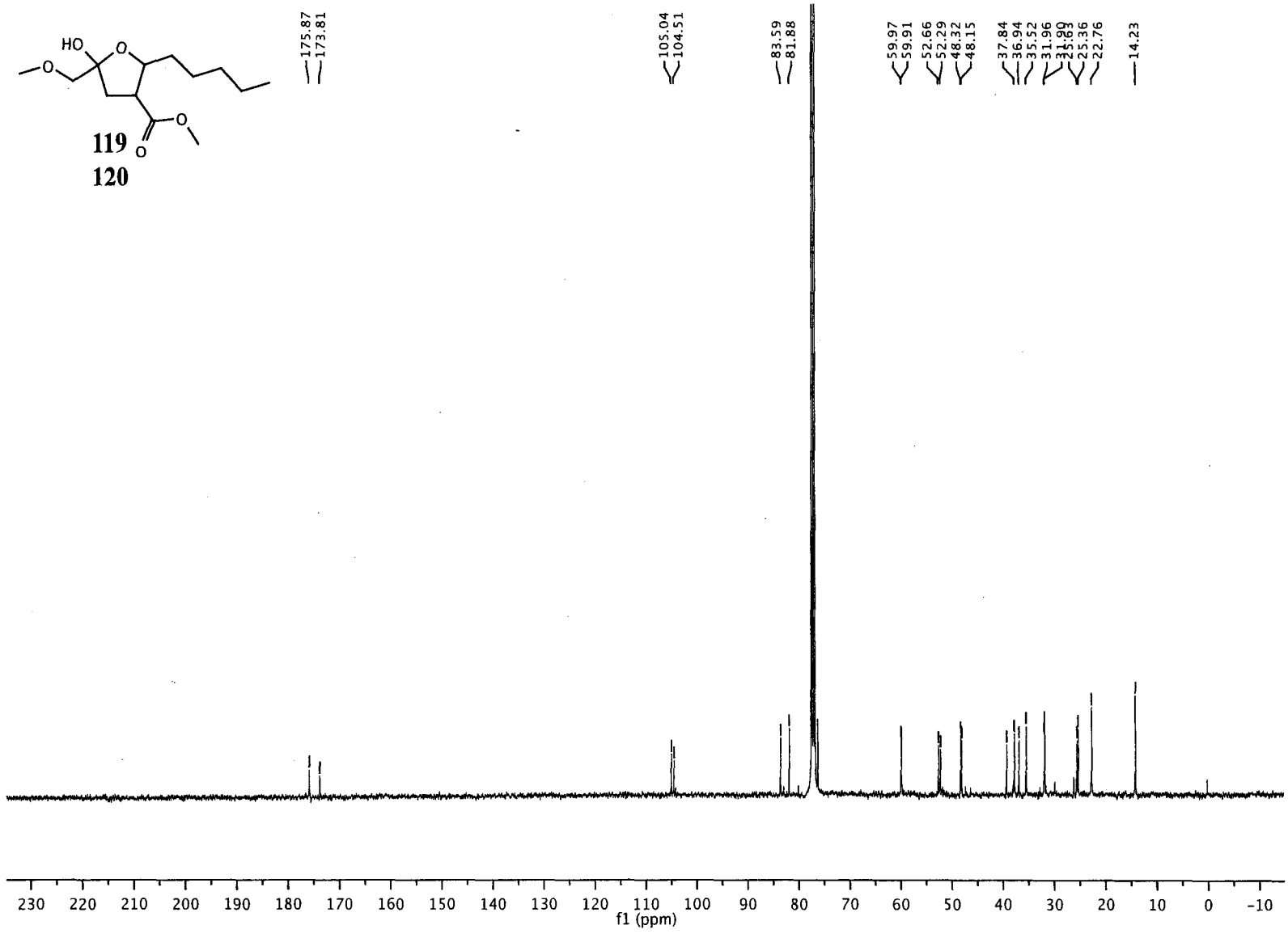
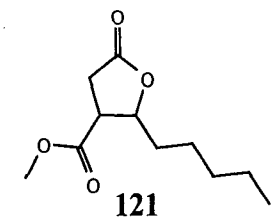
O

119
120

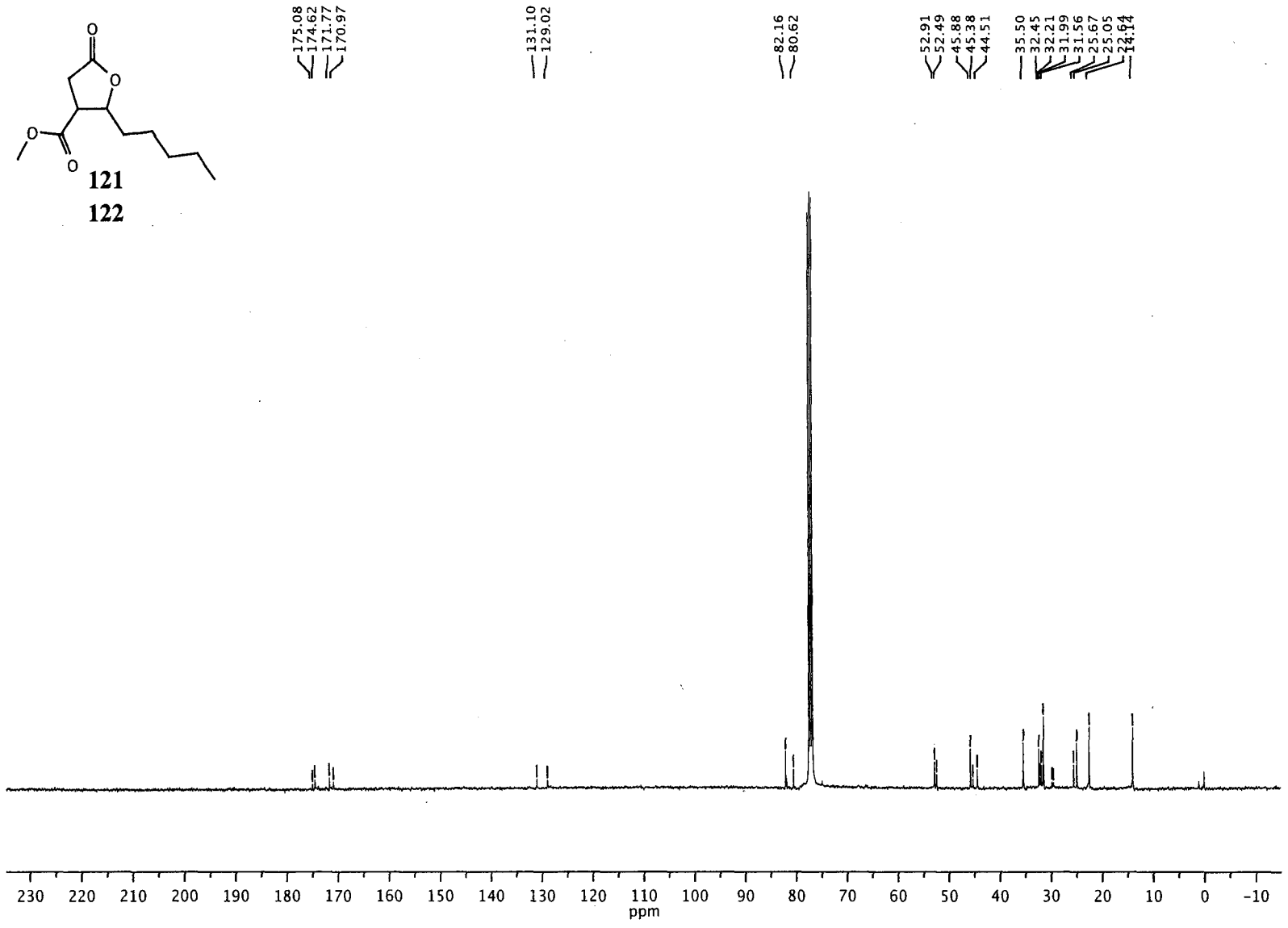

0.92
1.50
2.68
2.10
0.62
0.75
1.01
0.42
2.93
2.06
1.09
0.78
1.08
1.07
0.75
0.87
1.12
0.82
4.61
13.28
5.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

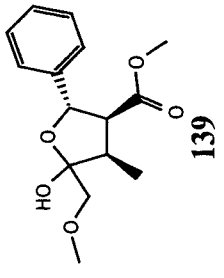

HO
O
O
O
O
119
120
175.87
173.81
105.04
104.51
83.59
81.88
59.97
59.91
52.66
52.29
48.32
48.15
37.84
36.94
35.52
31.96
25.36
22.76
14.23
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



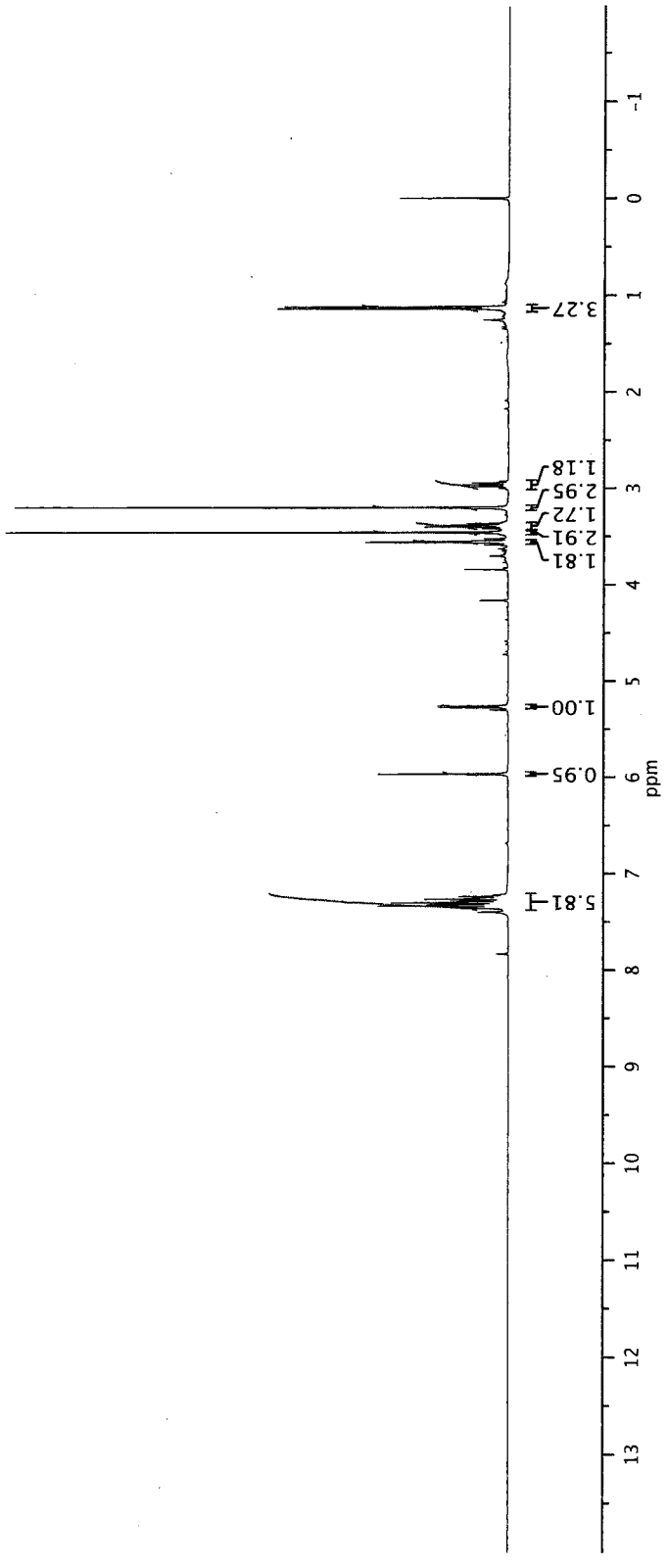
121
122

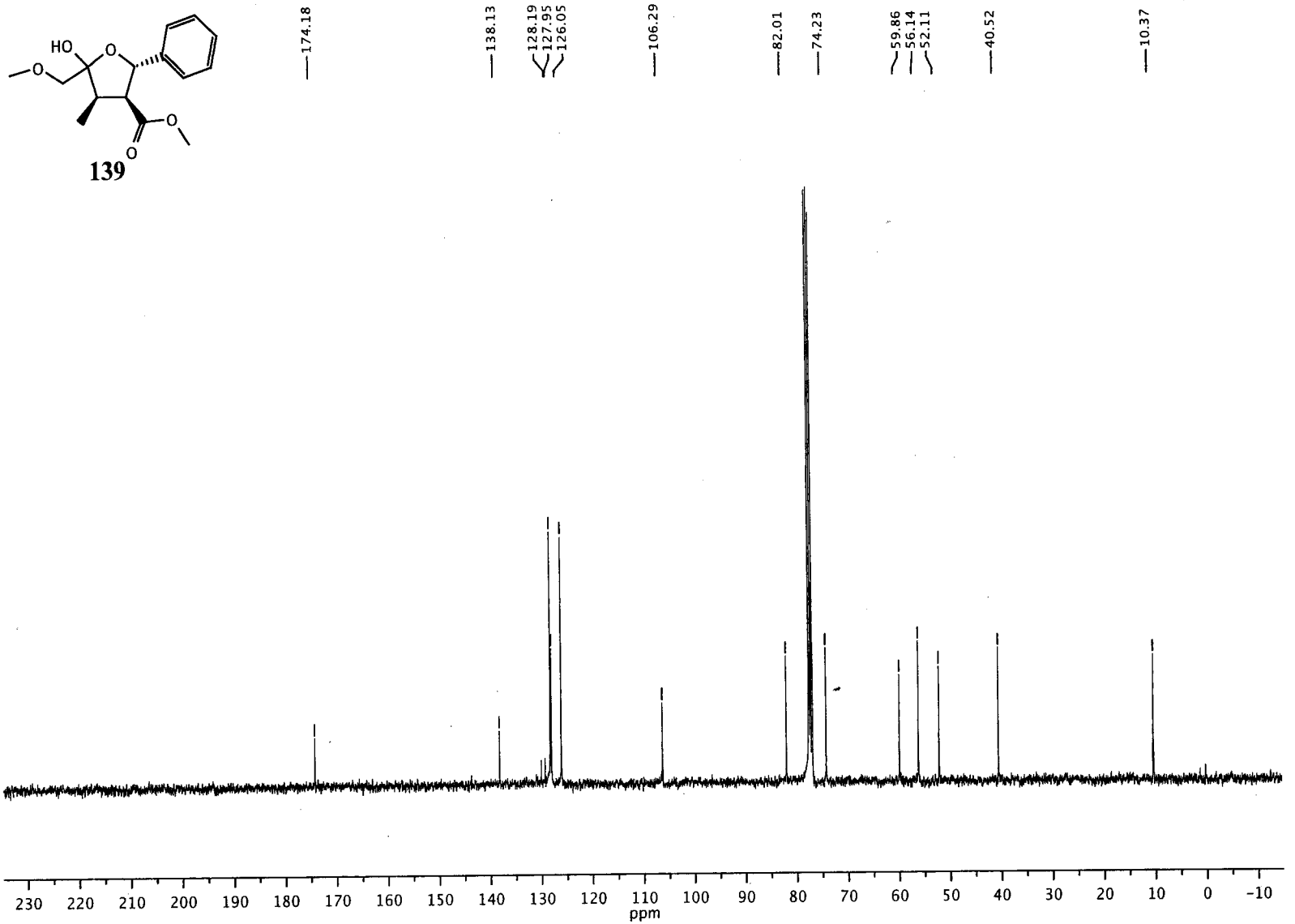
0.47
1.00
0.50
0.37
0.54
0.78
0.63
0.57
1.27
1.57
5.13
3.41
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

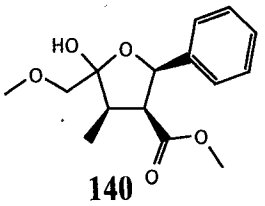

175.08
174.62
171.77
170.97
131.10
129.02
82.16
80.62
52.91
52.49
45.88
45.38
44.51
35.50
32.45
32.21
31.99
31.56
25.67
25.05
22.64
14.14
121
122
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



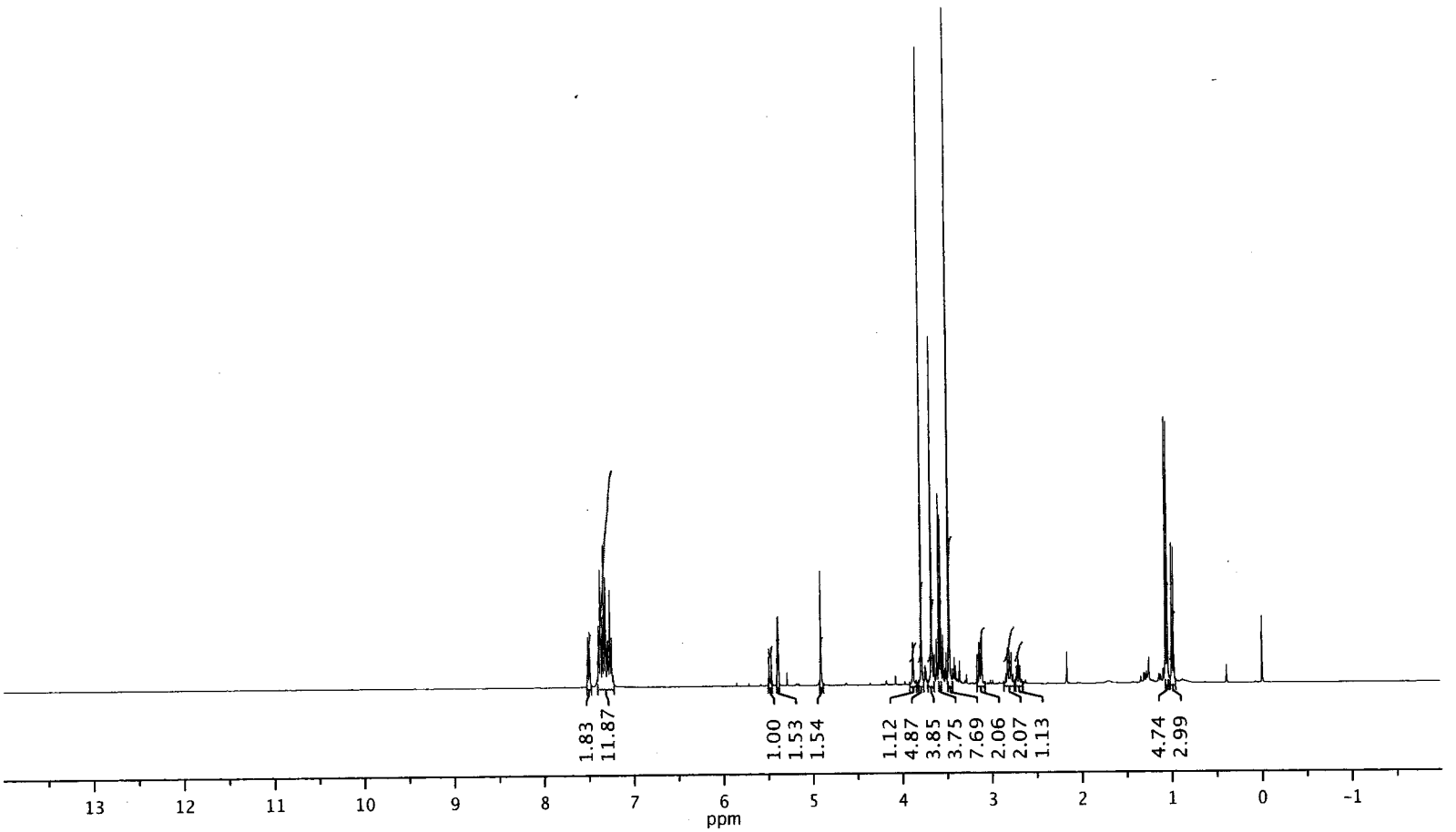
139

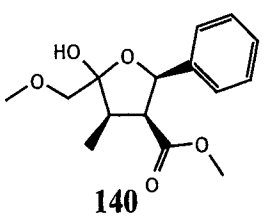



HO
O
O
O
O
139
174.18
138.13
128.19
127.95
126.05
106.29
82.01
74.23
59.86
56.14
52.11
40.52
10.37
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


HO
O
O
O
O

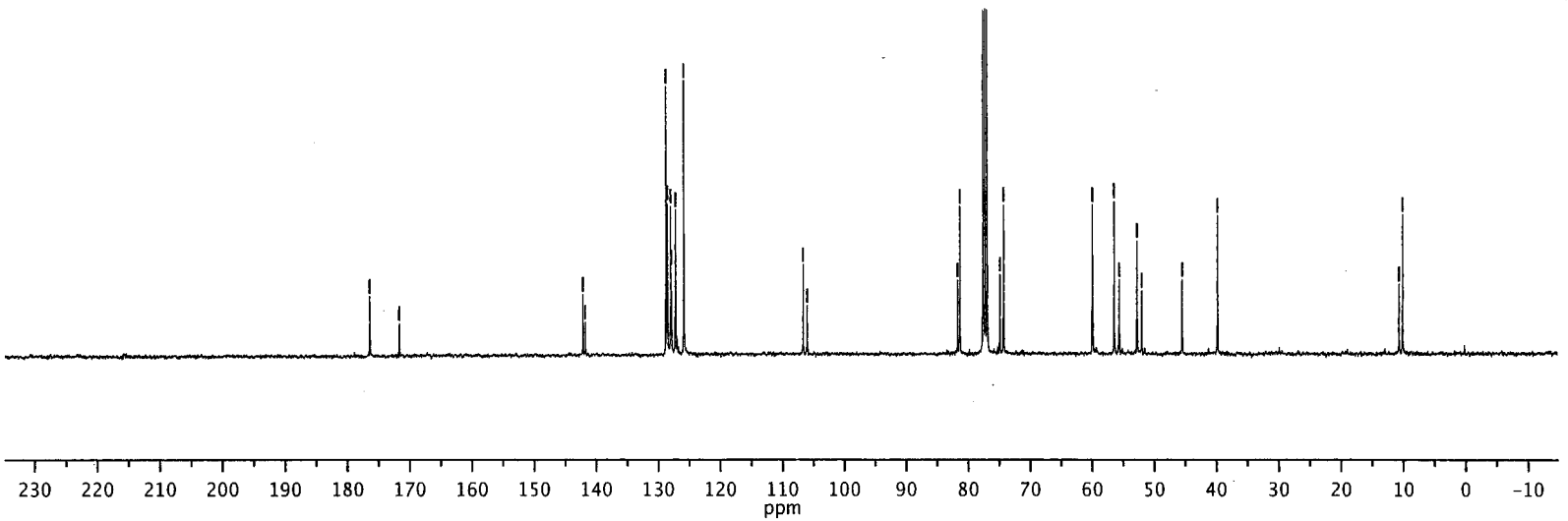
140

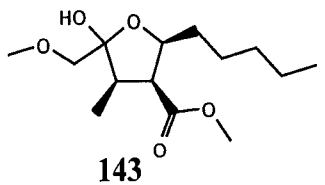

1.83
11.87
1.00
1.53
1.54
1.12
4.87
3.85
3.75
7.69
2.06
2.07
1.13
4.74
2.99
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm



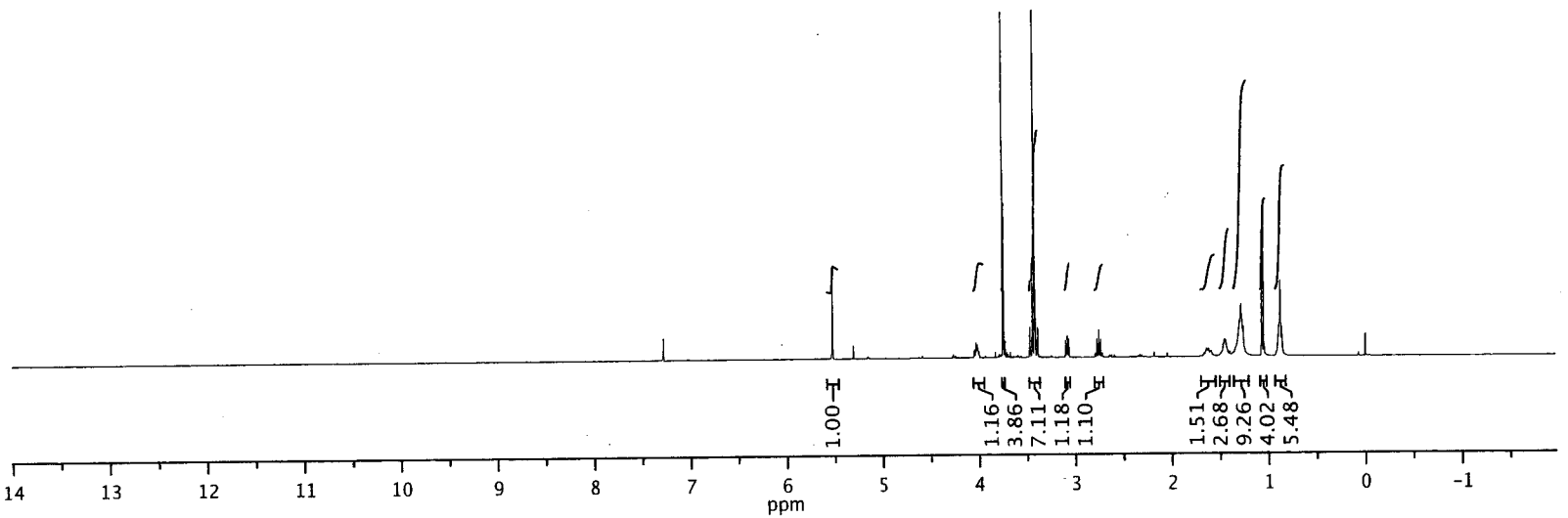
140

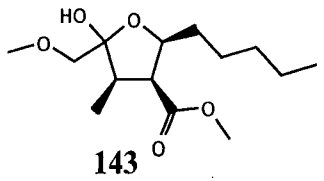
176.37
171.63
142.11
141.76
128.71
128.52
127.99
127.91
127.20
125.86
106.64
106.00
81.69
81.34
74.88
74.28
59.96
56.45
55.63
52.78
52.02
45.52
39.82
10.71
10.13




HO
O
O
O
O

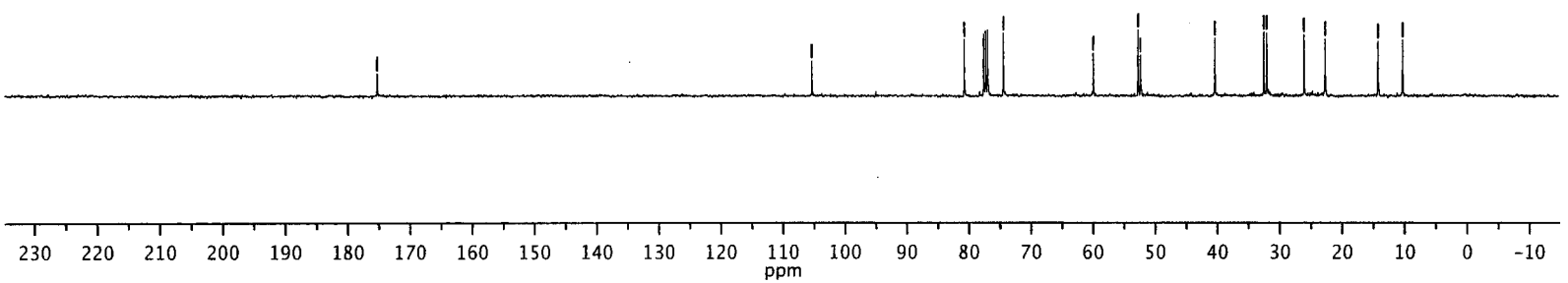
143

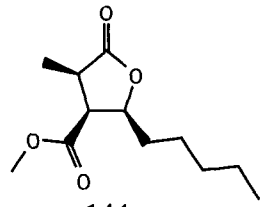

1.00
1.16
3.86
7.11
1.18
1.10
1.51
2.68
9.26
4.02
5.48
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


HO
O
O
O
O

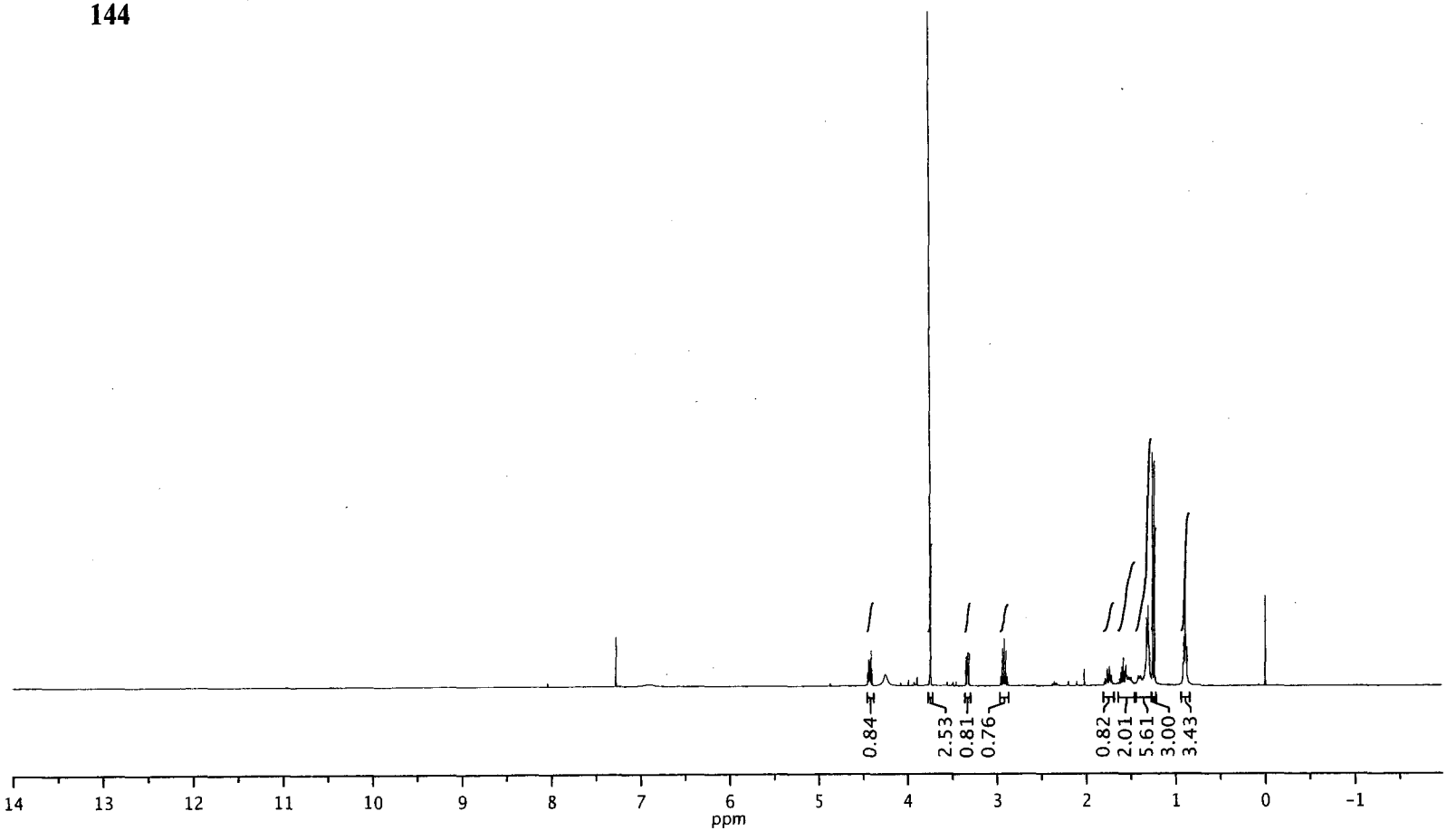
143

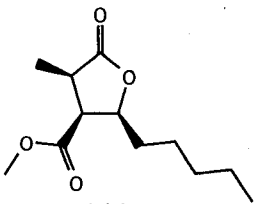

175.19
105.29
80.68
74.37
59.88
52.68
52.29
40.35
32.49
32.01
26.05
22.67
14.20
10.25


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



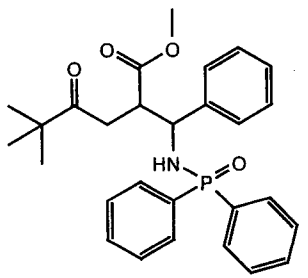
144


0.84
2.53
0.81
0.76
0.82
2.01
5.61
3.00
3.43
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

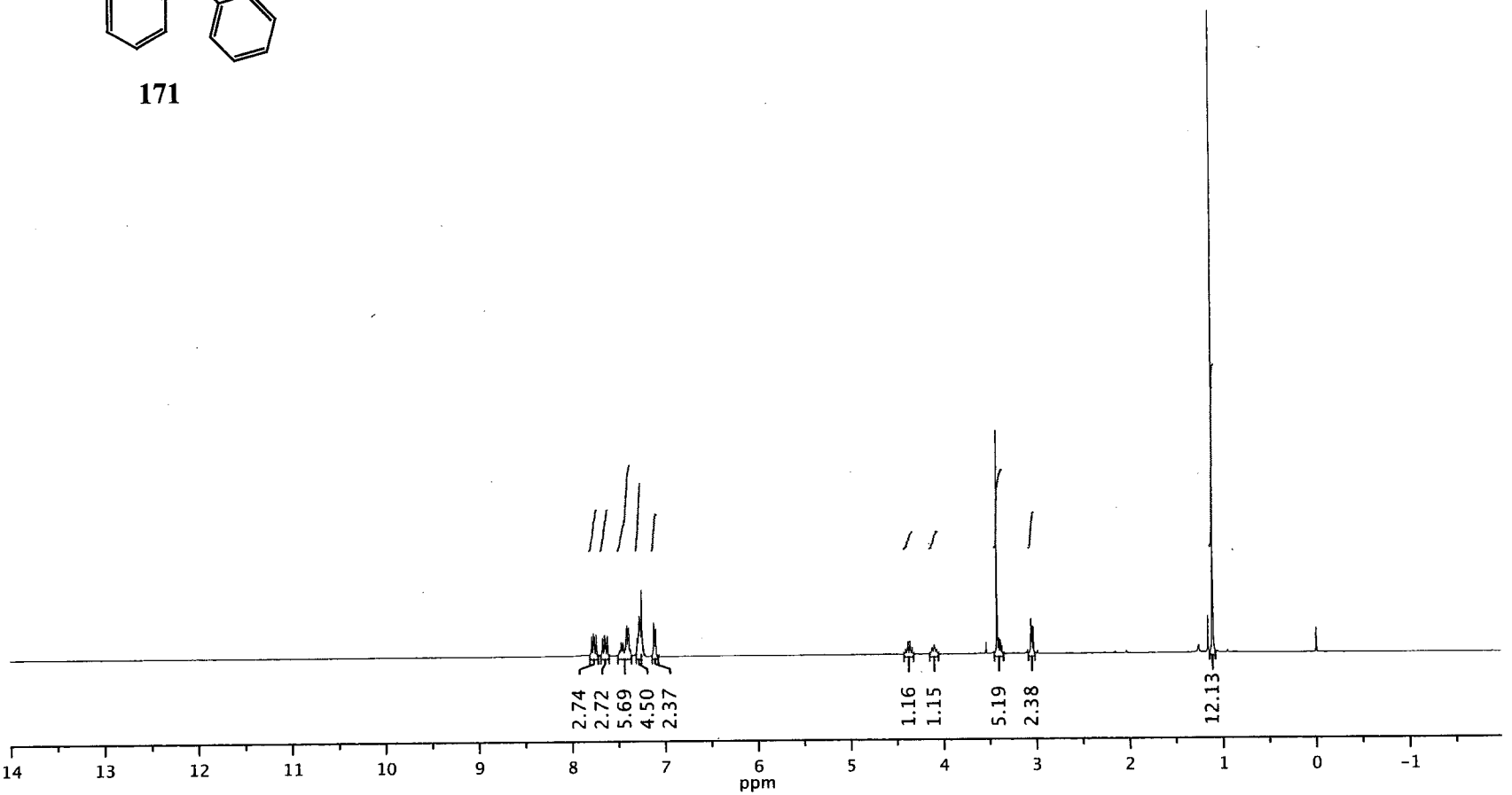


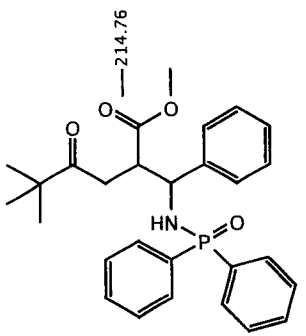
144

177.67
170.32
79.44
52.02
50.89
39.41
31.60
31.06
25.69
22.59
14.13
10.55
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


O
O
O
HN
P
O

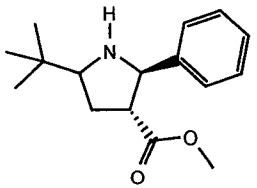
171


2.74
2.72
5.69
4.50
2.37
1.16
1.15
5.19
2.38
12.13
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

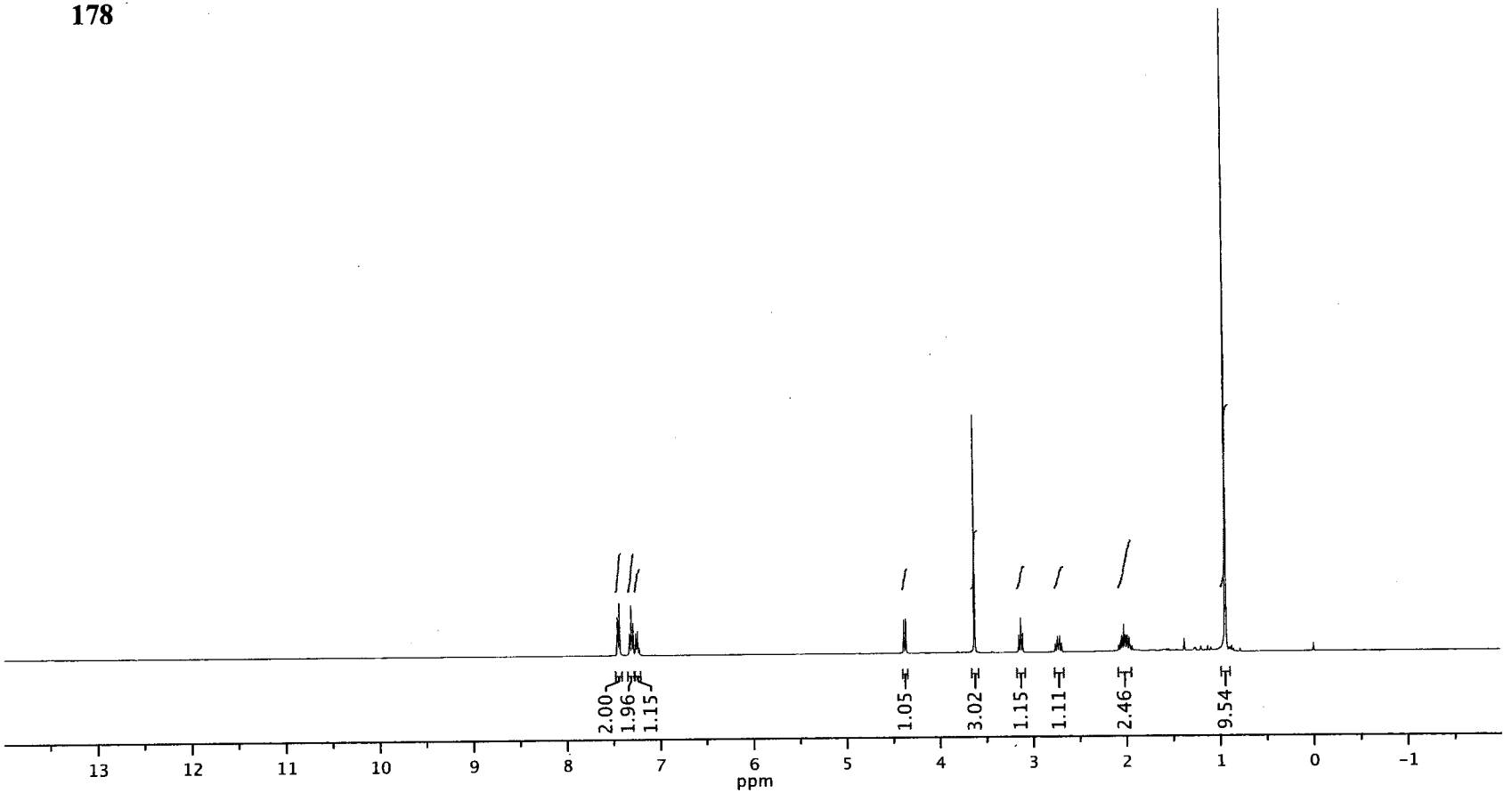

214.76
O
O
O
HN
P
O

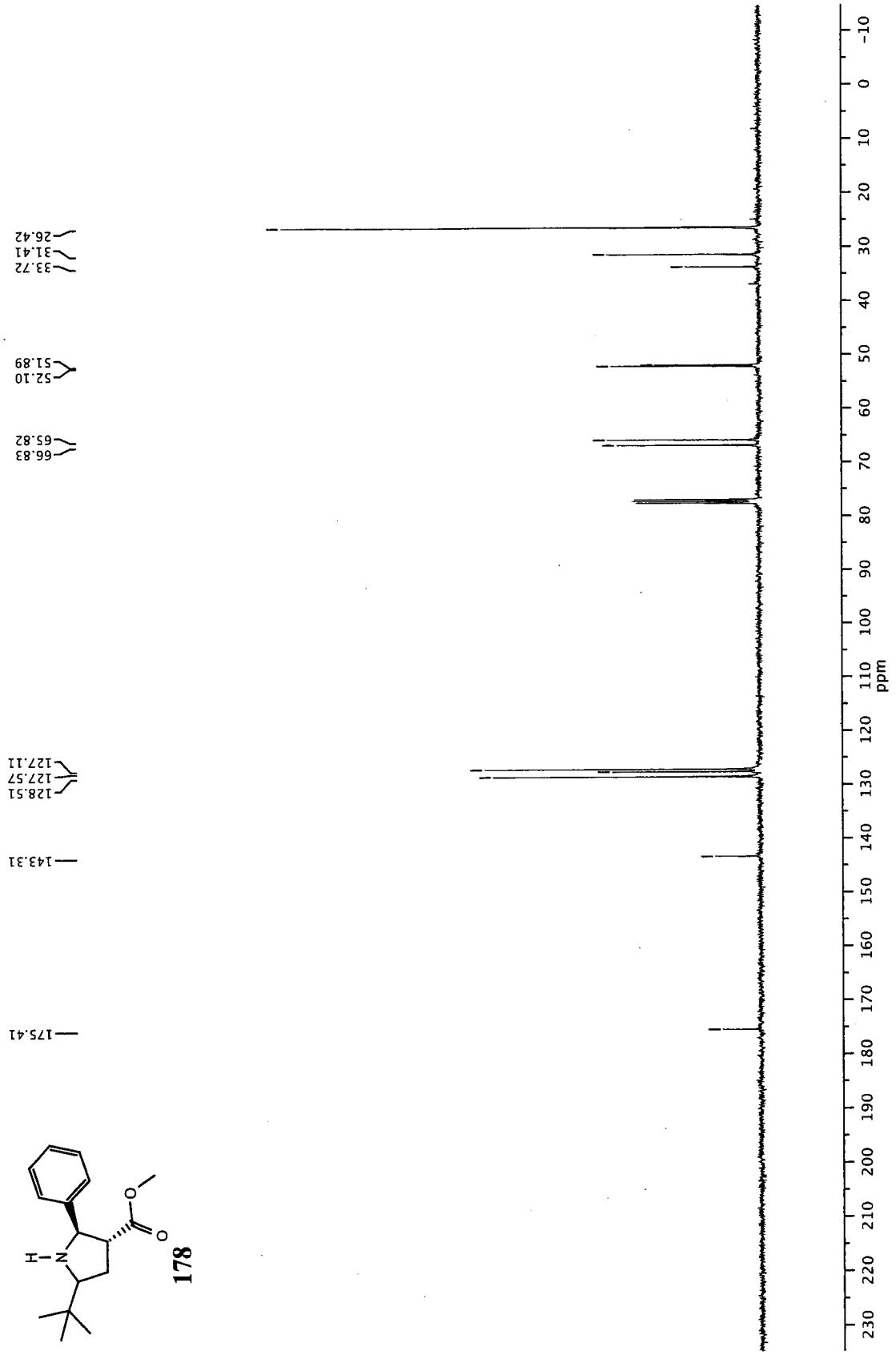
171

173.44
141.41
132.91
132.10
131.89
128.62
128.51
127.78
126.90
57.18
51.93
48.54
44.23
36.98
26.71
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

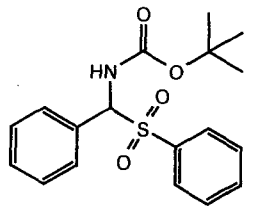


178

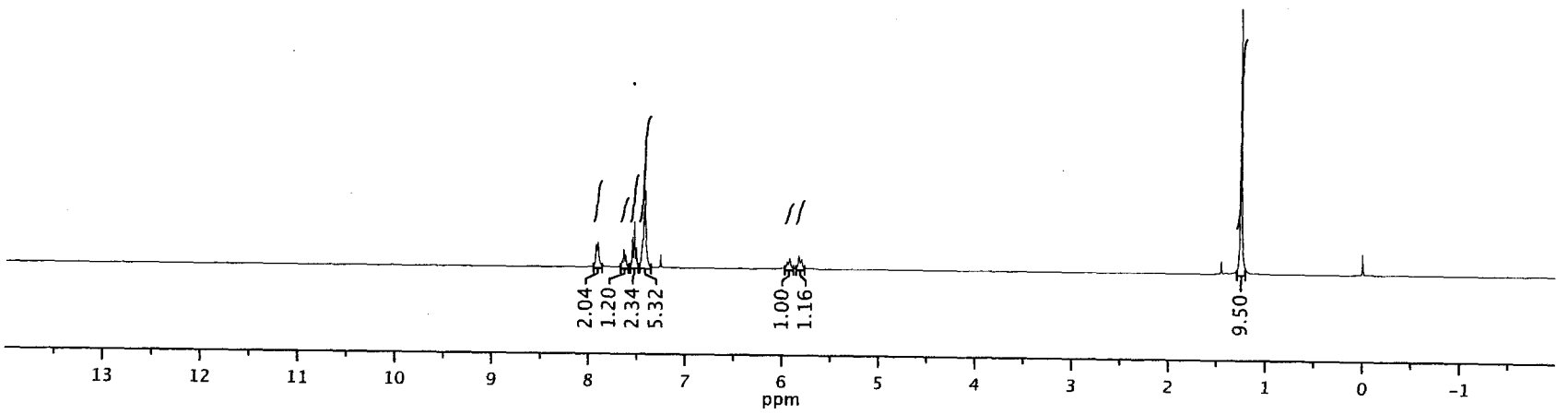


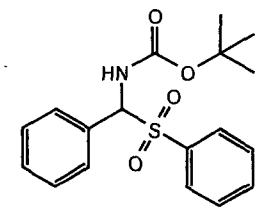

175.41
143.31
128.51
127.57
127.11
66.83
65.82
52.10
51.89
33.72
31.41
26.42
ppm

178



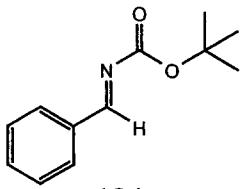
187a



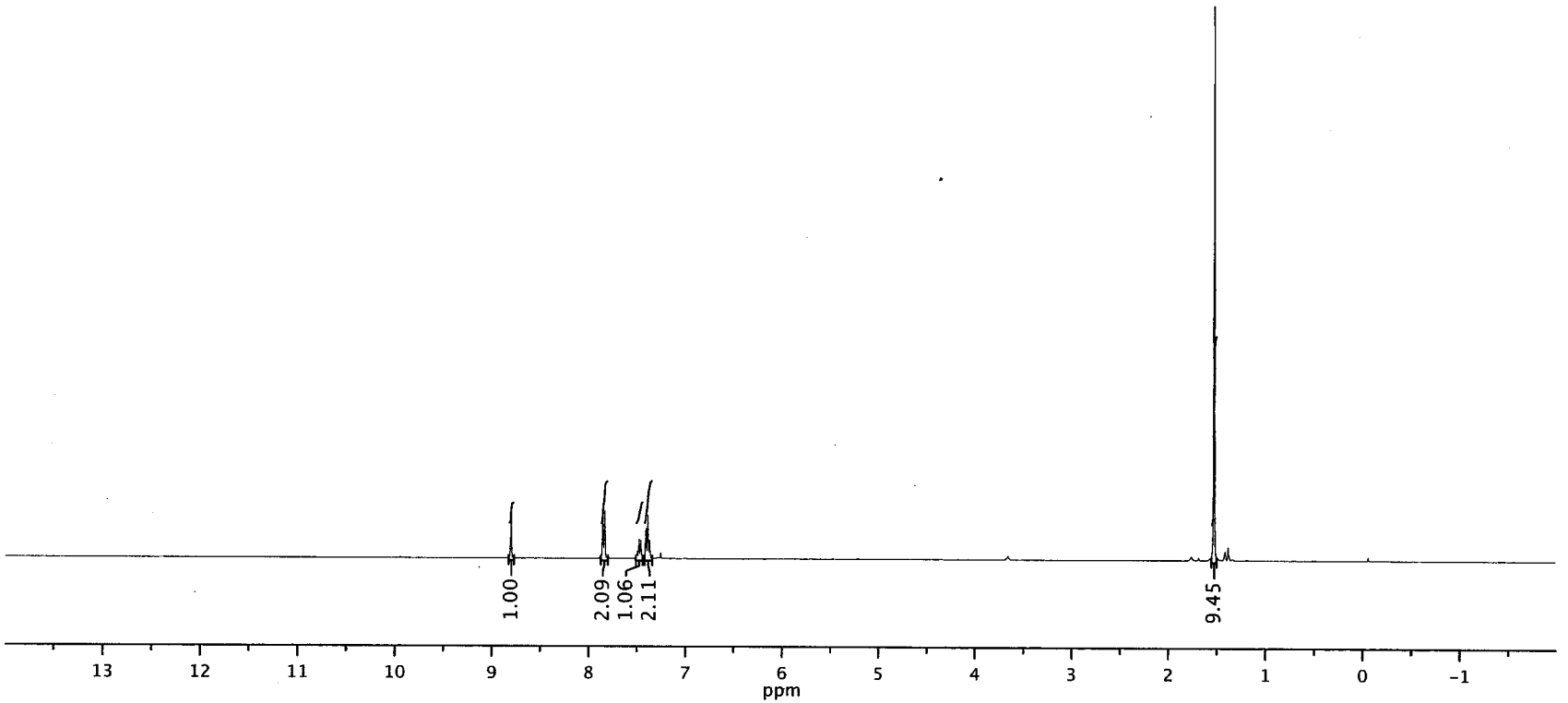


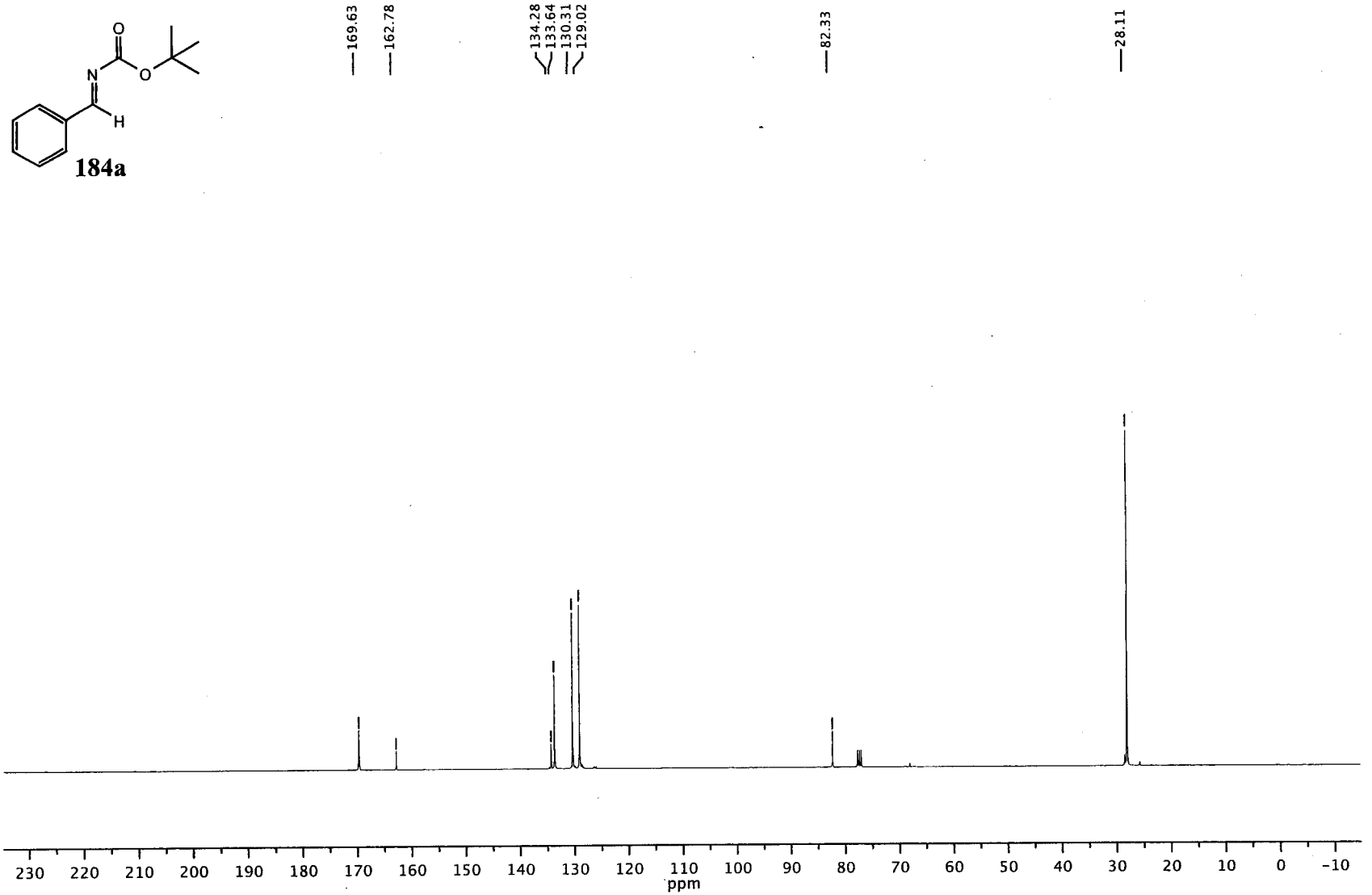
187a

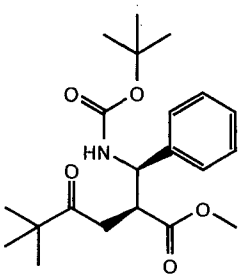
153.69
137.16
134.14
130.13
130.06
129.69
129.25
129.13
128.97
81.44
74.14
28.22
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



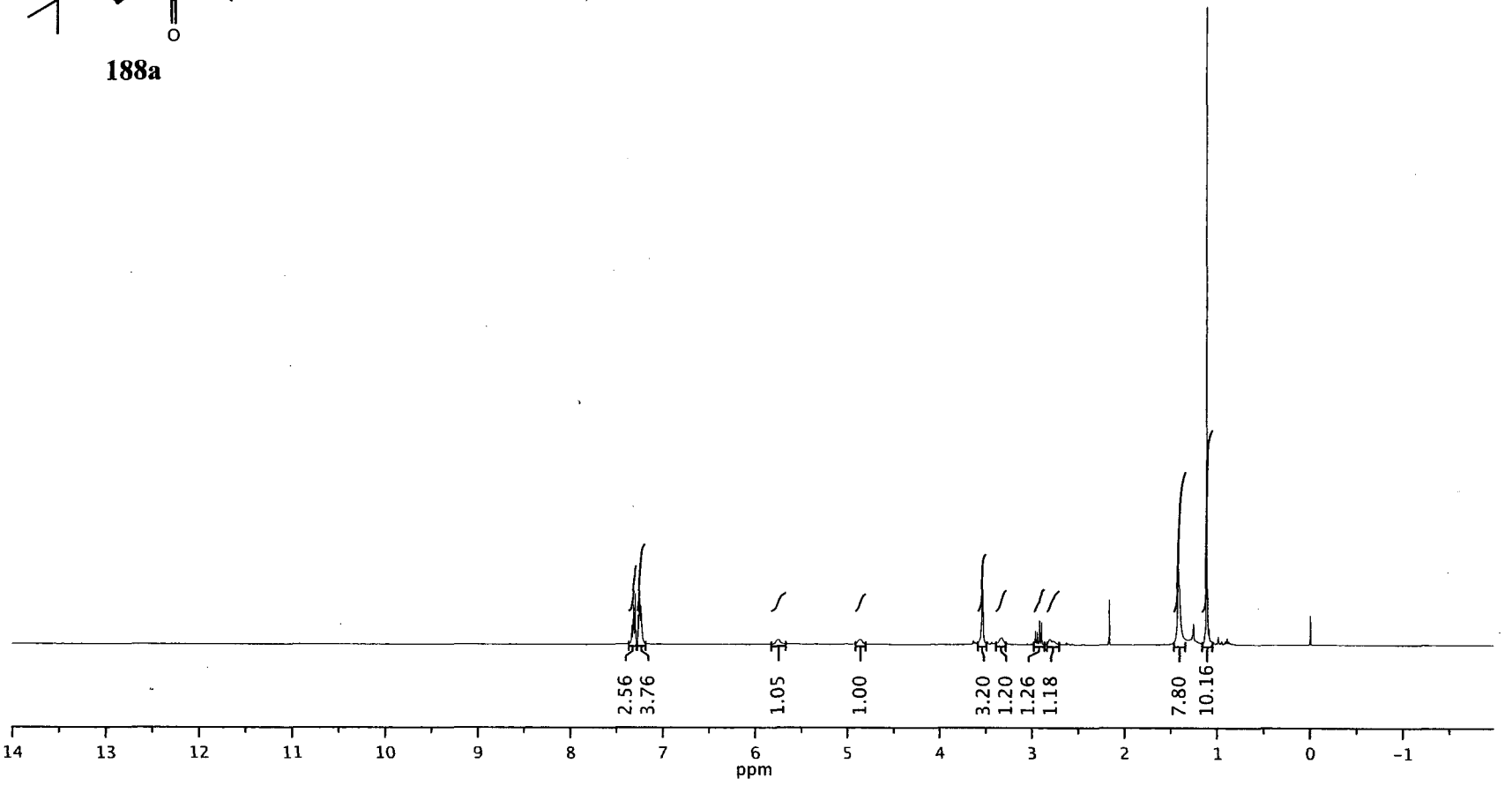
184a

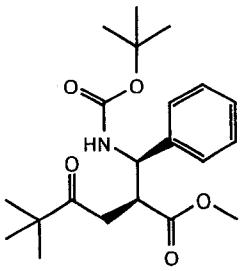



O
N
O
H
184a
169.63
162.78
134.28
133.64
130.31
129.02
82.33
28.11
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


O
O
HN
O
O
O

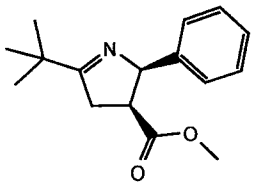
188a


2.56
3.76
1.05
1.00
3.20
1.20
1.26
1.18
7.80
10.16
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

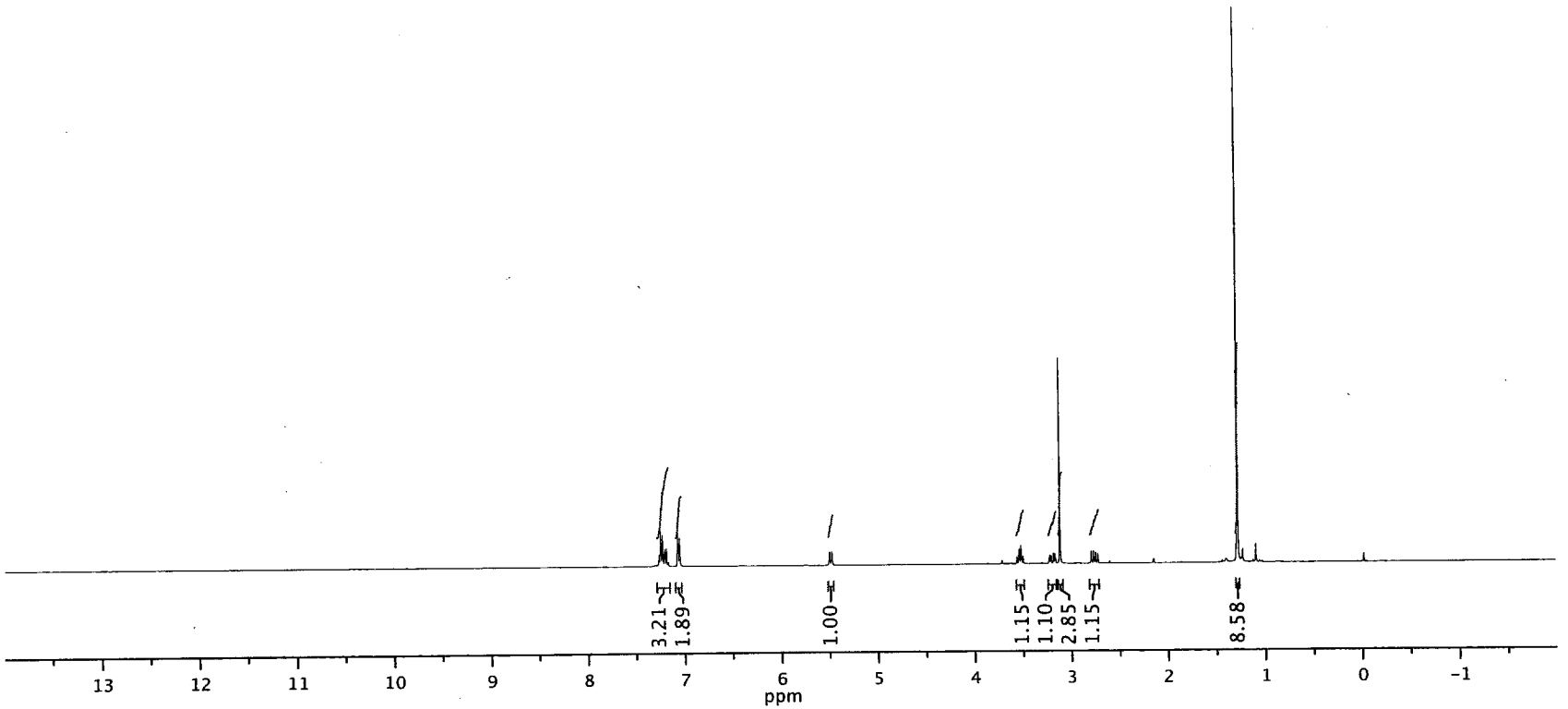

O
O
HN
O
O
O

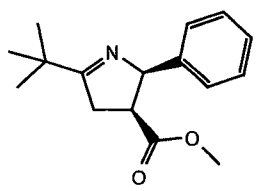
188a

213.42
174.50
155.44
140.76
128.73
127.68
126.32
79.82
55.04
52.04
46.19
44.24
37.41
28.53
26.65
26.53
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



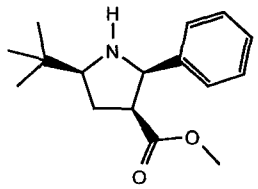
191a





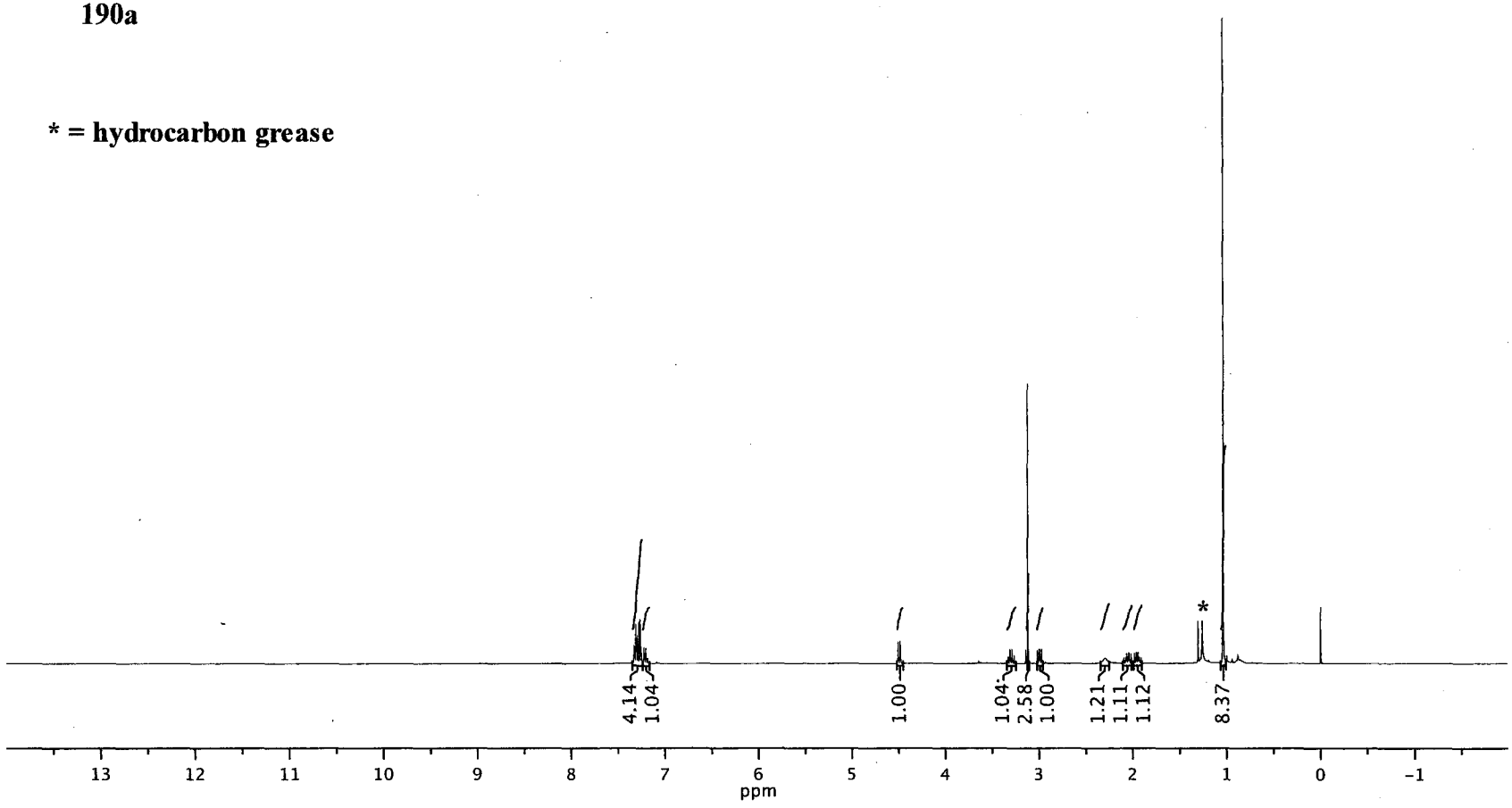
191a

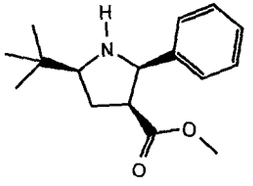
185.79
172.86
138.86
128.11
127.65
127.53
77.81
51.41
48.57
36.86
36.39
28.49
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



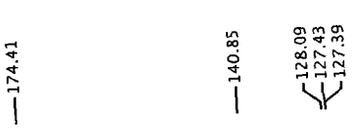
190a

*** = hydrocarbon grease**

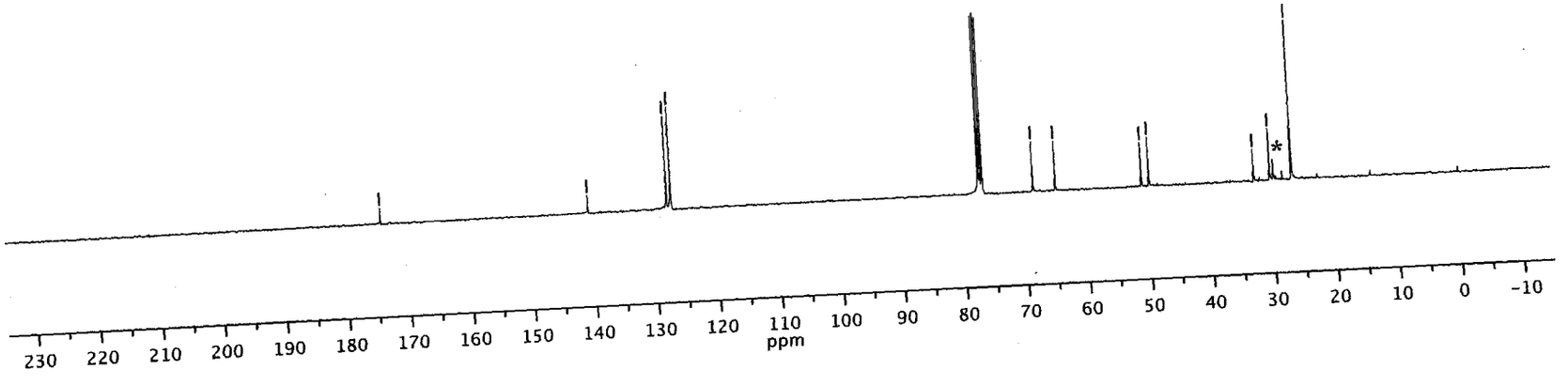


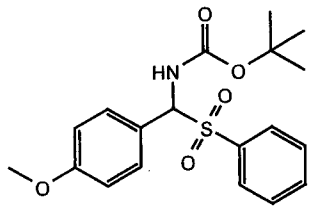


190a

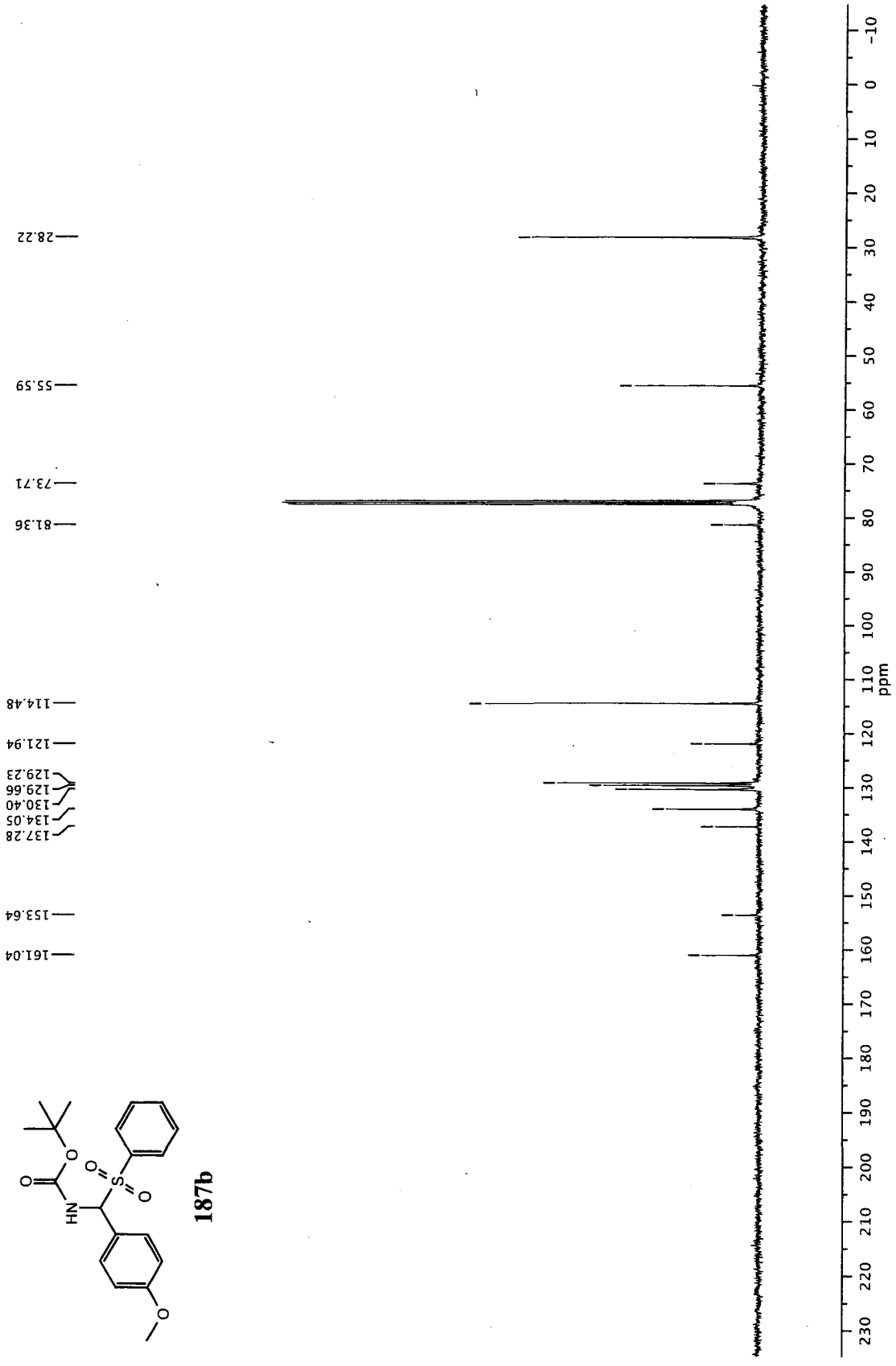


*** = hydrocarbon grease**

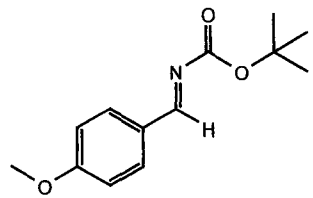




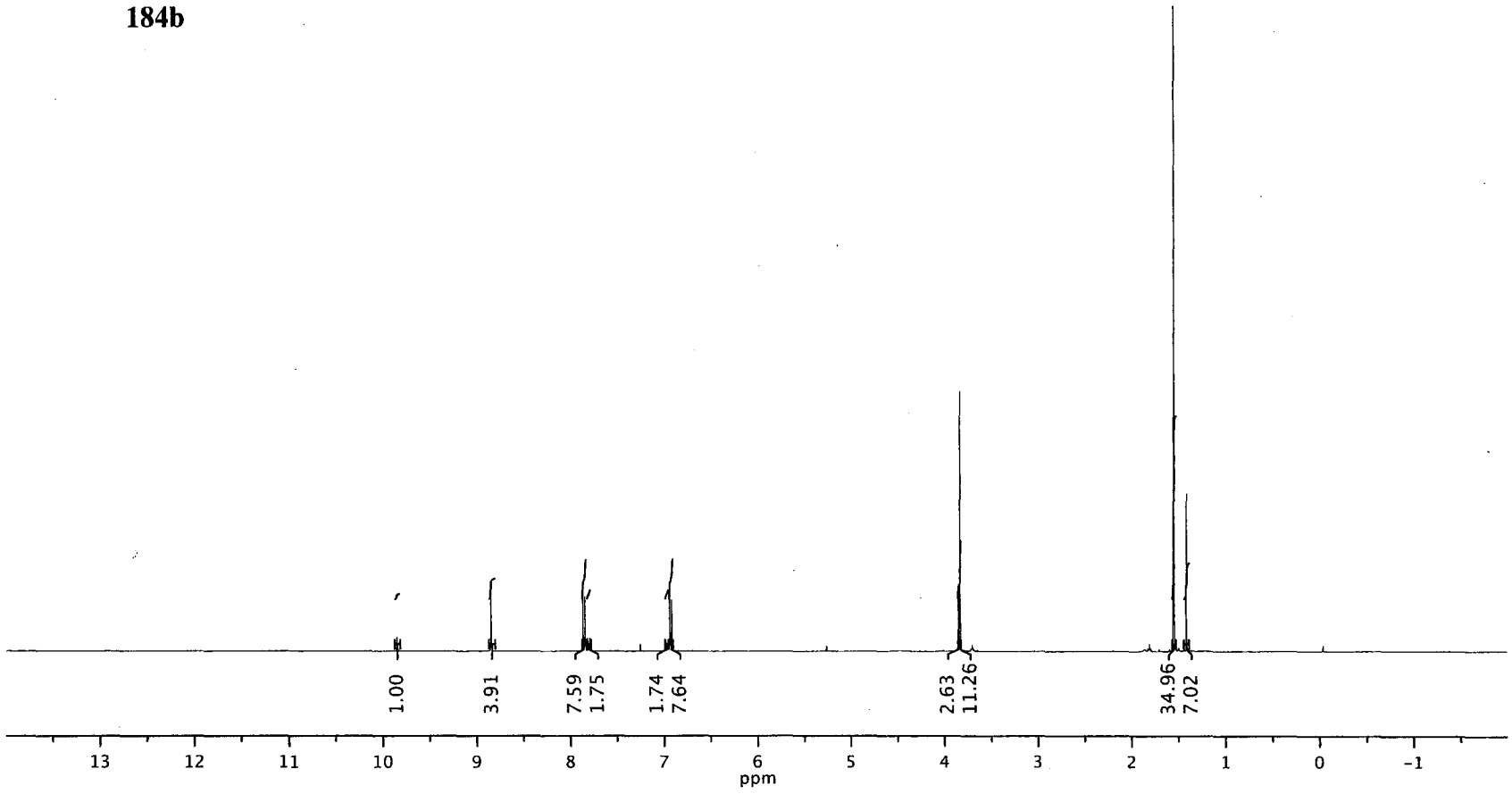
187b

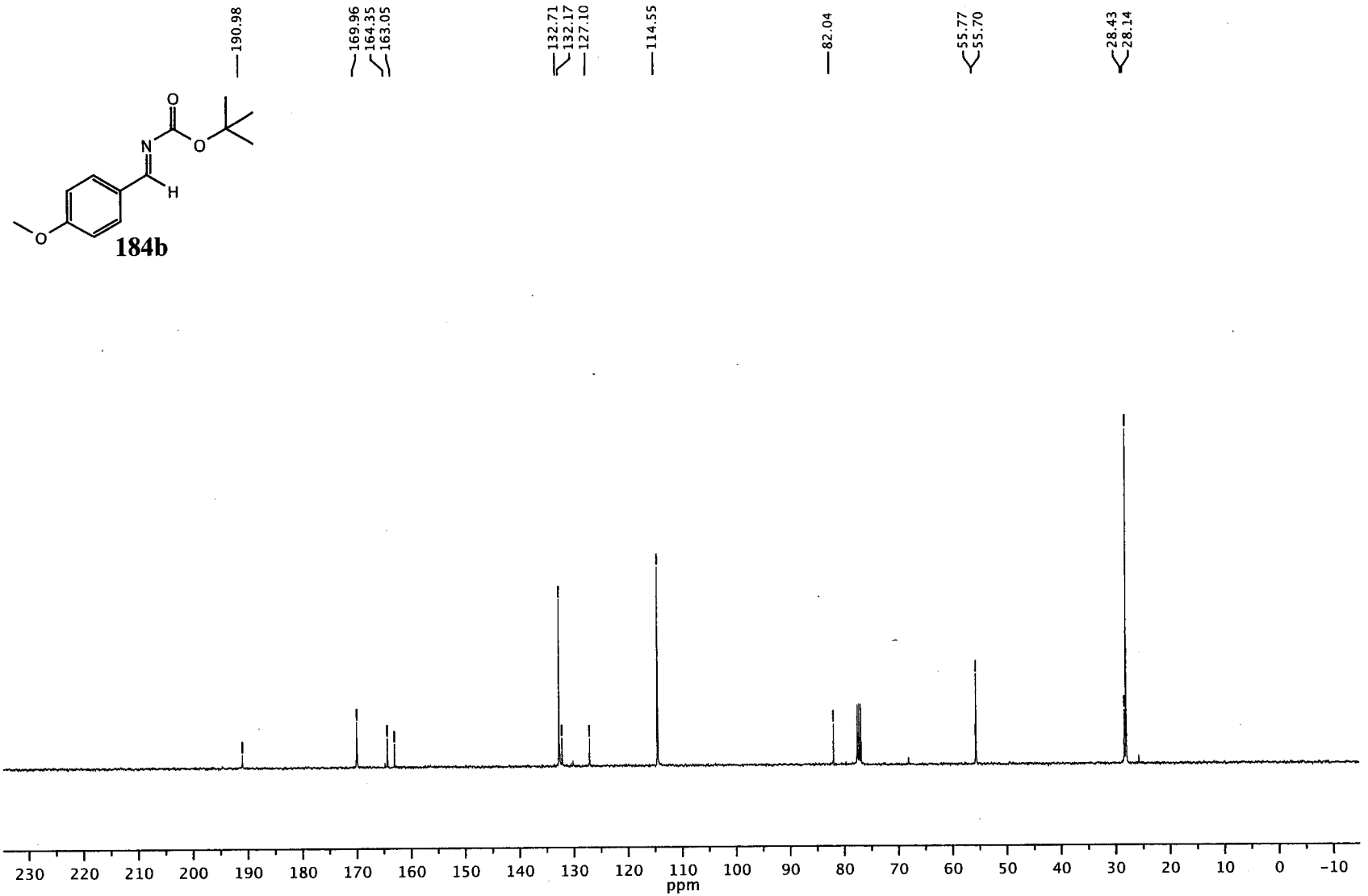

28.22
55.59
73.71
81.36
114.48
121.94
129.23
129.66
130.40
134.05
137.28
153.64
161.04
ppm
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230

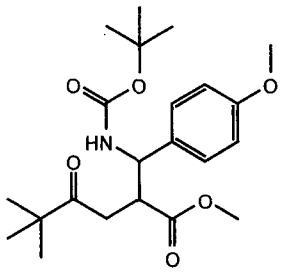
187b


O
N
O
H
O

184b

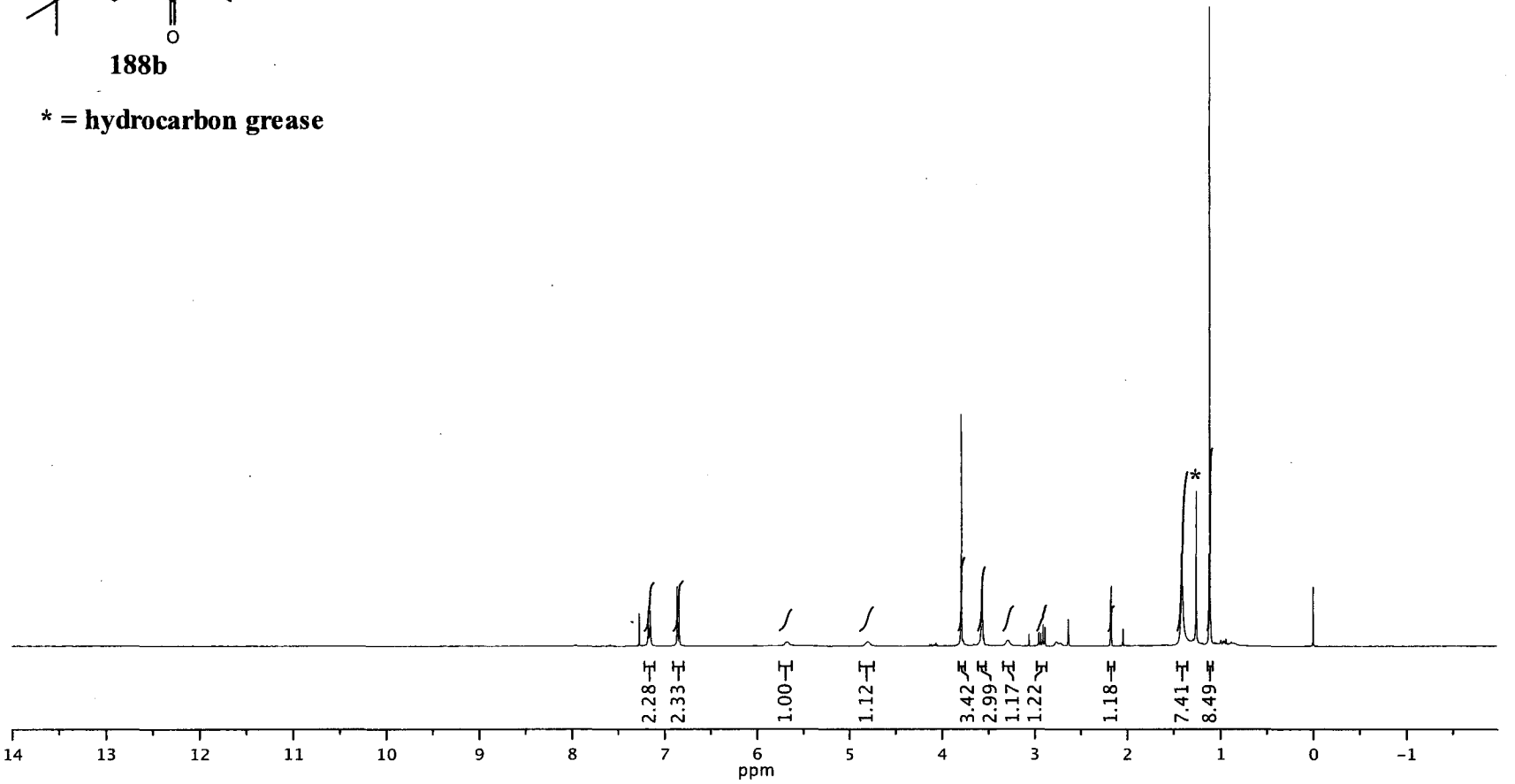

1.00
3.91
7.59
1.75
1.74
7.64
2.63
11.26
34.96
7.02
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

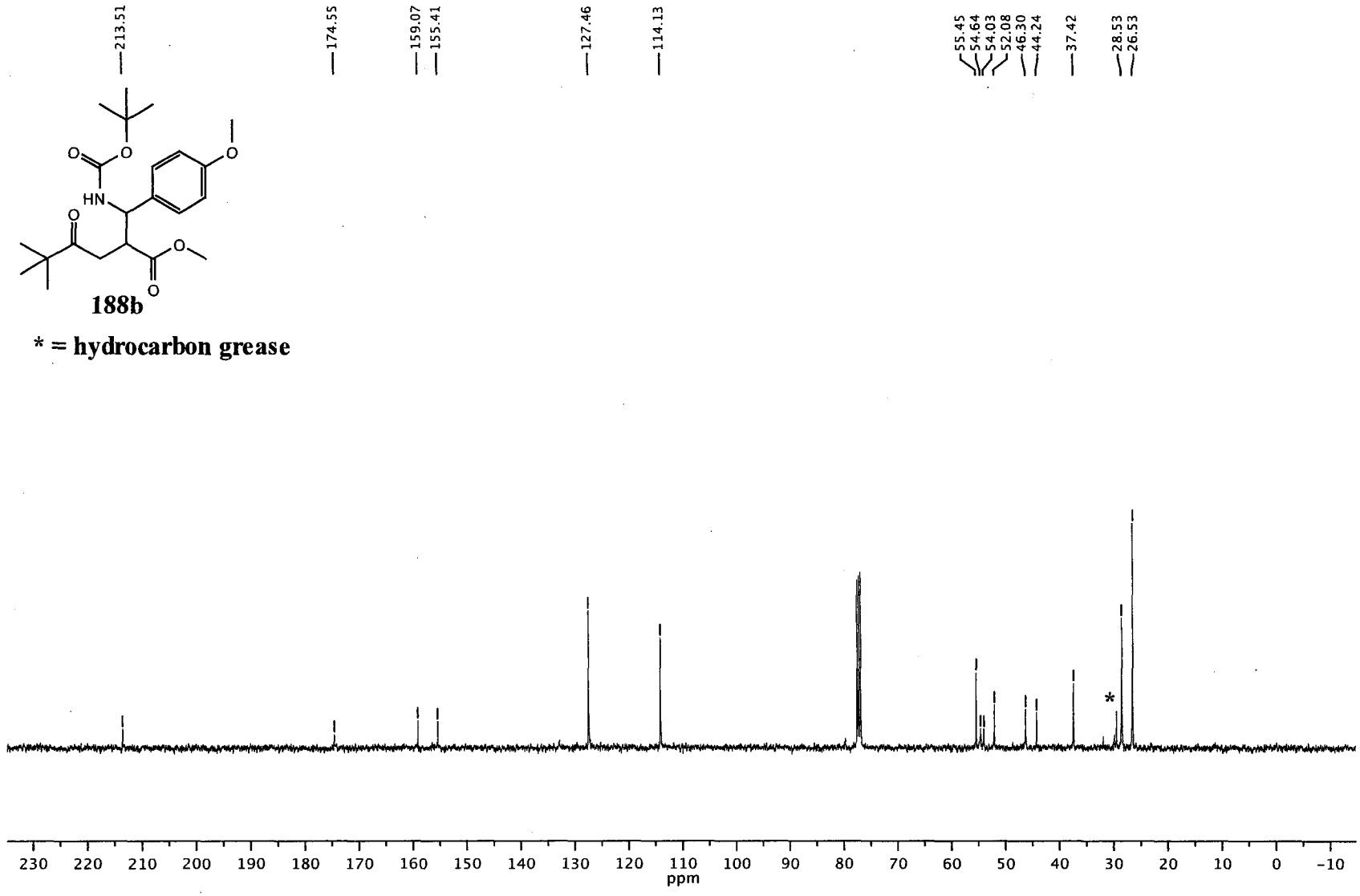

190.98
169.96
164.35
163.05
132.71
132.17
127.10
114.55
82.04
55.77
55.70
28.43
28.14
O
N
O
H
O
184b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

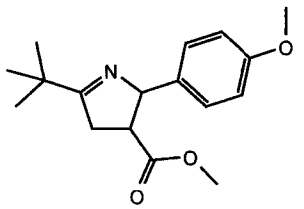


188b

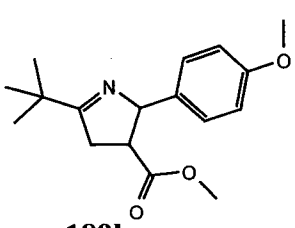
*** = hydrocarbon grease**




213.51
174.55
159.07
155.41
127.46
114.13
55.45
54.64
54.03
52.08
46.30
44.24
37.42
28.53
26.53
HN
O
O
O
O
O
O
O
188b
* = hydrocarbon grease
*
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

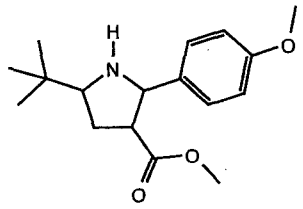


189b



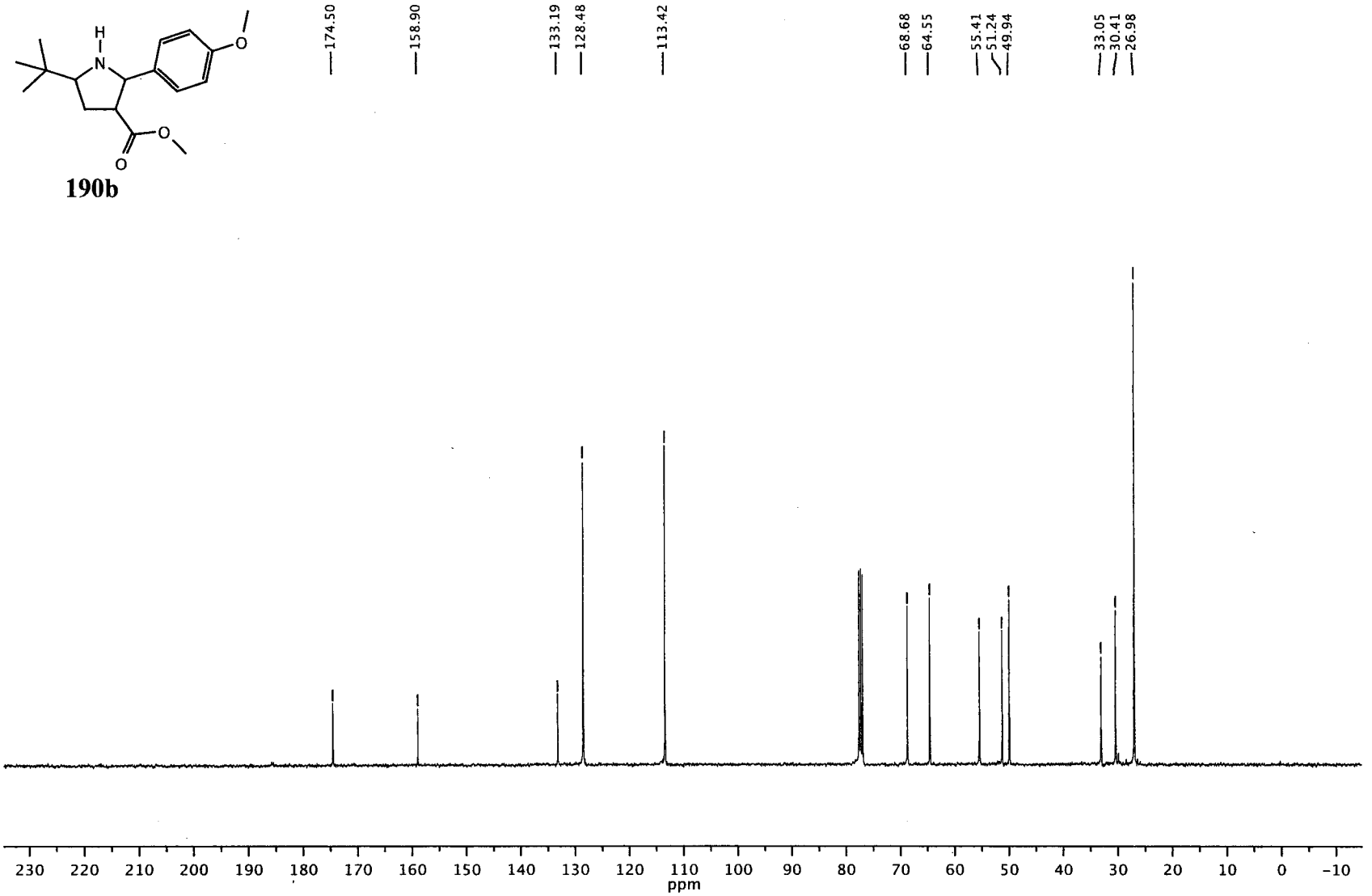
189b

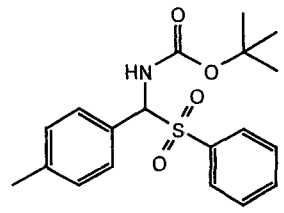
185.28
172.92
159.10
130.95
128.60
113.50
77.27
55.36
51.46
48.49
36.64
36.32
28.48
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



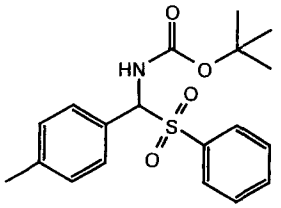
190b

1.93
1.82
1.00
2.90
1.10
2.69
1.05
1.20
1.96
8.26
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


174.50
158.90
133.19
128.48
113.42
68.68
64.55
55.41
51.24
49.94
33.05
30.41
26.98
190b
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

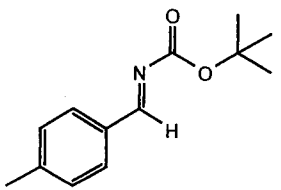


187c

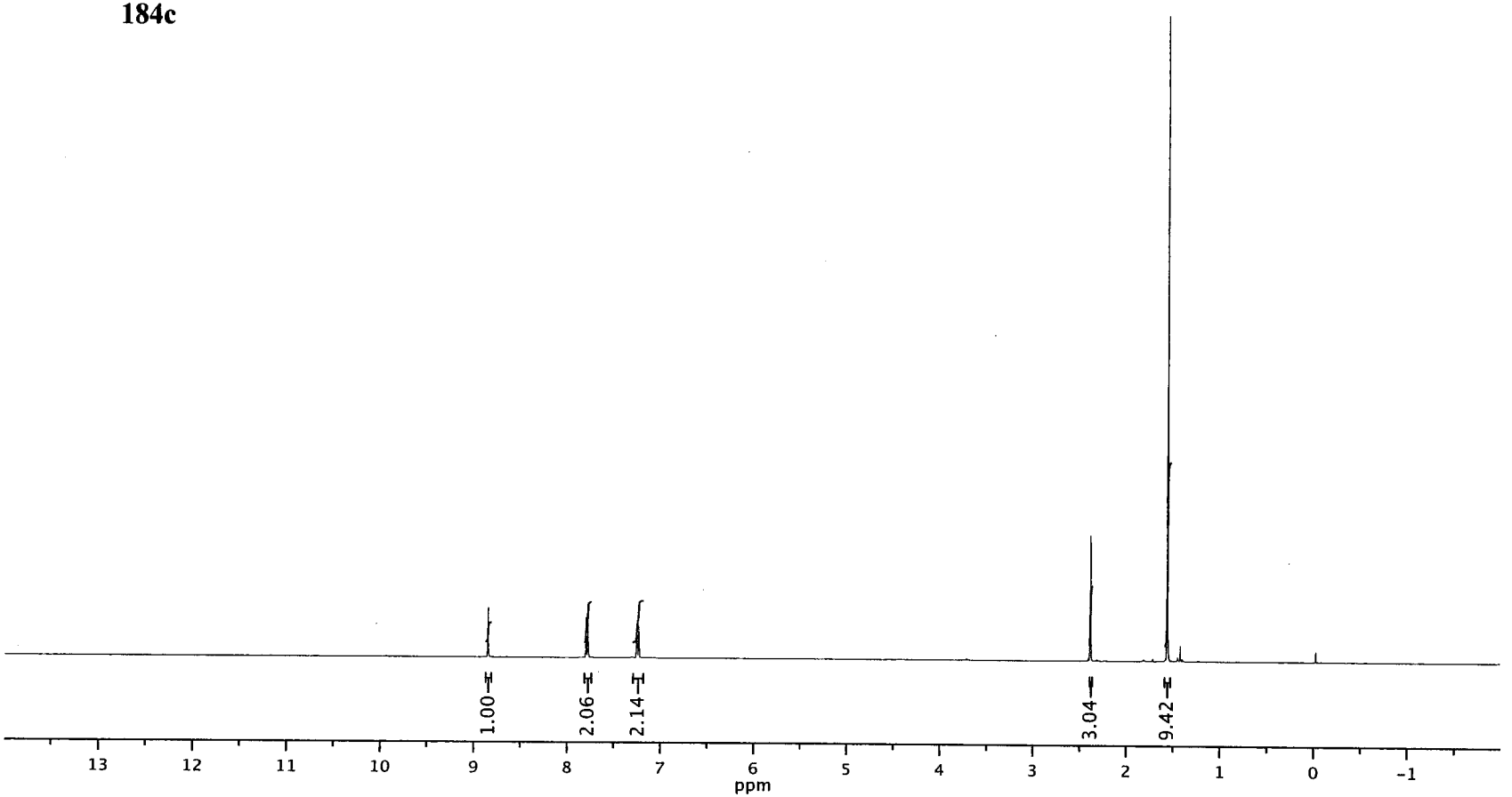


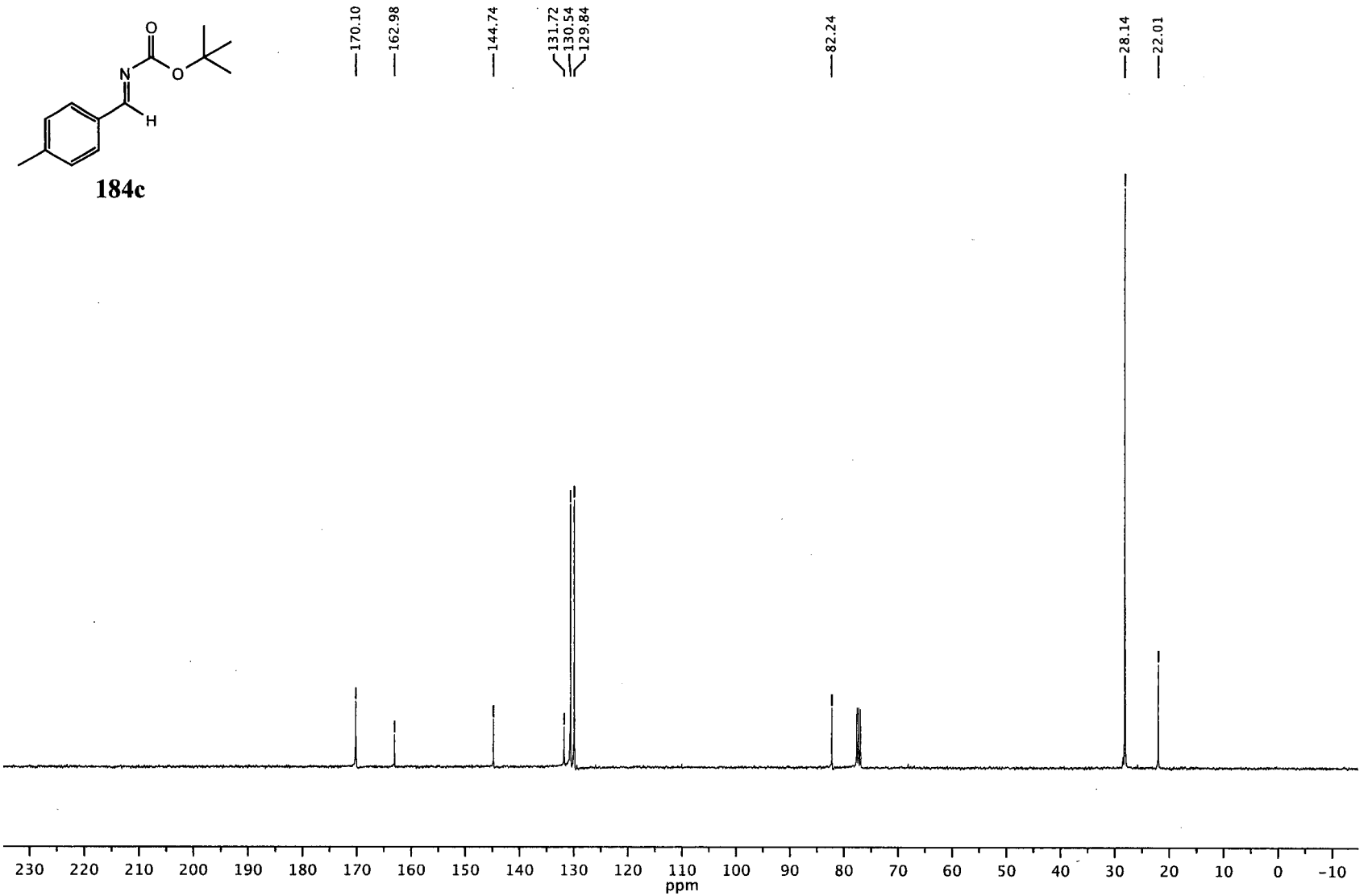
187c

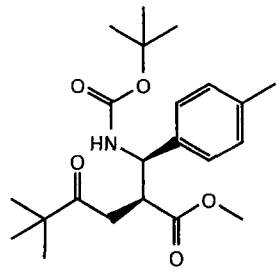
153.65
140.24
137.23
134.09
129.71
129.24
129.00
126.94
81.35
73.94
28.23
21.53
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



184c



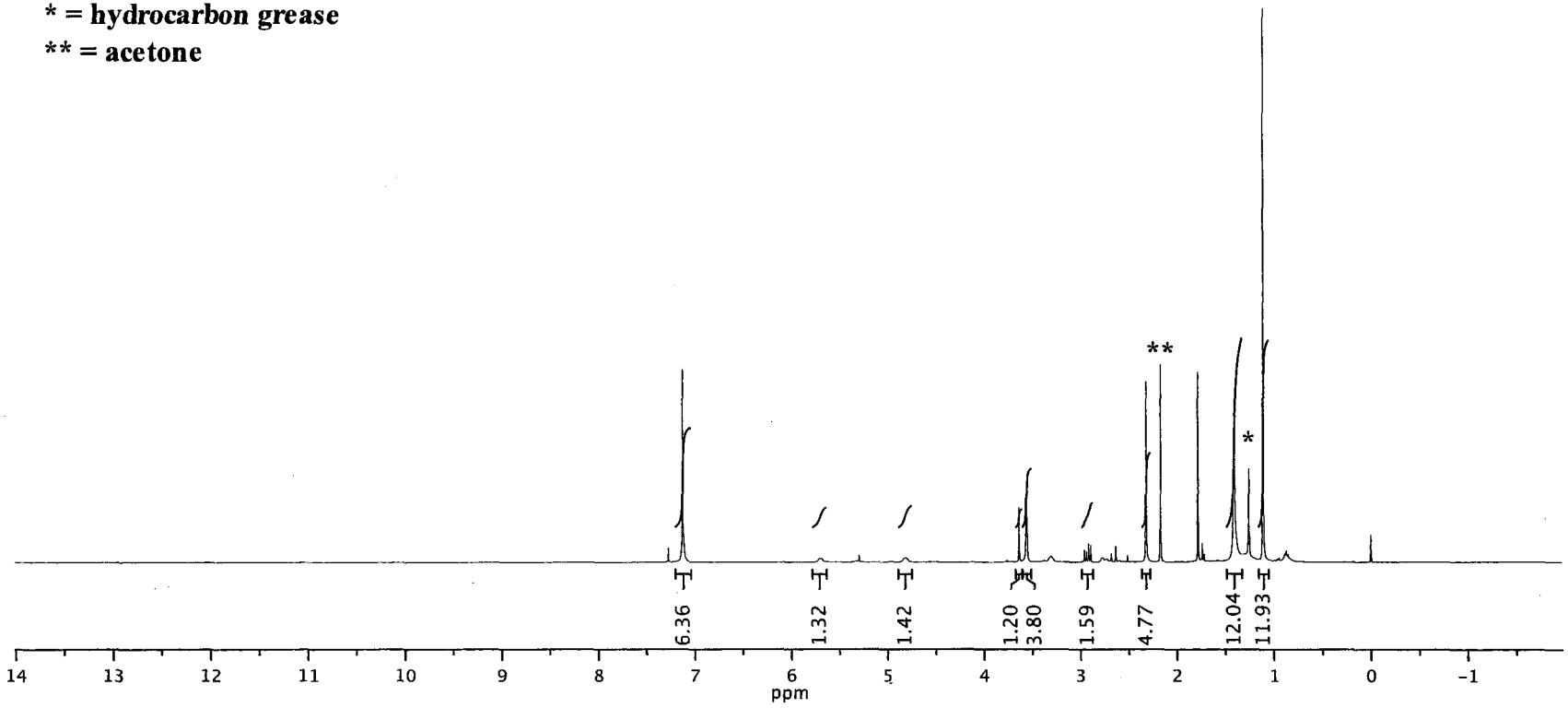

184c
170.10
162.98
144.74
131.72
130.54
129.84
82.24
28.14
22.01
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

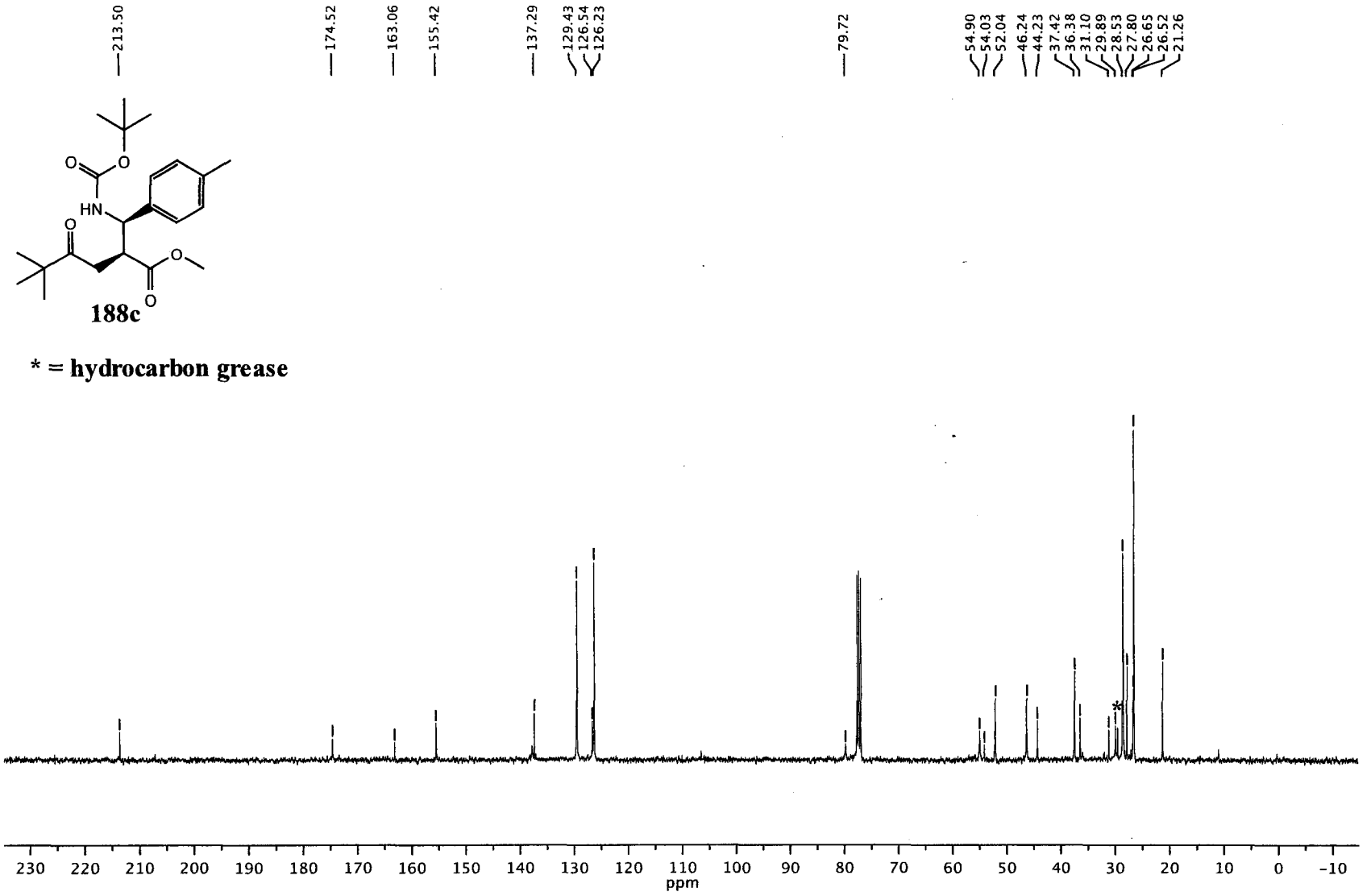


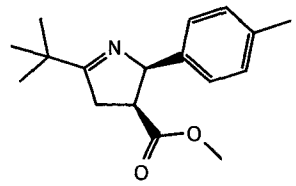
188c

*** = hydrocarbon grease**

**** = acetone**

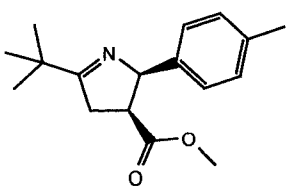



213.50
174.52
163.06
155.42
137.29
129.43
126.54
126.23
79.72
54.90
54.03
52.04
46.24
44.23
37.42
36.38
31.10
29.89
28.53
27.80
26.65
26.52
21.26
HN
O
O
O
O
O
188c
* = hydrocarbon grease
*
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



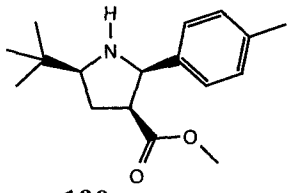
189c

*** = acetone**



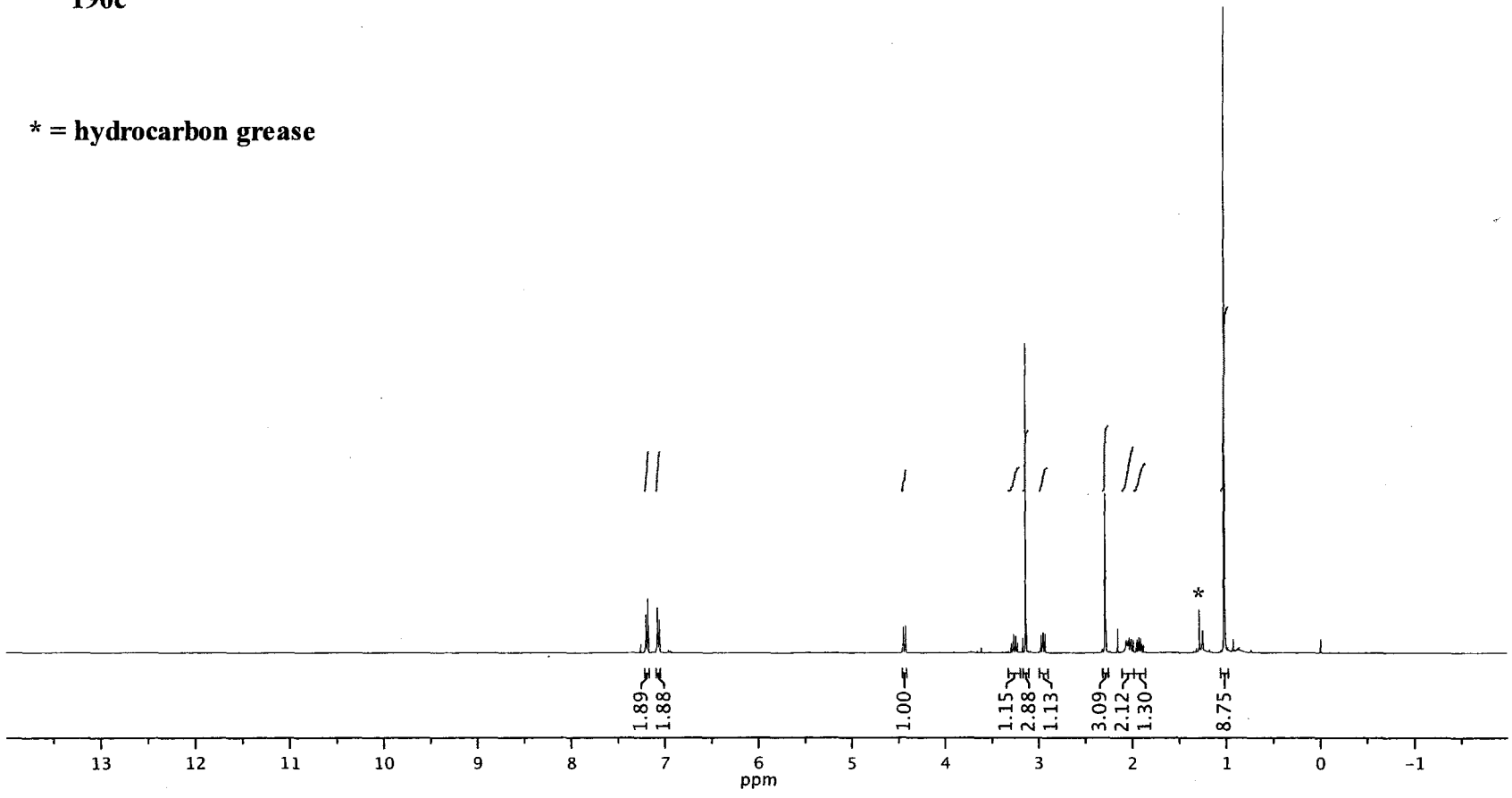
189c

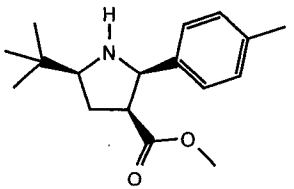
185.37
172.89
137.10
135.73
128.79
127.37
77.57
51.40
48.57
36.65
36.34
28.48
21.34
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



190c

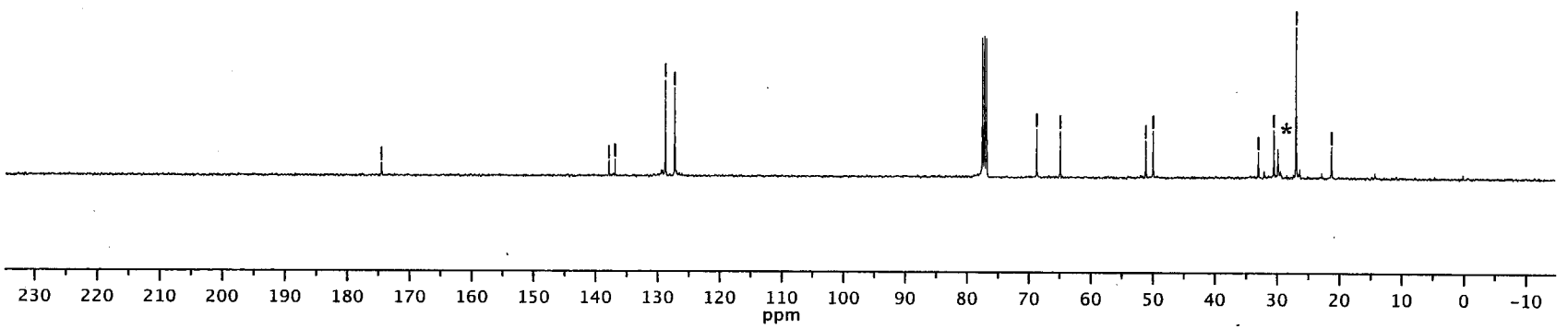
*** = hydrocarbon grease**

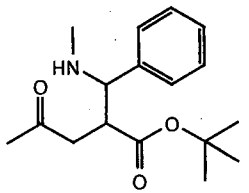




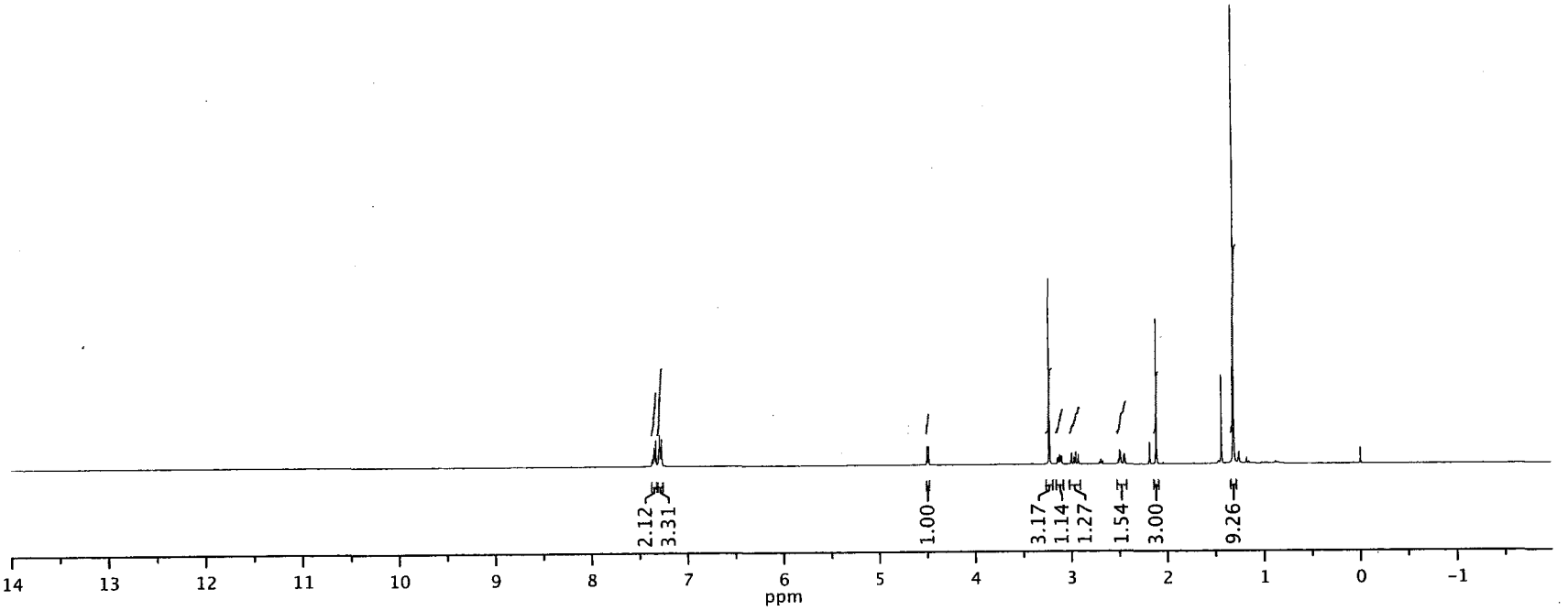
190c

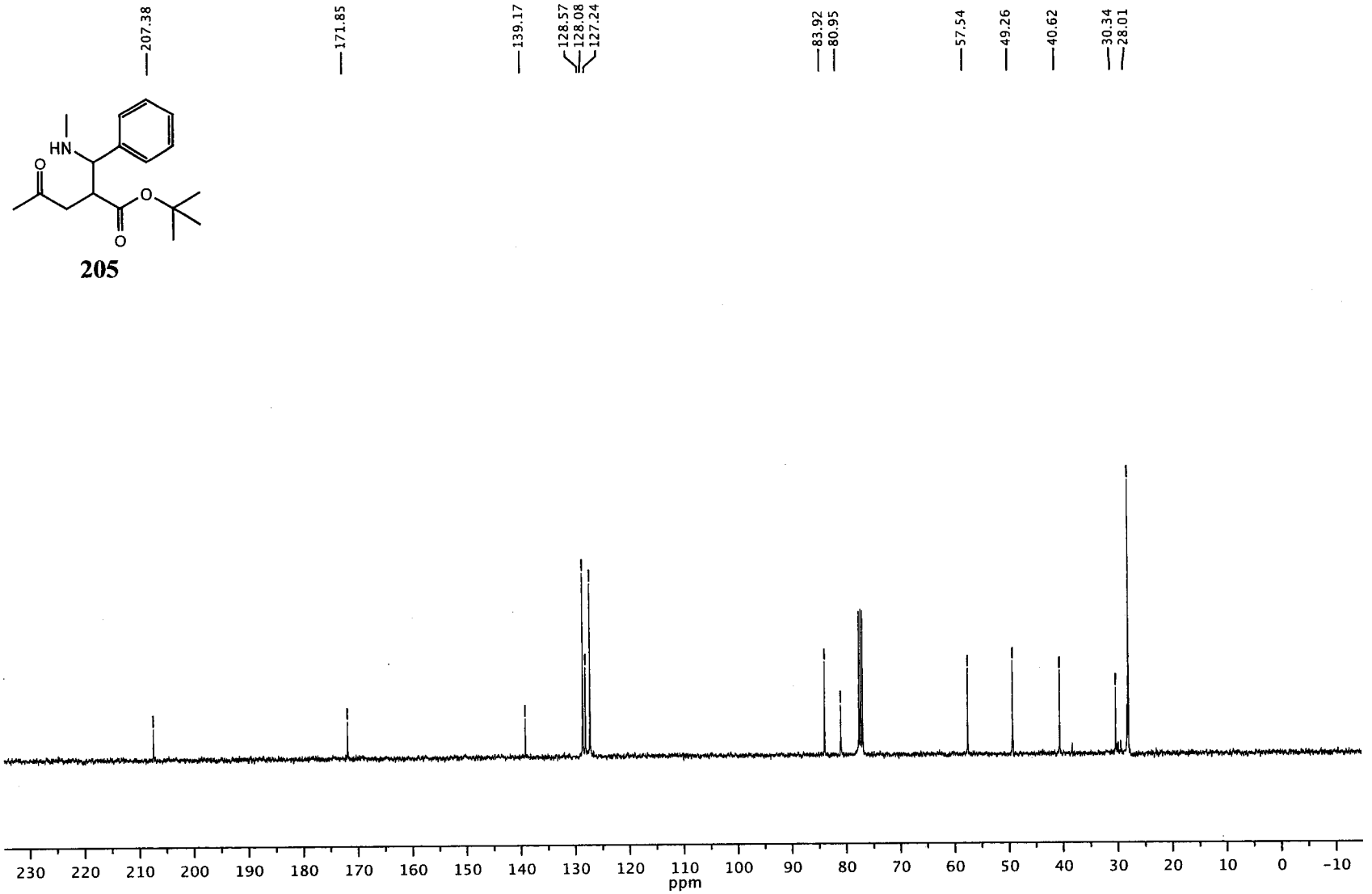
*** = hydrocarbon grease**



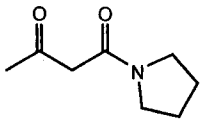

HN
O
O
O

205

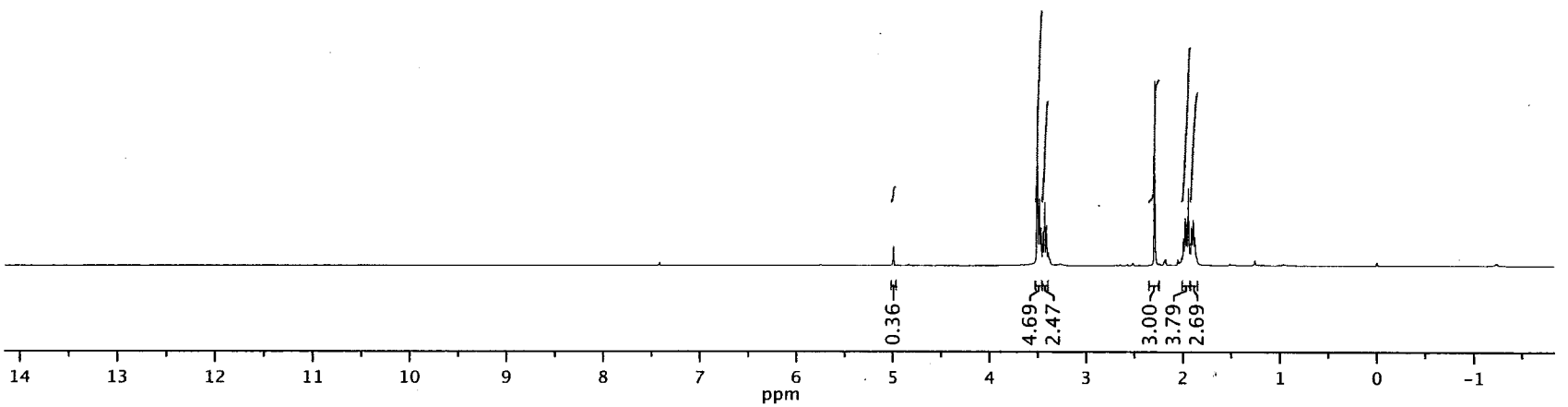

2.12
3.31
1.00
3.17
1.14
1.27
1.54
3.00
9.26
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

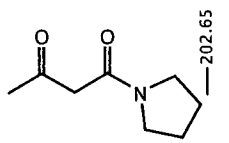

207.38
171.85
139.17
128.57
128.08
127.24
83.92
80.95
57.54
49.26
40.62
30.34
28.01
HN
O
O
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

205



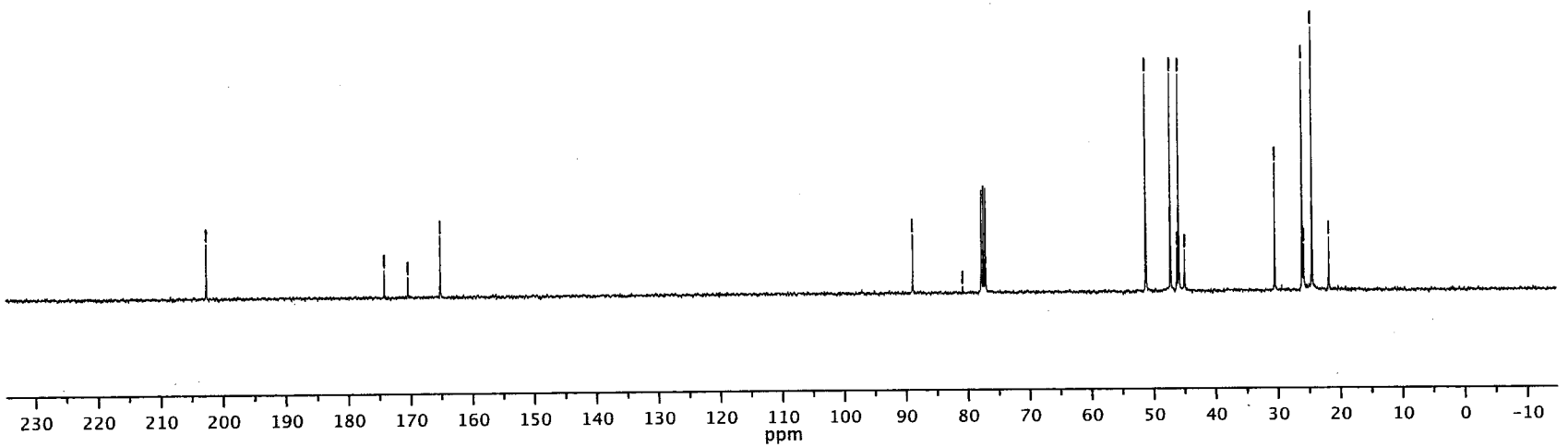
214

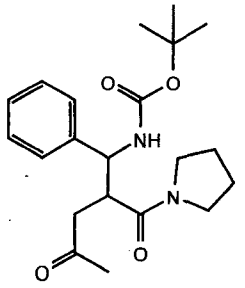



O
O
N
202.65

214

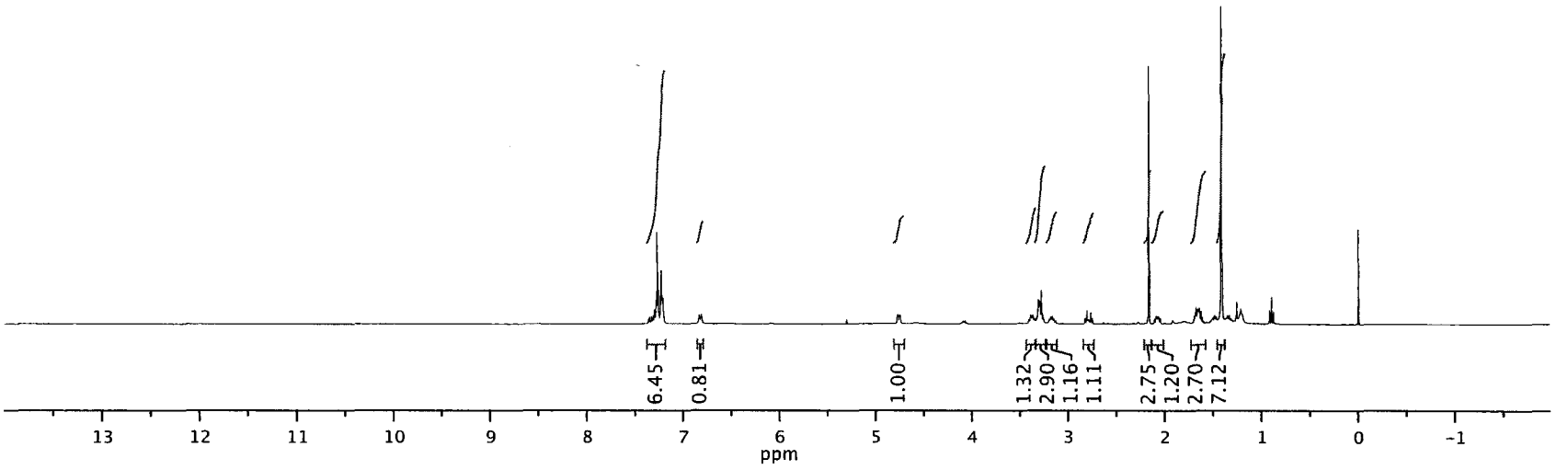

174.17
170.37
165.17
88.91
80.86
51.27
47.29
46.21
45.96
45.01
30.51
26.12
25.86
24.54
21.84

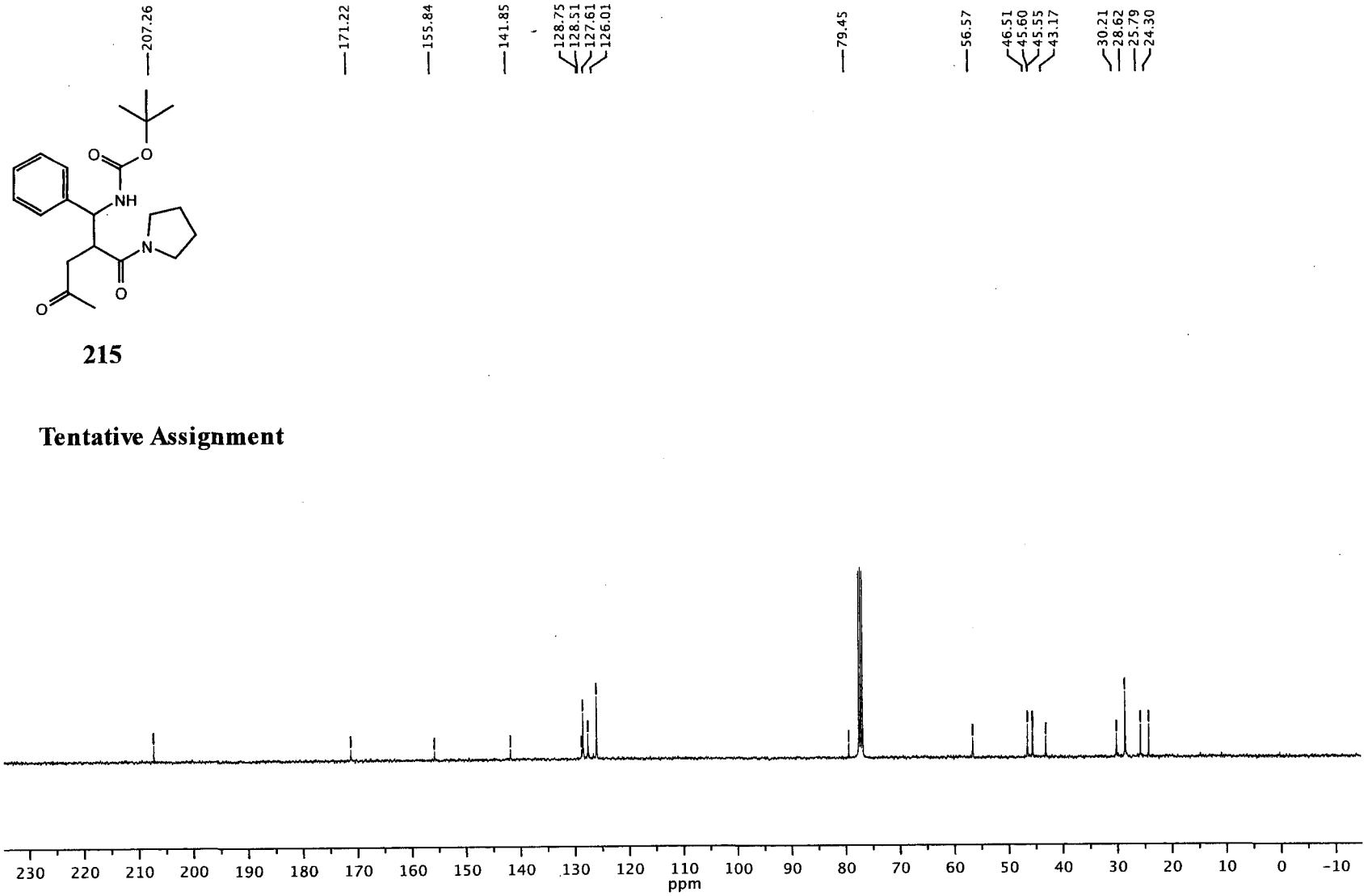

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



215

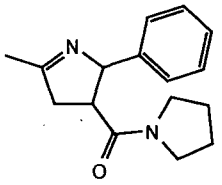
Tentative Assignment





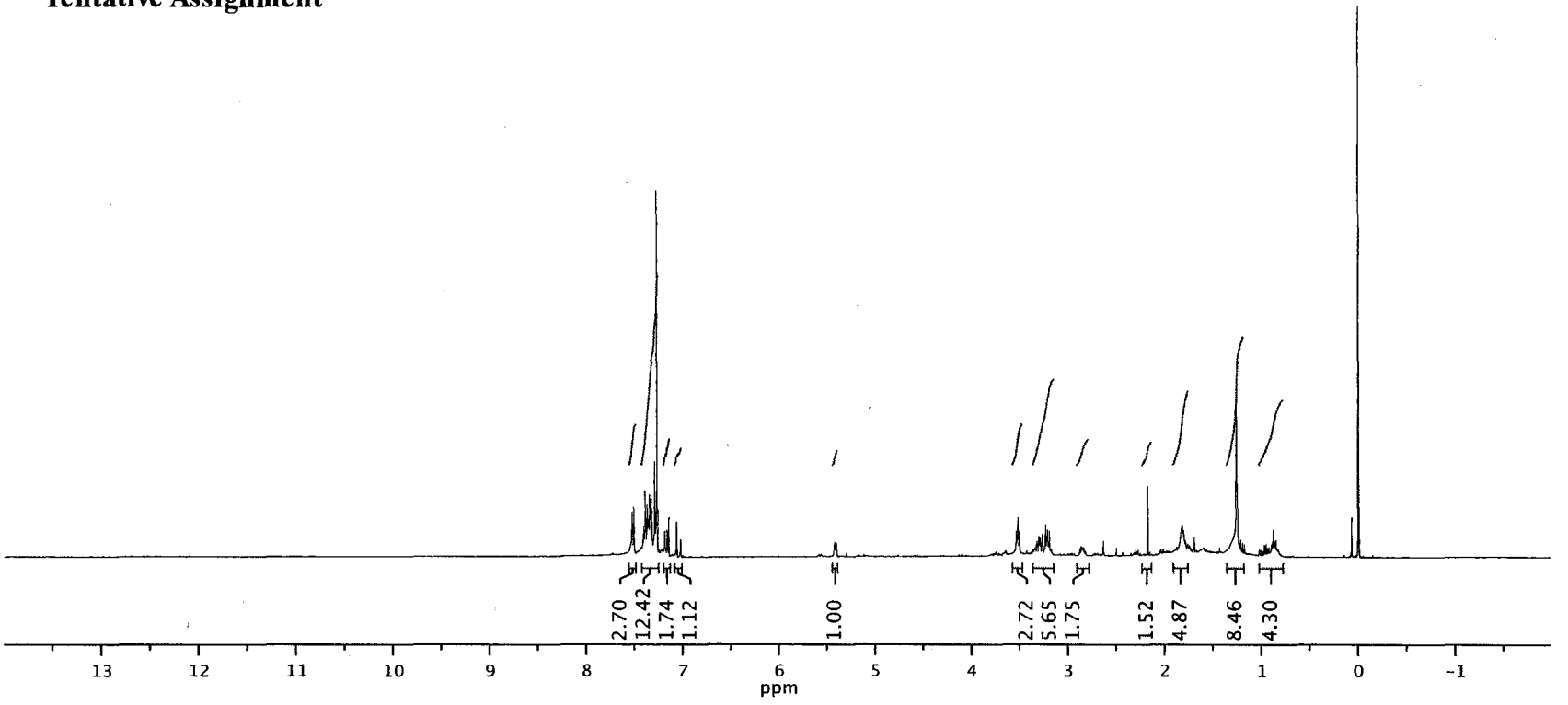
215

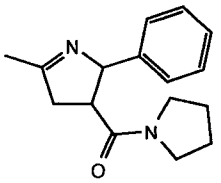
Tentative Assignment



216

Tentative Assignment

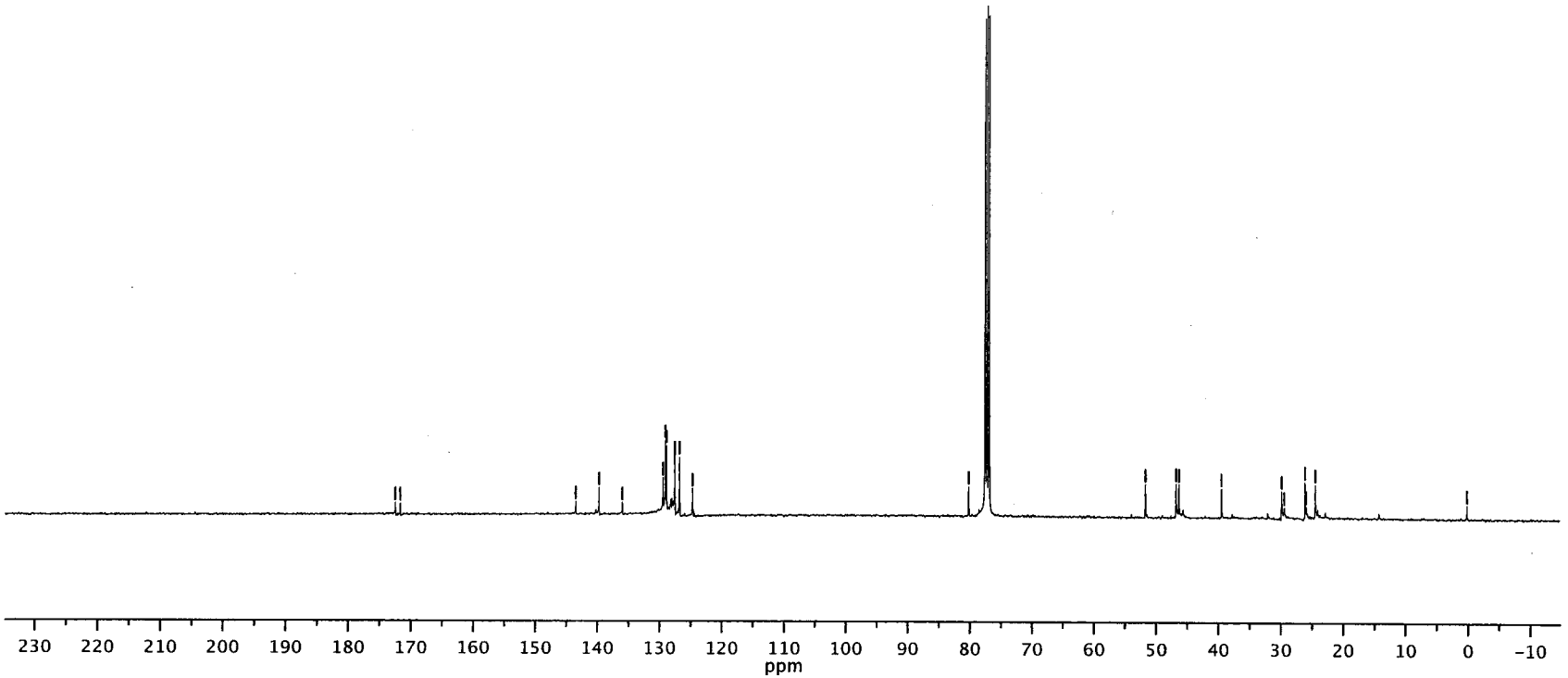


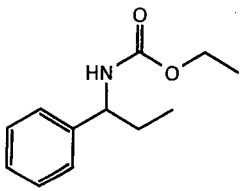


216

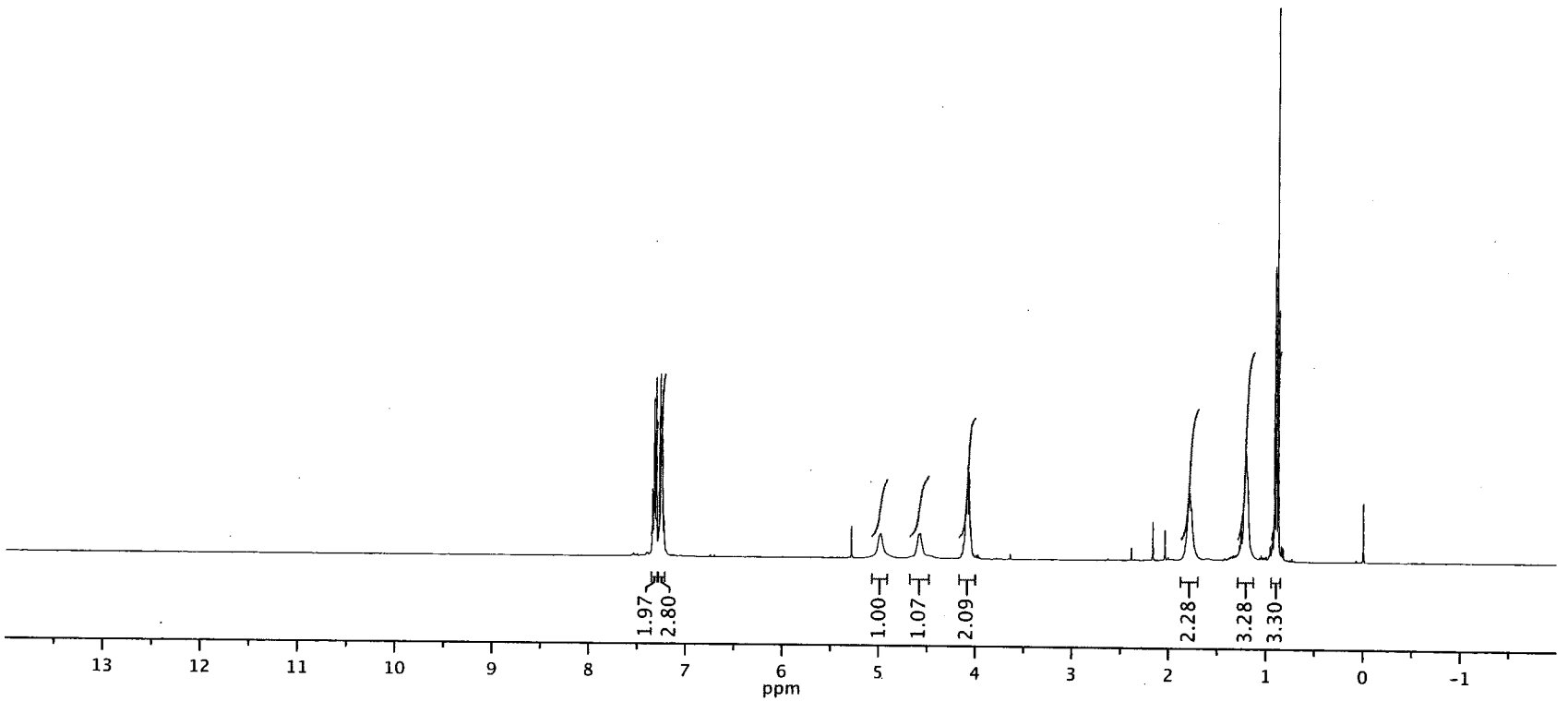
172.44
171.64
143.46
139.72
135.98
129.44
129.08
128.87
127.61
127.55
126.79
124.68
80.20
51.74
46.81
46.35
39.54
29.92
29.48
26.17
25.97
24.51
0.22

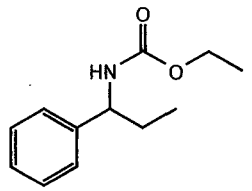
Tentative Assignment




O
HN
O

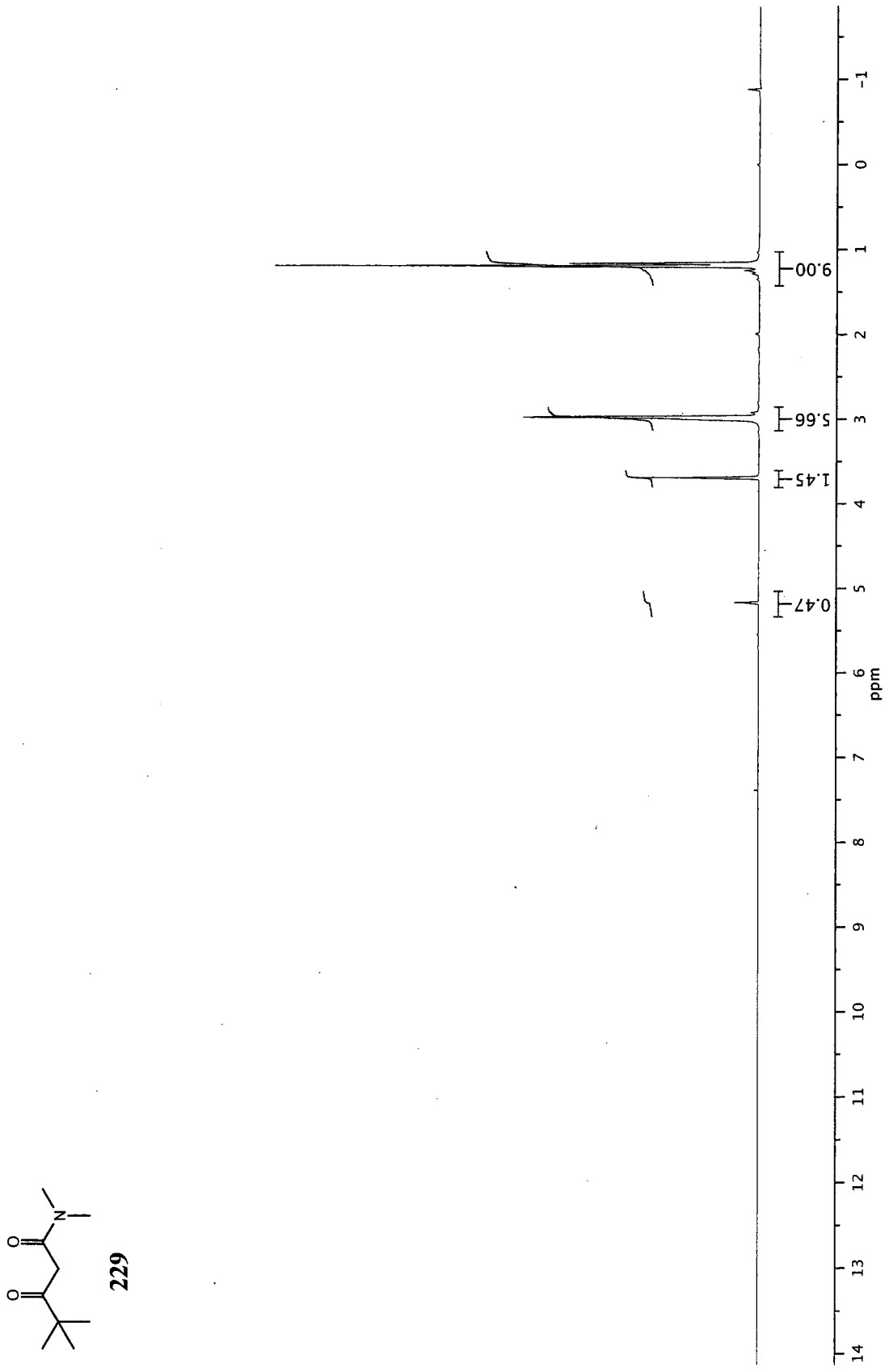
217


1.97
2.80
1.00
1.07
2.09
2.28
3.28
3.30
13
12
11
10
9
8
7
6
ppm
5
4
3
2
1
0
-1

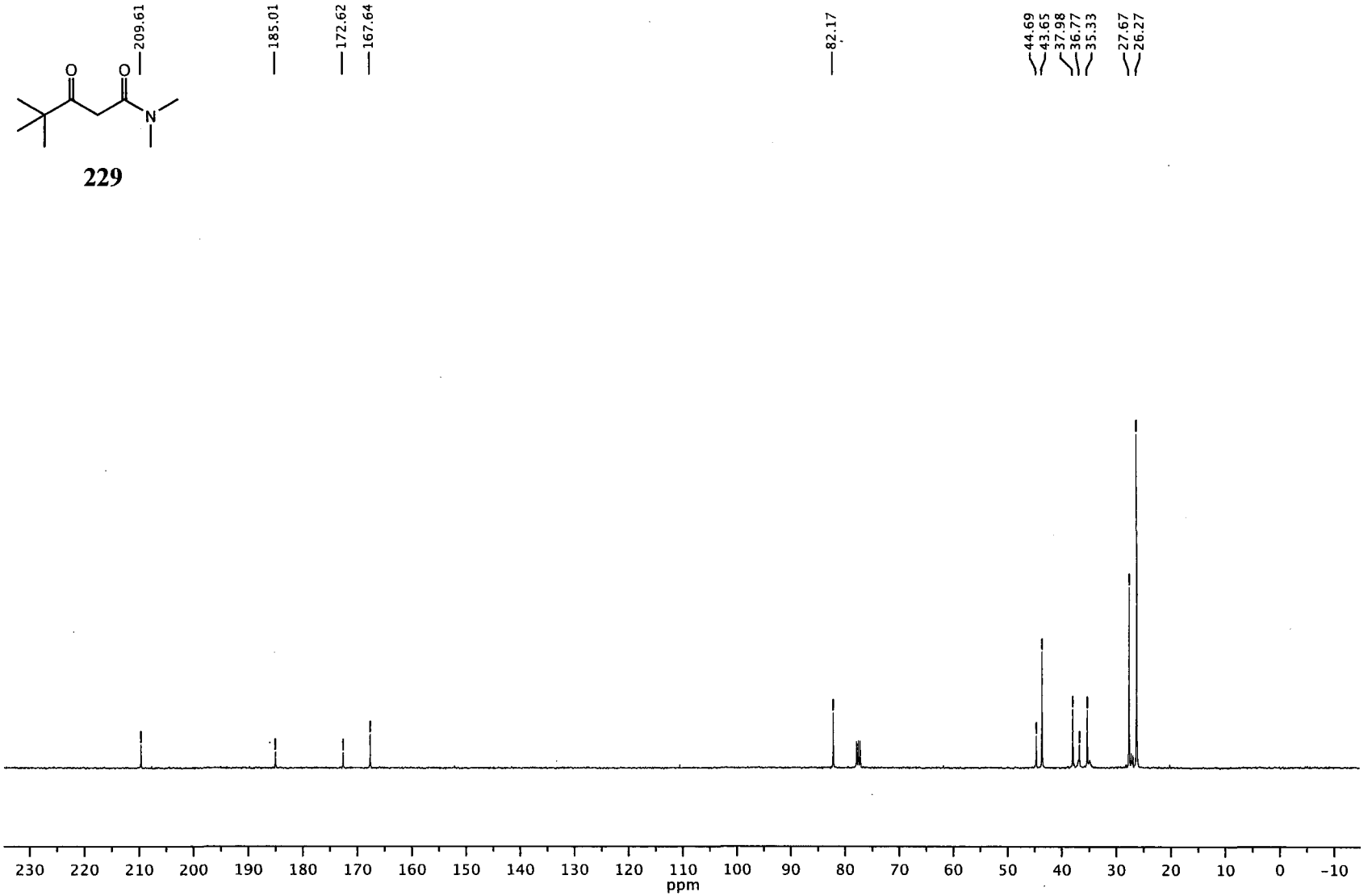

O
HN
O

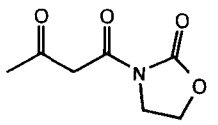
217

156.27
142.84
128.75
127.43
126.60
60.99
56.94
29.91
14.80
10.91
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

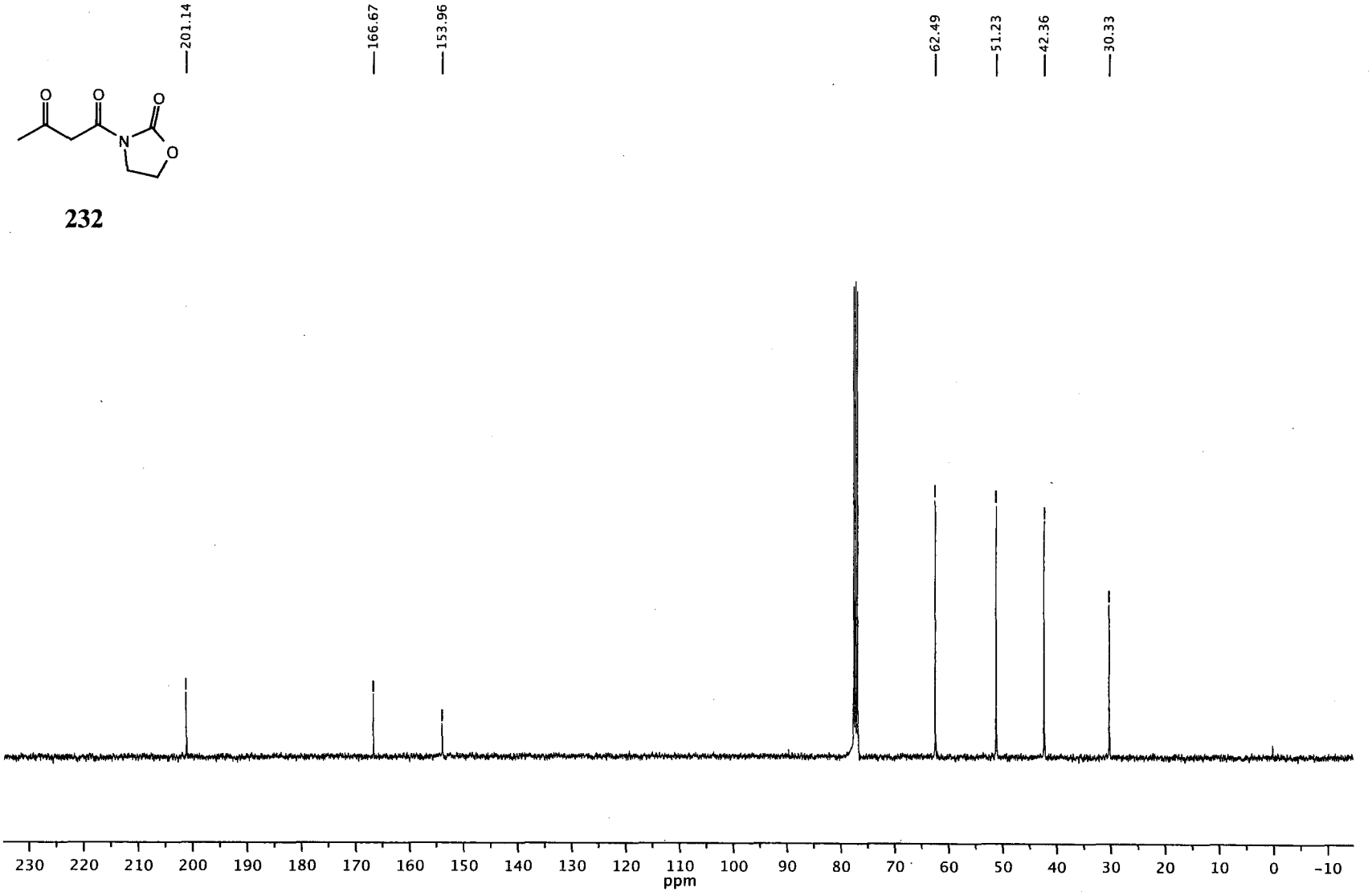


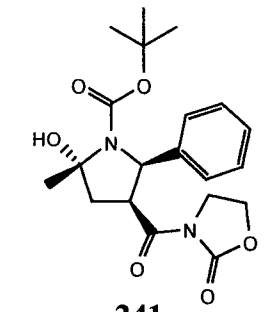
229


209.61
185.01
172.62
167.64
82.17
44.69
43.65
37.98
36.77
35.33
27.67
26.27
O
O
N
229
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

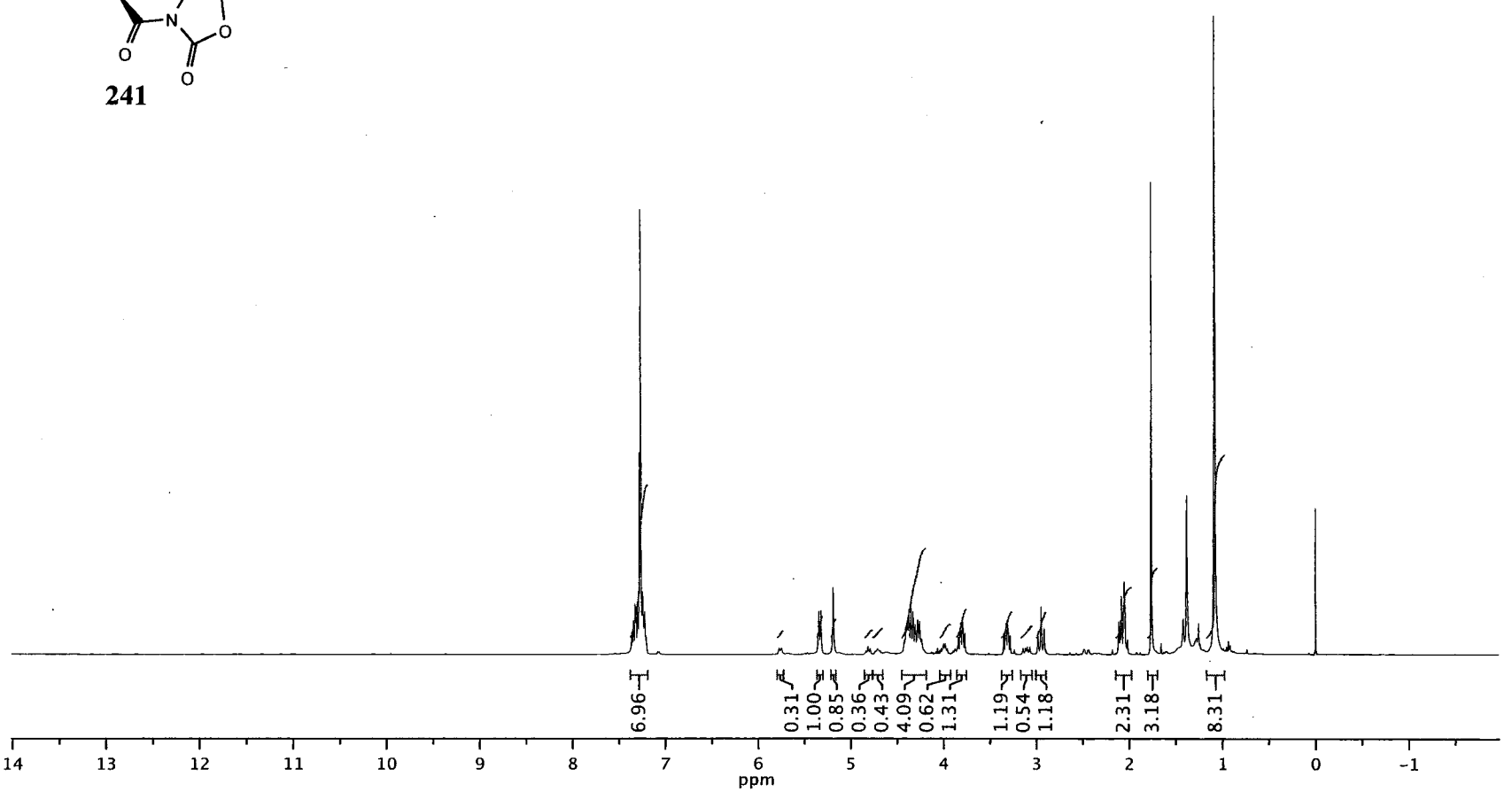


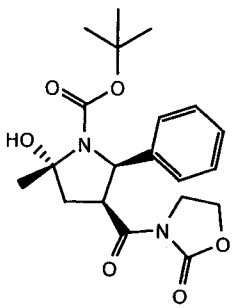
232


201.14
166.67
153.96
62.49
51.23
42.36
30.33
O
O
O
N
O
232
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


HO
N
O
O
O
N
O
O

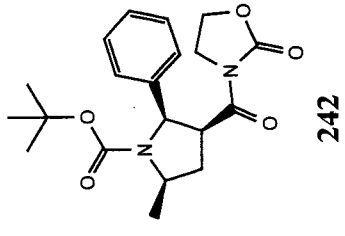
241


6.96
0.31
1.00
0.85
0.36
0.43
4.09
0.62
1.31
1.19
0.54
1.18
2.31
3.18
8.31
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

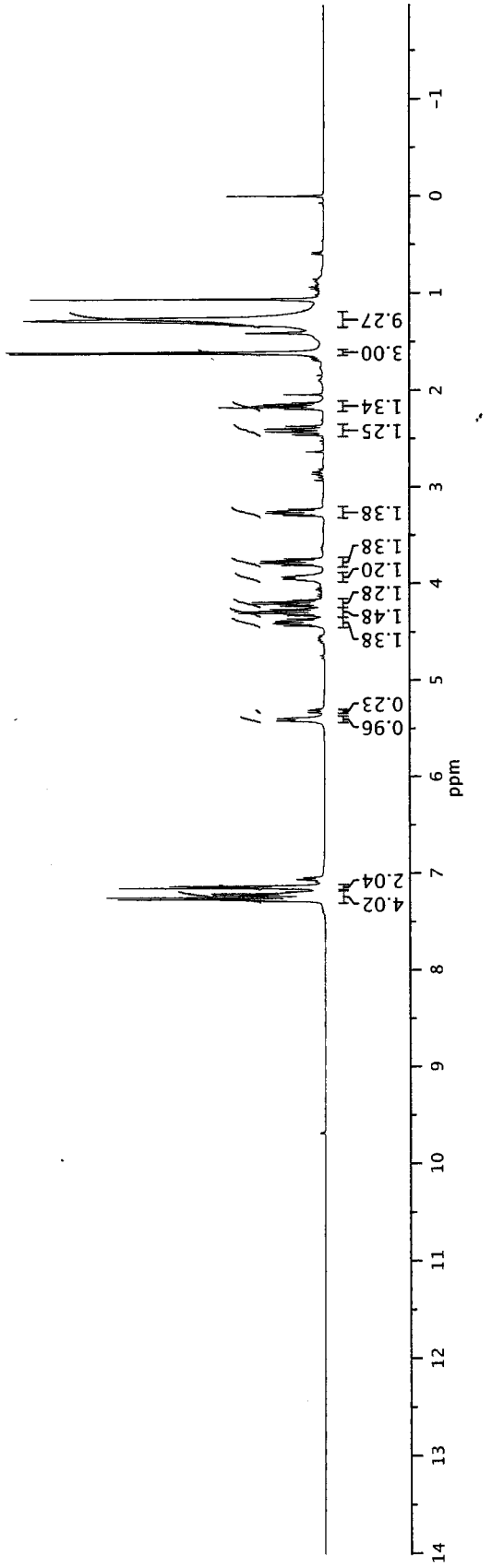


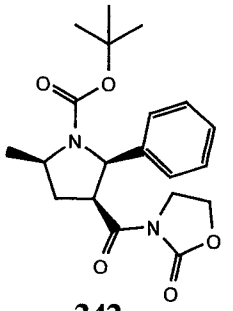
241

169.57
154.12
153.47
140.58
128.33
127.86
126.76
89.96
80.68
62.85
62.55
60.58
45.15
43.05
42.73
39.06
28.51
28.15
27.21
21.26
14.41
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



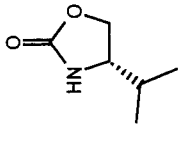
242



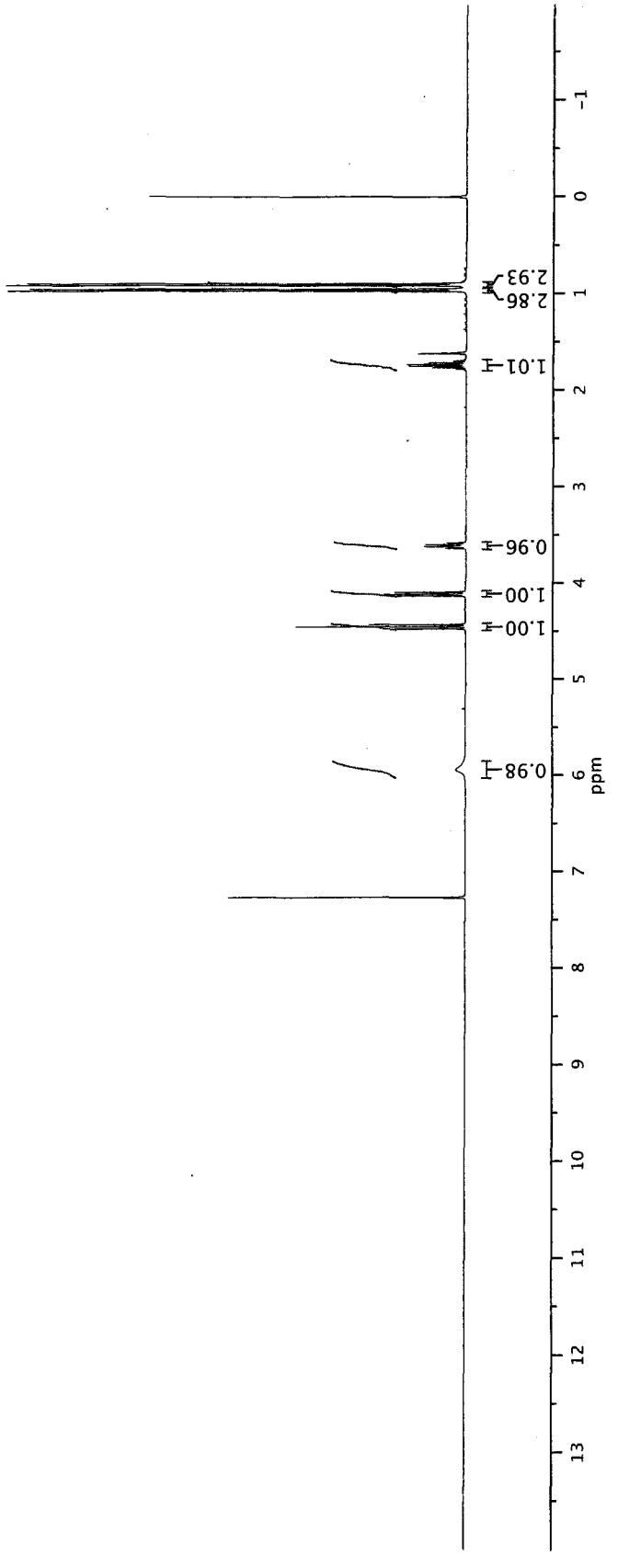


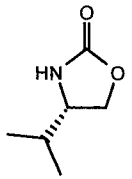
242

170.28
154.92
153.39
141.05
128.27
127.65
126.85
79.84
64.16
62.41
53.78
47.34
42.70
34.17
28.44
21.33
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



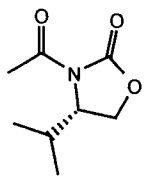
262



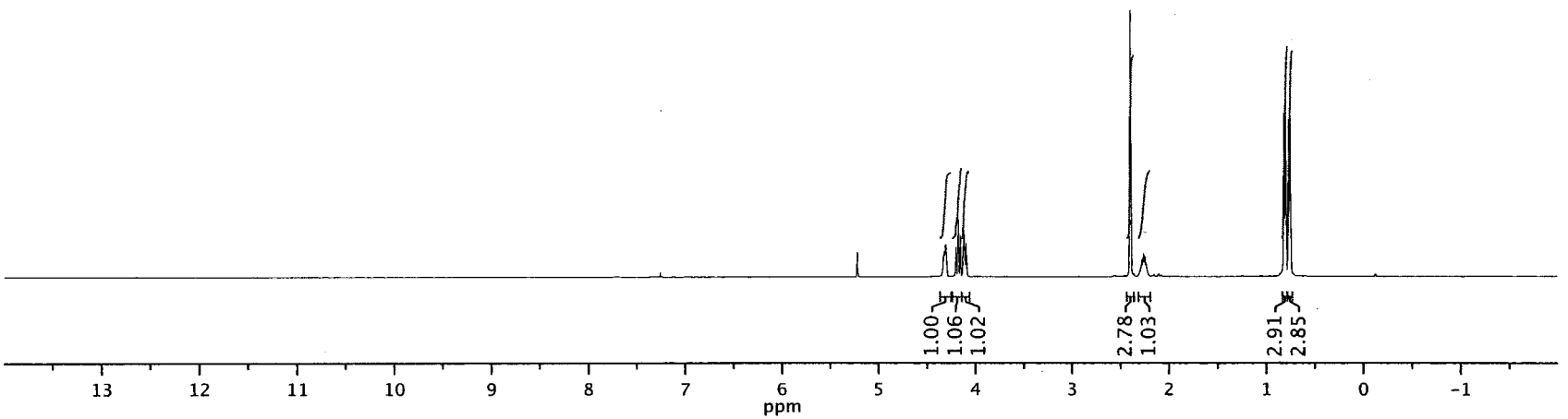

O
HN
O

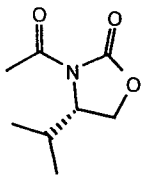
262

160.65
68.85
58.61
32.92
18.22
17.87
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



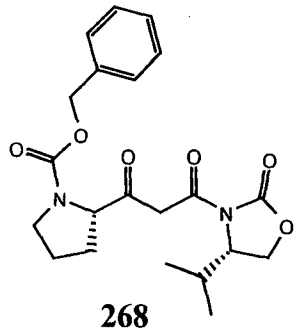
263





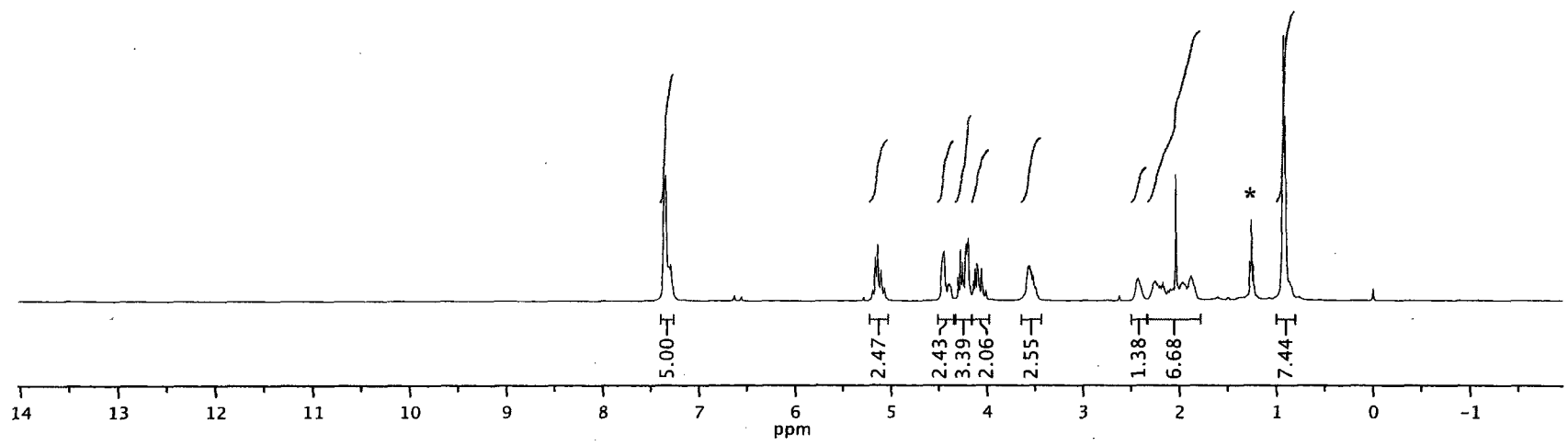
263

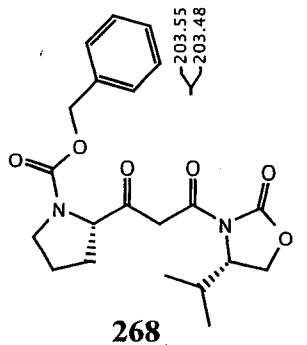
170.28
154.43
63.46
58.42
28.46
23.89
18.05
14.74
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



268

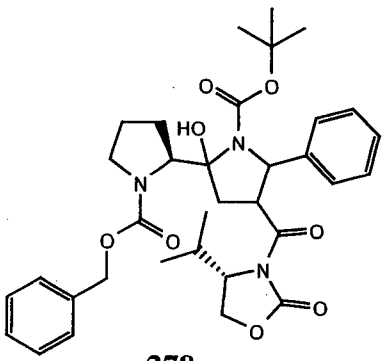
* = ethyl acetate



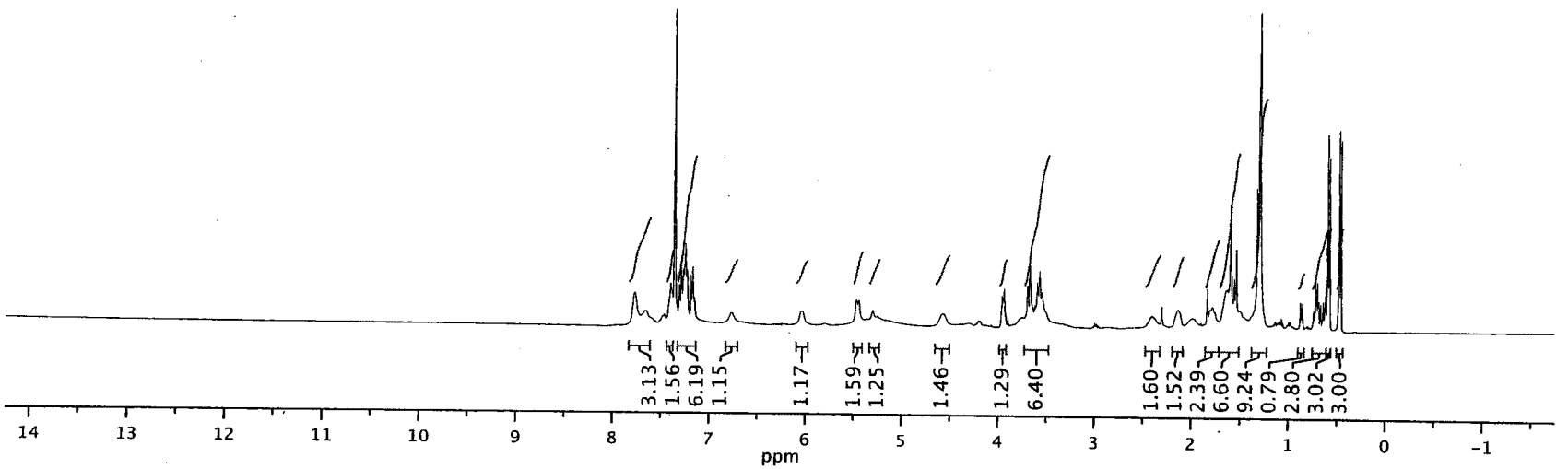


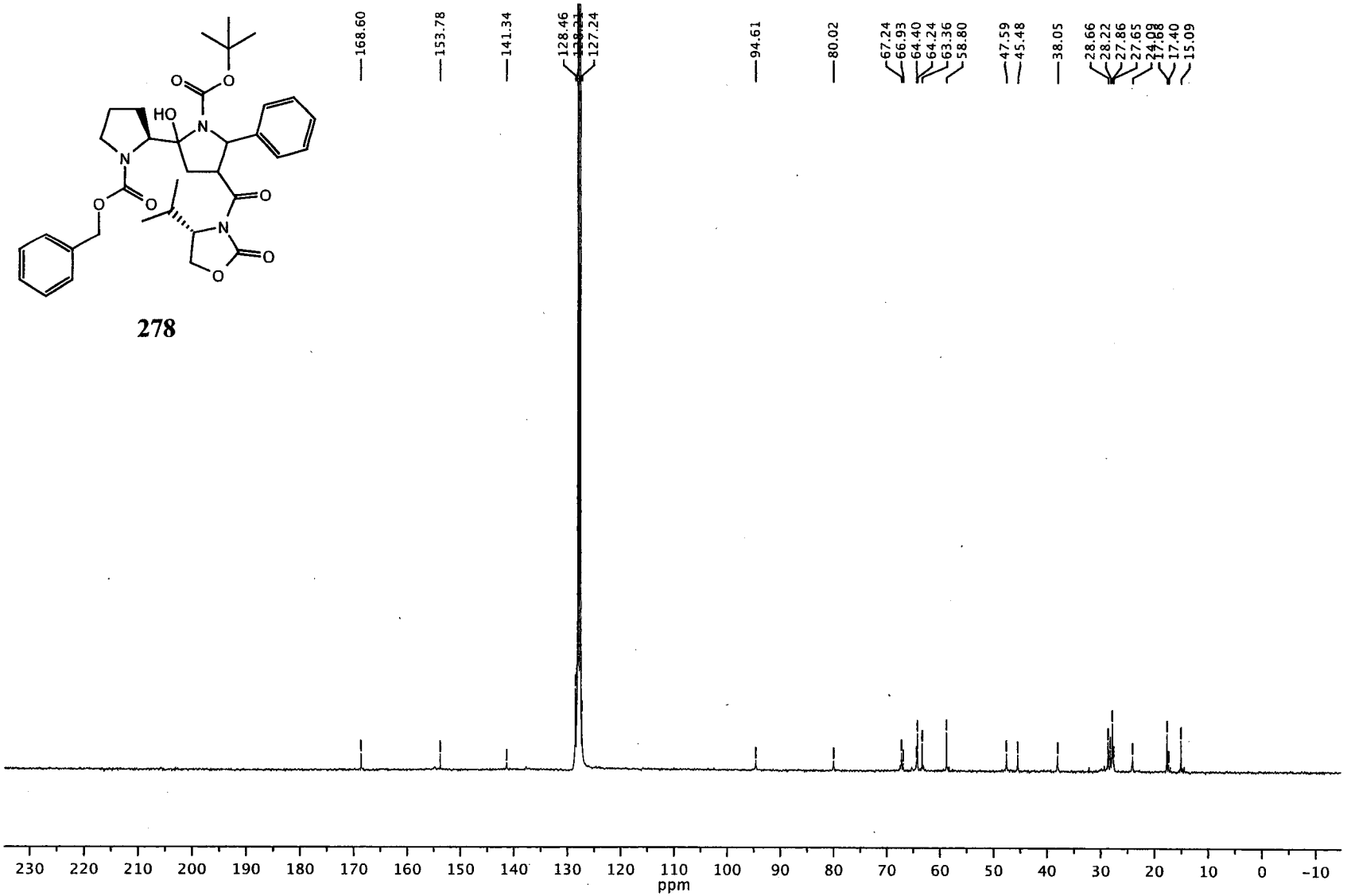
268

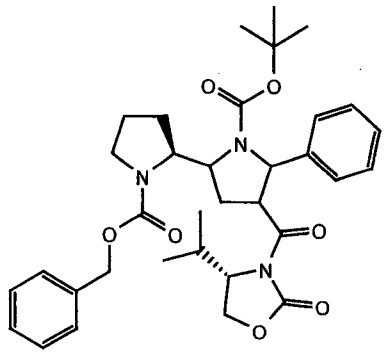
203.55
203.48
166.66
166.44
155.50
154.63
154.44
154.36
136.78
136.48
67.55
67.37
65.56
65.34
63.83
63.43
60.56
58.69
48.53
47.96
47.52
47.06
29.80
28.59
28.51
24.56
23.75
21.23
18.11
14.90
14.74
14.40
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


HO
N
N
N
O
O
O
O
O
O
O
O

278

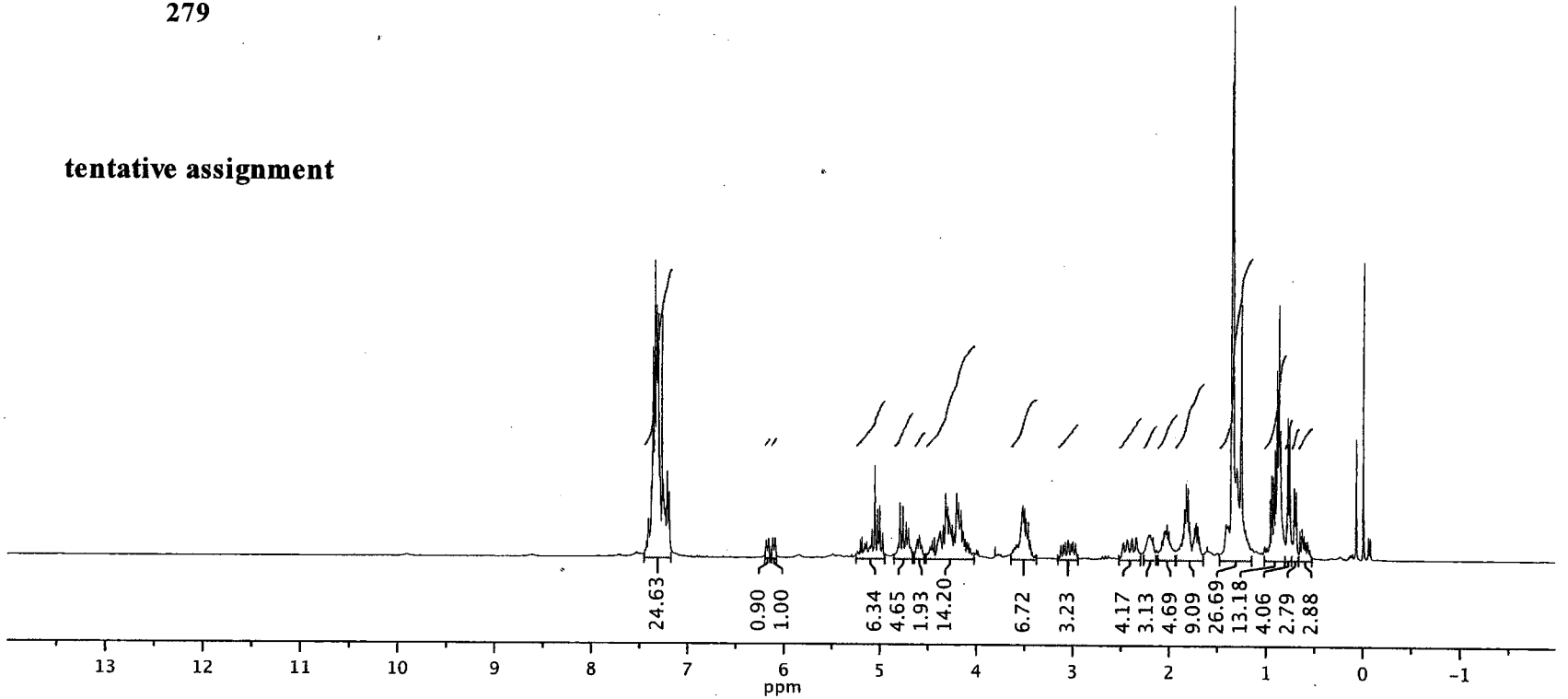

3.13
1.56
6.19
1.15
1.17
1.59
1.25
1.46
1.29
6.40
1.60
1.52
2.39
6.60
9.24
0.79
2.80
3.02
3.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

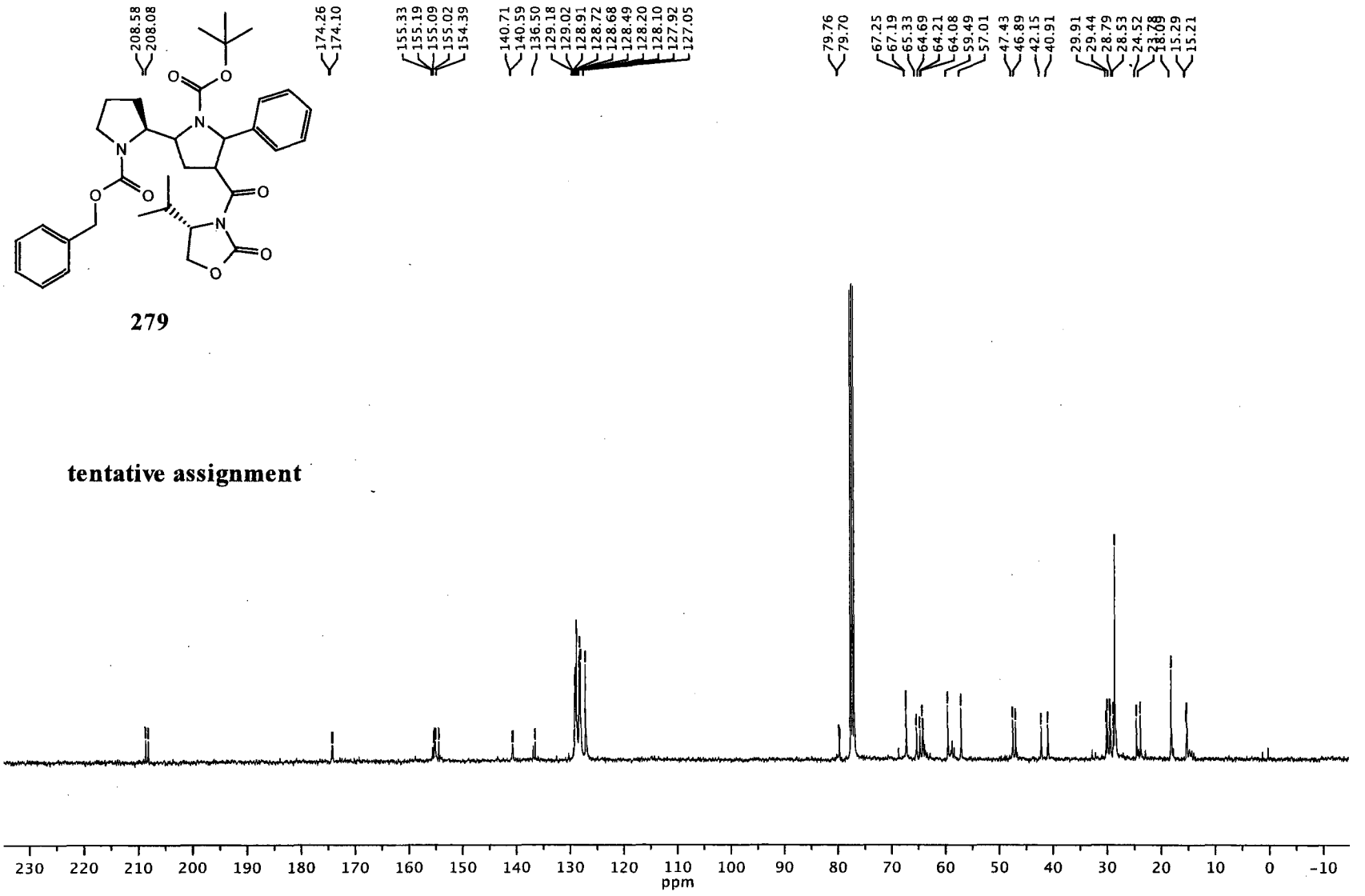

278
168.60
153.78
141.34
128.46
127.24
94.61
80.02
67.24
66.93
64.40
64.24
63.36
58.80
47.59
45.48
38.05
28.66
28.22
27.86
27.65
17.40
15.09
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



279

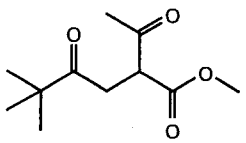
tentative assignment



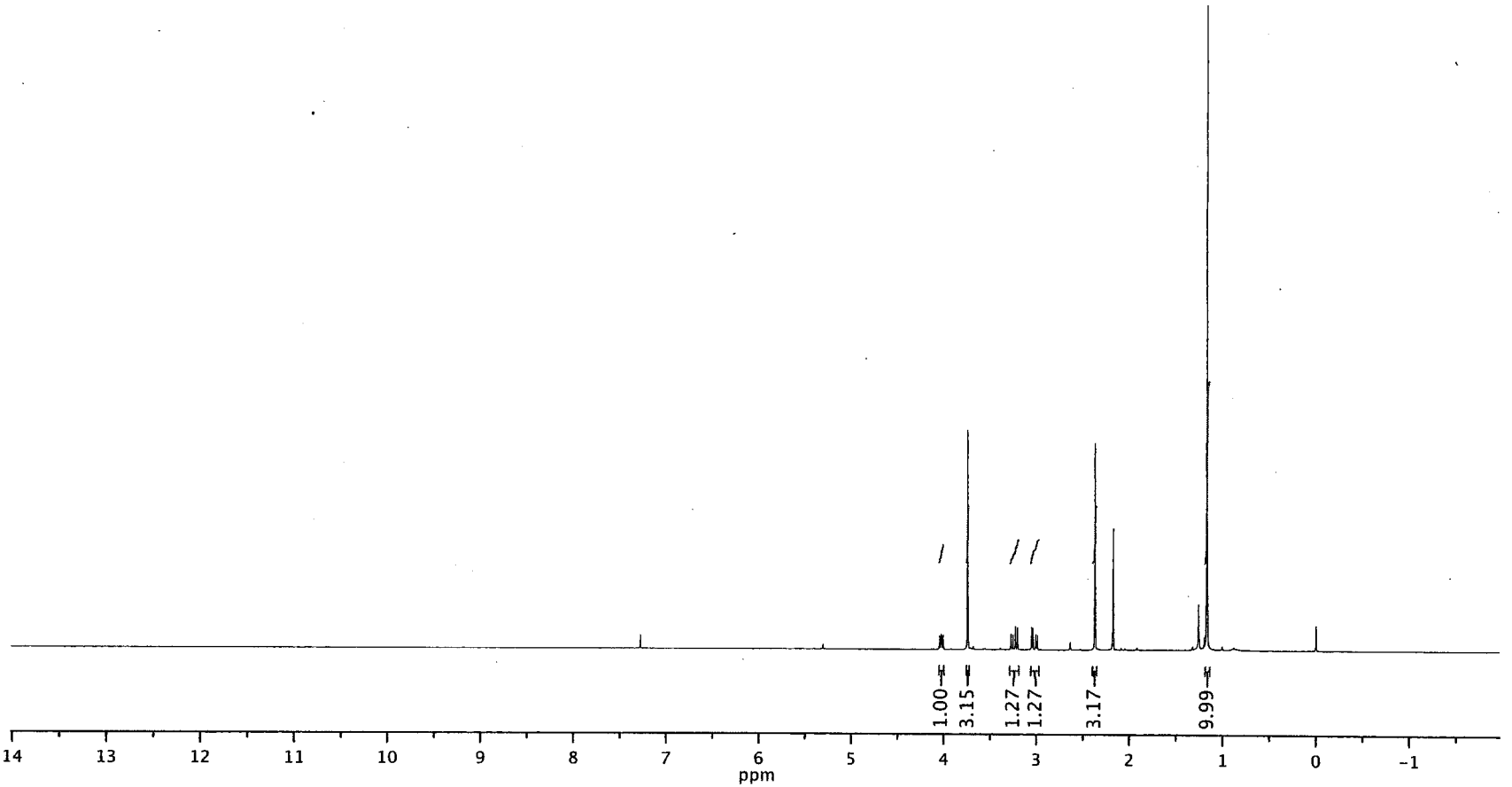


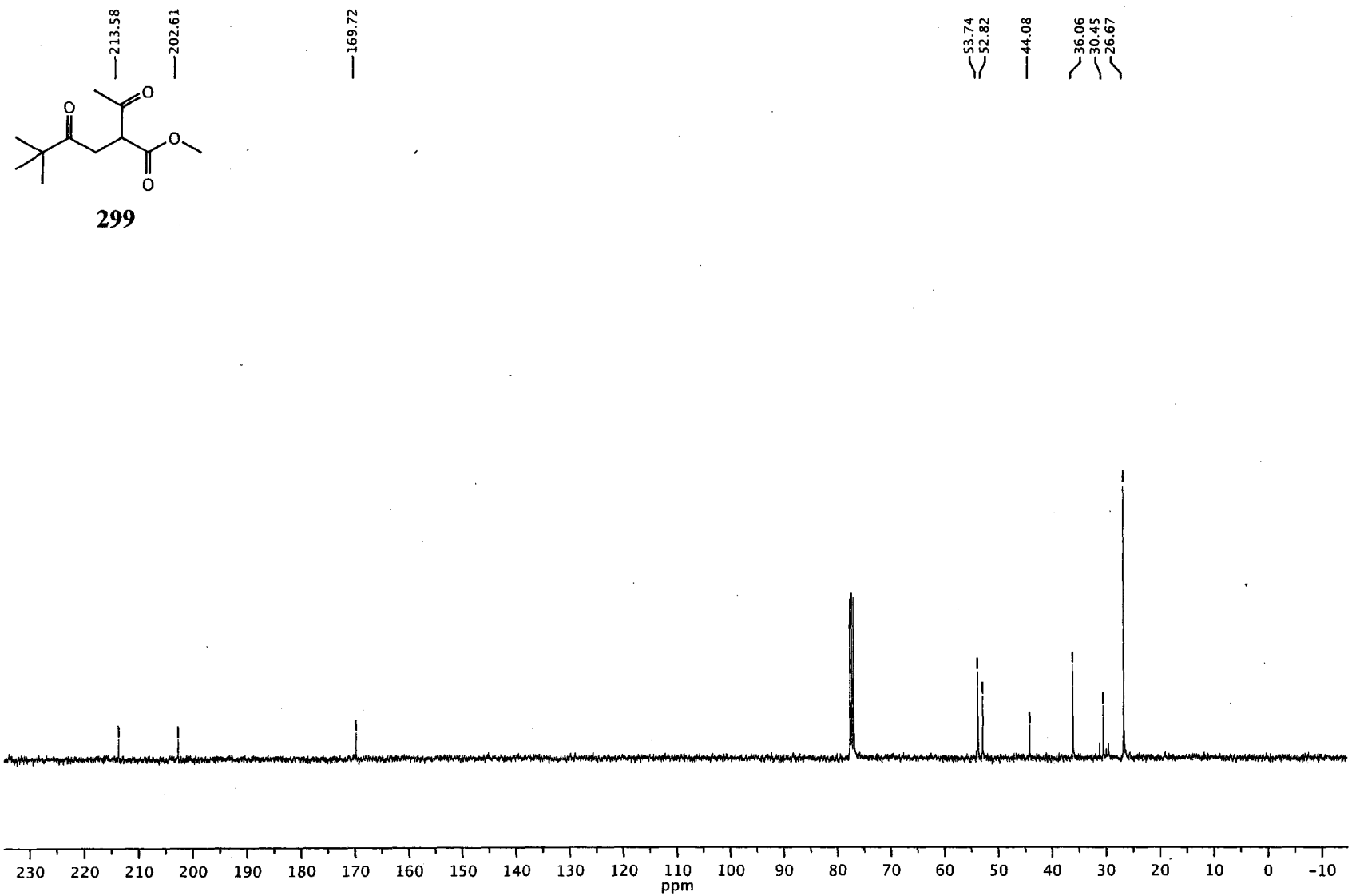
279

tentative assignment



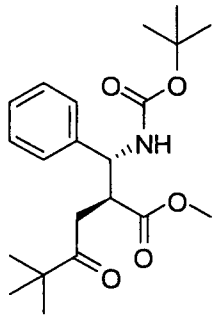
299



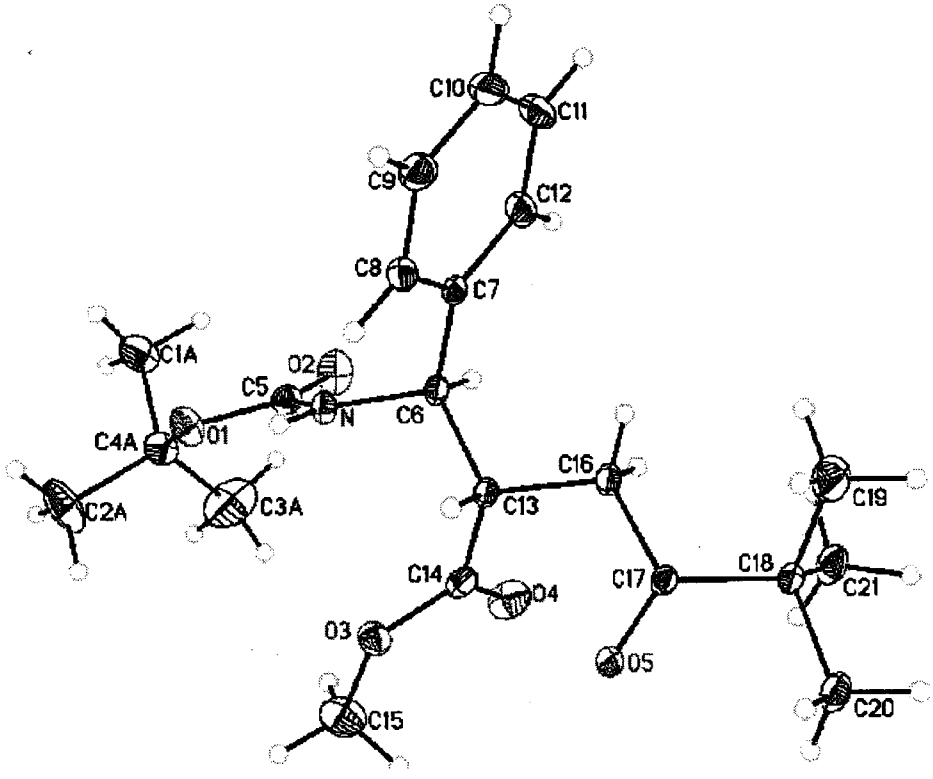

213.58
202.61
169.72
53.74
52.82
44.08
36.06
30.45
26.67
O
O
O
O
299
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

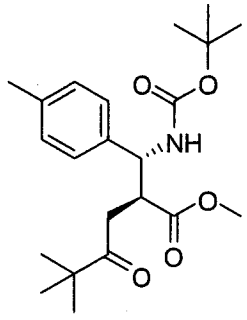
APPENDIX B

X-RAY CRYSTAL STRUCTURES

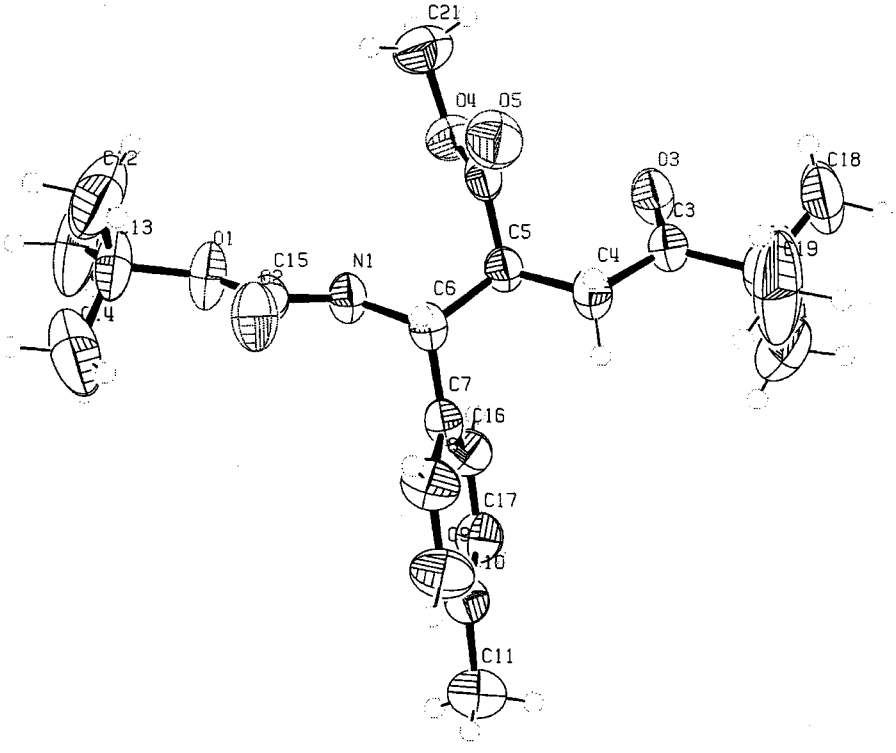


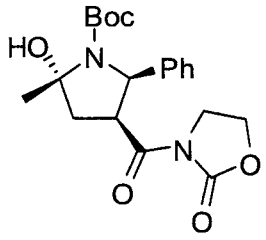
188a


C10
C11
C9
C12
C8
C7
C1A
O2
C5
N
C6
C4A
O1
C16
C13
C2A
C3A
C19
C14
O4
C17
C18
C21
O3
O5
C15
C20

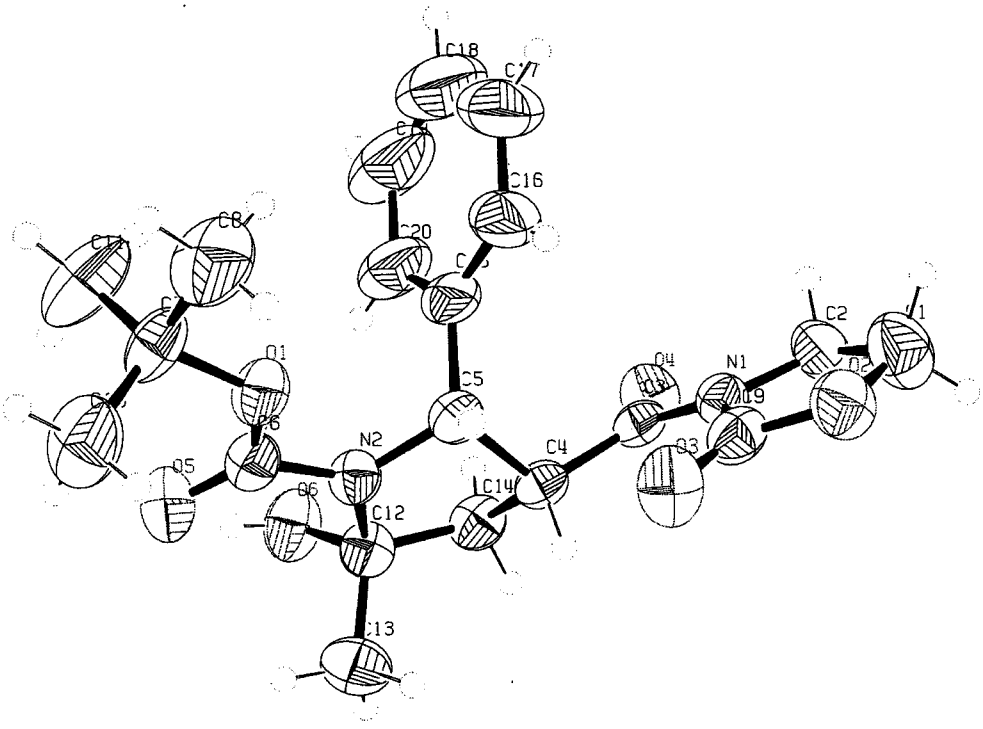

O
O
NH
O
O
O

188c


C21
O4
O5
O3
C18
C12
C13
O1
C15
N1
C5
C4
C3
C19
C6
C7
C16
C17
C10
C11


Boc
HO
N
Ph
N
O
O
O

241


C18
C17
C16
C20
C8
O1
C5
O4
N1
C2
C6
N2
C4
O5
O6
C14
C12
C13
O3