Spring 2011

I Progress towards the synthesis of plakortether B through a zinc-mediated homologation II Synthesis of novel hydroxy-cyclopropyl peptides isosteres

Ian Scott Taschner
University of New Hampshire, Durham

I. PROGRESS TOWARD THE SYNTHESIS OF PLAKORTETHER B THROUGH A ZINC-MEDIATED HOMOLOGATION

II. SYNTHESIS OF NOVEL HYDROXY-CYCLOPROPYL PEPTIDE ISOSTERES

BY

Ian Scott Taschner

B.S., University of Akron, 2005

DISSERTATION

Submitted to the University of New Hampshire

in Partial Fulfillment of

the Requirements for the Degree of

Doctor of Philosophy

in

Chemistry

May, 2011

This dissertation has been examined and approved.

Dissertation Director, Charles K. Zercher
Professor of Chemistry

Richard P. Johnson
Professor of Chemistry

Arthur Greenberg
Professor of Chemistry

Roy P. Planalp
Associate Professor of Chemistry

Donald C. Sundberg
Professor Emeritus

March 31, 2011
Date

DEDICATION

This dissertation is dedicated to Michael, Deborah, and Matt Taschner. My father has always been an inspiration to my chemical career and encouraged me throughout my graduate experience. My mother has always been there for me through the highs and the lows. No matter what path I decided to take, both of my parents were always extremely supportive and loving. My brother was there to keep me in check by reminding me that life is not all about work and that a little exercise can provide relief during the most stressful times. To my family (Rico and Brendelton, too), thank you for everything that was granted to me through my chemical career.

ACKNOWLEDGEMENTS

I would like to express gratitude to my graduate advisor, Professor Charles K. Zercher. His patience throughout my graduate studies has been vital to my understanding of chemistry. Starting with limited synthetic skills, Professor Zercher has molded me into an advanced chemist in the laboratory. Most importantly, he made time to help me with life situations and to overcome many of my shortcomings. For this, I thank Professor Zercher and his wonderful family.

I would also like to thank all of the chemistry professors at the University of New Hampshire. Professor Planalp has provided me with organometallic knowledge, as well as motivational music every Sunday from 2-4 pm, which helped to keep my focus in lab. Professor Weisman, though intimidating at first, has taught me very valuable mechanistic skills that have carried on throughout my graduate career. Professor Greenberg and Johnson have both sparked my interest in computational chemistry, which was obsolete when I first started in the chemistry program. Professor Wong has given me insight on basic inorganic chemistry that has been useful in the understanding of the zinc-mediated homologation. Professor Wong was also available to console with at anytime, especially during my second year.

I need to acknowledge my late and good friend Evan Southwick. He was an excellent chemist and friend in the beginning of my studies. Through him I have gained

an appreciation for life and hard work required to become a successful chemist. Much love.

I would like to express immense gratitude toward Dr. Thomas Jenkins and his family. Dr. Jenkins offered me an excellent opportunity to work at his company, Pharmacofore, under the guidance of Dr. Craig Husfeld. Working at Pharmacofore provided me with industrial experience and an appreciation for medicinal chemistry. Dr. Husfeld was a great mentor and most importantly a good friend. During my time at Pharmacofore, Dr. Jenkins and his family (Sherri, Alex, Max, Friar Lawrence, 8-foot, and Sister) opened their doors and provided me with a home away from home.

Brian Sliter and family have always been there to support me in the toughest of times during graduate school. During the rough times, his family always invited me to their home and provided me with amazing food. For this I owe them much gratitude and appreciation.

I also must show a great appreciation for the Zercher research group. Alex Jacobine, Wei-Min Lin, Karina Thorn, Matt Bixby, Jenn Mazzone, Brian Sliter, Tim Henderson, Matt Mower (CEO of Kemfinder), Pete "the beat" Moran, Carley Spencer, Deepthi Bhogadhi, Aida Ajaz, and Jared Pearl have been vital in my development as a synthetic chemist and have been great friends throughout. All of the fun and excitement I had in the lab is primarily due to these individuals.

Lastly, I would like to thank the best administrative assistants ever, Cindi Rohwer and Peg Torch.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

LDA	lithium diisopropylamide
Boc	*tert*-butoxycarbonyl
Cbz	benzyloxycarbonyl
PG	Protecting group
TFA	trifluoroacetic acid
CDI	carbonyl diimidazole
HOBT	1-hydroxybenzotriazole
TMS	trimethylsilyl
Pmb	*para*-methoxybenzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DMAP	*N,N*-dimethylaminopyridine
LAH	lithium aluminum hydride
CAN	ceric ammonium nirate

I. PROGRESS TOWARD THE SYNTHESIS OF PLAKORTETHER B THROUGH A ZINC MEDIATED HOMOLOGATION

II. SYNTHESIS OF HYDROXY-CYCLOPROPYL PEPTIDE ISOSTERES FOR ASPARTYL PROTEASE INHIBITION

BY

Ian Scott Taschner

University of New Hampshire, May, 2011

A streamlined synthetic pathway to target the core of plakortether B through a zinc-mediated homologation-aldol reaction has been developed. This chemistry was performed on a chiral β-keto amide, which was synthesized in a few steps. In a one-pot reaction the β-keto amide could be converted into a furanyl-ketal with high stereocontrol at two chiral centers. The homologation-aldol reaction was followed by a cyclization-allylation to obtain the plakortether backbone.

During the synthesis of plakortether B, a serendipitous byproduct was identified as a [3.1.0] bicyclic lactone. The lactone was seen as a precursor to a peptidomimetic that would contain an embedded hydroxycyclopropyl moiety. The formation of the bicyclic lactones was proposed to involve a cascade of homologation-cyclopropanation-

rearrangement-lactonization reactions. Amino acid-derived β-keto imides were synthesized in order to enhance the stereocontrol of the tandem lactonization reaction. The use of amino acid derived β-keto imides was beneficial in two ways; first it incorporates an amino acid directly into the peptide isotere and influences the diastereocontrol.

The homologation-cyclization-rearrangement-lactonization reaction of β-keto imides has proven to be successful for the formation of [3.1.0] bicyclic lactones as precursors to peptide isosteres.

CHAPTER I

INTRODUCTION

Isosteric peptides for enzyme inhibition

Since 1995, Saquinavir, the first FDA approved apartyl protease inhibitor, has been utilized to combat the Human Immunodeficiency Virus (HIV), a retro virus that directly leads to Acquired Immunodeficiency Syndrome (AIDS).[1] Effective pharmacological medications for inhibition of HIV have been derived from peptide isosteres. Use of structure activity relationships (SAR) along with peptide isosteres helped pave the way for an emergence of aspartyl protease inhibitors.

Implementation of classical isostere nomenclature was first proposed by Langmuir[2] to describe molecules that contain the same number of atoms and valence electrons. In medicinal chemistry, bioisosteres are defined as molecules that have the same general structure as the parent biological pharmacophore but differ in one or two atoms.[3]

Bioisosteric backbones that mimic natural peptides are depicted in **Figure 1**. Peptide isostere **1** contains a ketomethylene moiety which mimics the amide bond, but this isostere can withstand the hydrolytic cleavage by an aspartic protease. Another peptide mimic is the hydroxyethylene isostere (**2**), which mimics the tetrahedral intermediate **(Figure 2)** formed during the cleavage of an amide bond, but this isostere is also not susceptible to hydrolysis. Another peptide mimic developed for viral inhibition is a β-substituted hydroxyethylene isostere (**3**). Due to the mutation of the virus, HIV infected patients need to continuously change the drug "cocktail" throughout the rest of their lives to maintain homeostasis.[4] Hence, the ability to systematically change the lead compound is a major advantage during drug design.

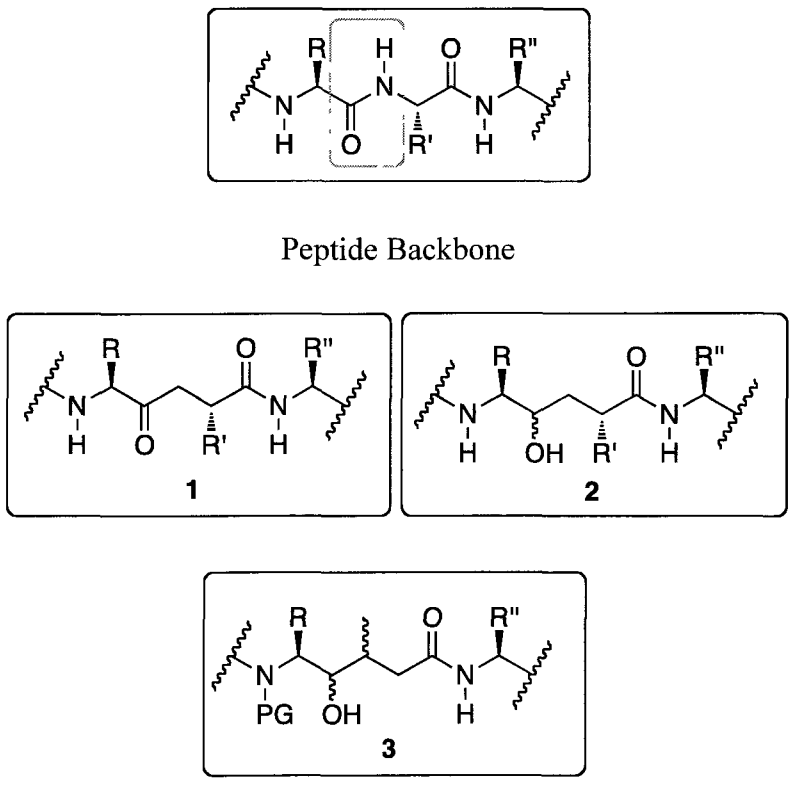


Figure 1. Representation of a peptide and peptide isosteres

The use of peptide isosteres for protease inhibition is extremely effective, but there are few direct ways to incorporate the ketomethylene group into a peptidic system. A variety of synthetic methods are reported in literature to incorporate ketomethylene functionalities into a peptide backbone, but these methods require numerous steps and most suffer from poor stereocontrol.

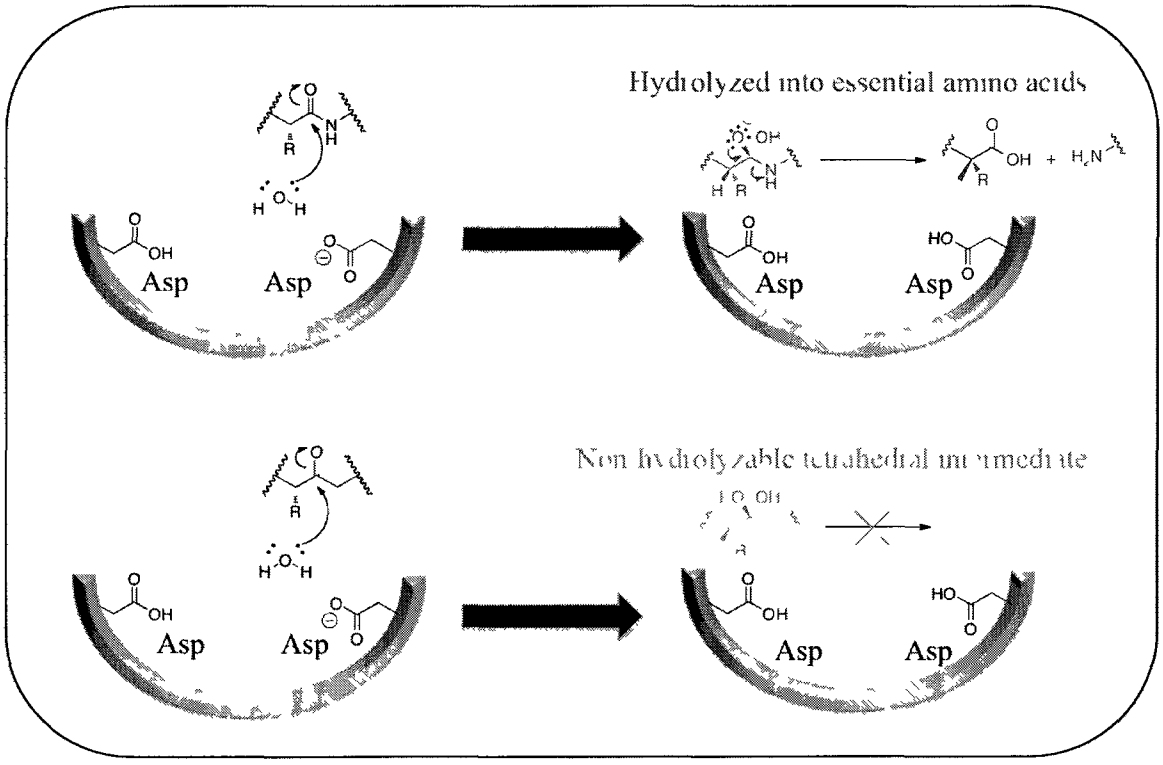
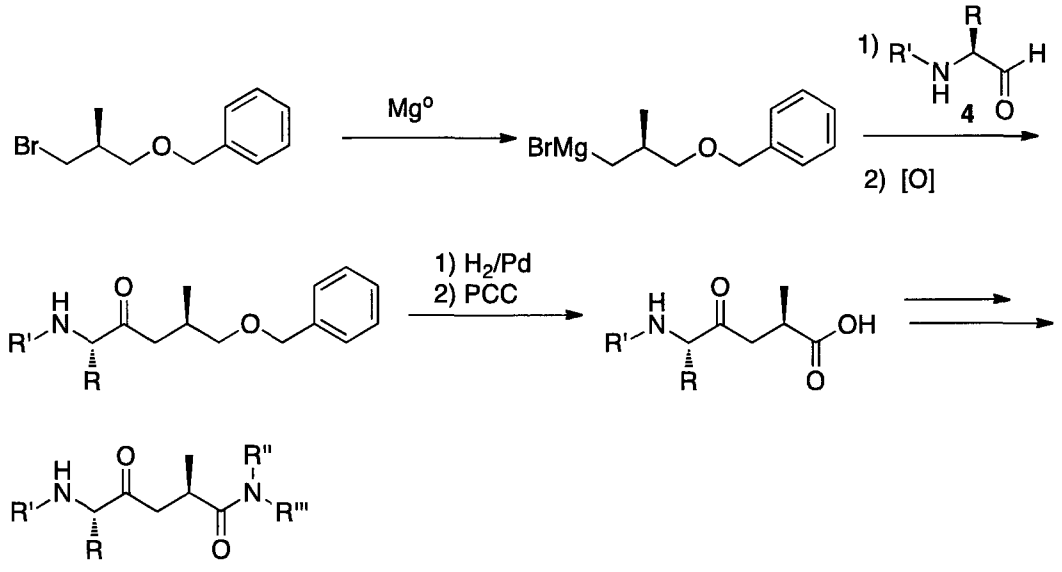


Figure 2. Aspartic Protease: Mimicry of tetrahedral intermediate

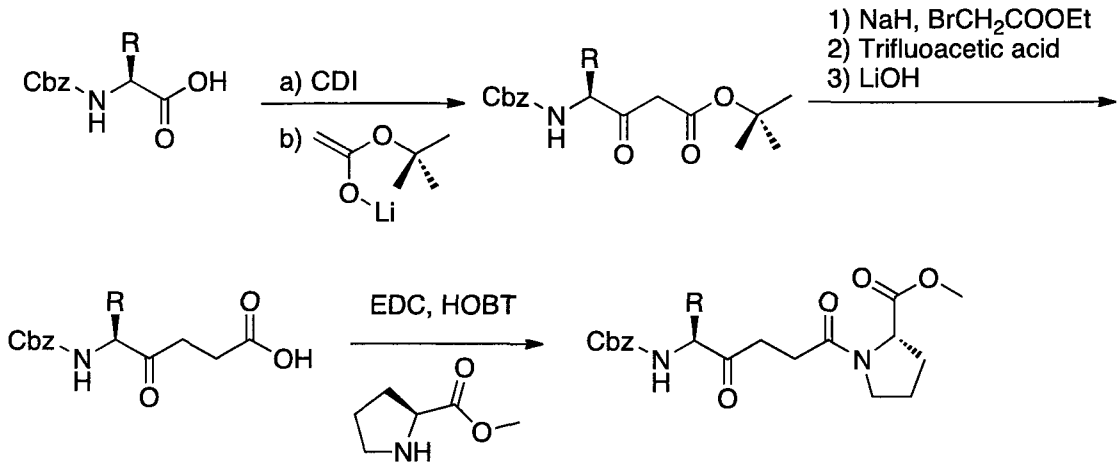
To fully utilize ketomethylene peptide isosteres as potential protease inhibitors, an efficient and direct methodology for their synthesis would be advantagous. Some initial methods described in literature include the use of a Grignard reagent **(Scheme 1)**,[5]

utilization of a modified Claisen condensation **(Scheme 2)**,[6] use of α-nitrocycloalkanones (**Scheme 3**),[7] and, lastly, a β-keto sulfone reaction **(Scheme 4)**.[8] These synthetic pathways leading to peptide isosteres can be lengthy and circuitous; furthermore, the approaches typically proceed with poor stereocontrol. Some of these methods that have been used for ketomethylene isostere formation are described below.



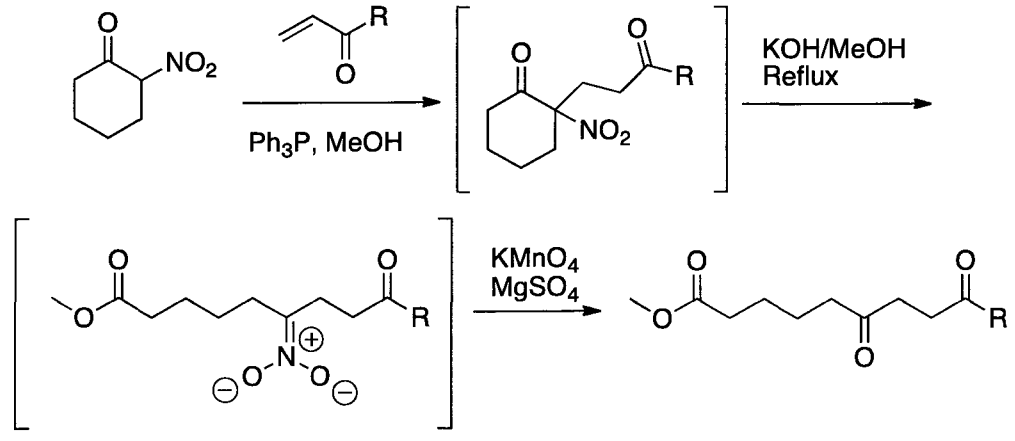
Scheme 1. Harbeson's approach to ketomethylene peptide isosteres

Harbeson reported a sequence in which an amino aldehyde **4** is reacted with a Grignard.[5] The amino aldehyde has the potential for epimerization of the α-carbon stereocenter, which would make this route unattractive due to the required separation of diastereomers. It is preferred to obtain enantio-pure peptide mimics to establish an explicit pharmacokinetic/pharmacodynamics (PK/PD) profile.



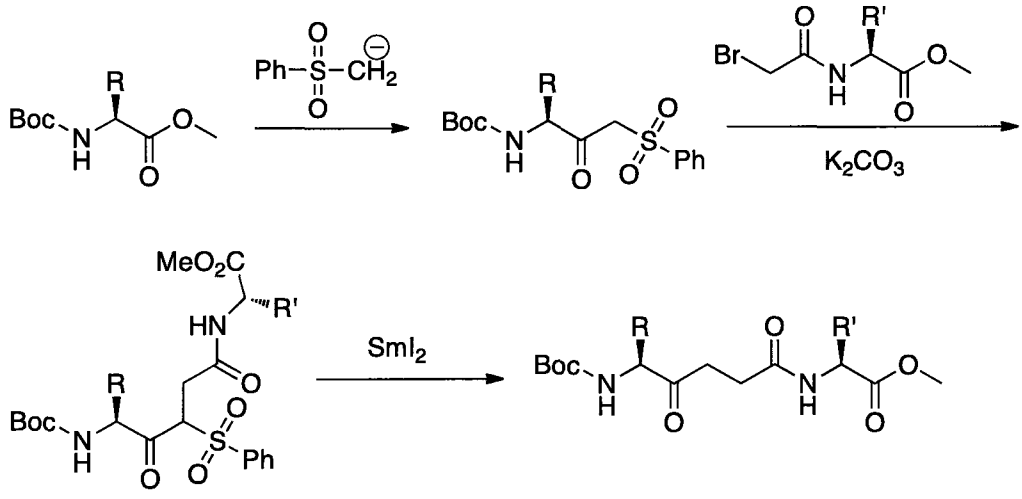
Scheme 2. Hoffman's approach to peptide isosteres

Hoffman reported a mixed Claisen condensation reaction to afford ketomethylene isosteres. A potential racemization of the amino acid stereocenter during the CDI/lithium enolate step could occur, hindering the overall method. After condensation, alkylation, and saponification, a coupling step is required. Another disadvantage of Hoffman's method is that stereocontrolled incorporation of the amides α-stereocenter is only possible through use of enantiopure α-bromo esters, of which few are commercially available.



Scheme 3. Ballini's approach

Ballini and coworkers approach to γ-keto esters offers a unique approach to obtain ketomethylene peptide mimics in a one-pot reaction. Michael addition of a α-nitrocycloalkanone into a α, β-unsaturated ketone followed by ring opening and oxidation affords the γ-keto esters in adequate yields. The major limitation to this pathway is the inability to incorporate amino acid functionality, which minimize the value of the overall synthetic method. Also, many functional groups would not be able to tolerate the harsh reaction conditions employed.

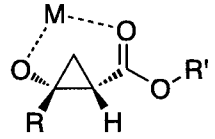


Scheme 4. Rudd's β-Keto Sulfone approach

Rudd's method to synthesize ketomethylene isosteres has the same drawback as the previous methods described. During the addition of the stongly basic sulfone anion, racemization of the amino acid stereocenter can occur. The major shortcoming to the

synthetic pathway is that incorporation of α-substituents with stereocontrol is not possible.

An alternative synthetic method to peptide isosteres would be homologation reactions that yield γ-keto esters. In contrast to the traditional approach of bringing the ketone and ester functionality together through a condensation reaction similar to the Hoffman and Rudd approaches,[9,10] fragmentation of a suitably substituted metal cyclopropoxide intermediate **5 (Figure 3)** would provide an alternate method for γ-keto ester formation. Approaches of this type have been reported by Bieraugel,[11] Saigo,[12,13] and Dowd.[14,15,16,17] The Bieraugel and Saigo methods reported the conversion of β-keto ester derivatives into their γ-keto ester counterparts by treatment with carbene equivalents. The Dowd method also utilized a β-keto ester starting material, but applies a radical mediated approach to the formation of the intermediate cyclopropoxide **5**.



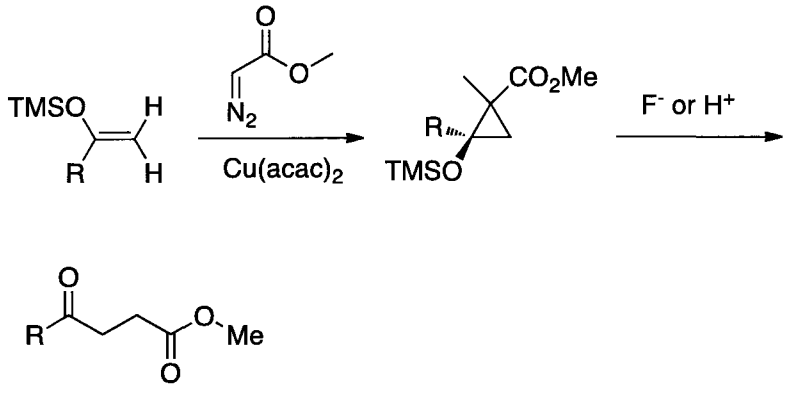
5

M = Transition metal

Figure 3. Zinc cyclopropoxide intermediate

A complimentary approach to cyclopropoxide **5** formation involves cyclopropanation of a ketone enolate derivative was reported by Reissig.[18] Reissig coined the term "donor-acceptor" cyclopropane to describe intermediate **5** (**Scheme 5**).

The "donor-acceptor" cyclopropane could be fragmented with aqueous acid or a fluoride source to yield corresponding γ-keto esters.



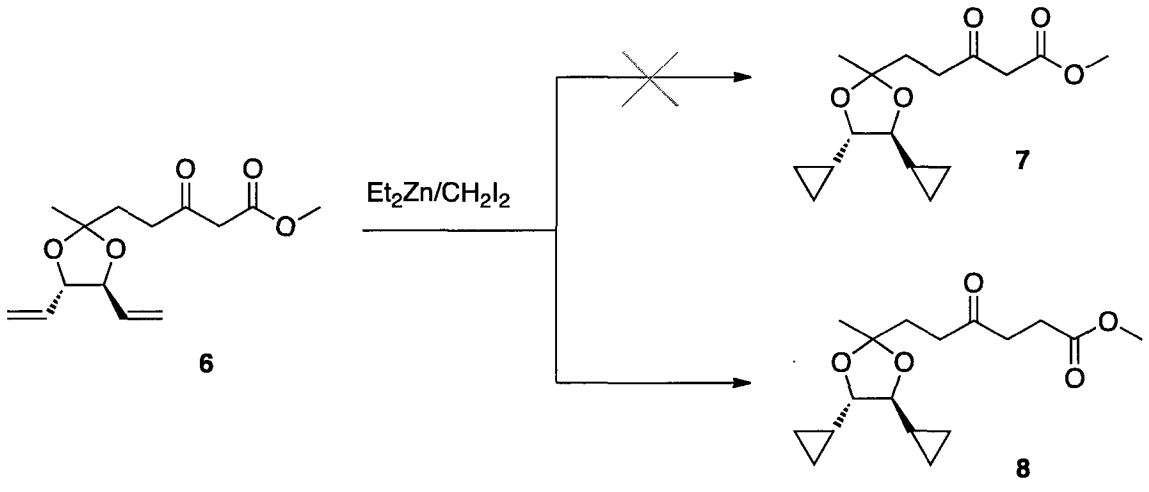
Scheme 5. Reissig's approach to γ-keto esters

Bieraugel, Saigo, and Dowd's homologation of β-keto esters are all believed to involve a "donor-acceptor" cyclopropane intermediate **5**. These methods require initial formation of an enamine or enolate equivalent, which can be time consuming and inefficient for the conversion to a γ-keto ester. A method developed in the Zercher laboratory has demonstrated that derivatization is not required, and that one-pot homologation of β-keto esters is possible.

Zinc Carbenoid-Mediated Homologation

A novel variation of the carbenoid-mediated homologation of β-keto esters was first reported by Brogan and Zercher in 1997.[19] This reaction **(Scheme 6)** was discovered during an attempt to cyclopropanate two olefins of β-keto ester **6**. Brogan employed a

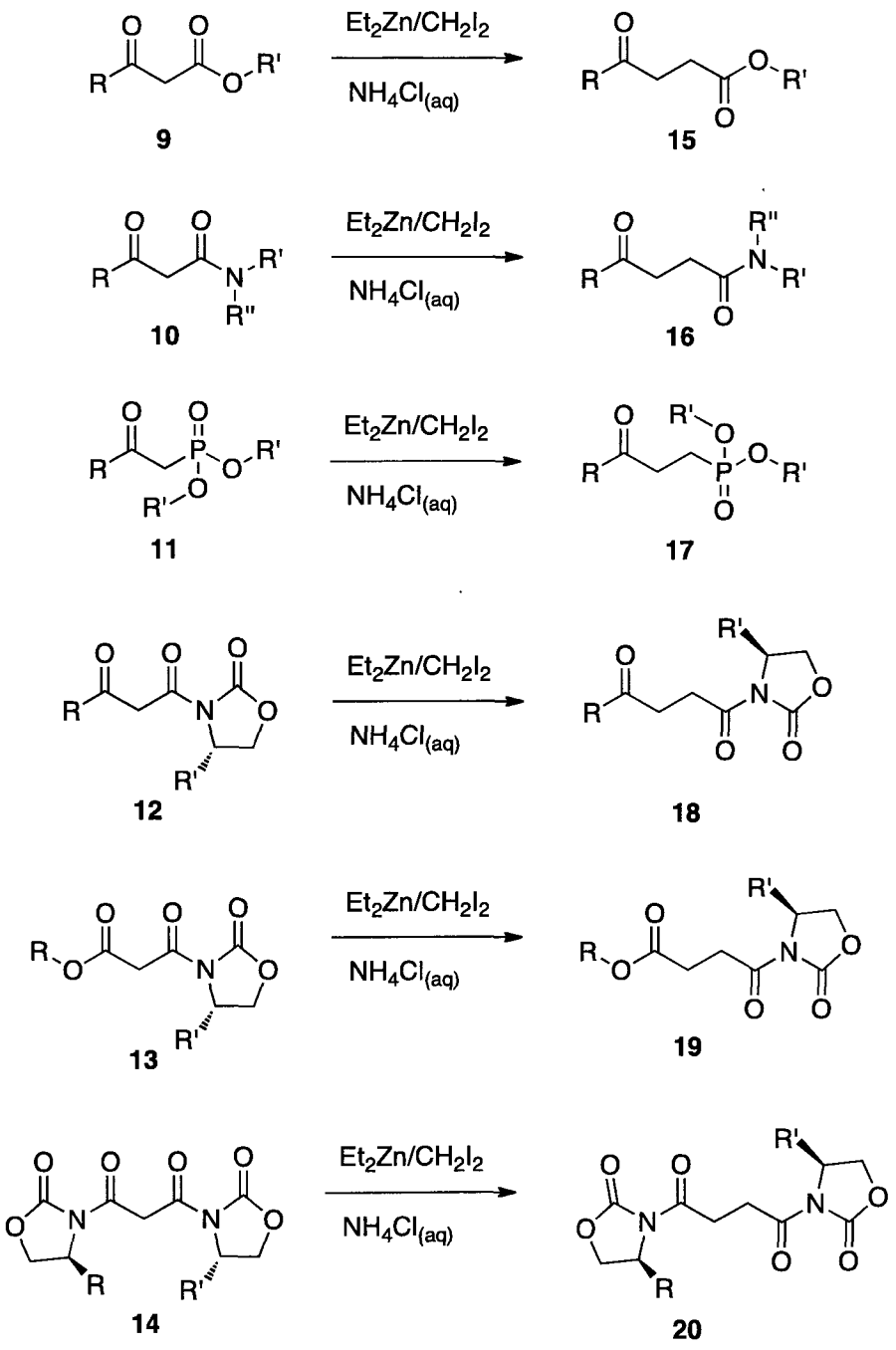
one-to-one mixture of diethyl zinc and diiodomethane in dichloromethane to form the Furukawa-modified Simmons-Smith carbenoid, which is reported in literature to readily cyclopropanate olefins.[20] Treatment of **6** with ethyl(iodomethyl)zinc carbenoid was expected to yield β-keto ester **7**, but when analyzed by ^{1}H and ^{13}C NMR spectroscopy the cyclopropanated γ-keto ester **8** was identified as the product.



Scheme 6. Zercher and Brogan's homologation discovery

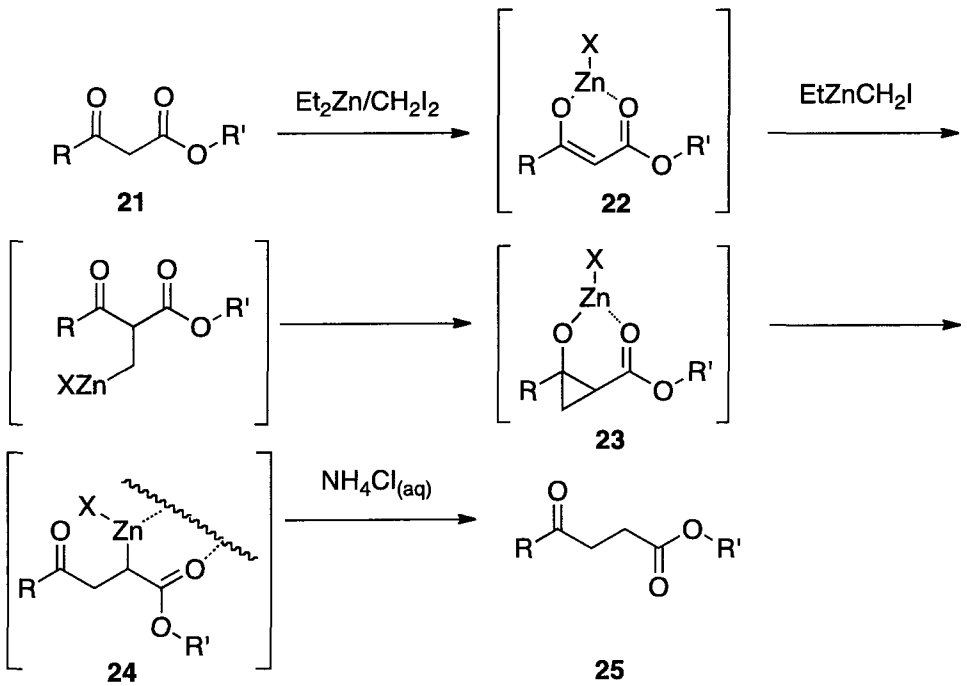
Once γ-keto ester **8** was identified as the product, the one-pot reaction was performed with a plethora of β-keto esters, all resulting in one-pot homologation to the γ-keto ester. This simple, yet efficient homologation is applicable to a variety of substrates, such as β-keto esters (**9**),[19] β-keto amides (**10**),[21] β-keto phosphonates (**11**),[22] β-keto imides (**12**),[23] α-carboxyester imides (**13**),[24] and α-carboxydiimides (**14**).[25] Substrates

9-14 (Scheme 7) are cleanly converted to their γ-keto/carboxyimide counterparts **15-20** in one pot within 30-60 minutes.



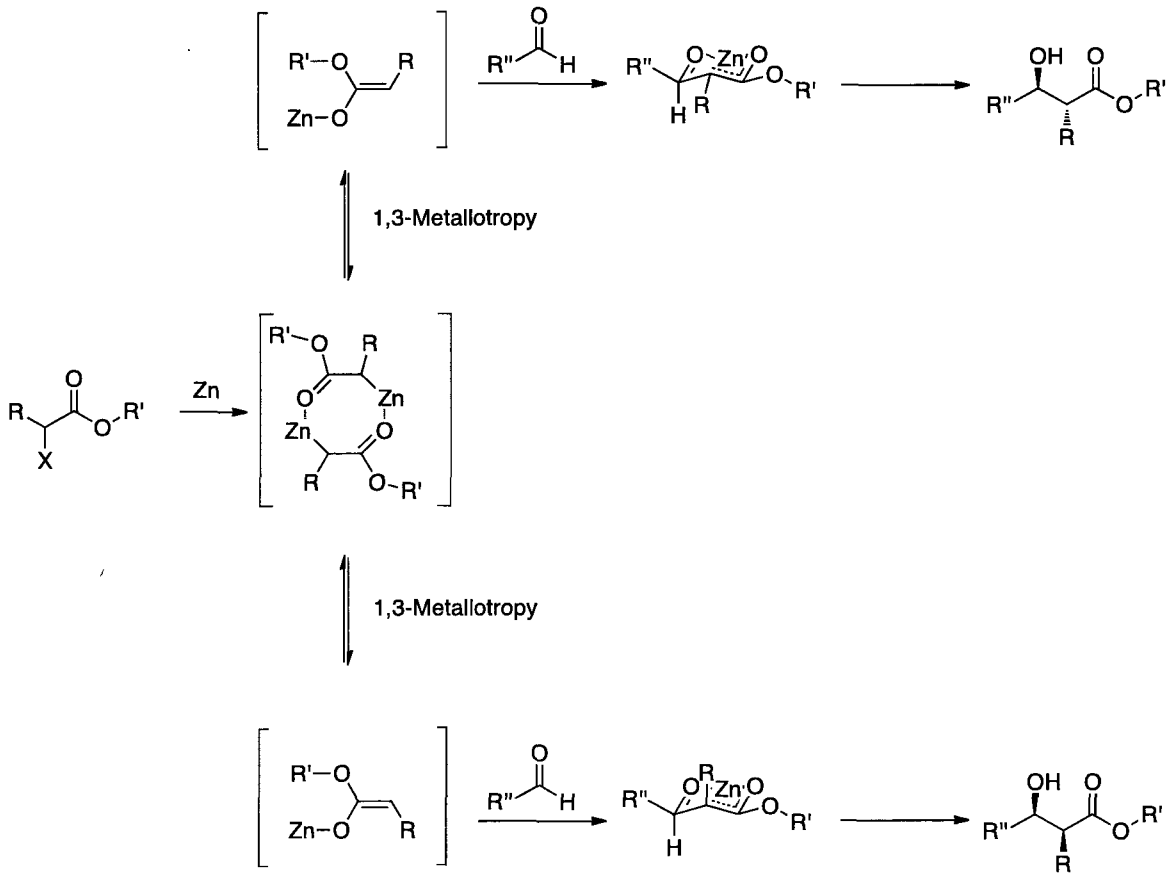
Scheme 7. β-Dicarbonyls exposed to ethyl(iodomethyl)zinc carbenoid

A multi-step mechanism has been proposed **(Scheme 8)**.[18] The β-keto ester **21** is deprotonated by ethyl(iodomethyl)zinc to provide a zinc-complexed enolate (**22**). The enolate (**22**) is alkylated by another equivalent of ethyl(iodomethyl)zinc, which is followed by an intramolecular nucleophilic attack of the keto functionality to render the "donor-acceptor" cyclopropane (**23**). Due to ring strain, the cyclopropane fragments to provide a latent enolate (**24**). Intermediate **24**, when quenched with a mild acid, affords the γ-keto ester (**25**). Computational investigations offer support to the proposed mechanism.[26]



Scheme 8. Proposed homologation mechanism of a β-keto ester

Structure **24** has been shown to exist as a Reformatsky-like intermediate.[27,28] The Reformatsky reaction (**Scheme 9**), developed in 1887, is a reaction which condenses aldehydes with α-halo esters in the presence of metallic zinc to yield β-hydroxy esters.[29] The organometallic intermediate, known as the Reformatsky intermediate, is prepared by treating a α-halo ester with dry, finely ground zinc dust. When an aldehyde or ketone is added to the solution of the Reformatsky intermediate, an aldol product is formed. Unlike the usual base-promoted reactions, the Reformatsky reaction utilizes a metal-halogen redox reaction to form the zinc enolate.



Scheme 9. Reformatsky Reaction

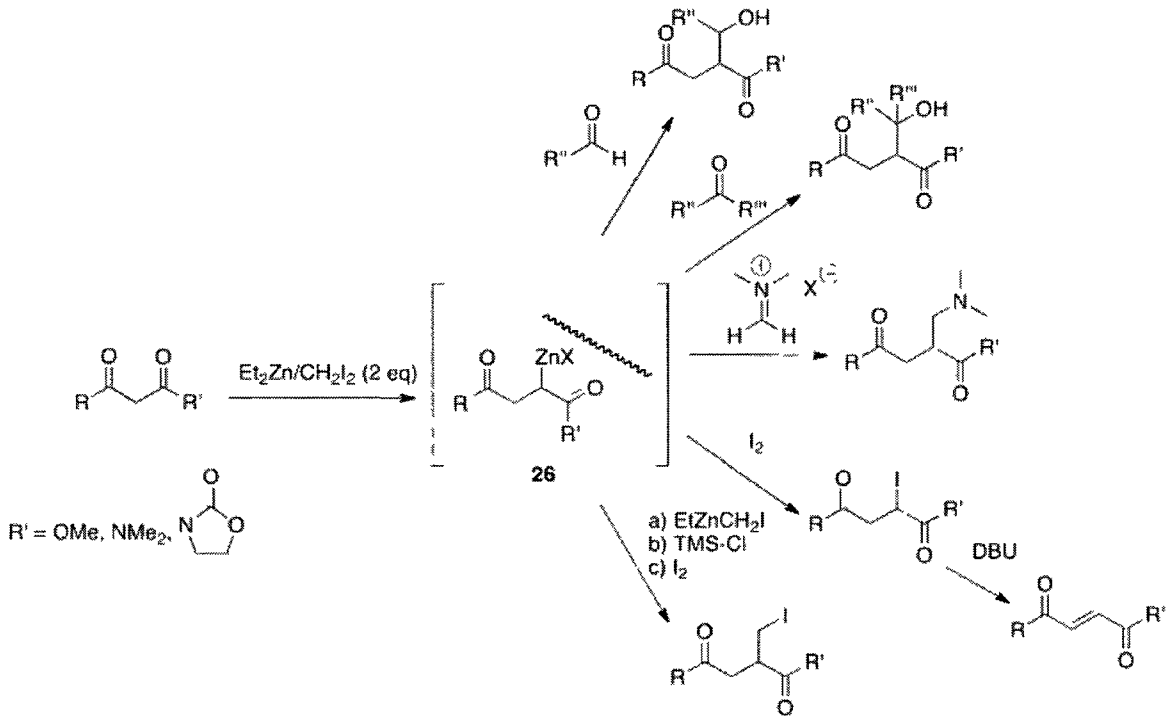
Since the discovery of the Reformatsky reaction, other metals have been used with similar results.[30] One drawback to the Reformatsky reaction is its moderate diastereoselectivity. On average, the ratio of diastereomers with aldehydes is 3:1 under kinetically-controlled conditions.[31] The poor diastereoselectivity is most likely caused by an equilibrium involving a 1,3-metallotropy **(Scheme 9)**,[32] which forms both the *E*-enolate and the *Z*-enolate. Higher diastereoselectivity in the reaction has been observed when one of the substrates is chiral.[33]

Tandem Zinc Carbenoid-Mediated Homologation Reaction

Using the hypothesis that the zinc-mediated chain extension proceeds through a nucleophilic zinc-organometallic intermediate (**24**), one-pot tandem reactions were developed in order to form α-substituted γ-keto esters. This method is referred to as the tandem chain extension (TCE). A variety of electrophiles can be used in order to quench the organometallic intermediate, such as excess carbenoid,[34] imines,[35] aldehydes,[36] ketones,[37] and iminium ions.[37] The TCE reaction can be applied to different substrates such as β-keto amides,[38] and β-keto imides **(Scheme 10)**.[38] When the electrophile is I_2, the reaction generates α-iodinated products, which can be isolated or induced to undergo elimination in the presence of a base to yield α, β-unsaturated compounds. These three

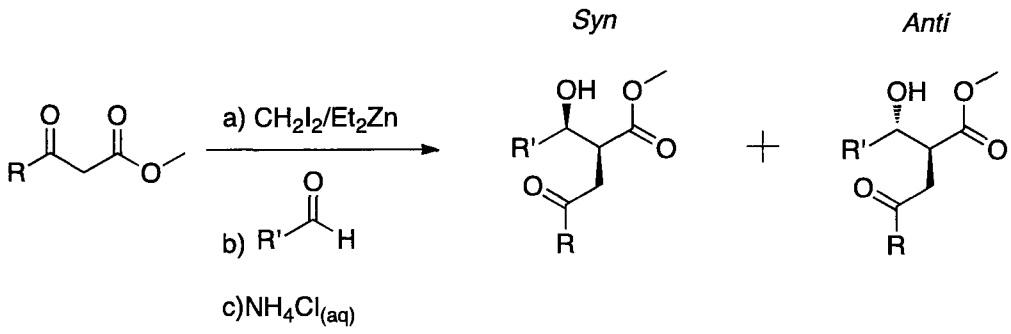
steps can be carried out in one-pot and have been coined tandem chain extension-oxidation-elimination.[39]

Treatment of β-keto esters with excess Furukawa reagent followed by the exposure to a catalytic amount of trimethylsilyl chloride provides access to an ester homoenolate.[40] This reaction was discovered serendipitously through the study of counter ion effects. Formation of the β-keto ester enolates by treatment with KHMDS resulted in the formation of α-methylated-γ-keto ester products. The identical product was observed when treating the intermediate organometallic with HMDS, the methylation event was attributed to the presence of the TMS group. Subsequently it was discovered that treatment of the enolate with catalytic TMS-Cl provided access to the ester homoenolate. When the homoenolate is quenched with a proton, the α-methylation is the major product. In order to determine that anionic character is present at the newly formed α-methyl group a quench was performed using D_2O, which yielded a deuterated α-methyl moiety. Treatment of the homoenolate with iodine provided access to α-iodomethyl substituents **(Scheme 10)**.[41]



Scheme 10. Electrophiles for TCE

The reaction between intermediate **26** and aldehydes has been studied extensively in order to determine the diastereoselectivity of the reaction **(Scheme 11)**. *Syn:anti* terminology will be utilized in order to communicate and characterize the diastereoselectivity of the reactions.[42] All of the reactions were carried out at 0°C, using 5 equivalents of ethyl(iodomethyl)zinc carbenoid formed from a 1:1 mixture of diethyl zinc and methylene iodide. The aldehyde was used in excess (1.5 equivalents) in comparison with the starting substrate. Using these conditions the TCE-aldol reaction of β-keto esters was shown to have a average *syn:anti* ratio of 9:1. When the temperature of the reaction was lowered to -78 °C, the ratio of *syn:anti* was increased to >20:1, suggesting that the homologation-aldol reaction operates under kinetic control.

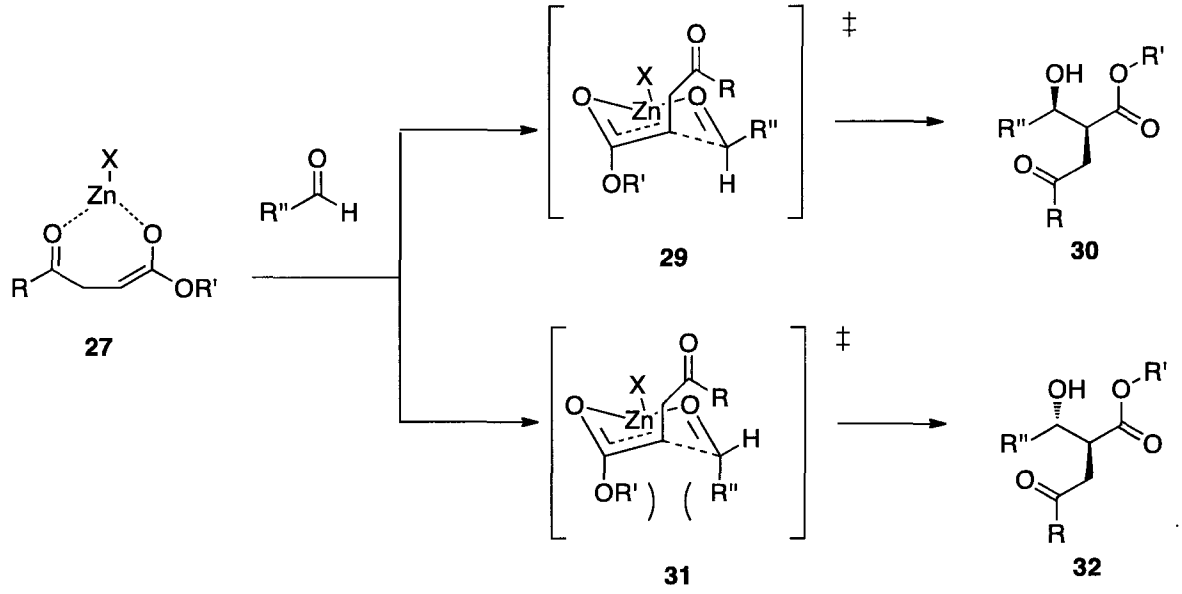


Scheme 11. Depiction of aldol stereochemistry

A Zimmerman-Traxler transition state model can be used to rationalize the selectivity of the tandem homologation-aldol reaction.[43] This transition state model is utilized for aldol reactions that are believed to proceed via a closed transition state. The aldol reaction is believed to proceed through a closed transition state with the aid of zinc (II).[44] A chair-like transition state was supported by Dewar's calculations on the Reformatsky reaction.[45] The similarity of the intermediate in the tandem chain extension-aldol (TCEA) reaction and the Reformatsky intermediate suggests common reaction pathways. Therefore, a closed transition state is appropriate to consider in the TCEA reactions.

Two enolates (*Z* (**27**) and *E* (**28**)) are possible intermediates in the aldol reaction. The *Z*-enolate (**27**) is postulated to be the dominant isomer in solution due to the potential chelation of the zinc by the ketone and the ester enolate (**Scheme 12**). When undergoing an aldol reaction through a closed transition state, the aldehyde can be oriented in two ways. The first involves positioning of the aldehydic R group in the pseudo-equatorial

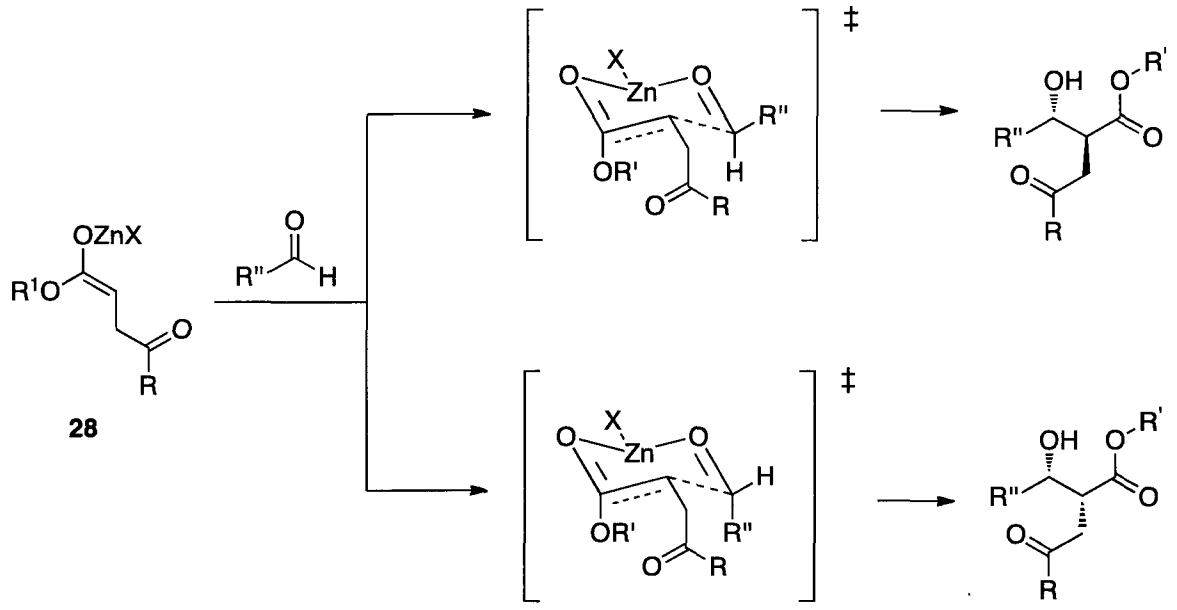
position (**29**), which would react with the *Z*-enolate to afford the *syn*-aldol product (**30**). The second involves the orientation of the aldehydic R group in the pseudo-axial position (**31**), giving rise to the *anti*-aldol product (**32**) when reacted with the *Z*-enolate.



Scheme 12. Zimmerman-Traxler model of the *Z*-enolate

Zinc chelation by the keto functionality is extremely important for the enhancement of diastereocontrol. Experiments run by Karelle Aiken clearly demonstrate that the presence of the keto moiety is necessary to obtain a high *syn*-selectivity.[28] The chelation of the keto functionality to zinc (II), which leads to the *Z*-enolate is proposed to be responsible for the *syn*-selectivity. While pseudo-axial approach (**31**) could be responsible for formation of the *anti*-aldol product, another possibility for the formation

of the minor *anti*-aldol product would be an aldol reaction involving an *E*-enolate (**28**) (**Scheme 13**).



Scheme 13. Zimmerman-Traxler model of the *E*-enolate

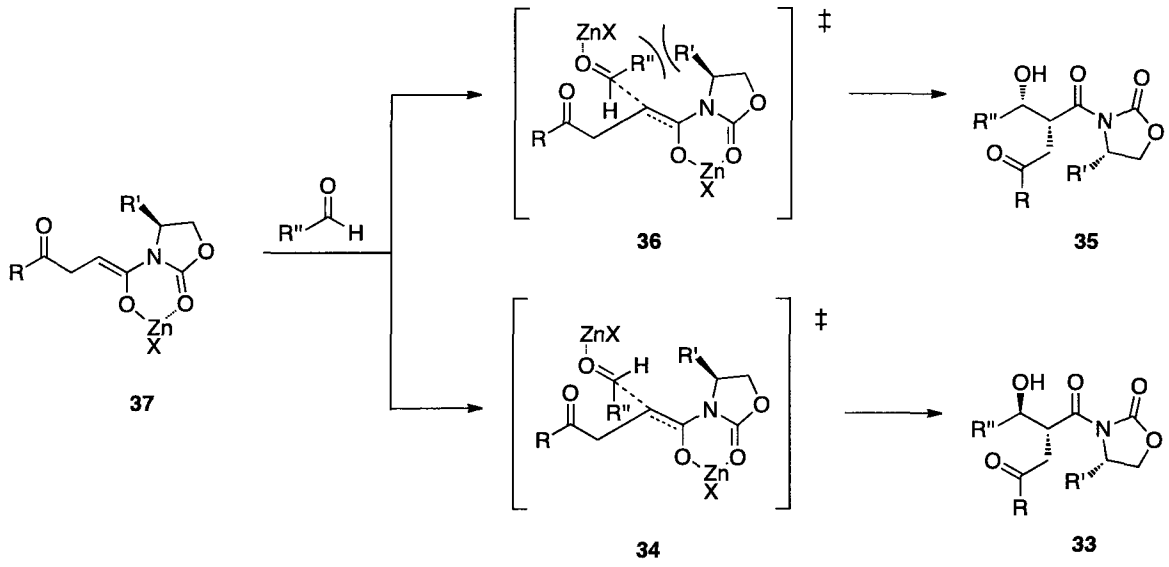
The *syn*-aldol product is the major product for β-keto ester or β-keto amide substrates. This is confirmed by experimental results[46] and rationalized through the use of the Zimmerman-Traxler models. However, when the substrate is switched to a β-keto imide, the diastereoselectivity is switched to favor formation of the *anti*-aldol isomer.[47] Heathkock reported a similar change in diastereocontrol with enolate of acylated oxazolidinones when excess Lewis base was present in the reaction mixture.[48] Heathkock reported that one equivalent of Lewis acid led to the *syn*-aldol product, but two equivalents of Lewis acid reversed the stereochemistry to the *anti*-aldol product.

Heathkock proposed that the aldol reaction takes place via a closed transition state when one equivalent of Lewis acid was used, but through an open transition state when two equivalents of Lewis acid were used. When two equivalents of a Lewis acid are used, the first would complex to the enolate and the second would aid in the activation of the aldehyde.

This hypothesis can be applied to the tandem homologation-aldol reaction of β-keto imides. The two imide carbonyl functionalities can chelate to zinc in solution, which would provide a more reactive nucleophile in comparison to the organometallic reagent. It is not known whether the imide derived intermediate exists as an enolate or as a Reformatsky-like organometallic species, but the imide enolate-equivalent has been shown to be more reactive than the corresponding ester or amide derived enolate equivalent. Since the chain extension reaction requires multiple equivalents of diethyl zinc, excess zinc (II) is present in solution. The excess zinc can serve as a Lewis acid to activate the aldehyde through an open transition state. The selective formation of *anti*-aldol products in the TCEA reaction are, therefore, rationalized to arise from an open transition state (**Scheme 14**).

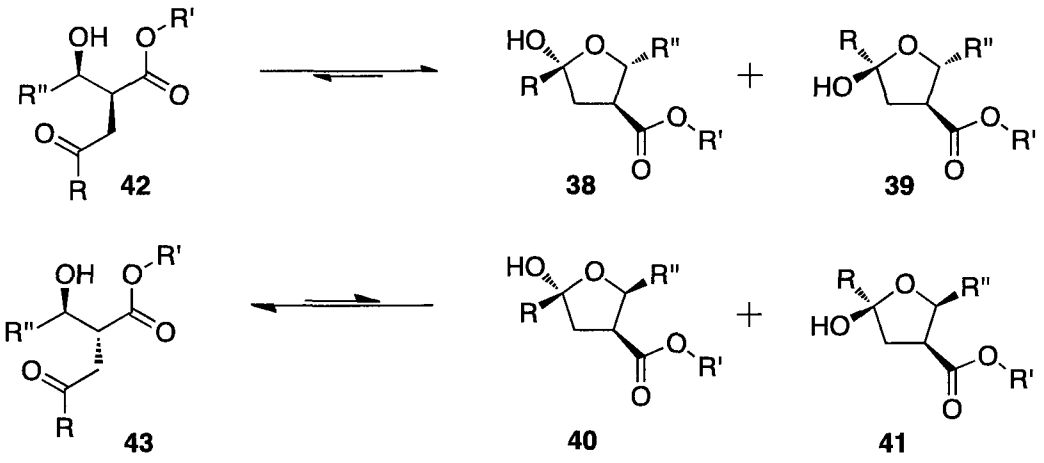
Steric considerations must also be taken into account when analyzing the open transition state. To obtain the *anti*-aldol (**33**) isomer, R" and the imide moiety must be oriented in a pseudo-*trans* position in the transition state (**34**). The *syn*-aldol isomer (**35**) would require that the R" and imide moieties be oriented in a pseuo-*syn* position creating unfavorable steric interactions in the transition state (**36**). When utilizing β-keto imides in the homologation-aldol reaction, the *E*-enolate can be disregarded due to the steric

interactions between the keto side chain and the oxazolidinone *Z*-enolate (**37**) is used in the model (**Scheme 14**).



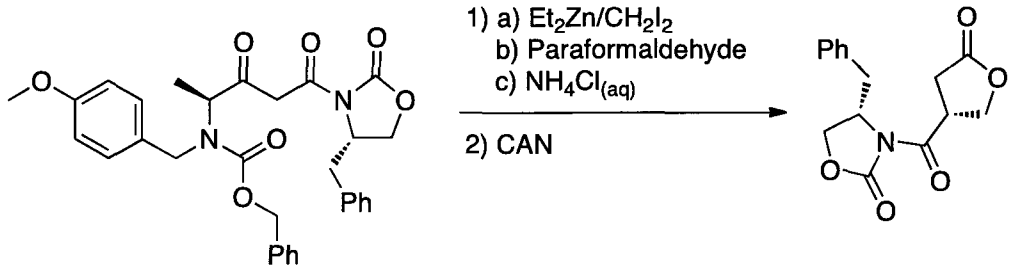
Scheme 14. Open Transition State of *Z*-Imide Enolate

The diastereoselectivity in the tandem homologation-aldol reaction with β-keto esters, amides, and imides can be difficult to quantify because hemi-ketals (**38**, **39**, **40**, and **41**) are in equilibrium with their corresponding open isomers (**42** and **43**) (**Scheme 15**). The *syn* isomer (**42**) exists predominantly as a closed hemi-ketals (**38** and **39**), a larger contribution of open form is observed for the *anti* isomer. This diastereomerically dependent equilibrium is likely dependent upon steric interactions between the ester and R" moieties.



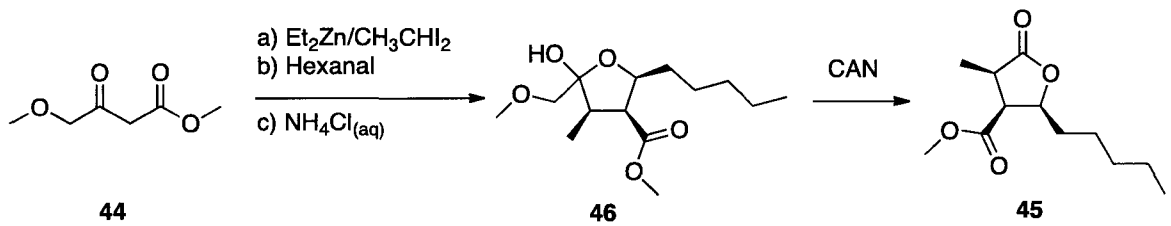
Scheme 15. Equilibrium of open chain and closed hemi-ketal isomers

The hemi-ketals (**38** – **41**) can be manipulated to facilitate assignment of stereochemistry of each individual isomer. One method, discovered by Lin, transforms hemi-ketals into substituted γ-lactones (**Scheme 16**) via an oxidative cleavage with the use of ceric ammonium nitrate (CAN).[49]

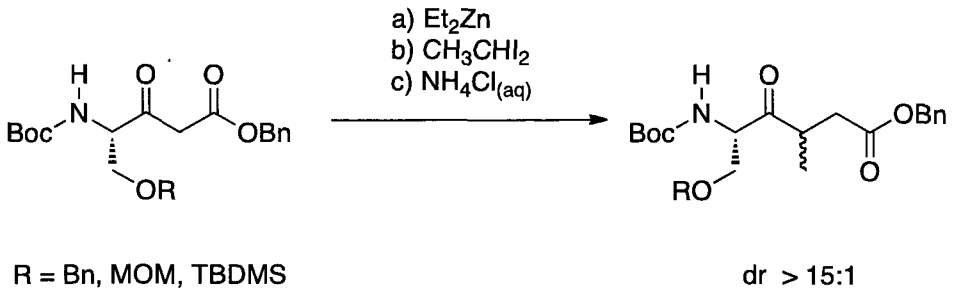


Scheme 16. CAN-mediated oxidative cleavage

Jacobine performed additional studies of the homologation-aldol reaction followed by the CAN-mediated oxidative cleavage. Substituted carbenoids were used to investigate the stereoselectivity of the homologation-aldol reaction in which a γ-heteroatom substituted β-keto ester (**44**) was used as the starting material. When a methyl-substituted carbenoid was used in combination with hexanal in the TCEA reaction, CAN oxidation provided the *cis, cis*-phaseolinic acid derivative (**45**) (**Scheme 17**). Through comparison to the literature,[50] Jacobine determined that the aldol reaction of substrate **44** proceeded with *anti* selectivity (**46**) (**Scheme 17**). With the relative stereochemistry controlled, Jenn Mazzone studied the absolute stereochemical control of the homologation reaction with a methyl-substituted carbenoid through use of serine derived β-keto esters (**Scheme 18**).[51] The serine backbone has induced high diastereoselectivity (≥15:1) in the incorporation of the β-methyl substituent.

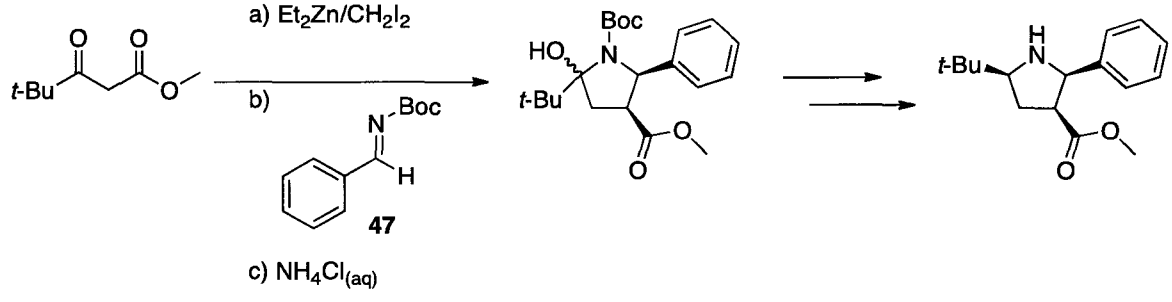


Scheme 17. Synthesis of *cis, cis*-phaseolinic acid derivative



Scheme 18. Use of a Serine derived β-keto ester

Jacobine also studied the use of an activated imine (**47**) as an electrophile in a tandem homologation reaction sequence. The imine-capture reaction ultimately led to the formation of β-proline derivatives through deprotection and reduction (**Scheme 19**). Jacobine observed that the homologation-imine capture reaction gave *anti* isomer as the major diastereomer when using a *t*-butyl carboxy-protected imine.

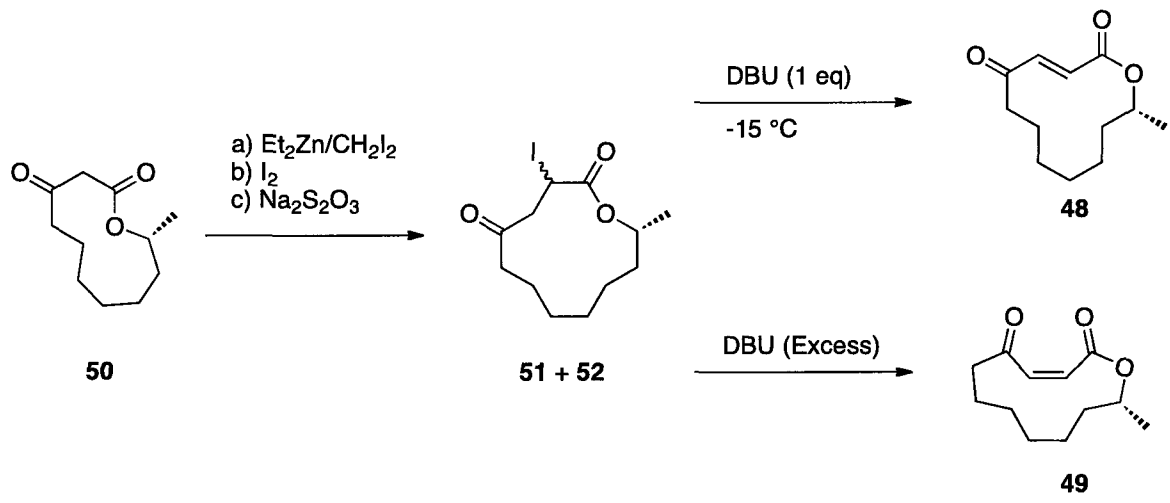


Scheme 19. Homologation-imine capture

Homologation for the formation of natural products and peptide isosteres

The zinc-carbenoid mediated homologation has been employed in the Zercher group as an efficient tool in the synthesis of natural products. The HIV-1 reverse

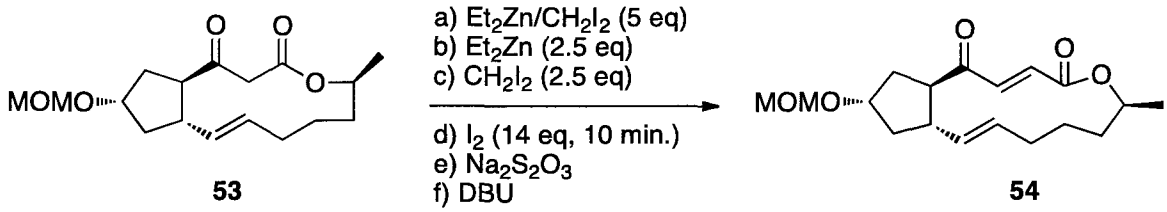
transcriptase inhibitors (+)-patulolide A (**48**) and (±)-patulolide B (**49**) were synthesized by Ronsheim through application of the chain extension oxidation-elimination methodology (**Scheme 20**).[52] The cyclic lactone (**50**) was homologated and the latent enolate was trapped with iodine to yield two diastereomers (**51** and **52**). When **51** and **52** were treated with excess DBU under thermodynamically-controlled conditions, (±)-patulolide B (**49**) was produced. Control of temperature, time, and equivalents during the elimination of the iodide produced (+)-patulolide A (**48**) as the sole product (**Scheme 20**).



Scheme 20. Synthetic route to (+)-patulolide A (**48**) and (±)-patulolide B (**49**)[54]

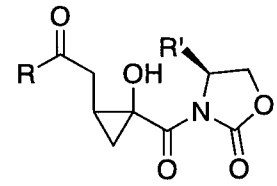
Lin synthesized a bicyclic vasorelaxant,[53] brefeldin A, exploiting the homologation-iodination-elimination methodology.[54] Once bicyclic lactone **53** was synthesized, a stoichiometrically-controlled homologation-iodination-elimination reaction sequence provided a methoxymethyl-protected *E, E*-bicyclic lactone (**54**)

(**Scheme 21**). Reduction of the ketone and removal of the methoxymethyl protecting group has been reported by Kim,[55] therefore the preparation of **54** constituted a formal synthesis of brefeldin A.



Scheme 21. Homologation-iodination-elimination reaction yielding a precursor to Brefeldin A

As mentioned earlier, preparation of ketomethylene-containing peptide isosteres has been a focal point in the Zercher research group.[41,23] Utilizing an amino acid-derived β-keto ester or imide, ketomethylene peptide isosteres can be accessed through the zinc-mediated homologation reaction. The ability to perform an aldol reaction *in situ* provides versatility and a wide range of functionality within the peptidomimetic backbone. In the process of studying the stereocontrolled α-functionalization, Lin[23] and Pu[41] serendipitously discovered a cyclopropanated byproduct (**55**) that was formed during the homologation reaction when utilizing β-keto imides as the starting material (**Figure 4**). More details will be discussed in chapter 3.



55

Figure 4. Cyclopropanated byproduct

CHAPTER II

PROGRESS TOWARD THE SYNTHESIS OF PLAKORTETHER B THROUGH A ZINC MEDIATED HOMOLOGATION

Plakortether B

The Caribbean specimen, *Plakortis simplex,* contain a rich variety of pharmacologically active metabolites. The marine sponges are the main source of a number of related natural products (**Figure 5**) (**56-63**) with an embedded tetrahydrofuranyl backbone. These natural products exhibit several interesting biological activities, such as antibacterial,[56] antimalarial,[57] and antitumor.[58] The lipid-soluble metabolites are derived from the cyclic peroxide, plakortin (**56**). This primary metabolite has been shown to inhibit the growth of *Escherichia coli* and play a major role in the inhibition of *Plasmodium falciparum*, a parasite that initiates malaria.[56]

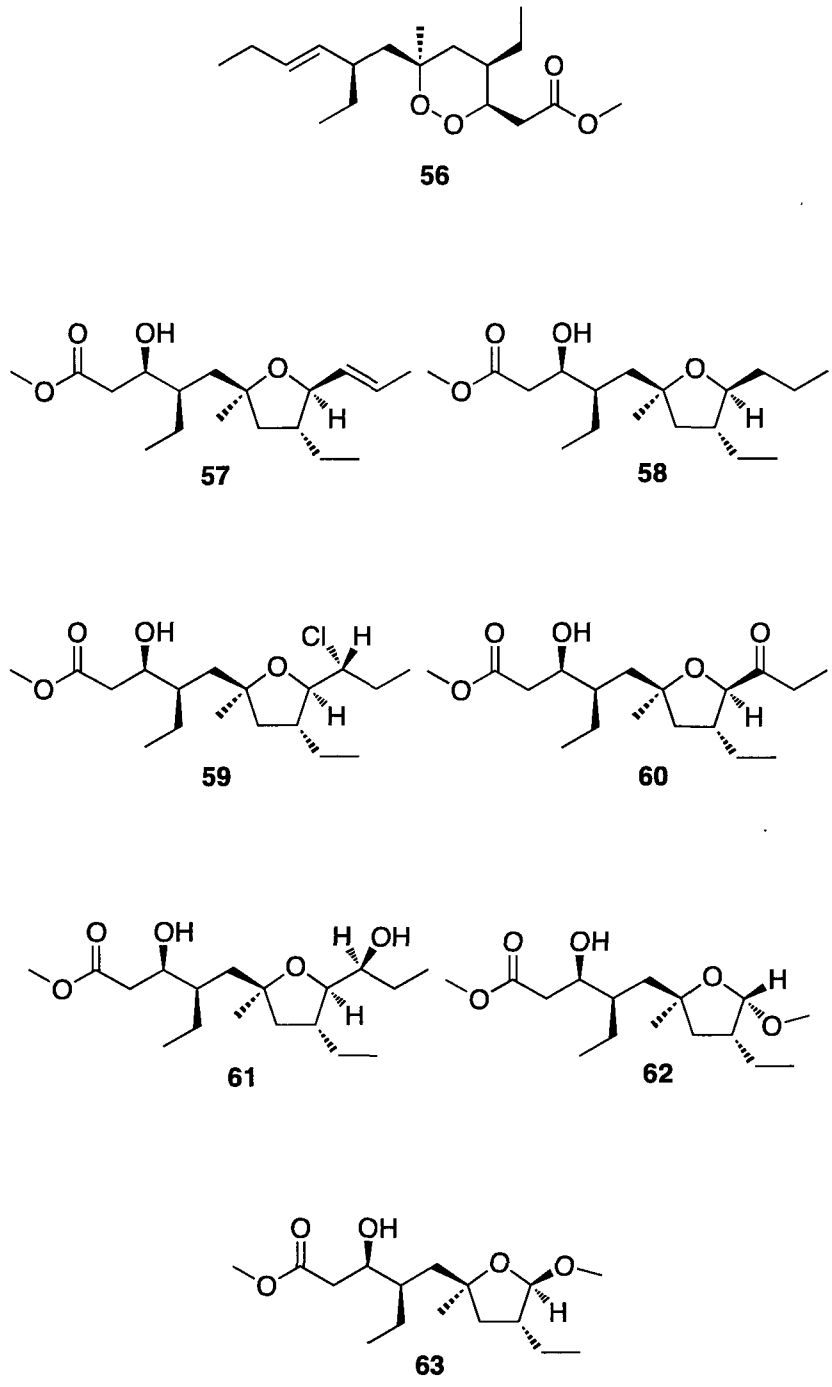
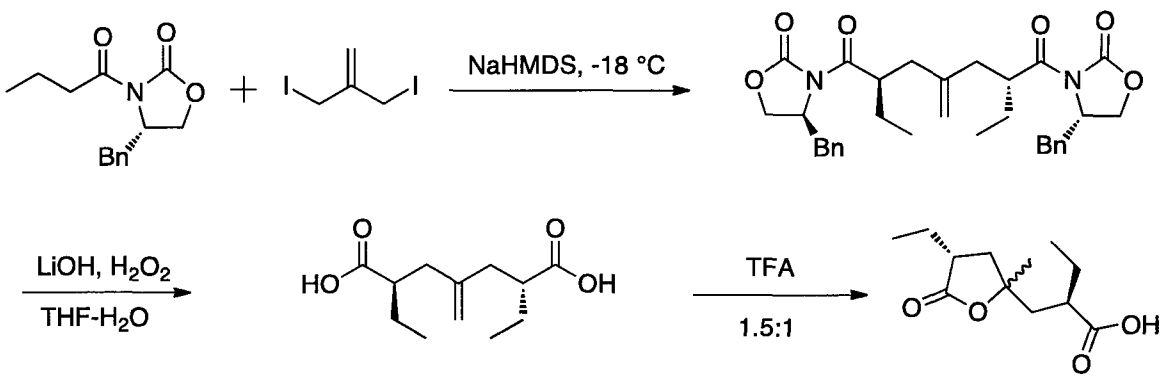


Figure 5. Plakortin and Plakortether A, B, C, D, E, F and G respectively

Syntheses of **62** and **63** have been accomplished through a lengthy series of basic chemical reactions. Novikov and co-workers utilized a C_2-symmetric diiodide followed by an asymmetric alkylation reaction and an acid mediated lactonization to afford the plakortether backbone (**Scheme 22**).[59] The acid-mediated cyclization was poorly diastereoselective in the formation of the backbone of **62** or **63**. The homologation methodology developed in the Zercher group allows for the formation of an advanced intermediate with an embedded tetrahydrofuranyl backbone in a few simple steps. The tandem homologation-aldol reaction also provides high *syn*-aldol selectivity, required for plakortether B, which was determined through NMR analysis and X-ray crystallography, and will be discussed later in this chapter.



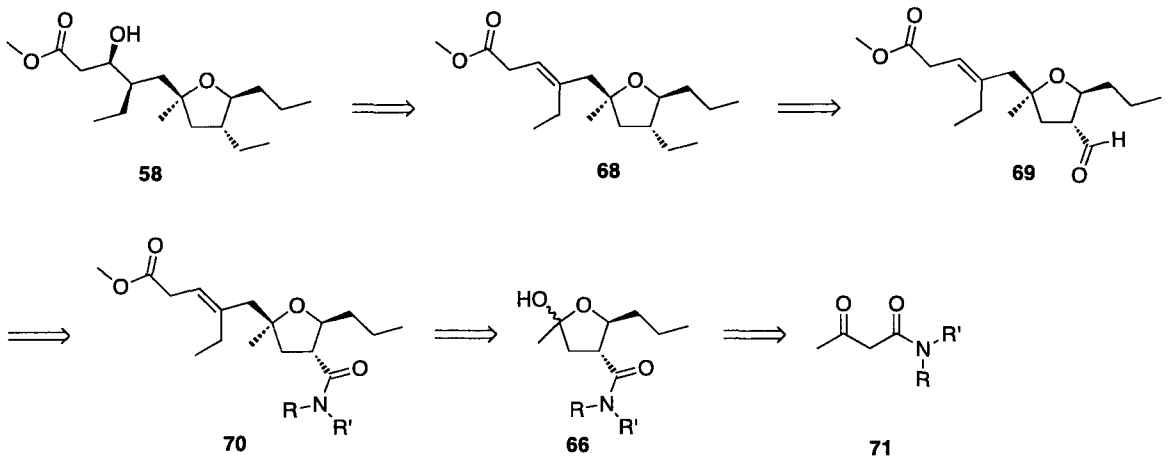
Scheme 22. Novikov's synthetic pathway to the backbone of plakortethers F and G

Incorporation of the tandem homologation-aldol

A variety of homologation reactions have been performed in the Zercher research group with numerous β-keto carboxy groups. Two different starting substrates were

utilized in the initial study of the tandem homologation-aldol reaction, methyl pivaloylacetate (**64**) and methyl acetoacetate (**65**). Both of these substrates exhibited similar results in the tandem homologation-aldol reaction, although methyl acetoacetate was the required starting material to access the plakortether backbone (**66**). Many different electrophiles have been utilized in the tandem homologation-aldol reaction, such as acetone, benzaldehyde, and butyraldehyde (**67**). An electrophile of prime interest is butyraldehyde (**67**), due to the potential for approaching the substitution patterns of the natural product plakortether B (**58**).

A retrosynthetic analysis of Plakortether B is illustrated in **Scheme 23**. Plakortether B (**58**) can come from the stereoselective chiral hydroboration-oxidation of the tri-substituted olefin of **68**. Compound **68** would be formed by use of a Wittig reaction followed by a selective reduction of the mono-substituted alkene on **69**. Aldehyde **69** would arise from a selective amide reduction on compound **70**. Attachment of the methyl ester containing side chain to the furanyl ring would come about from allylation of the Lewis acid mediated oxocarbenium ion formed from compound **66**. Use of the homologation-aldol reaction upon a chiral β-keto amide (**71**) would afford a diastereoselective route for the synthesis of the backbone of plakortether B (**Scheme 23**).

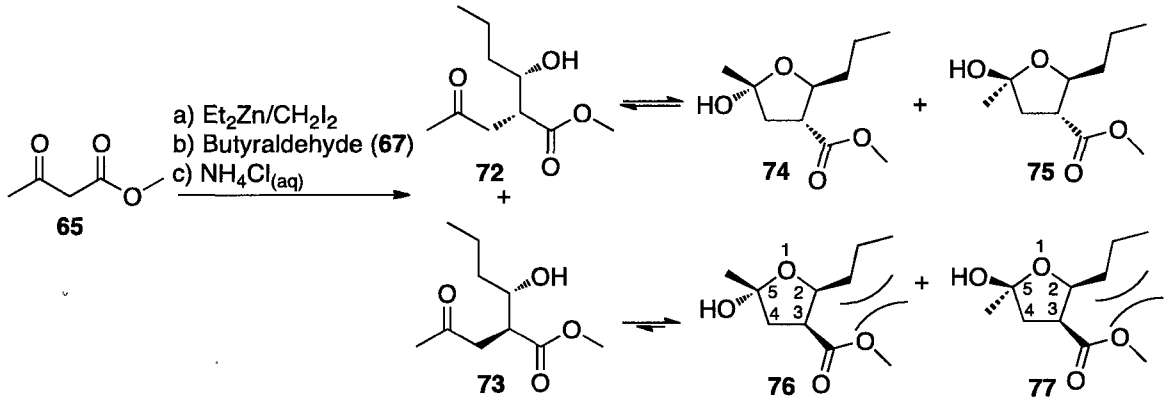


Scheme 23. Retrosynthetic analysis for the synthesis of plakortether B

The plakortether backbone (**66**) was viewed as being accessible through the use of the tandem homologation reaction utilizing butyraldehyde (**67**) as the electrophile (**Scheme 24**). Formation of the *syn* aldol isomer would give the desired trans stereochemistry in the tetrahydro furanyl ring. While the aldol product was formed in a 9:1 ratio in 50% yield, rigorous determination of the stereochemistry of the major isomer was required. Stereochemical assignment at this stage was difficult and further reactions were necessary to determine which is the *syn* (**72**) and *anti* (**73**) isomer.

NMR spectroscopy was the first tool employed in an effort to determine the stereochemistry of the aldol products. After the homologation-aldol reaction with butyraldehyde, the two diastereomers were separated via column chromatography. The ^{1}H NMR spectrum for the major isomer was extremely complex due to the formation of two epimeric hemi-ketals (**74** and **75**) (**Scheme 24**). The same challenge was encountered with the minor diastereomer, even though the two closed hemi-ketals (**76**

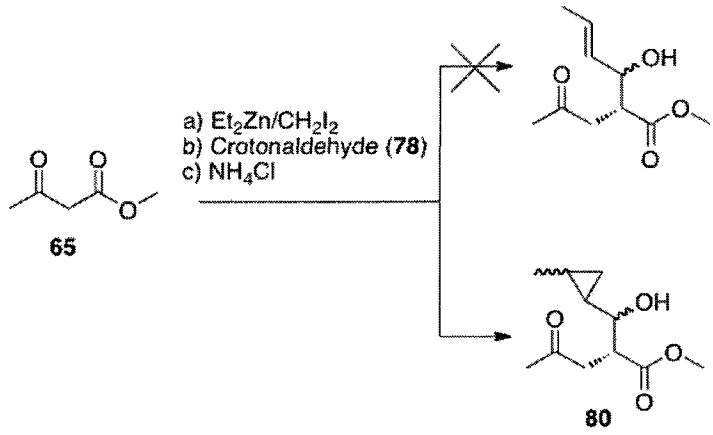
and 77) (**Scheme 24**) were not as prominent in the ^{13}C NMR spectrum. A greater amount of open form (**73**) has been reported to occur for the *anti*-aldol isomer (**73**) then for the *syn*-aldol form (**72**).[46] This is presumably due to the observation that the minor isomer possessed more open-chain form supported the assumption that the *anti* isomer (**73**) was the minor product (**Scheme 24**).



Scheme 24. Depiction of hemi-ketals from the tandem homologation-aldol reaction

Another attempt at assigning stereochemistry of the *syn* (**72**) and *anti* (**73**) isomers, involved use of crotonaldehyde (**78**) as the electrophile in the tandem homologation-aldol reaction. Vicinal coupling constants of the open chain form have been useful in the identification of the *syn* and *anti* aldol isomers. The presence of the diastereotopic protons on the butyraldehyde side chain led to difficulty in determining the vicinal coupling constant. Crotonaldehyde was selected in order to simplify the coupling patterns in the ^1H NMR spectra of the aldol product. However, the use of crotonaldehyde

ended up complicating the spectra due to the reaction of excess zinc carbenoid with the allylic alkoxy moiety generated in situ thereby forming a cyclopropane ring (**80**) (**Scheme 25**). The use of crotonaldehyde as the electrophile was thus terminated.

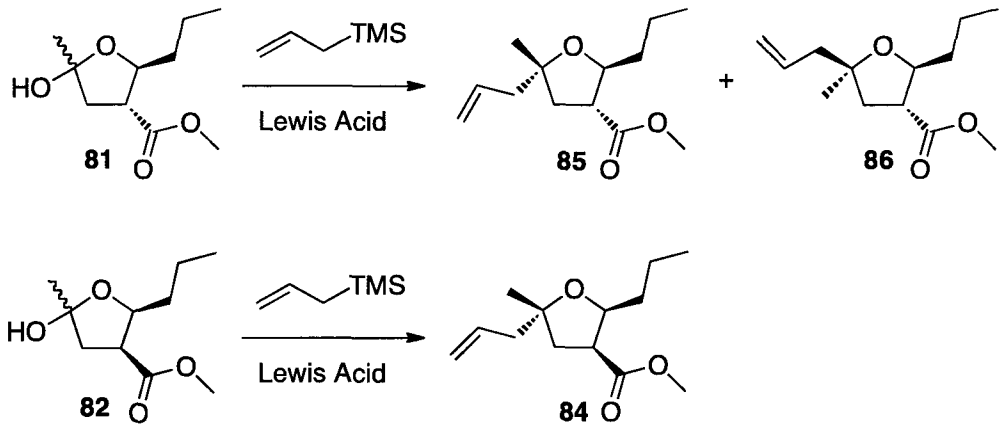


Scheme 25. Use of crotonaldehyde in the tandem homologation-aldol reaction

Cyclization-allylation

The stereochemistries of **72** and **73** were eventually elucidated by performing subsequent chemistry on the corresponding hemi-ketals (**81** and **82**). We anticipated that cyclization and allylation of the aldol products should enable the stereochemical determination of both isomers. Additionally, development of the allylation methodology was viewed as a key step in the synthesis of the plakortether backbone. The cyclization-allylation reaction (**Scheme 26**) of **81** and **82** was performed using allyltrimethylsilane and a Lewis acid.[60,61] The allylation reaction proceeds through a Lewis acid generated, sp^2-hybridized planar oxocarbenium ion (**83**) (**Figure 6**). Due to the planarity of the

intermediate, the allylation-cyclization reaction should have significant facial discrimination when performed on the *anti* aldol product (**82**), while the *syn* aldol isomer (**81**) would be expected to be less discriminatory.



Scheme 26. Allylation of hemi-ketals

Other research groups have studied the stereoselective addition of nucleophiles into oxocarbenium ions (**83**). Reissig and coworkers have also reported the synthesis of substituted tetrahydrofurans from corresponding hemi-ketals (γ-lactols).[62] Hydroxyalkylation of enolates generated from a siloxycyclopropylcarboxylate followed by fluoride-induced ring opening yielded their γ-lactols. Under the influence of $BF_3 \cdot Et_2O$ these γ-lactols were reacted with a range of silated nucleophiles. The anomeric hydroxyl group can be substituted with a cyano, allyl, or allenyl unit to yield a highly substituted tetrahydrofuran derivative.[62] A variety of studies have been performed in efforts to understand the diastereocontrol in these additions. For example, Woerpel and coworkers

studied the electronic effects of five-membered ring oxocarbenium ions (**Figure 6**).[63] The research group determined that the C-3 alkoxy group in a pseudoaxial orientation maximizes the electrostatic effects. In all cases, the major product was formed by a stereocontrolled inside attack on the lowest energy conformer (**Figure 6**). Systematically varying the substitution of the ribose-derived acetal, the Worpel group determined that the alkoxy group at C-3 principally governs the selectivity.

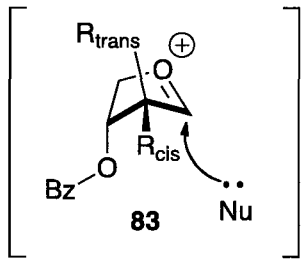
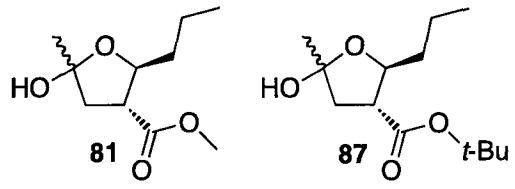


Figure 6. Five membered furanyl oxocarbenium ion

Through use of the cyclization-allylation reaction, the *anti* aldol product (**82**) was determined to be the minor product in the tandem homologation-aldol reaction. When the minor diastereomer was subjected to allytrimethylsilane and boron trifluoride ($BF_3 \cdot Et_2O$), a single stereoisomer (**84**) was observed by ^1H NMR. The high stereoselectivity can be rationalized by steric encumbrance associated with the propyl and methyl ester moieties in the 2 and 3 positions on the furanyl oxocarbenium ion (**Scheme 26**).

The cyclization-allylation reaction also allowed for the assignment of the *syn* aldol isomer (**81**) as being the major product in the tandem homologation-aldol reaction. The *syn* isomer (**81**) produced two diastereomers in the allylation reaction. Studies by ^1H NMR showed the two isomers, (**85**) and (**86**), to be present in an approximate 1:1 ratio when $BF_3 \cdot Et_2O$ was used as a Lewis acid. The temperature of the reaction was lowered in an attempt to improve the diastereoselectivity of the cyclization-allylation reaction involving the *syn*-aldol isomer. The optimal temperature determined for promoting diastereoselectivity was -78 °C; however, only a minor increase in diastereoselectivity was observed (**Table 1**).

Another aspect of the cyclization-allylation reaction that was studied was the performance of different Lewis acids. Three different Lewis acids were studied: $BF_3 \cdot Et_2O$, titanium tetrachloride ($TiCl_4$), and tin tetrabromide ($SnBr_4$). The Lewis acid, $BF_3 \cdot Et_2O$, yielded the two diastereomers in an approximate 1:1 ratio. When $TiCl_4$ was used, neither starting material nor products were obtained. This suggests that $TiCl_4$ causes decomposition of the starting hemi-ketal. When $SnBr_4$ was used, the two diastereomers were present in about a 2:1 ratio, suggesting $SnBr_4$ to be the Lewis acid of choice for further allylation-cyclization reactions (**Table 1**).



Lewis Acid	Substrate	Temperature	Product Ratio
BF_3	**81**	-78 °C – 25 °C	1:1
BF_3	**81**	-78 °C	1:1.2
BF_3	**87**	-78 °C – 25 °C	Elimination
BF_3	**87**	-78 °C	Elimination
$TiCl_4$	**81**	-78 °C – 25 °C	NA
$TiCl_4$	**81**	-78 °C	NA
$TiCl_4$	**87**	-78 °C – 25 °C	NA
$TiCl_4$	**87**	-78 °C	NA
$SnBr_4$	**81**	-78 °C – 25 °C	1:1.5
$SnBr_4$	**81**	-78 °C	1:2
$SnBr_4$	**87**	-78 °C – 25 °C	Elimination

Table 1. Lewis acid mediated allylation, varied conditions

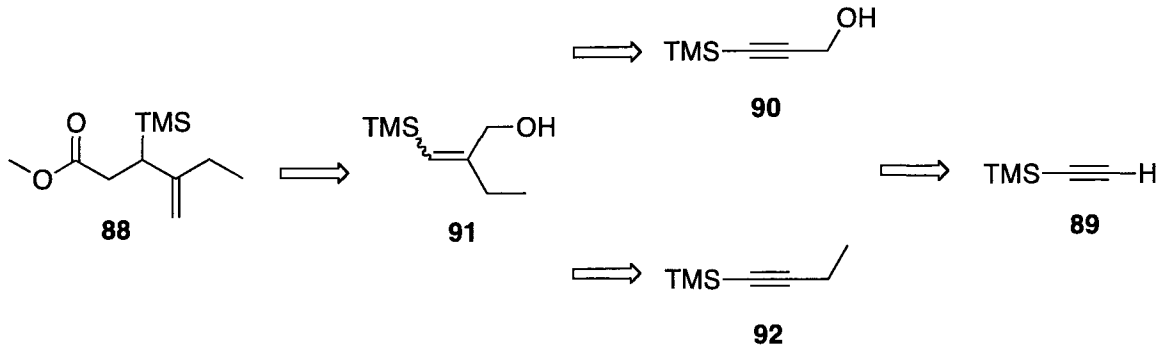
The use of different starting materials in the tandem homologation and the allylation-cylization reactions was studied in an effort to understand diastereoselectivity. When *t*-butyl acetoacetate was used, the tandem homologation reaction proceeded with the anticipated *syn* selectivity to produce hemiketal **87**. When exposed to the allylation-cyclization step, the acid sensitive *t*-butyl ester was eliminated. Decomposition was observed with both Lewis acids, $BF_3 \cdot Et_2O$ and $SnBr_4$.

Substituted Allyl Silane

A direct approach to the diastereoselective formation of the plakortether skeleton would involve convergency. A substituted allylsilane (**88**), with increased steric bulk, may aid in diastereoselective addition to the oxocarbenium ion. Furthermore, the substituted allylsilane (**88**) would offer the advantage of convergency. The targeted substituted allylsilane can be formed two different ways from simple starting materials.

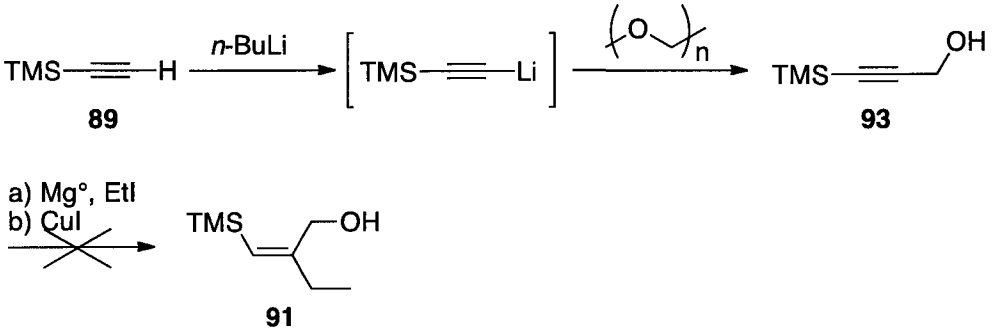
The first method involves deprotonation of an acetylenic silane (**89**) and bubbling in formaldehyde gas, formed from cracking paraformaldehyde.[65] Nucleophilic attack by an ethyl moiety on the propargyl alcohol (**90**) will provide a tri-substituted vinylsilane (**91**).[66] This alkene can then participate in a Claisen rearrangement with an orthoester to provide the targeted substituted allyl silane (**88**) (**Scheme 27**).

The second approach would intiate with the deprotonation of an acetylenic silane (**89**) and addition of an ethyl halide. This product (**92**) could react with a borane reagent, which would be followed by carbene insertion and oxidation to provide the targeted vinylsilane (**91**).[64] This substrate can then undergo a Claisen rearrangement in the presence of an orthoester to yield a substituted allylsilane (**88**) (**Scheme 27**).



Scheme 27. Retrosynthetic analysis of a substituted allylsilane

Trimethyacetylene (**89**) was deprotonated and exposed to formaldehyde, produced by cracking paraformaldehyde, which afforded hydroxymethyl-substituted trimethylsilylacetylene (**93**) (**Scheme 28**).[65] The next step utilizes an ethyl-substituted organocuprate, which is reported to add in a *syn* fashion to the carbon-carbon triple bond.[66] The first time the reaction was run only starting material was obtained. A soxhlet extraction was employed to purify the copper (I) iodide using dry THF to leach out iodine and water impurities.[67] After the purification of copper (I) iodide, the organocuprate reaction was performed again, and starting material was obtained once again. This synthetic pathway was abandoned as a route to the vinyl silane (**91**).

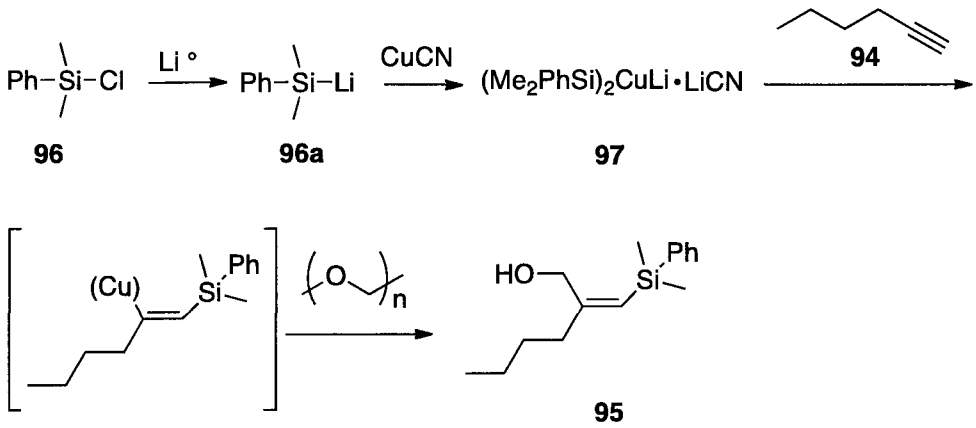


Scheme 28. First synthetic approach to a vinyl silane

Concomitantly, a literature search identified a pathway to directly synthesize a vinylsilane in a single step via silylcupration of acetylenes.[68] Silylmetalation of multiple bonds is an attractive and efficient strategy to gain access to vinyl and allyl silanes.[69] This metallation provided an easy entry to the synthesis of vinylsilanes, since it allows the introduction of two substituents across a carbon-carbon triple bond. The regio- and stereoselectivity of this process has been exhaustively studied and is exceedingly well established.[70] Silylcupration of alkynes involves a *syn*-addition of the silylcuprate, where the silicon is bonded to the less-substituted carbon.[71] Numerous electrophiles can be reacted with the vinyl metal intermediate to produce the vinylsilane skeleton.

The first silylcupration control study used 1-hexyne (**94**) and paraformaldehyde (**Scheme 29**). Paraformaldehyde was not reported as an electrophile in the literature procedure, but was essential for the formation of **95**. Trimethylsilyl chloride would be the least expensive silyl reagent to use in the transformation, but literature reports have shown that the use of trimethylsilyl chloride led to extremely low yields or no conversion

to product.[68] Instead of using trimethylsilyl chloride as the silane precursor, the reaction required the use of dimethylphenylsilyl chloride (**96**).

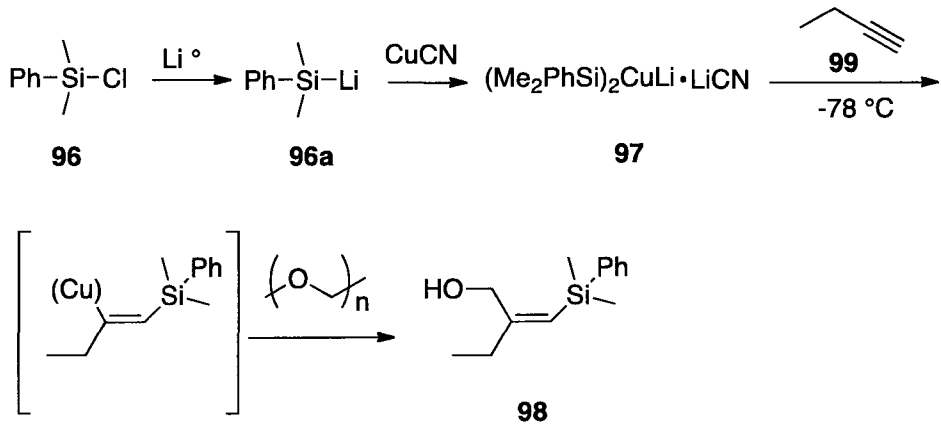


Scheme 29. Silylcupration of 1-hexyne

The reaction started with the formation of lithiated dimethylphenylsilane (**96a**), which was carried out by addition of lithium wire to a solution of dimethylphenylsilylchloride (**96**) in THF at 0 °C. Once the THF solution turned reddish-brown it was time to form the silylcuprate (**97**). The solution of the lithiated silane was transferred by cannula to a THF solution of dry copper (I) cyanide at 0 °C. After twenty minutes, 1-hexyne (**94**) was added in one portion. Formaldehyde was generated (via cracking paraformaldehyde under high temperatures) and bubbled through the solution at

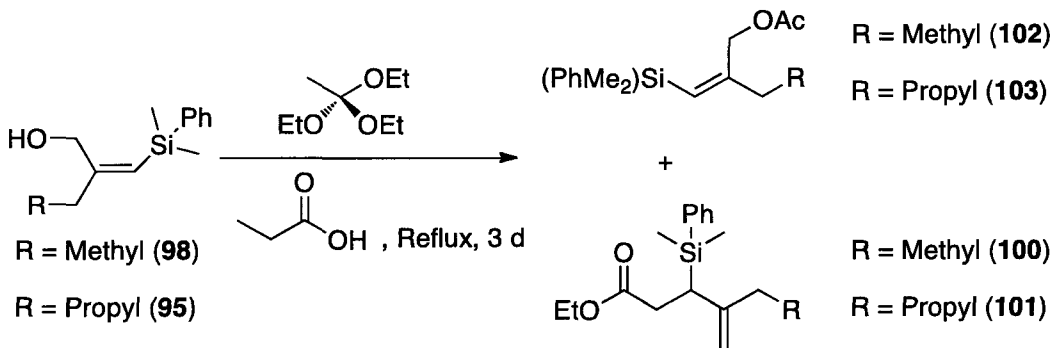
0 °C (**Scheme 29**). Upon work up and column chromatography the vinyl silane (**95**) was isolated in 40 – 60 % yields.

In order to obtain the vinylsilane (**98**) of interest, use of 1-butyne (**99**) as the alkyne and paraformaldehyde as the electrophile must be integrated into the silylcupration reaction. Use of 1-butyne (**99**) was not reported in the methodology study, likely due to the fact that 1-butyne (b.p. = 8.08 °C) is a gas at room temperature. When performing the silylcupration, 1-butyne had to be condensed into a glass vessel that was kept at -78 °C and added via syringe promptly to the silylcuprate (**97**). After paraformaldehyde was bubbled through the solution, the vinylsilane (**98**) was obtained and purified (**Scheme 30**).



Scheme 30. Silylcupration of 1-butyne

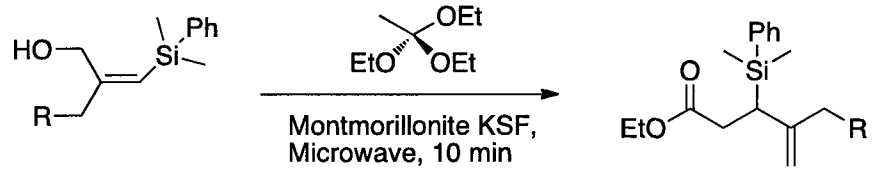
With the successful preparation of vinylsilanes (**95** and **98**), the formation of an allyl silane appropriate for the plakortether side chain was now in reach. A Johnson-Claisen rearrangement, which utilizes an orthoester and catalytic propionic acid, was anticipated to afford a substituted vinylsilane.[72] This reaction was carried out separately with **95** and **98**, which underwent a [3+3] sigmatropic rearrangement to yield the allylsilanes (**100** and **101**) (**Scheme 31**). When the crude allylsilanes (**100** and **101**) were purified on silica, the respective acetoxyvinylsilane (**102** and **103**) would co-elute with the corresponding allylsilanes (**100** and **101**). The yield of the reaction was also extremely low, so variations were considered in order to obtain the pure allylsilane and in high yields.



Scheme 31. Conventional Johnson-Claisen rearrangement

For a wide variety of reactions, microwave irradiation has been shown to provide more efficient reaction times while reducing the amount of byproducts.[73] Microwave-

induced Johnson-Claisen rearrangements have been reported in literature.[74] When substrates **98** and **95**, montmorillonite KSF, and triethylorthoacetate in DMF were subjected to microwave irradiation, the reaction yielded quantitative amounts of the corresponding allylsilanes (**100** and **101**) (**Scheme 32**).



R = Methyl (**98**)

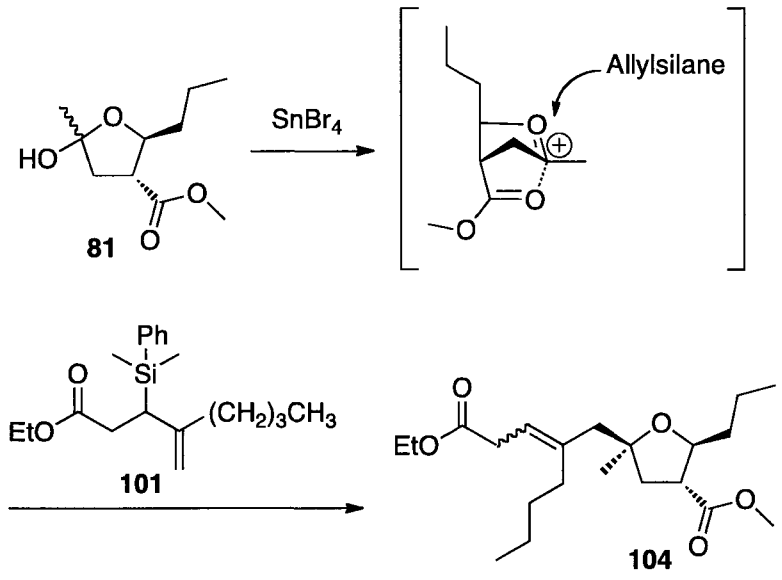
R = Propyl (**95**)

R = Methyl (**100**)

R = Propyl (**101**)

Scheme 32. Microwave mediated Johnson-Claisen rearrangement

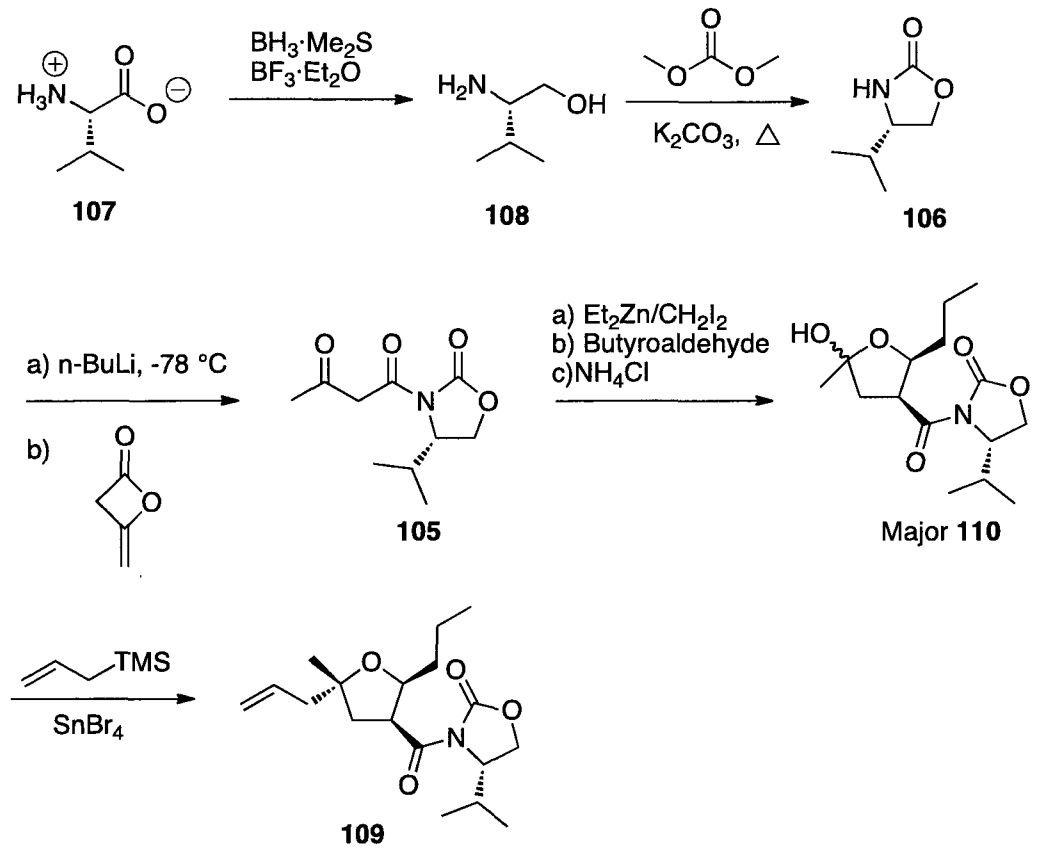
A test reaction was performed with hemiketal **81** and allyl silane **101** in the presence of $SnBr_4$ to yield the substituted tetrahydrofuran **104** (**Scheme 33**). With the added steric bulk of the substituted allylsilane (**101**), modification of the diastereomeric ratio was expected. Analysis of the allylation reaction suggested that one diastereomer was formed in excess. Anchimeric assistance of the tetrahydrofuranyl's ester moiety would serve to block one face of the furanyl system. If anchiomeric assistance is operative the major product of the allylation reaction would be predicted to be the necessary stereochemistry for formation of the plakortether core (**Scheme 33**).



Scheme 33. Control allylation study

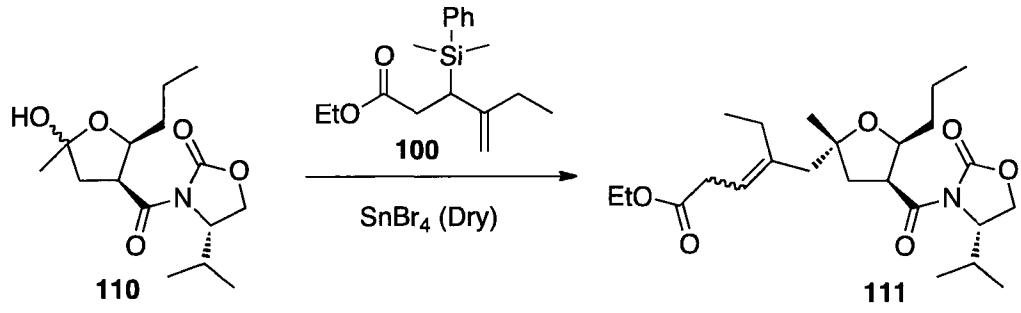
Now that formation and addition of the substituted allysilane (**101**) was demonstrated, control of the absolute stereochemistry was essential for the tandem homologation-aldol reaction. Chiral β-keto imides have been utilized in the tandem homologation-aldol reaction to control the absolute stereochemistry. Synthesis of the β-keto imide (**105**) was possible through a route involving diketene and a chiral oxazolidinone (**106**). The oxazolidinone (**106**) was formed by reduction of L-valine (**107**) with lithium aluminum hydride (LAH), followed by cyclizing the amino alcohol (**108**) with dimethylcarbonate in the presence of potassium carbonate (**Scheme 34**). After formation of the chiral oxazolidinone (**106**), the addition of diketene at -78 °C resulted in the corresponding β-keto imide (**105**) (**Scheme 34**).

The β-keto imide (**105**) was then subjected to the tandem homologation-aldol reaction and the two diastereomers of product were separated on silica (**Scheme 34**). The use of aliphatic aldehydes as electrophiles in the tandem homologation-aldol reaction of β-keto imides has not been studied. Lai had reported *anti*-aldol selectivity when using benzaldehyde as the electrophile, but the *anti*-selectivity reported by Heathcock in a study of aldol reactions has focused on the importance of Lewis-basic (aromatic) aldehydes.[46] The role of an aliphatic aldehyde would play in the diastereoselection was unclear. The major aldol diastereomer of the tandem homologation-aldol reaction was subjected to $BF_3 \cdot Et_2O$ and trimethylallylsilane, and a single tetrahydrofuranyl product (**109**) was isolated. Based on this selectivity, the *anti*-aldol isomer (**110**) was assigned as the major product in the tandem homologation-aldol reaction. Therefore, the use of a chiral β-keto imide was not viable for the synthesis of the plakortether backbone.



Scheme 34. Formation, homologation-aldol, and allylation of a chiral β-keto imide

Even though the reaction was viewed as unsuitable for an approach to the plakortether core, the *anti*-aldol product (**110**) was reacted with the substituted allylsilane (**100**). Initial reactions resulted in protodesilation of the silane (**100**) and a return of the aldol-derived starting material. Water, or some other proton source, must have been introduced to the reaction. Tin (IV) bromide was determined to be the source of water contamination. Fresh, dry tin (IV) bromide was used and the reaction resulted in the addition of the allylsilane (**100**) to the oxocarbenium ion yielding **111** (**Scheme 35**).

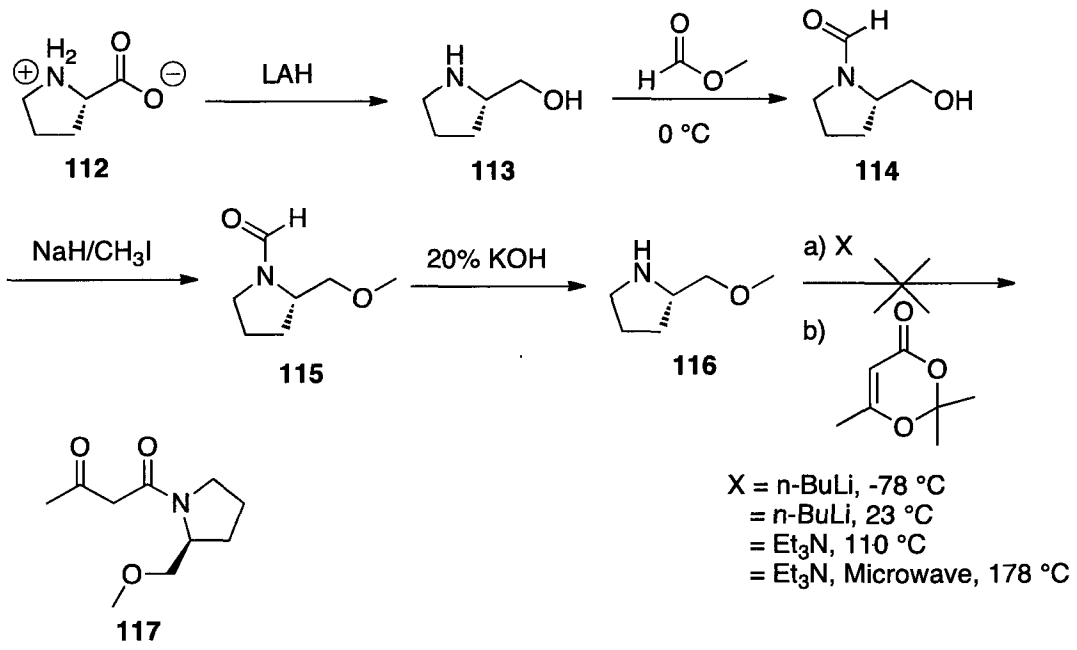


Scheme 35. Use of *anti*-aldol product (**110**) with the substituted allylsilane (**100**)

In order to provide absolute stereocontrol in a *syn*-aldol reaction, a different chiral starting material was needed. Since the β-keto imide did not result in the *syn* isomer as the major diastereomer, use of a β-keto amide was the next substrate to be studied in the homologation-aldol reaction. Lin had reported the use of proline methyl ester as the stereocontrolling element in a *syn*-selective tandem homologation-aldol reaction. The decision was to use the proline skeleton, but to modify the ester functionality. An *Organic Syntheses* preparation was employed to form the chiral amine.[75] Reduction of L-proline (**112**) with LAH provided the 2-(hydroxymethyl)pyrrolidine (**113**), which was protected as the formamide (**114**) to allow for the synthesis of a methyl ether (**115**). Potassium hydroxide was used to liberate the formamide and generate the free amine (**116**) (**Scheme 36**).

The next step was to acetoacylate the chiral auxiliary with diketene. Unfortunately, diketene was no longer commercially available and another reagent was needed to acylate the chiral amine. The acetone adduct of diketene was commercially

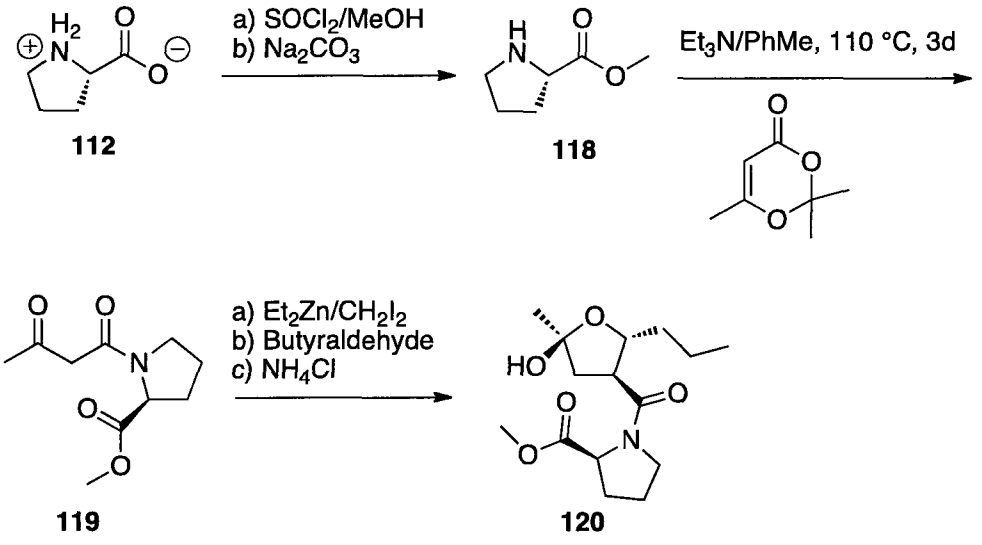
available and has been reported to acetoacylate alcohols to provide β-keto esters.[76] The diketene adduct was added to the chiral amine (**116**) in refluxing toluene, yet none of the β-keto amide (**117**) was formed. Many different reaction conditions were attempted to form **117**, including running the reaction at room temperature, refluxing in toluene with triethylamine, and microwave irradiation. All of these conditions returned the starting amine (**116**) and produced decomposition byproducts. In an effort to minimize loss of the chiral auxiliary, the test reaction with the acetone-adduct of diketene were performed with L-proline methyl ester (**118**).



112 113 114 115 116 117

Scheme 36. Attempts to synthesize a chiral β-keto amide

The methyl ester of L-proline (**118**) was obtained via an acid catalyzed esterification of L-proline (**112**) in methanol.[77] The methyl ester of L-proline (**118**) was produced as the HCl salt and was liberated to the freebase with potassium carbonate. The freebase was added to the diketene acetone adduct and refluxed in toluene for three days (**Scheme 37**). Column chromatography was used to isolate the β-keto amide (**119**) in low yields. The β-keto amide (**119**) was used in the tandem homologation-aldol reaction (**Scheme 37**). After the two aldol diastereomers were separated by column chromatography, the major isomer (**120**) solidified. Utilization of a diffusion chamber (methylene chloride: pentane) allowed for the formation of an X-ray quality crystal. The crystal structure of the major isomer revealed the homologation-aldol reaction of β-keto amides to be *syn*-selective (**Figure 7**). Even though the L-proline induced stereocontrol provided the incorrect absolute configuration for the formation of the naturally occurring plakortether B, subsequent model studies could still be performed.



Scheme 37. Synthesis and use of a chiral β-keto amide

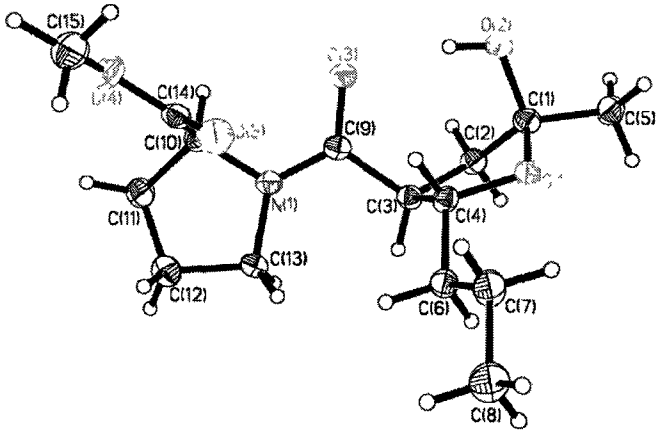
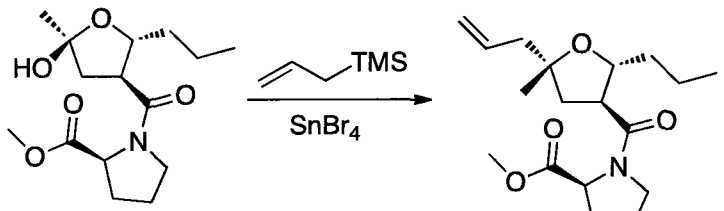


Figure 7. Crystal structure of **120**

Once the stereocontrol of the proline-derived auxiliary was established, allylation of the hemi-ketal (**120**) was studied. Removal of the amide moiety would simplify the ^1H NMR spectra through elimination of rotameric forms and would eventually be required for completion of the synthesis of plakortether B. The decision of keeping the amide moiety, however, was to provide steric bulk and the potential for anchiomeric assistance during the allylation reaction. Both features would favor addition of the allylsilane to the desired face of the tetrahydrofuran ring. Hemi-ketal (**120**) was introduced to a solution of trimethylallylsilane and $BF_3 \cdot Et_2O$. The reaction solution was stirred for twelve hours, which yielded **121** (**Scheme 38**). The stereochemistry of **121** could not be established by ^1H NMR due to the rotameric forms in solution. Functional group transformation of the amide moiety at this stage would be beneficial for simplification of the spectra and for progress toward plakortether B.

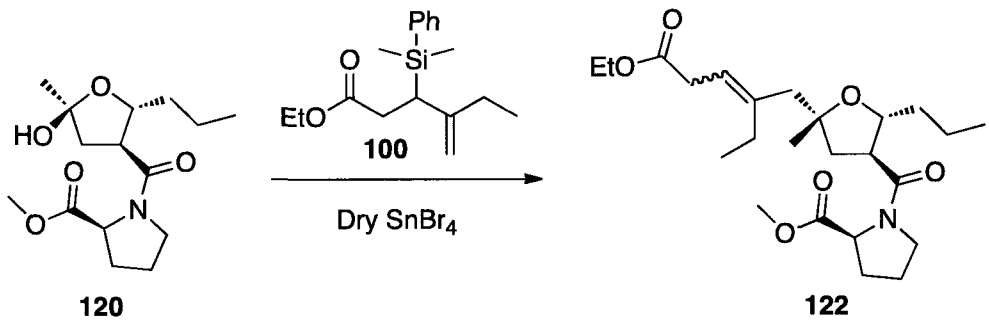


120 **121**

Scheme 38. Reductive-allylation of hemi-ketal **120**

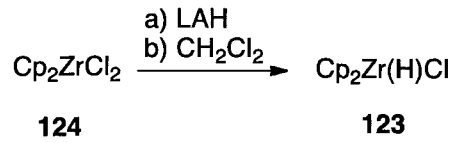
The reductive allylation of the enantiopure hemi-ketal (**120**), exploiting the substituted allylsilane (**100**) and $BF_3 \cdot Et_2O$, was used to form an advanced intermediate

(**122**) related to the plakortether backbone (**Scheme 39**). The product (**122**) contained many moieties that require functional group interconversion. Selective alteration of the amide functionality is key in order to maintain the integrity of the molecule as a whole. Of particular concern were the ester and alkene functionalities introduced in the allylation reaction. Most reagents used to reduce an amide bond, including borane and aluminum hydrides, are commonly used to react with esters and amides but have little functional group tolerance. The use of zirconocene hydrochloride (**123**) (Schwartz reagent),[78] which has been shown to reduce tertiary amides to form an aldehyde.[78]



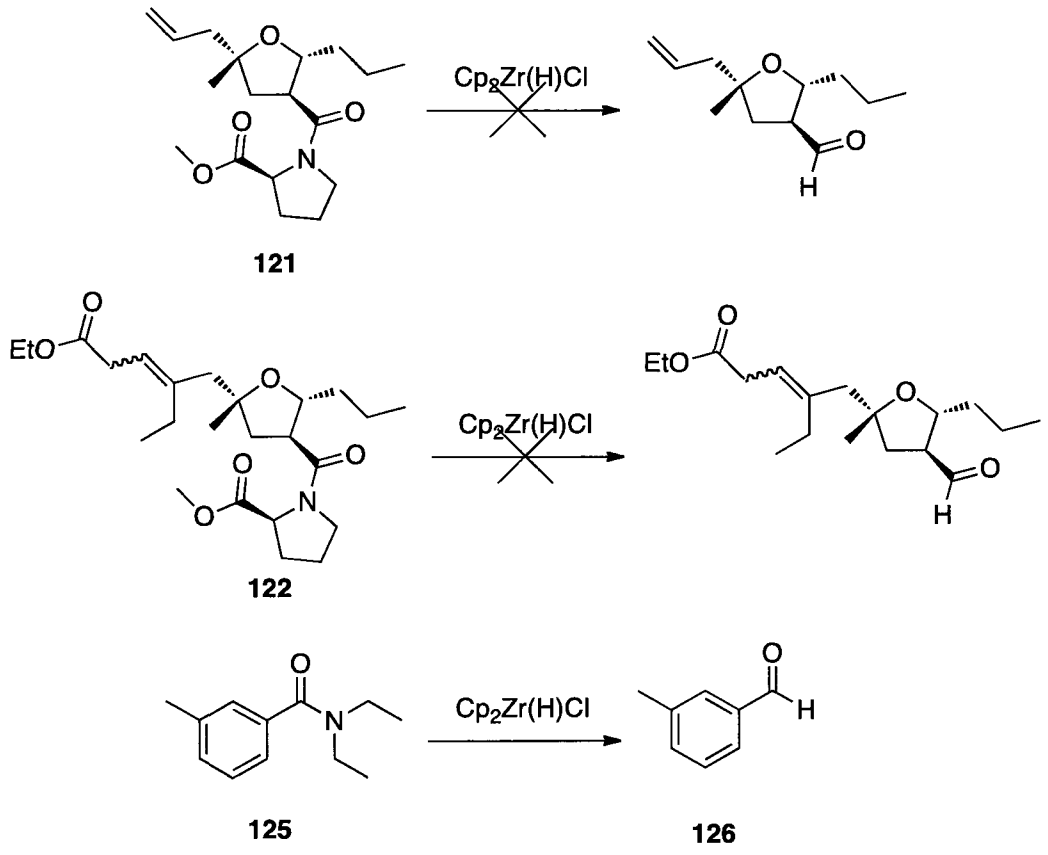
Scheme 39. Reductive-allylation of **120** with substituted allylsilane **100**

The Schwartz reagent has been utilized in organic synthesis to selectively reduce alkenes and alkynes.[79] The Schwartz reagent was formed by the reduction of zirconocene dichloride (**124**) in the presence of stoichiometric lithium aluminum hydride (LAH). This reduction forms zirconocene dihydride, which upon addition of methylene chloride generates the Schwartz reagent in near quantitative yields (**Scheme 40**).[80]



Scheme 40. Formation of the Schwartz reagent (**123**)

The Schwartz reagent was tested on **121** in order to determine the stability of the alkene under the reductive reaction conditions (**Scheme 41**). When the reaction was worked up, only starting material (**121**) was isolated. This failed reduction was thought to be due to the poor quality of the Schwartz reagent. *N, N*-Diethyl-*m*-toluamide (**125**) (DEET) was used as a test reagent to determine the integrity of the Schwartz reagent. Under the same reaction conditions, the reduction of DEET to its aldehydic counterpart (**126**) proceeded cleanly and in high yield, indicating that the Schwartz reagent was active. The reaction of **121** and the Schwartz reagent was then allowed to proceed for twelve hours and still no reduction was observed. The reduction of **122** with the Schwartz reagent was also studied (**Scheme 41**). As with **121**, no reduction was detected, and the ^{1}H NMR showed decomposition of the starting material (**122**).



Scheme 41. Attempted reduction of amides with Swartz reagent

Investigation into the synthesis of plakortether B utilizing the tandem homologation-aldol reaction as the key step has resulted in the identification of a diastereoselective approach to the hemi-ketal (**120**). Hemi-ketal (**120**) can be modified to yield a highly substituted tetrahydrofuran (**122**), providing a scaffold to perform chemical transformations in order to synthesize plakortether B. The plakortether backbone can be synthesized in three steps with every carbon incorporated except one from the starting β-keto amide (**119**). If the amide moiety of **122** can be reduced chemoselectively, the use of

a Wittig reaction followed by a selective reduction of the terminal alkene would afford the ethyl moiety embedded in the natural product (**58**). The final step that would need to be performed would be a diastereoselective hydroboration-oxidation of the tri-substituted alkene to render the enantiomer of plakortether B. Depending on the geometry of the alkene in **68** an inversion of the alcohol functional group might be nessissary. To synthesize the correct enantiomer, a β-keto amide derived from D-proline would have to be utilized in the tandem homologation-aldol reaction.

CHAPTER III

SYNTHESIS OF NOVEL HYDROXY-CYCLOPROPYL PEPTIDE ISOSTERES FOR ASPARTYL PROTEASE INHIBITION

Peptide Isosteric Replacements

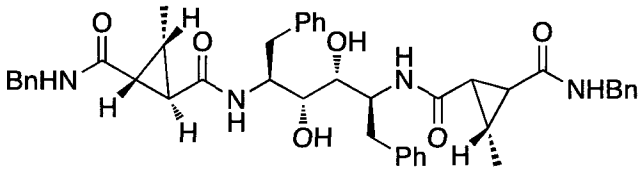
Peptide isosteres are useful tools to probe enzyme-substrate interactions for the design of pharmacophores.[81] A challenge in bioorganic chemistry is to determine the three-dimensional structure details of the peptide and the active site of a receptor. The replacement of the peptide bond with nonhydrolyzable functionality has been a crucial design principle in medicinal chemistry.[82] For example, Wipf and Xiao have transformed trisubstituted (*E*)-alkenylpeptidomimetics (**127**) to their corresponding cyclopropyl (**128**) replacement (**Figure 8**). Their rational for using the cyclopropyl moiety was that the alkenyl functionality is susceptible to isomerization, oxidation, and general chemical lability.[83] Peptide isosteric replacements have been extensively used toward recognition and inhibition of aspartyl proteases.

127 128

Figure 8. Synthesis of cyclopropyl peptidomimetics

Human immunodeficiency virus (HIV) is a crucial and complex target for the medicinal chemistry community. The drug arsenal that is currently used for HIV therapy consists of twenty-five approved therapeutics that act as inhibitors.[84] These drugs are separated into six classes that act as aspartyl protease inhibitors or non-nucleoside reverse transcriptase inhibitors.[85]

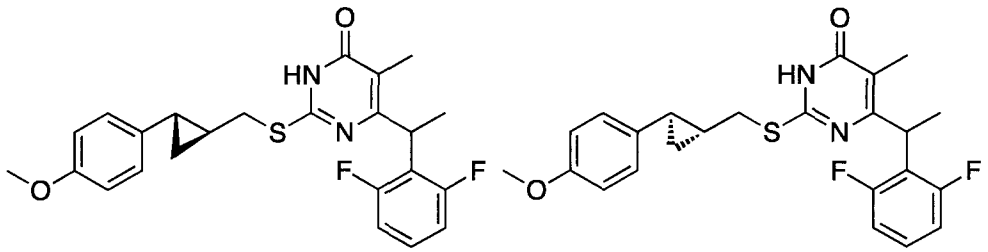
Martin and co-workers targeted the aspartic protease of HIV-1 with cyclopropanated peptidomimetics.[86] The use of topographical probes, such as a rigid cyclopropane moiety, provides insights into the biologically active conformation. Martin and co-workers have successfully synthesized a C_2 symmetric dicyclopropanated peptidomimetic (**129**) that is selective for HIV-1 protease (K_is 0.16 – 0.21) (**Figure 9**). Peptide isostere **129** was also bound to HIV-1 protease and the bound conformation was determined through X-ray analysis.



129

Figure 9. Peptidomimetic **129**

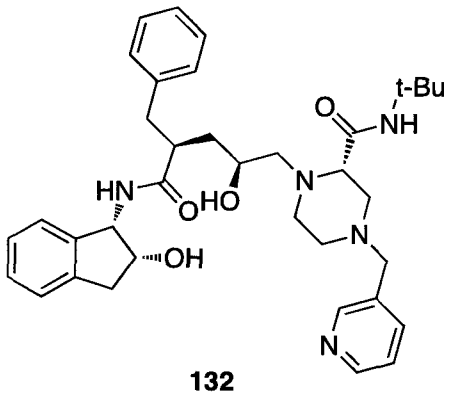
Botta and coworkers synthesized two novel reverse transcriptase inhibitors that were highly selective in cell assays.[87] The group utilized simple chemical transformations along with SAR studies mimicking known therapeutics to afford potent HIV inhibitors **130** and **131** **(Figure 10).** The incorporation of two stereoisomers dramatically lowered the ID_{50} (mean infectious dose) in the cell culture assays when compared to known HIV inhibitors. The incorporation of a cyclopropyl moiety was the most effective and showed the lowest concentration for complete inhibition.



130 **131**

Figure 10. HIV-1 reverse transcriptase inhibitors **130** and **131**

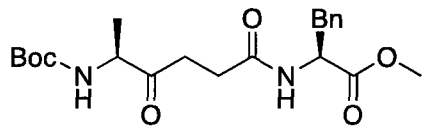
Many of the aspartyl protease inhibitors are derived from peptide isosteres that are unable to be hydrolyzed into essential amino acids. Many of the therapeutics for aspartyl proteases are designed to mimic intermediates within HIV's aspartyl protease. This design model is depicted in the approved drug Indinavir (**132**), (**Figure 11**) with the H-bonding and sp^3 hybridization of the hydroxyethylene unit. The use of mimics in protease inhibition are often limited by low protein/receptor selectivity and low IC_{50}.[88] Rationales offered for the poor binding and selectivity is due to the free rotation around the isosteric carbon-carbon bond and loss of Coulombic interactions within the bound substrate.[89] The successful combination of design principle that maximize selectivity through reducing bond rotation and maintaining Coulombic interactions is key to future success.



132

Figure 11. Indinavir

Previous work within the Zercher group has resulted in the development of a one-pot method for the formation of ketomethylene isosteres.[23] Formation of ketomethylene-containing isosteres by previous methods had been tedious and lengthy. Lin, however, was able to synthesize **133** as a single diastereomer, by application of a zinc-mediated homologation reaction (**Figure 12**). Peptide isostere **133** was non-hydrolyzable, but free rotation around the carbon-carbon isosteric replacement was believed to have negatively impacted the binding efficiency.[90]

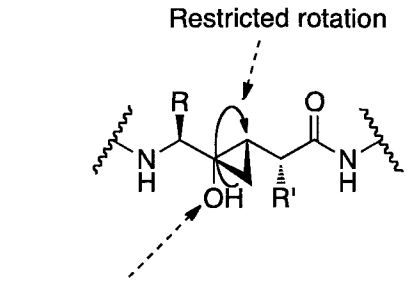


133

Figure 12. Ketomethylene isostere

A new principle for the design of peptide isosteres that are non-hydrolizable, provide restricted rotation, and mimic the aspartyl protease hydrolysis intermediate has been developed. The principle is based on incorporation of a hydroxy cyclopropyl moiety that would satisfy the above conditions. Another important application is the ability to selectively functionalize individual carbons in a stereoselective fashion to provide inhibitors that may be less vulnerable to mutation-resistance of an aspartyl protease.

In the study reported herein, a tandem reaction sequence has been utilized to form bicyclic lactones, which upon opening, provide peptide isosteres that contain a cyclopropanol moiety. This functionality possesses restricted rotation around the carbon-carbon bond as well as H-bonding capabilities (**Figure 13**). The cyclopropyl moiety can be seen as an isosteric replacement for carbon-carbon double bonds and is more stable to hepatic oxidation than that of an alkene.[91]



134

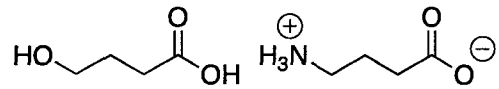
Figure 13. Novel peptide isostere

A method that can be readily utilized for selecting bioactive pseudopeptides to their cooresponding target is the use of Ramachandran plots. Gupta and Payne have shown that through simple conformational analysis a Ramachandran plot can be obtained to depict the relative Boltzmann distributions of a select isostere. This plot can show the relative conformation of the isostere in a beta-sheet, alpha helix, or left-handed helix.[92] With the aid of X-ray crystallography a bound substrate can be selectively removed from the protein and determined its overall conformation. With novel peptide isosteres the

described computational tool can allow prediction of all possible conformations possible to better analyze the binding potential of the substrate.

γ-Hydroxybutyrate (GHB)Analogs

The endogenous neurotransmitter γ-hydroxybutyrate (**135**) (**Figure 14**) is utilized for the treatment of cataplexy associated with narcolepsy and has displayed therapeutic potential for treating drug dependence.[93,94] The exact mechanism of action for GHB is unknown, but a structurally similar compound γ-aminobutyric acid (**136**) (GABA) (**Figure 14**) has been shown to be a major inhibitor of dopamine in the central nervous system.[95] Modulation of the GABA receptors is known to produce anxiolytic responses and allows patients with numerous disorders to live a stable life.



135 **136**

Figure 14. GHB (**135**) and GABA (**136**)

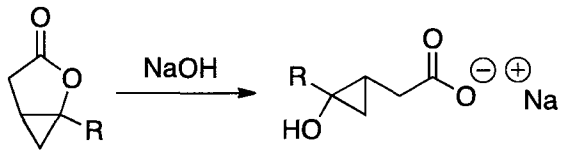
The GABA receptors are ligand-gated chloride ion channels comprised of five transmembrane subunits that mediate the expression of dopamine.[96] These ion channels are also the sites at which benzodiazepines bind and exert their anxiolytic effects. Benzodiazepine agonists have an extremely high efficacy, but display no selectivity within the GABA subunits.[97] Each of these subunits displays differing efficological

effects upon the central nervous system. GHB itself has low affinity for the GABA receptors, but recently there has been evidence of a GHB receptor, which has been postulated to cause many of the pharmacological effects associated with the drug.[98] Therefore, treatment of anxiety and cataplexy has been extensively studied with GHB and analogous compounds to selectively bind to an individual subunit (GABA and/or GHB receptors).

Clausen and coworkers have studied the basic structure activity relationships (SAR) on GHB in order to selectively determine the binding affinities through hydrophobic/hydrophilic interactions.[99] Adding aryl moieties to the 4-position of GHB was determined to drastically lower the K_i values, which gave insight to the binding mode. They hypothesized a hydrophobic pocket within the GABA receptors aid in the high affinity associated with their aryl analogs. When they eliminated the hydroxyl group at the 4-position of GHB and the respective analogs, the inhibition constants were raised ten fold. This indicated that the hydroxyl moiety is necessary for efficient binding to the receptors through the use of H-bonding interactions.

The ability to generate cyclopropanated lactones provides the means to produce cyclopropanated analogues of GHB. The bicyclic lactone (**137**) can be synthesized in one pot and hydrolyzed with a base such as sodium hydroxide to obtain sodium salts of the GHB analogs (**Scheme 42**). Another advantage to the homologation-cyclopropanation methodology is that the starting substrates can easily be modified to address the H-bonding, Coulombic, and hydrophobic/hydrophilic interactions via

appropriate selection of starting material. The 4-hydroxyl moiety can be seen as being embedded within the bicyclic lactone (**137**), which is a necessity for efficient binding.

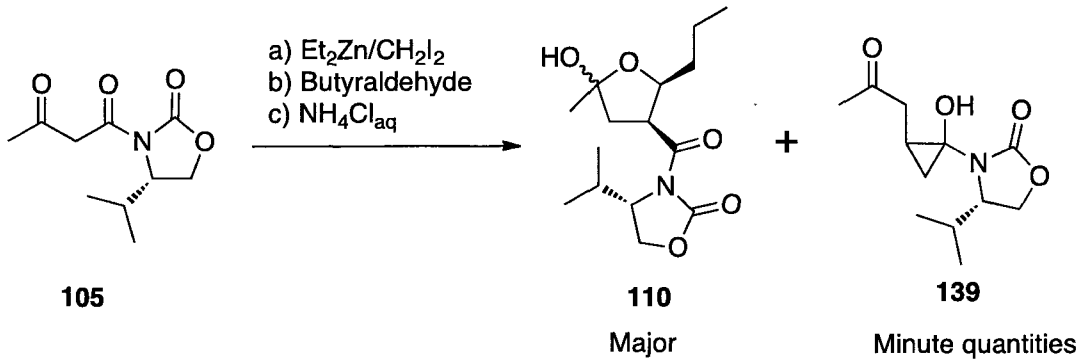


137 **138**

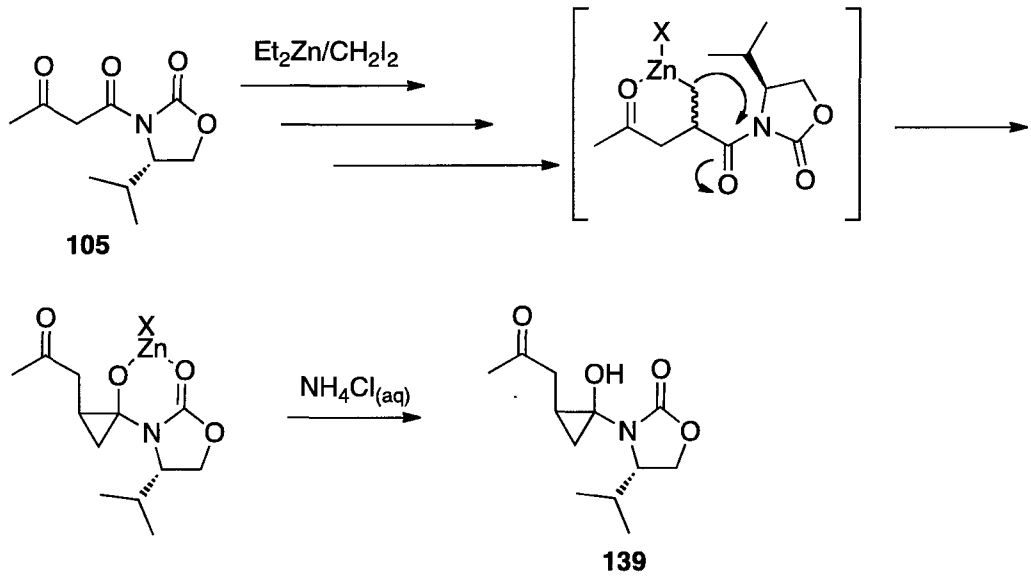
Scheme 42. Proposed opening of the bicyclic lactone (**137**) to form GHB analogs (**138**)

Serendipitous discovery of bicyclic lactones

Previous Zercher group members performing the tandem homologation-aldol or tandem homologation-homoenolate formation of a β-keto imides have isolated a cyclopropanol byproduct in minute amounts.[41,104] During a homologation-aldol reaction performed with a β-keto imide (**105**) to approach the plakortether backbone, the cyclopropanol byproduct (**139**) was also isolated in small quantities (**Scheme 43**). Based on an understanding of the proposed homologation mechanism, the cyclopropanol byproduct (**139**) could be envisioned as forming through a homoenolate, which performs an intramolecular cyclization into the imide carbonyl (**Scheme 43**).



Scheme 43. Serendipitous discovery of a cyclopropanol (**139**) derivative

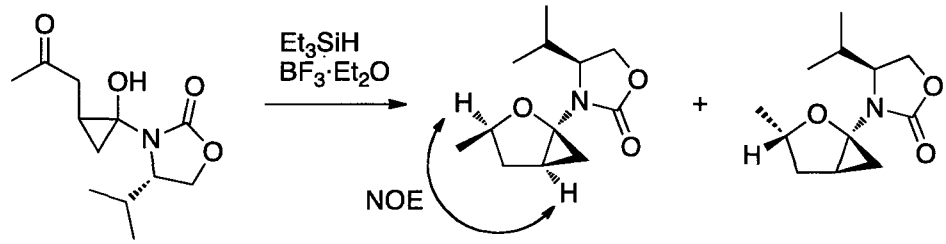


Scheme 44. Proposed mechanism for the formation of **139**

Upon isolation of **139**, a variety of potential applications of the cyclopropanol could be envisioned. Access to enantiopure homoenolates constituted one potential application. Reduction of the hydroxyl functionality, followed by reduction of the imide,

could provide access to enantiopure cyclopropyl amines. The unique cyclopropanol motif provided the possibility for many chemical transformations to afford access to enantiopure reagents that would be further utilized in separate chemical reactions.

One chemical reaction performed on the cyclopropyl alcohol (**139**) was a reduction using triethylsilane and boron trifluoride. When the ^{1}H NMR of the crude reaction mixture was analyzed, two cyclopropylfuranyl diastereomers (**140** and **141**) were observed (**Scheme 45**). The two diastereomers (**140** and **141**) were separated via flash chromatography and **140** was determined to be the major isomer through an NOE experiment.

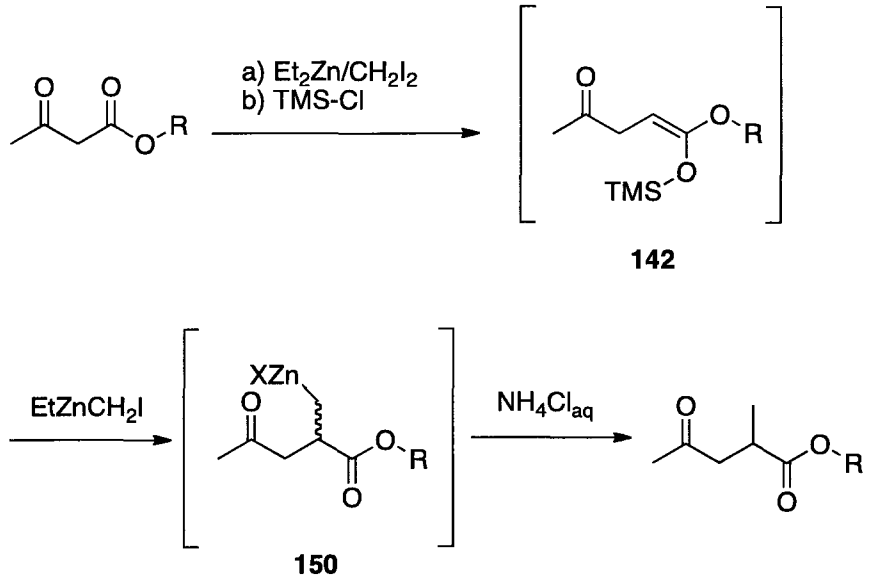


139 **140** Major **141**

Scheme 45. Silane reduction of **139**

Many attempts were made to increase the yield of the cyclopropanol derivative (**139**); however, most of these attempts resulted in the formation of only a small quantity of product (**139**) or no cyclopropane-containing product. A key observation reported by Hilgenkamp was that α-alkylation of the homologated β-keto ester was enhanced via use

of a TMS-Cl.[21] The use of a TMS-Cl was hypothesized to break up the zinc bound oligomer and produced a more reactive enolate equivalent (**142**) (**Scheme 46**). The more reactive enolate would then be capable of reacting with the zinc carbenoid to form the homoenolate.

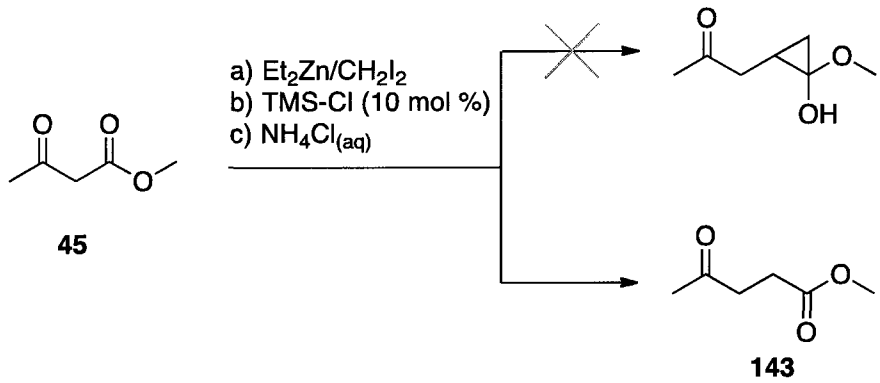


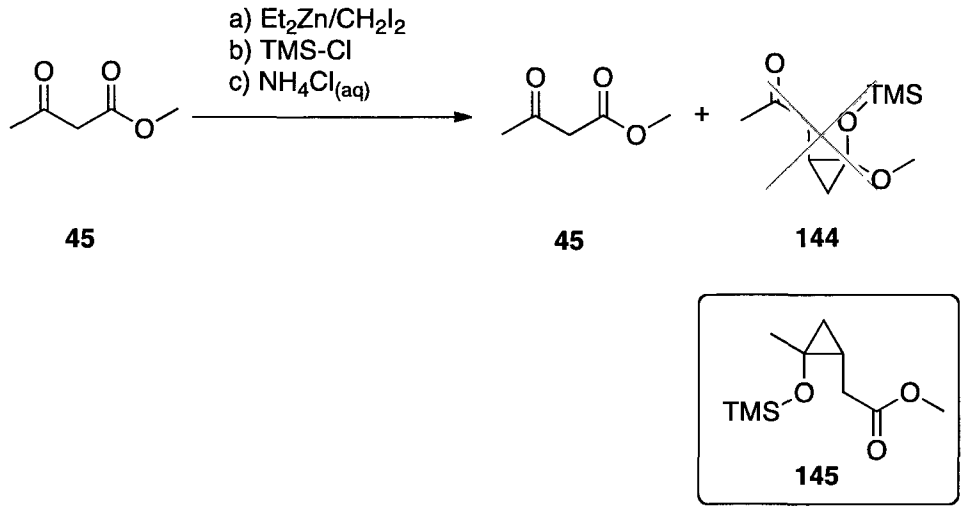
Scheme 46. Use of TMS-Cl as a Lewis acid

Utilization of TMS-Cl in catalytic amounts (0.1 mol equivalents) in the reaction of a β-keto ester has been shown to be effective for alkylation at the alpha carbon with the electrophilic carbenoid. The time course of the TMS-Cl catalyzed tandem homologation-homoenolate formation reaction was essential for α-methylation. Hilgenkamp reported the exposure of five equivalent excess of ethyl(iodomethyl)zinc to β-keto ester for a thirty minute reaction period, followed by the addition of TMS-Cl and

another thirty minute reaction period resulted in a ~70% yield of the α-methyl γ-keto ester.

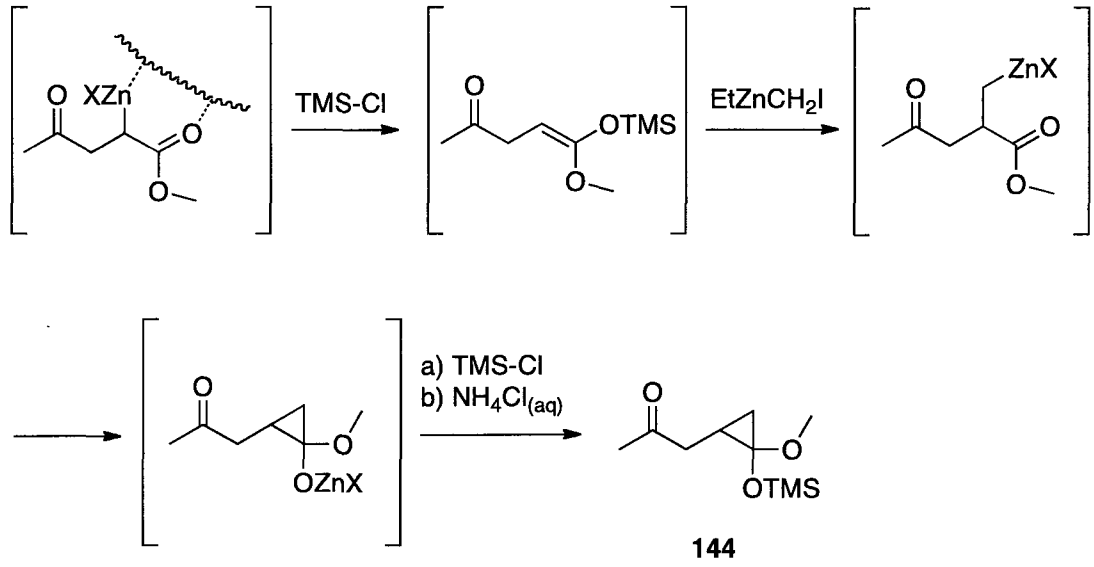
In an attempt to use a β-keto ester (methyl acetoacetate (**45**)) as a starting substrate use of catalytic TMS-Cl (0.1 mol equivalents) and five equivalents ethyl (iodomethyl)zinc were employed. The one difference from Higenkamp's method was that the reaction time was extended to twenty-four hours. The resulting product was the homologated γ-keto ester (**143**) (**Scheme 47**). The next variation was the use of stoichiometric amounts of TMS-Cl with excess ethyl(iodomethyl)zinc. After column chromatography, small amounts of a product, initially predicted to be a cyclopropyl mixed-acetal (**144**) were isolated. Analysis by ^{13}C NMR revealed that the only carbonyl resonance in the spectrum was in the range of an ester moiety, which led to the assignment of the cyclopropyl silyl ether (**145**) as the structure.





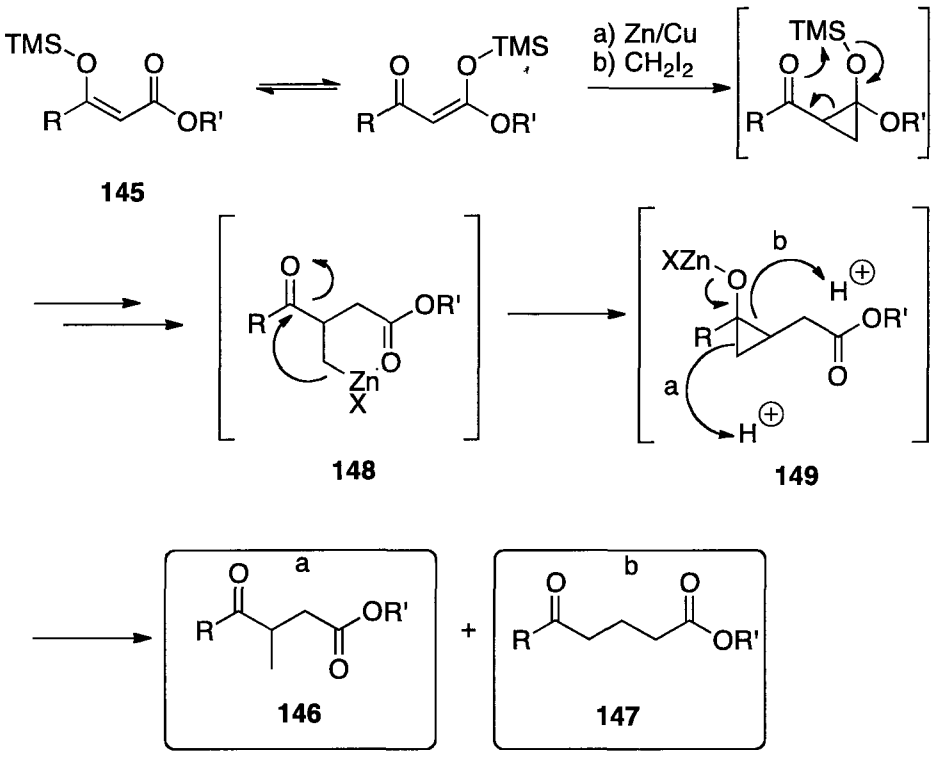
Scheme 47. Homologation-cyclopropanation conditions

In the homologation-cyclopropanation reaction of methyl acetoacetate (**45**), a latent zinc enolate is generated alpha to the ester moiety. The addition of TMS-Cl is proposed to disrupt the oligomeric species, thereby enabling alkylation with an equivalent of the electrophilic carbenoid, to form a zinc homoenolate. If this homoenolate were to undergo an intramolecular cyclization into the ester carbonyl, followed by trapping with the stoichiometric amount of TMS-Cl, a mixed acetal would be produced (**144**) (**Scheme 48**). The isolation of this mixed acetal **144** has never been observed in the reaction of β-keto esters.



Scheme 48. Mechanistic prediction of the homologation-cyclopropanation

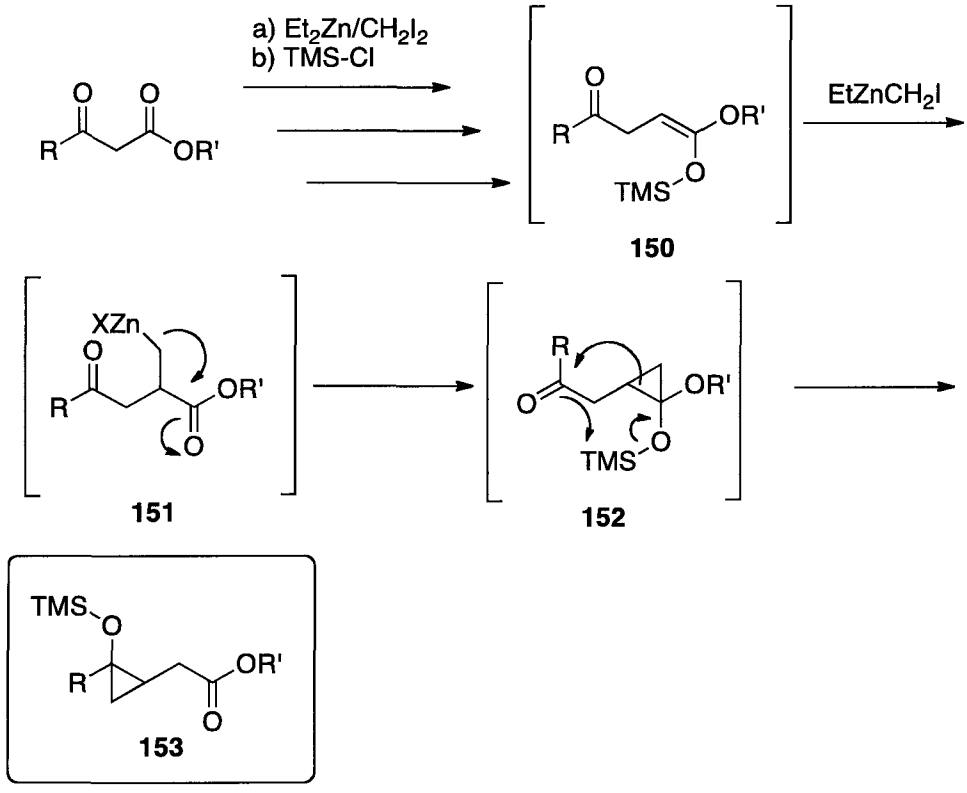
Saigo's reported studies of a homologation reaction in which TMS-enol ether (**145**) derived from a β-keto ester, was subjected to the Simmons-Smith carbenoid.[100] Along with isolation of the anticipated γ-keto ester, a β-methylated γ-keto ester (**146**), and a δ-keto ester (**147**) were also observed. Saigo proposed that anionic character alpha to the keto moiety was generated. Reaction with excess zinc carbenoid would provide a homoenolate (**148**). The homoenolate (**148**) could undergo an intramolecular cyclization to form a zinc cyclopropoxide (**149**). Addition of a proton and fragmentation the cyclopropoxide would afford the β-methylated γ-keto ester (**146**) or the δ-keto ester (**147**) in small amounts (**Scheme 49**).



Scheme 49. Saigo's isolated by-products **146** and **147**

Based upon the formation of the cyclopropyl silyl ether (**145**) and the results from Saigo's homologation reaction, a mechanism was proposed for the twenty-four hour TMS-promoted homologation-alkylation of β-keto esters with the Furukawa reagent. After the initial homologation the latent silyl-enol ether (**150**) is reacted with another equivalent of zinc carbenoid in solution to render a homoenolate. Homoenolate **151** can then undergo an intramolecular cyclization into the ester carbonyl to afford a cyclopropyl silyl enol ether (**152**) that can rearrange to form another cyclopropyl silyl enol ether (**153**) with the keto moiety (**Scheme 50**). Based on this mechanistic proposal, incorporation of

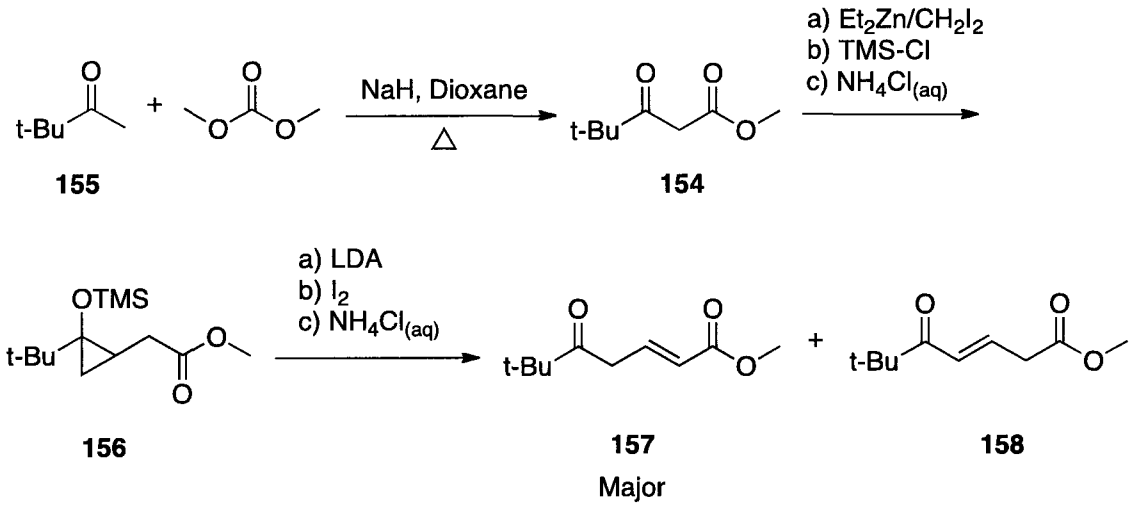
steric bulk adjacent to the ketone could facilitate formation of the silyl mixed acetal and prevent rearrangement to the isomeric cyclopropane.



Scheme 50. Proposed rearrangement during the TMS-promoted homologation-alkylation

For this reason, methyl pivaloylacetate (**154**) was studied in the homologation-cyclopropanation reaction. The synthesis of methyl pivaloylacetate (**154**) was straightforward and was performed on a multigram scale.[101] Refluxing sodium hydride, pinacolone (**155**), and dimethyl carbonate in dioxane afforded methyl pivaloylacetate (**154**) in a 66% yield (**Scheme 51**). The homologation-cyclopropanation reaction was performed on substrate **154** to determine if steric hindrance could play a role and favor

formation of the mixed acetal. Even with the added steric bulk, the product was the cyclopropyl silyl ether (**156**) (**Scheme 51**).

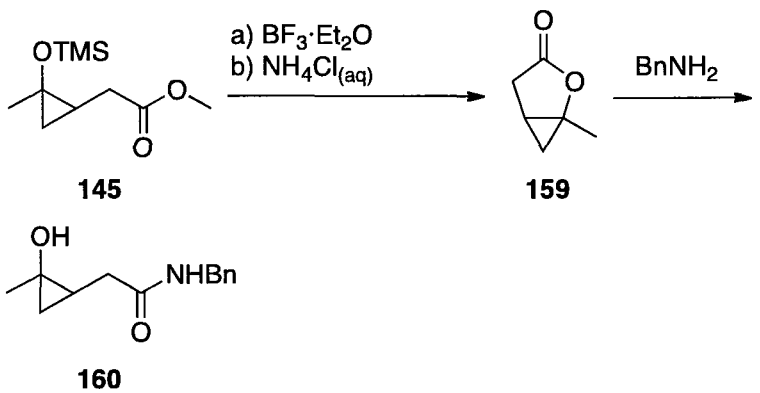


Scheme 51. Use of a sterically hindered β-keto ester (**154**)

The cyclopropylsilyl ether (**156**) was subjected to a α-iodination-elimination reaction to yield (*E*)-methyl 6,6-dimethyl-5-oxohept-2-enoate (**157**) (**Scheme 51**).[102] Product **157** underwent a minor isomerization to (*E*)-methyl 6,6-dimethyl-5-oxohept-3-enoate (**158**) when the reaction was quenched with concentrated hydrochloric acid. Formation of **157** was consistent with the major product from the homologation-cyclopropanation reaction being the cyclopropylsilyl ether (**156**).

The cyclopropylsilyl ether (**145**) was introduced to a Lewis acid-mediated cyclization reaction (**Scheme 52**).[103] This reaction produced a bicyclic lactone (**159**) in near quantitative yield. The bicyclic lactone (**159**) underwent a ring opening with the

addition of benzyl amine, forming *N*-benzyl-2-(2-(*tert*-butyl)-2-hydroxycyclopropyl) acetamide (**160**). This constituted the first compound that could be manipulated into a peptide isostere that would contain the hydroxy-cyclopropanol functionality.



Scheme 52. Reductive cyclization followed by ring opening

A drawback to the formation of the cyclopropanol isostere was that the stereochemistry was not controlled. To gain access to an enantiopure bicyclic lactone, a chiral β-dicarbonyl starting substrate would need to be synthesized. The second limitation was that the homologation-cyclopropanation-silation reaction was extremely low yielding. The low yield was later attributed to deprotection of the silyl ether from the slightly acidic silica gel used to purify **145** via flash chromatography. This was confirmed through the use of 2D thin layer chromatography (**Figure 15**).

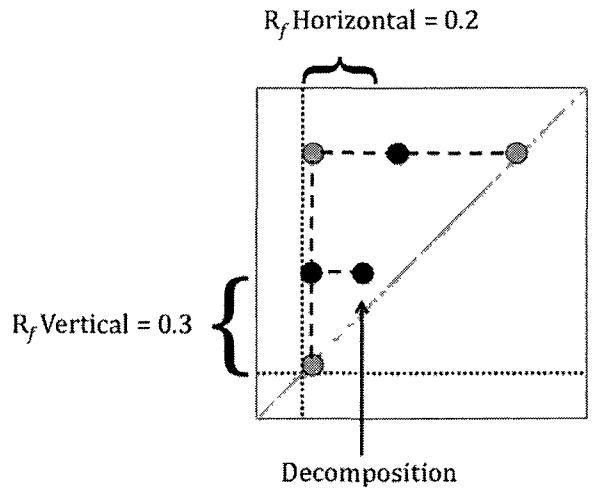


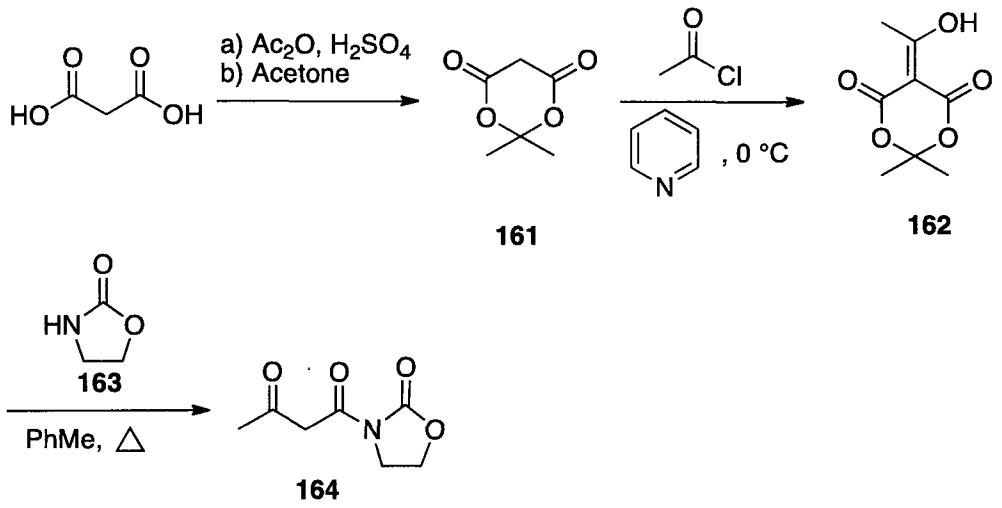
Figure 15. 2D TLC plate to confirm decomposition of **145**

With low yields and instability of the β-keto ester-derived cyclopropyl silyl ether **145**, use of another starting β-keto substrate was explored. β-Keto imides have shown to cyclopropanate in the absence of TMS-Cl which made them attractive targets.[41] Preparation of a β-keto imide through the use of diketene has been performed in the past. [23] Due to the discontinuation of commercially available diketene a new route was required to obtain a β-keto imide.

Acetoacylation via Meldrum's acid

An acetoacylation reaction with the acetone adduct of diketene was proposed to afford the β-keto imide in a similar fashion to diketene. This reaction, though direct, was extremely poor yielding and cumbersome. Acylated Meldrum's acid has been reported to acetoacylate alcohols and amines, resulting in the formation of β-keto esters and amides, respectively.[104] Meldrum's acid (**161**) was synthesized in gram quantities from malonic

acid, acetic anhydride, acetone, and catalytic sulfuric acid.[104] After recrystalization from ethanol, Meldrum's acid was subjected to acetyl chloride and pyridine to yield the acylated Meldrum's acid adduct (**162**) in quantitative yield.[104] To test the acetoacylation reaction, Meldrum's acid adduct (**162**) was refluxed in toluene with 2-oxazolidone (**163**), which gave 1-(2-oxooxazolidin-3-yl)butane-1,3-dione (**164**) in 89% yield (**Scheme 53**).

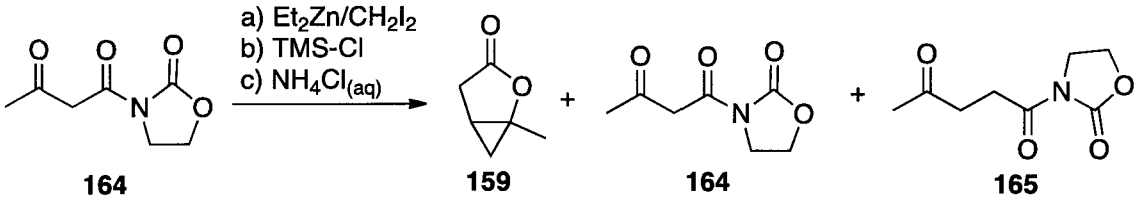


Scheme 53. Formation of a β-keto imide

Tandem homologation-alkylation-cyclization-lactonization

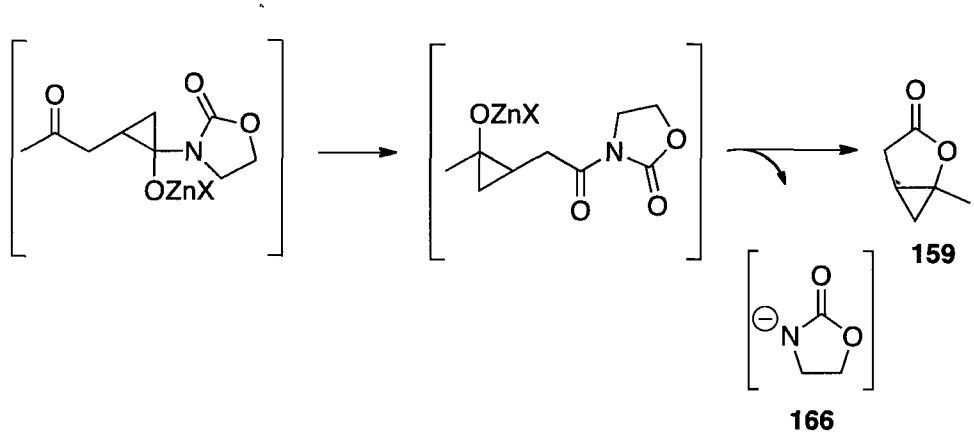
To test the homologation-cyclization reaction, the achiral β-keto imide (**164**) was introduced to three equivalents of the ethyl(iodomethyl)zinc carbenoid and catalytic amounts of TMS-Cl (**Scheme 54**). Quin-Ling Pu has shown that catalytic amounts of TMS-Cl in the presence of β-keto imides promoted formation of a homoenolate, which was postulated to cyclize to the cyclopropane after a period of time. When the

homologation-cyclization reaction was performed on **164**, the product that was isolated after a twelve hour reaction period was not the predicted cyclopropanol. A bicyclic lactone (**159**) was isolated in a 12% yield (**Scheme 54**). Two other products, identified by ^{1}H NMR analysis of the crude reaction mixture, were determined to be starting material (**164**) and the homologated γ-keto imide (**165**). The next step in the study was to optimize the yield and diminish the amount of unreacted starting material.



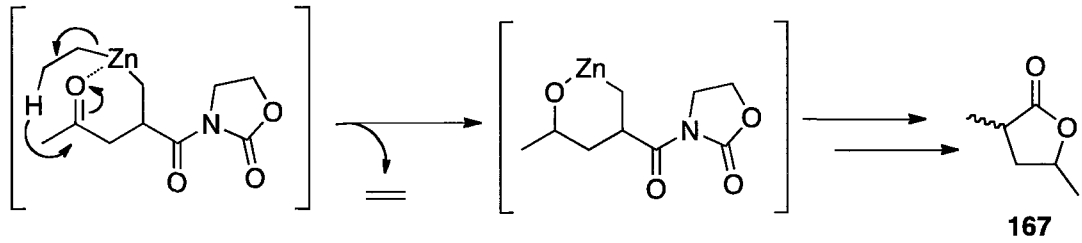
Scheme 54. Homologation-Cyclopropanation

TMS-Cl was theorized to contain some HCl, which would be expected to quench some of the carbenoid. When TMS-Cl was omitted from the reaction, the yield of the bicyclic lactone (**159**) slightly increased to 15%. The continued presence of starting material, even in the presence of a large excess of carbenoid, was troubling. If a byproduct generated in the reaction were capable of destroying the carbenoid, this could account for the continued presence of starting material. During the lactonization step, expulsion of an oxazolidone anion (**166**) occurs in the formation of the bicyclic lactone (**159**) (**Scheme 55**). If this anion could react with the remaining carbenoid, the continued presence of unreacted starting material could be rationalized.



Scheme 55. Mechanistic proposal of the homologation-cyclopropanation

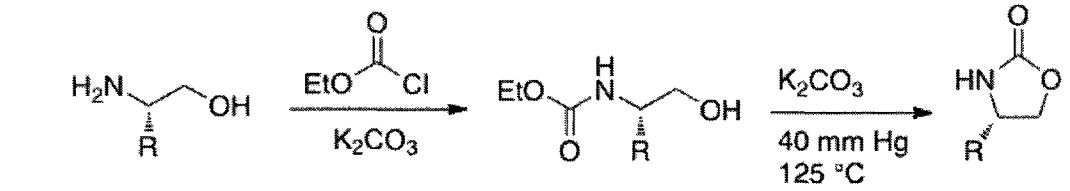
A control study was performed with 2-oxazolidone and ethyl(iodomethyl)zinc to determine if it acts as a carbenoid scavenger. The Furukawa reagent (1 equivalent) was stirred for twelve hours with 2-oxazolidone (1 equivalent). Upon work up, both the starting 2-oxazolidone and *N*-methylated 2-oxazolidone were identified via ^{1}H NMR. Based on this evidence, five equivalents of the ethyl(iodomethyl)zinc were used in subsequent homologation reactions in an effort to compensate for the carbenoid decomposition caused by the oxazolidone anion (**166**). When the reaction was performed with five equivalents of the Furukawa reagent, all of the starting β-keto imide was consumed but the bicyclic lactone (**159**) co-eluted off of the chromatograph column with another lactonized product. The impurity was identified as α-methyl-γ-valerolactone (**167**). This byproduct could be generated by an intramolecular or intermolecular Meerwein-Ponndorf-Verley-like reduction (**Scheme 56**).[105]



Scheme 56. Intramolecular Meerwein-Ponndorf-Verley like reduction

One method envisioned to prevent a Meerwein-Ponndorf-Verley-like reduction involved removal of the ethyl ligand on the Furukawa-modified zinc carbenoid. Exchange of the carbenoid's ethyl ligand for a trifluoroacetoxy moiety has been reported, and this modified carbenoid has proven effective in the homologation of β-dicarbonyl substrates.[106] Another variation on the carbenoid involves the use of a 2:1 mixture of diiodomethane and diethylzinc, which produces an ambiphilic bis(iodomethyl)zinc carbenoid.[107] This latter variation offers two advantages: first, the electronic nature of the carbenoid is similar to the Furukawa-modified carbenoid and second, the absence of the ethyl ligand prevents the possibility of a Meerwein-Ponndorf-Verley-like-reduction. Utilization of the bis(iodomethyl)zinc carbenoid in the homologation-lactonization reaction on substrate # resulted in an increased yield of the bicyclic lactone (**159**) and no indication of a Meerwein-Ponndorf-Verley like reduction. With the yield of the bicyclic lactone (**159**) at approximately 50 %, an enantiopure β-keto imide was utilized to determine if a chiral oxazolidinone could be used to control absolute stereochemistry within the tandem homologation-cyclization reaction.

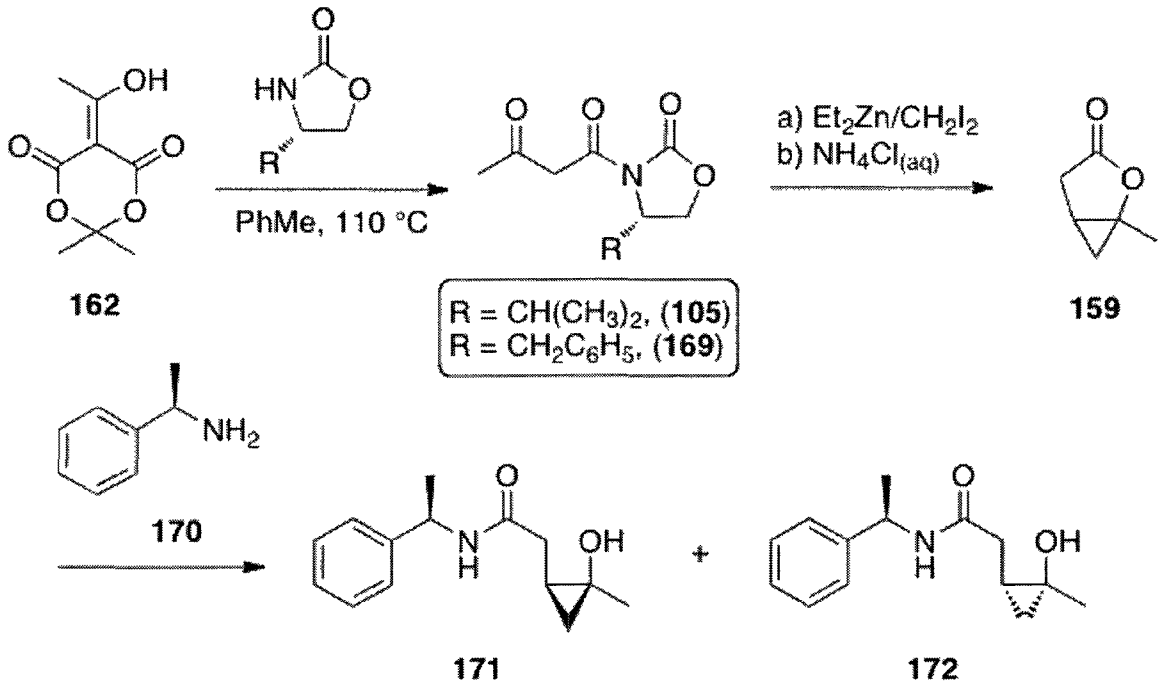
Chiral β-keto imides have been used in the Zercher research group to control the stereochemistry in the tandem homologation-aldol reaction.[23] The availability of gram quantities of β-keto imides was necessary in order to perform the full complement of studies. Reduction of an amino acid to the corresponding amino alcohol can be achieved in high yields through the use of lithium aluminum hydride (LAH) or through a borane reduction.[108,109] Closure of the amino alcohol to the respective oxazolidinone has been performed with triphosgene or diethyl carbonate.[110] Use of these methods have major drawbacks and limitations. Triphosgene is a potentially hazardous reagent (formation of phosgene in the course of the reaction) and the diethyl carbonate method results in poor yields of the oxazolidinone (**106**). More recently, the synthesis of chiral oxazolidinone (**106**) has been reported to proceed in high yields through the formation of a carbamate, followed by a base-catalyzed intramolecular cyclization (**Scheme 57**).[111]



Scheme 57. Formation of chiral oxazolidones **106** and **106a**

Amino alcohols (**108** and **168**) derived from L-valine and L-phenylalanine were both converted to their respective chiral oxazolidinones (**106** and **106a**) utilizing the procedure developed by Wu and coworkers. First, the amino alcohol was acylated with ethyl choroformate in the presence of potassium carbonate to obtain a hydroxy-carbamate (**106'** and **106a'**), which was treated with catalytic amounts of potassium carbonate under vacuum (40 mmHg) at 125 °C until gas evolution ceased. After simple column chromatography the pure oxazolidone was obtained in high yield.

The two chiral oxazolidinones (**106** and **106a**) were then subjected to the acylated Meldrum's acid (**162**) in refluxing toluene to afford the acetoacylated oxazolidinones (**105** and **169**) (**Scheme 58**). The β-keto imides (**105** and **169**) were then subjected to the homologation-lactonization reaction in the presence of five equivalents of bis (iodomethyl)zinc (**Scheme 58**). The bicyclic lactone (**159**) was isolated in roughly 50% yield. Optical rotation measurements was then performed on **159** to determine if the absolute stereochemistry of the oxazolidinone was transferred to the bicyclic lactone. The results were inconclusive, since the low concentration of the bicyclic lactone in solution provided a miniscule and irreproducible optical rotation.



Scheme 58. Use of a Chiral β-keto imide to control absolute stereochemistry

Another method to analyze the enantioselectivity of the homologation-lactonization reaction on substrates **105** and **169** involved chemical modification of the lactone (**159**). As reported in **Scheme 58**, bicyclic lactone **159** could be opened through the use of benzylamine. Use of an enantio-pure chiral amine to open up a lactone (**159**) would yield two diastereomers that could be quantified in the ^1H NMR spectrum of the crude reaction mixture. Use of α-(methyl)benzyl amine (**170**) as the chiral reagent provided two diastereomers (**171** and **172**) in a 2.3:1 ratio, as determined by ^1H NMR (**Figure 16**). From this ratio, the enantioselectivity of the homologation-lactonization reaction could be traced back to provide a 2.3:1 ee.

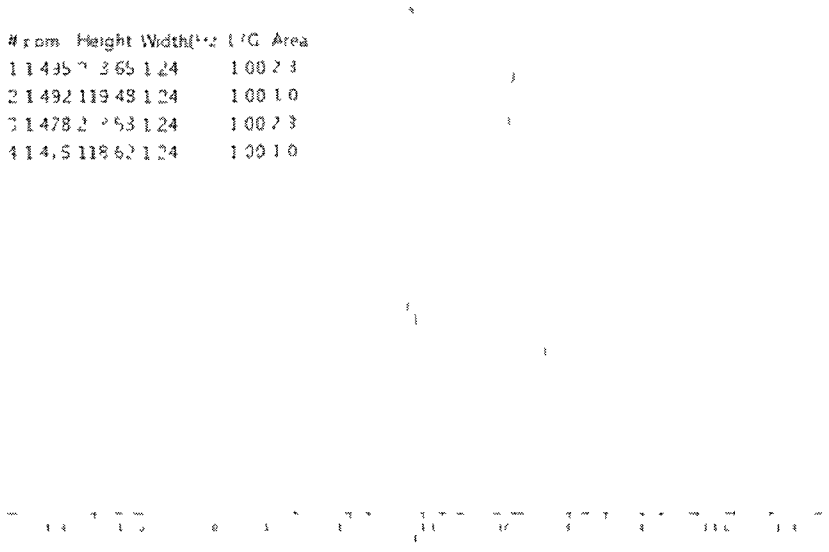
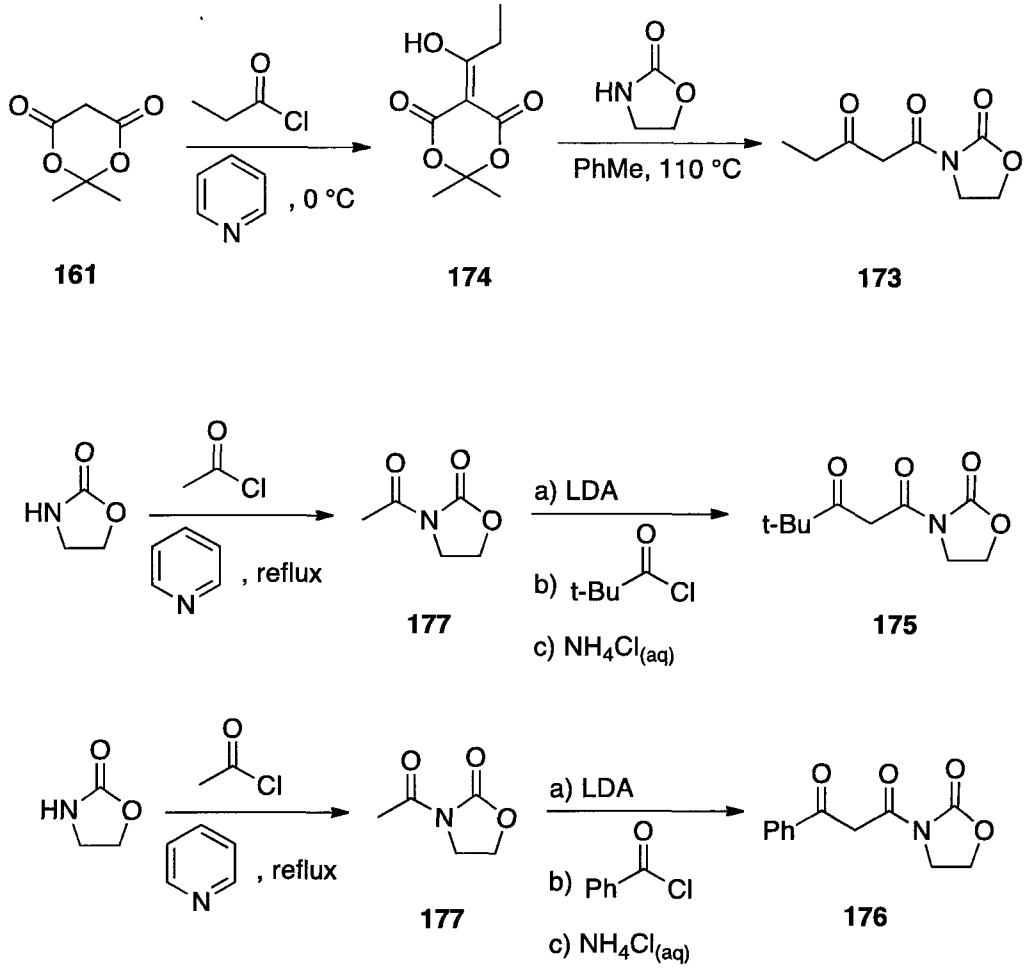


Figure 16. Line fit in MNOVA to determine the diastereoselectivity

Different β-keto imides were then synthesized by changing the functionality adjacent to the ketone moiety to build a library of similar compounds. The first derivative to be studied was 1-(2-oxooxazolidin-3-yl)pentane-1,3-dione (**173**), which was produced by acylating Meldrum's acid with propionyl chloride to form 5-(1-hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**174**),[104] followed by treatment with 2-oxazolidone in refluxing toluene. The β-keto imide (**173**) was produced in high yield (**Scheme 59**). The next derivative that was synthesized was 4,4-dimethyl-1-(2-oxooxazolidin-3-yl)pentane-1,3-dione (**175**). Synthesis of compound **175** was first attempted through the Meldrum's acid route. Efforts to acylate Meldrum's acid with pivaloyl chloride were unsuccessful and returned the starting Meldrum's acid. The

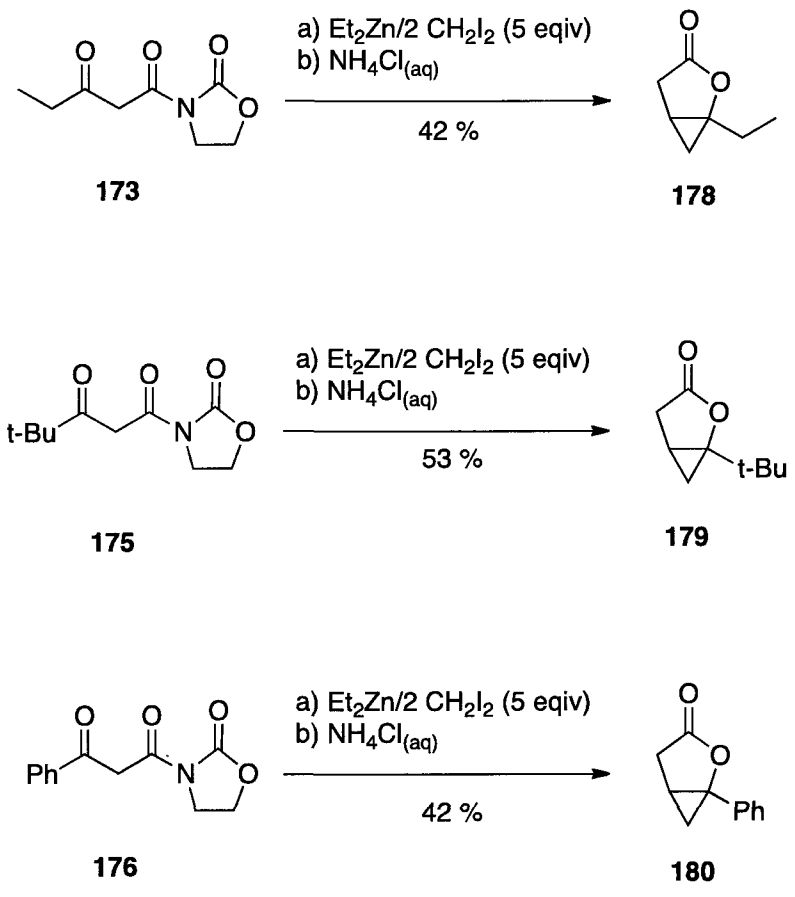
targeted compound (**175**) was eventually generated through a mixed Claisen reaction. Acylation of 2-oxazolidinone was achieved by refluxing pyridine and acetyl chloride for twelve hours (**Scheme 59**). Deprotonation of the acetylated oxazolidinone with LDA produced an enolate, which was transferred by cannula into a solution of THF and pivaloyl chloride. The β-keto imide (**175**) was generated in moderate yields (**Scheme 59**).

The last derivative to be added to the library was an aryl functionalized β-keto imide. Again, formation of this substrate was attempted through the Meldrum's acid route by using benzoyl chloride as the electrophile, although this was unsuccessful. Unreacted Meldrum's acid and acetophenone, which was postulated to arise from the decomposition of the acylated Meldrum's acid, were the major components of the reaction mixture. Once again, use of a mixed Claisen route was successful in the formation of the aryl β-keto imide (**176**) (**Scheme 59**). The major drawback to the mixed Claisen route is the necessity of using excess acylated oxazolidinone (**177**).



Scheme 59. Synthesis of β-keto imide analogs

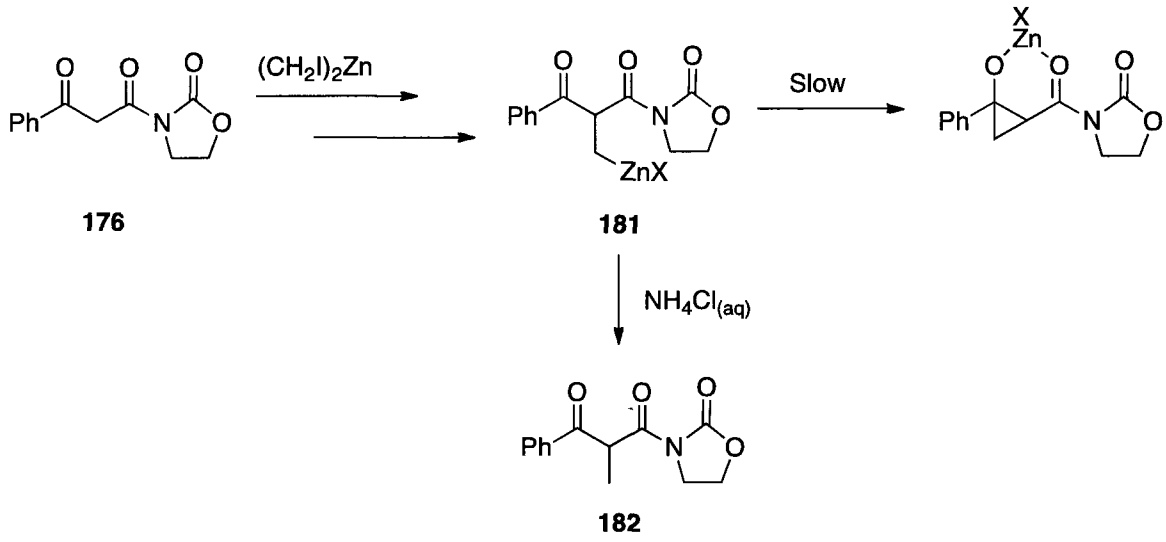
The β-keto imide analogs (**173**, **175**, and **176**) were all subjected to the homologation-lactonization reaction with the use of bis(iodomethyl)zinc. Substrates **173** and **175** gave modest yields of their corresponding bicyclic lactones (**178** and **179**) **(Scheme 60)**. Reaction of β-keto imide **176** led to a surprisingly low yield of the bicyclic lactone **180**, which was also difficult to purify and required two separate flash chromatography columns.



Scheme 60. Bicyclic lactone derivatives

One reason that **176** reacts inefficiently to provide the lactone may be related to the decreased efficiency in the homologation of ethyl benzoylacetate. When zinc homoenolate (**181**) cyclizes, the resonance stability between the aryl group and the keto moiety will be reduced (**Scheme 61**). The ^1H NMR of the crude reaction mixture showed presence of a α-methylated β-keto imide (**182**), which suggests that slow intramolecular

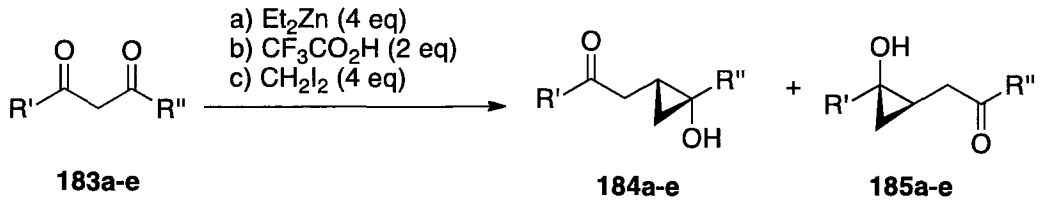
cyclization of the homoenolate derived from aryl β-keto imides was partially responsible for the decreased yield of lactone (**180**).



176 **181** **182**

Scheme 61. Slow homologation using aryl ketones

The use of a modified zinc carbenoid to convert 1,3-diketones into their corresponding 1,2-disubstituted cyclopropanols was reported by Xue.[112] A combination of aryl and aliphatic ketones were used in numerous substrates. Two different constitutional isomers could be produced for non-symmetrical diketones, yet in all cases with an aryl and aliphatic diketone, the major cyclopropanol isomer was formed adjacent to the aliphatic moiety (**Table 2**).



183a-e **184a-e** **185a-e**

Entry	R'	R"	% 184a-e	% 185a-e
183a	C_6H_5	Me	93	0
183b	*p*-$MeOC_6H_4$	Me	95	0
183c	*p*-ClC_6H_4	Me	70	14
183d	*p*-$MeOC_6H_4$	$CH_3CH_2CH_2$	94	0
183e	C_6H_5	$CH_3CH_2CH_2$	45	12

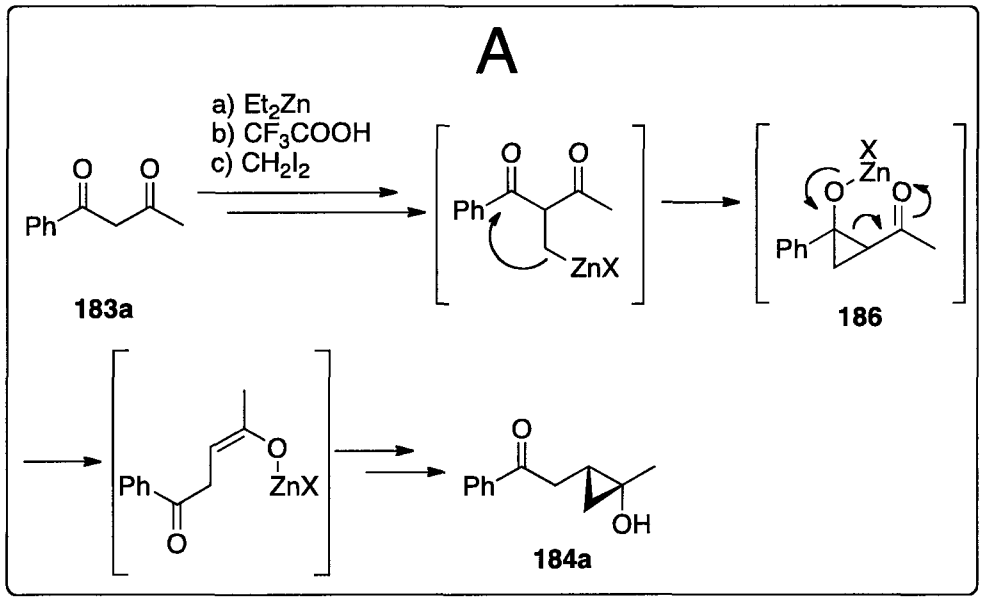
Table 2. Homologation-cyclopropanation of 1,3-diketones[112]

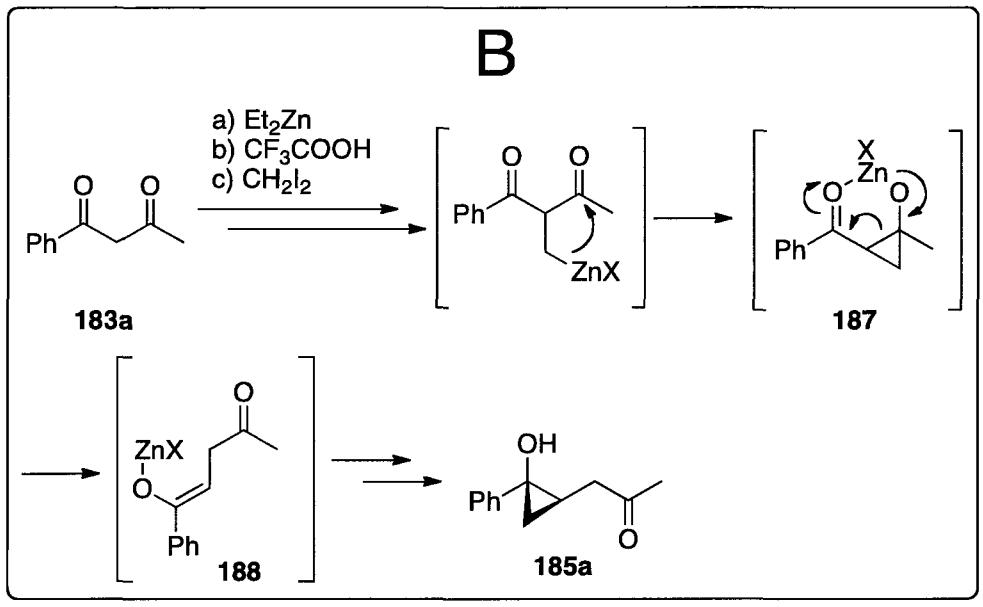
Illustrated in **Scheme 62** are the two proposed routes to the synthesis of cyclopropanols **184a** and **185a**. Formation of the major cyclopropanol product is depicted to form through route A (**Scheme 62**). The donor-acceptor cyclopropoxide **186** required for the formation of the major product would result from cyclization on the aryl ketone. This process would sacrifice the resonance energy between the aryl and keto moieties, and earlier studies point to the inefficiency of this route.[19]

The donor-acceptor cyclopropoxide (**187**) formed in Route B would result from cyclization into the more electrophilic aliphatic ketone. Basic principle suggest that the zinc homoenolate should preferentially cyclize into this carbonyl (**Scheme 62**). When **187** opens to afford the enolate (**188**), the product should be the aryl cyclopropanol **185a**.

The examples in **Table 2** show the major products to be the aliphatic cyclopropanols (**184a-e**). In other words, the major cyclopropanol product appears to result from formation of the donor-acceptor cyclopropane that is least likely to form.

The major cyclopropanol products (**184a-e**) possess resonance stabilized ketones and possess the *syn*-orientation between the alkyl-ketone and hydroxyl substituents. A thermodynamically-driven equilibrium was proposed for this homologation-cyclopropanation reaction. If the two possible products exist in equilibrium, this would explain the formation of the more stable product.

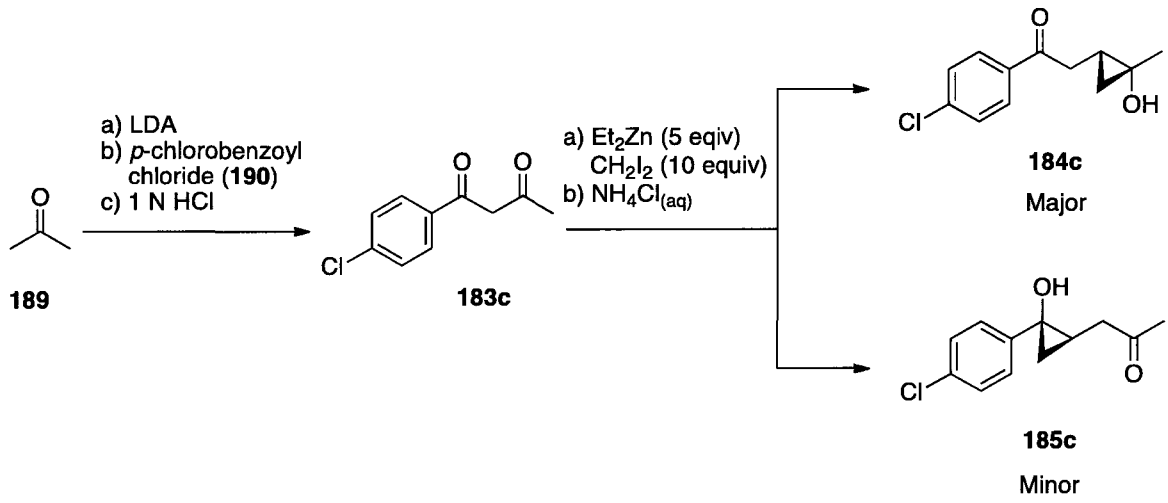




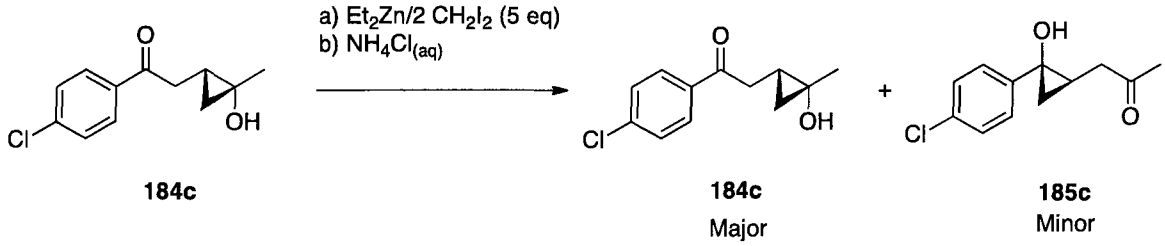
Scheme 62. Two possible pathways for the formation of a cyclopropanol

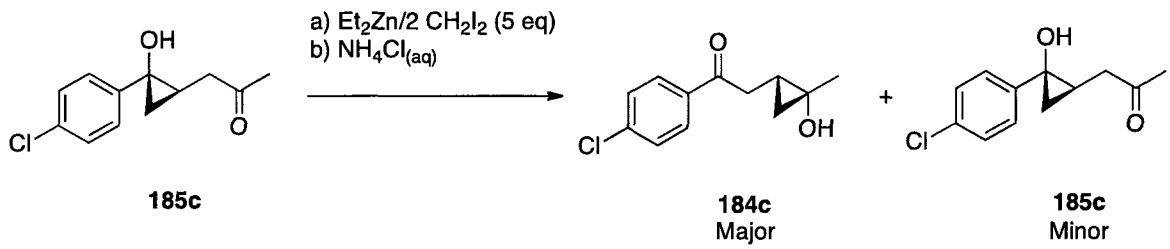
A chemical test to probe the hydroxy-cyclopropane rearrangement of compounds generated from non-symmetric 1,3-diketones was undertaken. Xue and co-workers had reported that 1-(4-chlorophenyl)butane-1,3-dione (**183c**) gave a 70:14 constitutional isomeric ratio when treated with an electrophilic zinc carbenoid ($CF_3COOZnCH_2I$) (**Table 2**), so this substrate was selected for our studies.[112] β-Diketone **183c** was synthesized through a mixed Claisen reaction between acetone (**189**) and *p*-chlorobenzoyl chloride (**190**) in a 38% yield (**Scheme 63**). When **183c** was subjected to bis (iodomethyl)zinc, the major (**184c**) and minor (**185c**) cyclopropanols, which were present in the crude reaction mixture in a 7:1 ratio, were separated via flash chromatography. Pure compound **184c** (major isomer) was reexposed to bis(iodomethyl)zinc and the ^1H NMR of the reaction product showed a mixture of the major (**184c**) and minor (**185c**)

cyclopropanol isomers (**Scheme 64**). In order to probe the reversibility of the rearrangement, it was necessary to take the minor isomer (**185c**) and demonstrate its conversion to the major isomer (**184c**). When pure **185c** (minor isomer) was introduced to bis(iodomethyl)zinc and the reaction worked up, cyclopropanol isomer **184c** was the major product, as determined by analysis of the crude ^{1}H NMR spectrum (**Scheme 64**).[113] This further established the likelihood that a rearrangement was occurring during the homologation-cyclopropanation reaction.



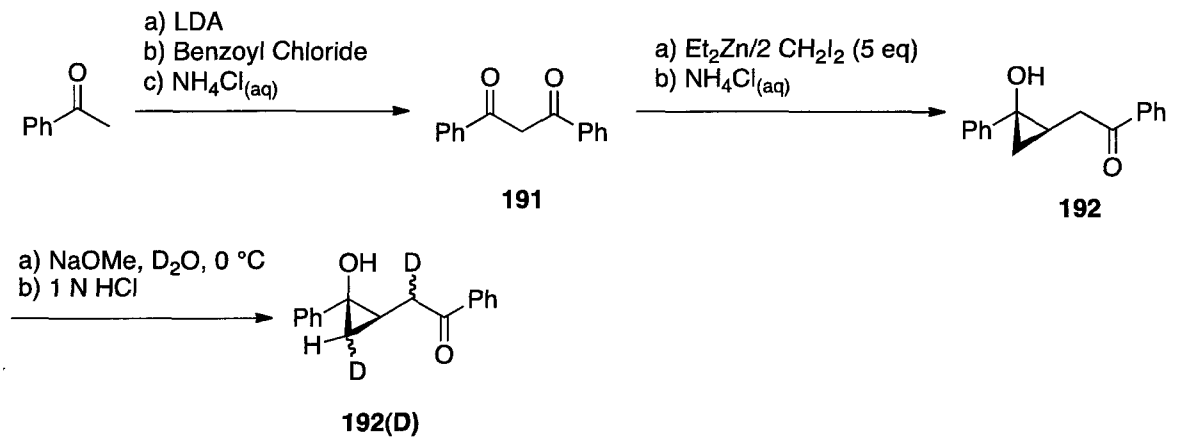
Scheme 63. Synthesis of **183c** followed by homologation-cyclopropanation





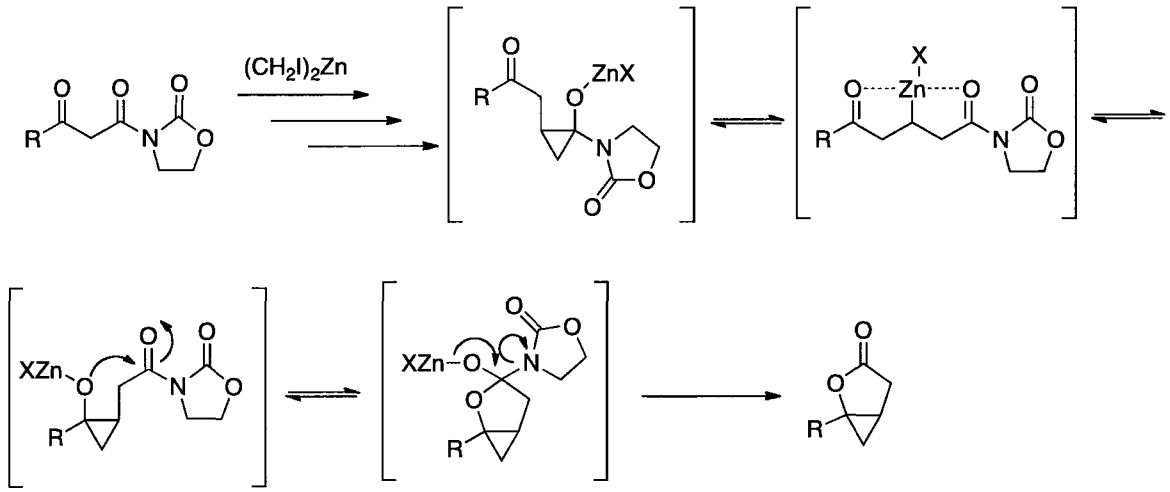
Scheme 64. Additional exposure to bis(iodomethyl)zinc

Employment of a C_2 symmetric 1,3-diketone and deuterium labeling would help provide further evidence of a possible rearrangement within the homologation-cyclopropanation reaction. A mixed Claisen reaction was the quickest route for the preparation of dibenzoylmethane (**191**). Acetophenone was deprotonated with LDA and transferred by cannula into a solution of benzoyl chloride and THF to obtain a 40% yield of dibenzoylmethane (**191**) (**Scheme 65**). Dibenzoylmethane (**191**) was then subjected to bis(iodomethyl)zinc and upon purification, a 67% yield of the 1,1,2-trisubstituted cyclopropanol was obtained (**192**) (**Scheme 65**). The cyclopropanol (**192**) was then added to a solution of sodium methoxide in deuterium oxide in an effort to exchange deuterium for hydrogen and to determine if base would catalyze the rearrangement. When analyzing the ^1H NMR spectra of the crude reaction mixture, the cyclopropyl (methylene) resonances, as well as the alpha proton resonances were diminished. The multiplicities of both resonances were also increased in complexity. This provided verification that deuterium was incorporated at both sites, which was consistent with the rearrangement proposed for the 1,3-diketone systems.



Scheme 65. Deuterium labeled control study

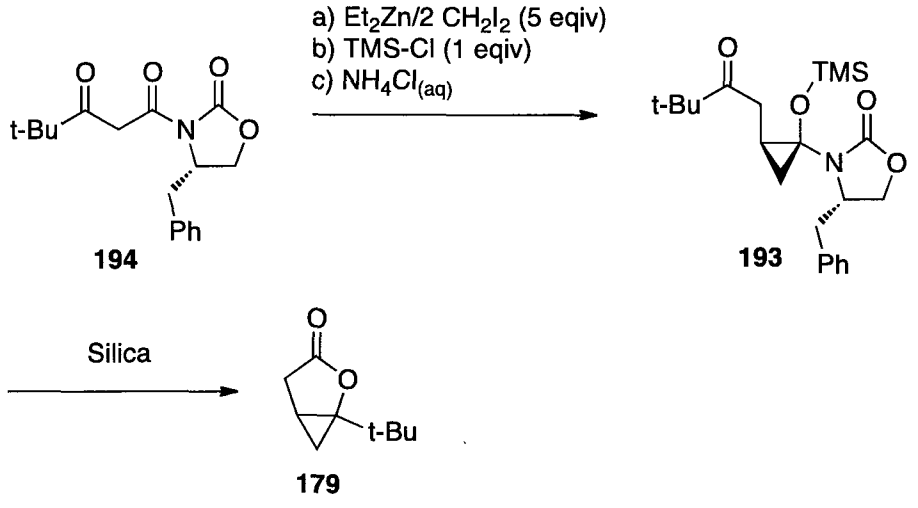
The results of the previous studies were used as a mechanistic guide for the homologation-lactonization reaction performed with bis(iodomethyl)zinc and β-keto imides. With the possibility that equilibration plays a role in the homologation-cyclopropanation reaction of diketones, we proposed that a similar rearrangement may also be involved in the reaction that leads to lactone formation. The mechanism is similar to that described for the β-diketone substrates, but incorporates a cyclopropoxide rearrangement involving the keto and imide moieties (**Scheme 66**). The reaction was then classified as a cascade-like reaction and was coined as the homologation-cyclopropanation-rearrangement-lactonization (HCRL) reaction.



Scheme 66. Proposed mechanism of the homologation-cyclopropanation-rearrangement-lactonization

In an effort to explore the hypothesis that rearrangement of cyclopropanes plays a role in the HCRL reaction, the intermediate cyclopropane (**193**) was trapped. Enolate facial selectivity in the formation of the homoenolate and in the addition to the imide carbonyl would expected to be influenced by the chiral oxazolidinone. Stoichiometric amounts of TMS-Cl were added to the HCRL reaction in order to trap the cyclopropoxide (**Scheme 67**). When attempting to purify the putative TMS-cyclopropyl ether (**193**) on a column, acid-catalyzed desilation occurred and the bicyclic lactone **179** was generated, possibly through rearrangement of cyclopropoxides (**Scheme 67**). Only 2% of the TMS-cyclopropyl ether **193** was isolated. When the TMS-intermediate was subjected to 2D TLC on silica, decomposition was confirmed to be problematic. The formation of **193** was performed again, and the silica used for column chromatography was basified with

treatment of 5 % triethylamine in ethyl acetate. When the reaction mixture was purified using the deactivated silica, the TMS-cyclopropyl ether (**193**) was isolated in a 44% yield.



Scheme 67. Decomposition of the putative TMS-cyclopropyl ether **193**

Upon ^1H NMR analysis of the crude reaction mixture of silylcyclopropyl ether **193** only one diastereomer was observed. After column chromatography, **193** was subjected to a pentane diffusion chamber and a single crystal was grown and analyzed by X-ray diffraction (**Figure 17**). Analysis of the crystal structure revealed that diastereomer **193** was preferentially formed, consistent with the enolate facial selectivity reported by Lin and Lai.[46,47]

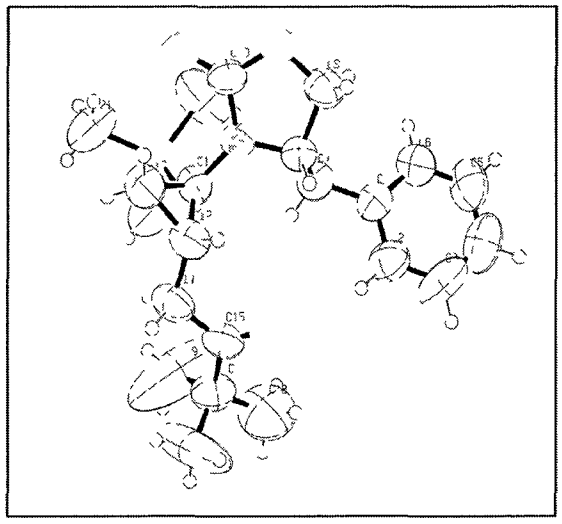
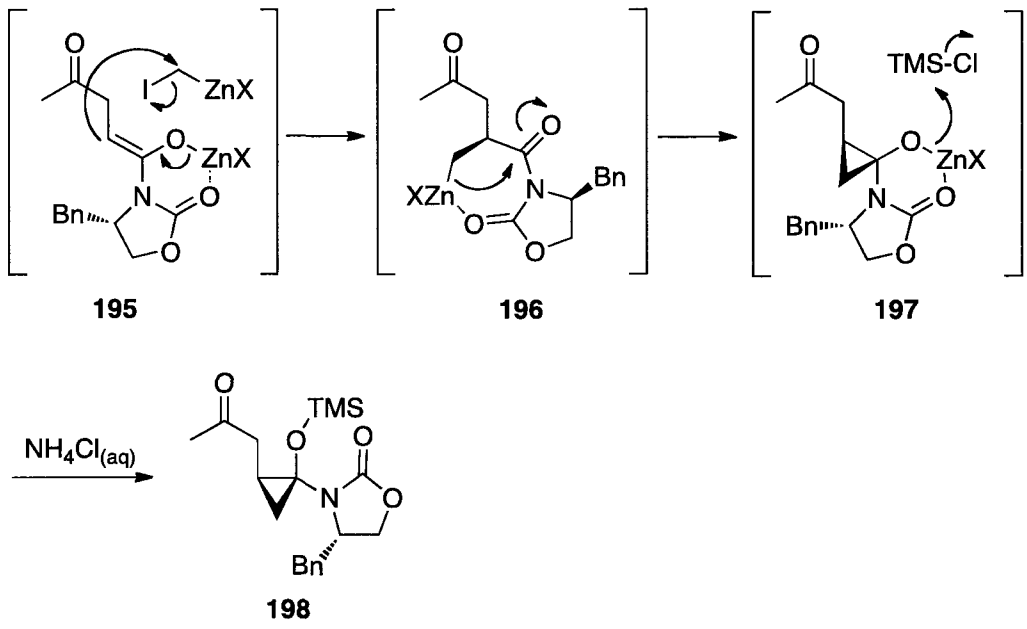


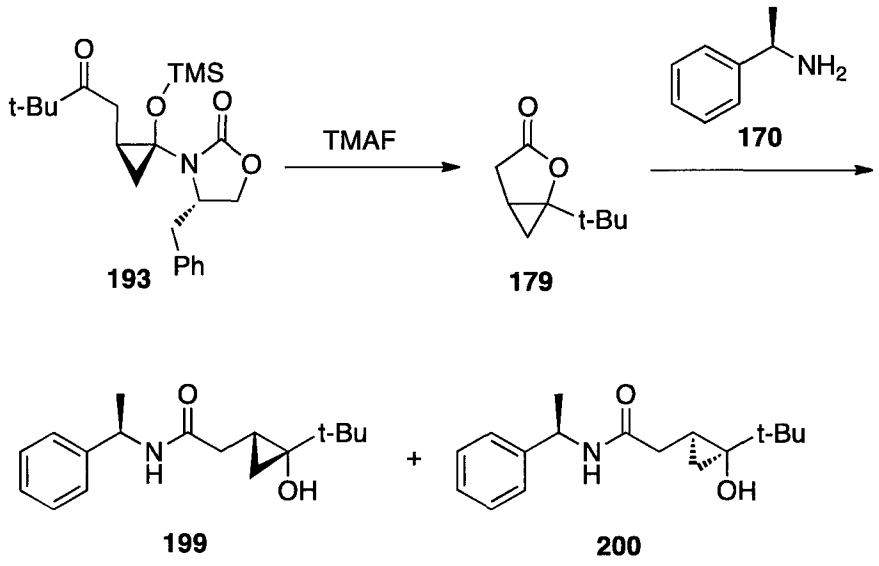
Figure 17. X-ray crystal structure depicting the absolute stereochemistry of the TMS-cyclopropyl ether **193**

Use of the sterochemical information provided by the X-ray structure (**Figure 17**) a mechanism was proposed (**Scheme 68**). The starting chiral β-keto imide **194** was homologated in accordance with the previous mechanism (**Scheme 44**). The *Z*-enolate (**195**) would be predicted to form due to 1,3-allylic strain of the *E*-enolate. The diastereoselective alkylation to form the zinc homoenolate (**196**) would be directed by the chirality of the imide functionality. Chelation of zinc (II) by the imide carbonyls would increase the electrophilicity of the imide carbonyl, which would be suitable for the homoenolate (**196**) attack. The cyclopropyl alkoxide (**197**) could O-silate with TMS-Cl in solution to yield the TMS protected cyclopropanol (**198**). Alternatively, the TMS-group could be complexed with the carbonyl prior to cyclopropanation.



Scheme 68. Proposed diastereoselective mechanism for the formation of **198**

In an effort to generate the free alcohol, treatment of **193** with trifluoroacetic acid (TFA) resulted in decomposition of **193** presumably by decomposition of the cyclopropane. However, use of tetramethylammonium fluoride (TMAF) as a desilating agent did remove the TMS group and produced the bicyclic lactone **179** (**Scheme 69**). Production of a naked anion was followed by rearrangement and lactonization. To test the stereochemical fidelity of the resulting bicyclic lactone (**179**), α-(methyl)benzyl amine was employed. The diastereomeric ratio of the opened bicyclic lactones (**199** and **200**) was determined to be ~2.3:1. Therefore, even when the first alkylation-cyclopropanation was controlled, the resulting lactone **179** stereochemical fidelity was compromised.



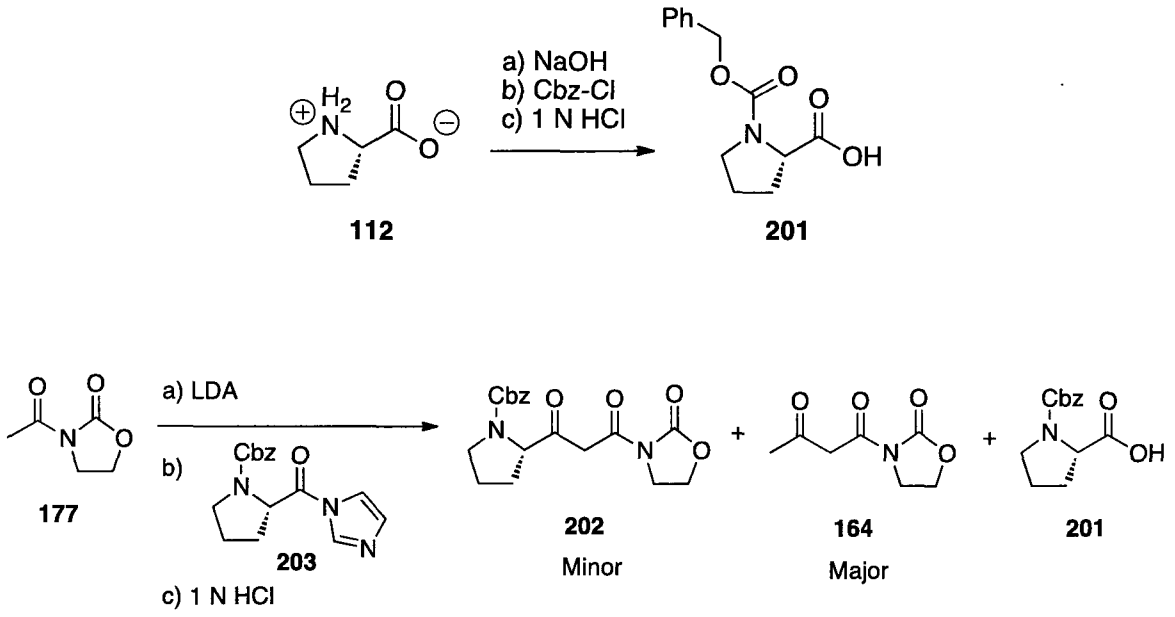
Scheme 69. TMAF induced Desilation-rearrangement-lactonization

The chirality within the oxazolidone moiety of the β-keto imide provided minor stereocontrol in the HCRL reaction. Jennifer Mazzone, a research student in the Zercher laboratory, has developed a methodology by which to control β-stereochemistry when using a methyl substituted zinc carbenoid in the homologation of β-keto esters. Although incorporation of a phenylalanine or valine stereocenter adjacent to the ketone provided modest diastereocontrol, serine-derived substrates were quite effective.[114] Using this result as a guide, the next target was the synthesis of an amino acid-derived β-keto imide.

Synthesis of amino acid-derived β-keto imides

Amino acid derived β-keto imides have been synthesized by previous Zercher members.[115] The researchers used a mixed Claisen reaction, which was often quite

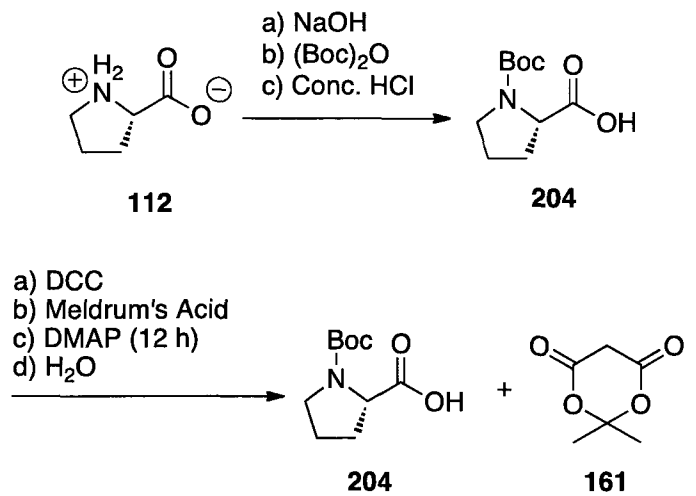
challenging. Drawbacks to the mixed Claisen include difficulty in reproducibility, the necessity of using excess starting enolate, expense, and difficulty in purification. The reaction was, however, direct and would give the desired amino acid-derived β-keto imide. A test reaction was conducted with L-proline (**112**), in which L-proline (**112**) was protected as the benzyl carbamate (**201**) in order to facilitate conversion to the β-keto imide (**202**) (**Scheme 70**). Acylated 2-oxazolidinone (**177**) was slowly added to a solution of LDA, which was then quickly transferred by cannula to a flask that contained carbonyl diimidizole (CDI)-activated Cbz-proline (**203**). The resulting solution was stirred at room temperature for thirty minutes and quenched with 1 N HCl. Upon purification, starting material, Cbz-proline (**201**), and 1-(2-oxooxazolidin-3-yl) butane-1,3-dione (**164**) were isolated as the major products. The desired product, (*S*)-benzyl-2-(3-oxo-3-(2-oxooxazolidin-3-yl)propanoyl)pyrrolidine-1-carboxylate (**202**) was isolated in a 23 % yield (**Scheme 70**). The low yields and necessity of using three equivalents of acylated 2-oxazolidinone made this route very unattractive.



Scheme 70. Cbz-protection of L-proline followed by a mixed Claisen reaction

When consulting the literature for additional methods for synthesizing **202**, a reaction that used Meldrum's acid adducts was found to provide enantioselective tetramic acid derivatives from amino acids.[116, 117] Jouin's protocol starts with *N*-protected amino acids and uses *N,N*-dimethylaminopyridine (DMAP) and *N,N'*-dicyclohexylcarbodiimide (DCC) under neutral conditions to acylate Meldrum's acid. Thermolysis results in intramolecular cyclization that leads to the corresponding tetramic acid in quantitative yield. In order to prevent tetramic acid formation, amino acid substrates must not possess a free N-H. Double protection of amino acids or use of a mono-protected proline residue would allow use of this method without concern of tetramic acid formation. The procedure reported by Jouin and co-workers for the coupling and isolation of the Boc-proline functionalized Meldrum's acid adduct was employed; however, upon analysis of

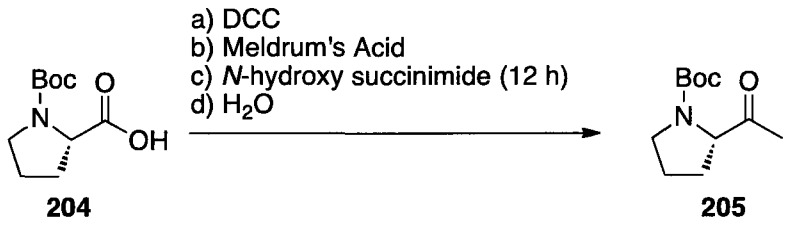
the ^{1}H NMR spectrum of the crude reaction mixture, only starting material was observed (**Scheme 71**).



Scheme 71. Initial coupling attempt

Several research groups have reported the use of acylated Meldrum's acid produced from carboxylic acids, but these substances are primarily noncharacterized intermediates that are used for the preparation of β-keto esters and amides.[118,119] *N*-Hydroxysuccinimide has also been reported to be an efficient substitute for DMAP in the acylation of Meldrum's acid with DCC.[120] The reaction was performed using *N*-hydroxy succinimide and the resulting ^{1}H NMR showed evidence of acylated Boc-proline (**205**), which indicated that Meldrum's acid was being acylated, but addition of water was followed by loss of two equivalents of carbon dioxide and acetone was providing the methyl ketone (**205**) (**Scheme 72**). The same reaction was carried out using *N*-

hydroxybenzotriazole as the nucleophilic additive, but when the reaction was worked up under neutral aqueous conditions the decomposition was still observed. The formation of acylated Boc-proline derivative (**205**) appeared to be occurring, although decomposition of the Meldrum's acid adduct appeared to be unavoidable.



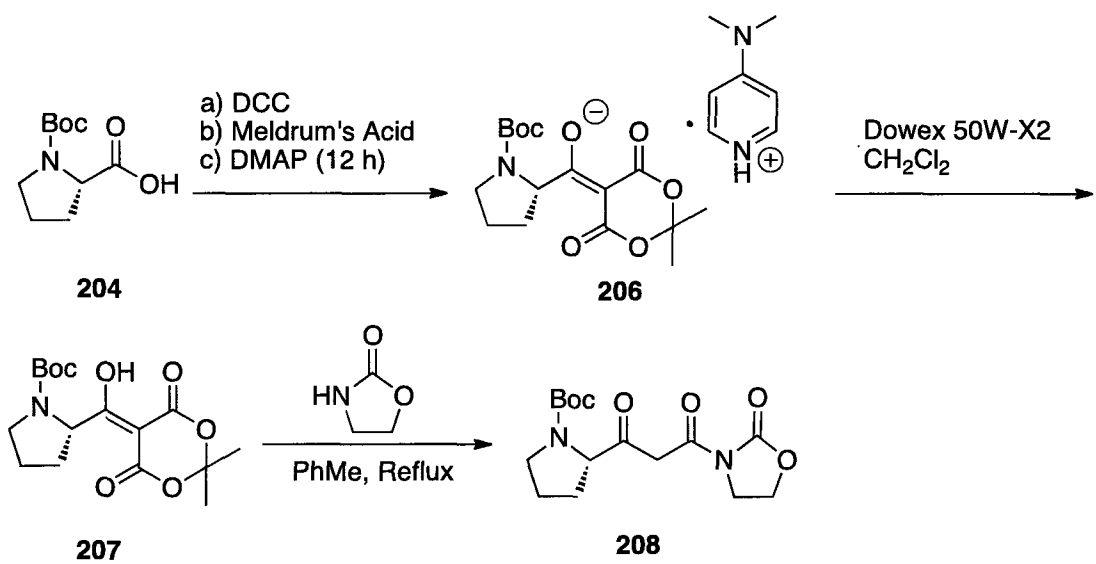
204 **205**

Scheme 72. Use of *N*-hydroxy succinimide as a nucleophilic additive

Lastly, Raillard and co-workers reported the mild coupling of carboxylic acids to Meldrum's acid, in which they reported that the conventional aqueous work-up of the Meldrum's adduct results in decomposition of product.[121] Their use of DMAP provided the DMAP salt of the Meldrum's acid adduct, which was shown to have high stability. Raillard reported that the DMAP-Meldrum's acid salts could be suspended in deuterated chloroform at room temperature for six months with only 10 % decomposition. Raillard treated the salt with an acidic polymeric residue to generate the free Meldrum's acid adduct, which was then refluxed in toluene with dibenzylamine to afford the corresponding amino acid-derived β-keto amide.

Using Raillard's methodology, activation of Boc-proline (**204**) with stoichiometric amounts of DCC, and displacement of the cyclohexylurea by Meldrum's acid followed

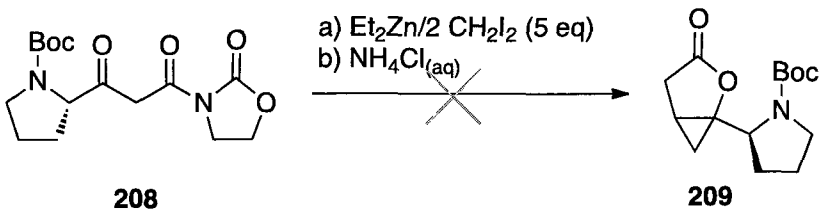
by addition of DMAP resulted in the clean formation of the DMAP salt of the Boc-proline-Meldrum's acid adduct (**206**) in 89% yield. Use of DOWEX® 50W-X2 ion exchange resin released the free acid of Boc-proline-Meldrum's Acid (**207**), which was immediately exposed to 2-oxazolidone in toluene. The reaction mixture was heated to reflux for one hour, which yielded Boc-proline derived β-keto imide (**208**) (**Scheme 73**). The Meldrum's acid coupling route was run on a larger scale to obtain gram quantities of **208**.



Scheme 73. Meldrum's acid coupling

β-Keto imide **208** was subjected to the HCRL reaction in the presence of bis (iodomethyl)zinc in an effort to form the Boc-proline-derived bicyclic lactone (**209**) (**Scheme 74**); however, no bicyclic lactone was isolated. From analysis of the ^{1}H NMR

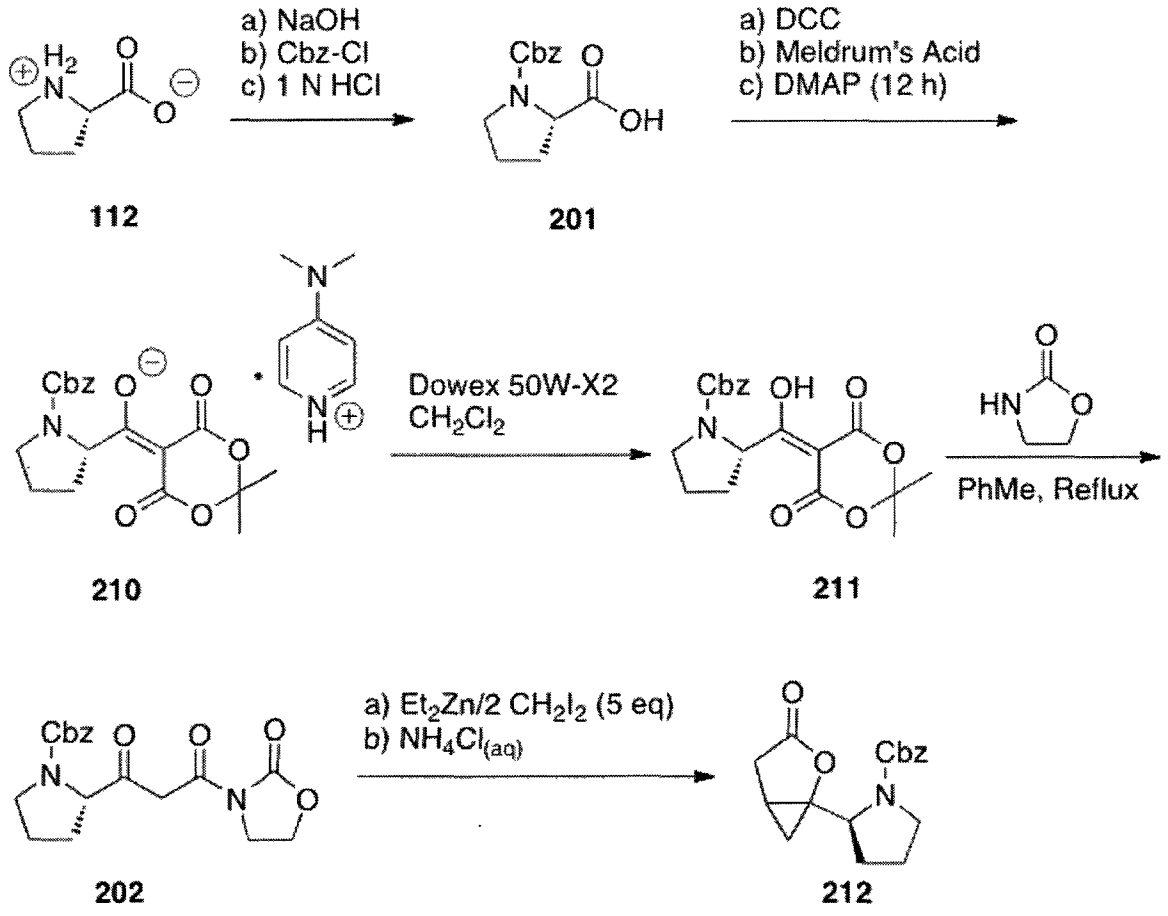
of the crude reaction mixture, the Boc moiety seemed to have been lost, and a complex mixture of products were formed.



208 **209**

Scheme 74. HCRL of β-keto imide **208**

Since loss of the *t*-butyl carbamate had occurred, possibly due to the Lewis acidity of the zinc (II) salts,[122] the use of a benzylcarboxy (Cbz) moiety as an alternative protecting group was explored. Protection of L-proline (**112**) with Cbz-Cl resulted in the formation of *N*-Cbz-proline (**201**) (**Scheme 75**). Upon addition of DCC, Meldrum's acid, and DMAP the resulting DMAP salt (**210**) was isolated in 89% yield. The salt was exposed to Dowex® 50W-X2 ion exchange resin to release the free acid (**211**) (**Scheme 75**). Upon refluxing with toluene in the presence of 2-oxazolidone, the Cbz-proline derived β-keto imide (**202**) was isolated in 82% yield (**Scheme 75**). β-Keto imide **202** was subjected to the HCRL reaction in the presence of bis(iodomethyl)zinc to generate the Cbz-proline-derived bicyclic lactone (**212**) (**Scheme 75**).

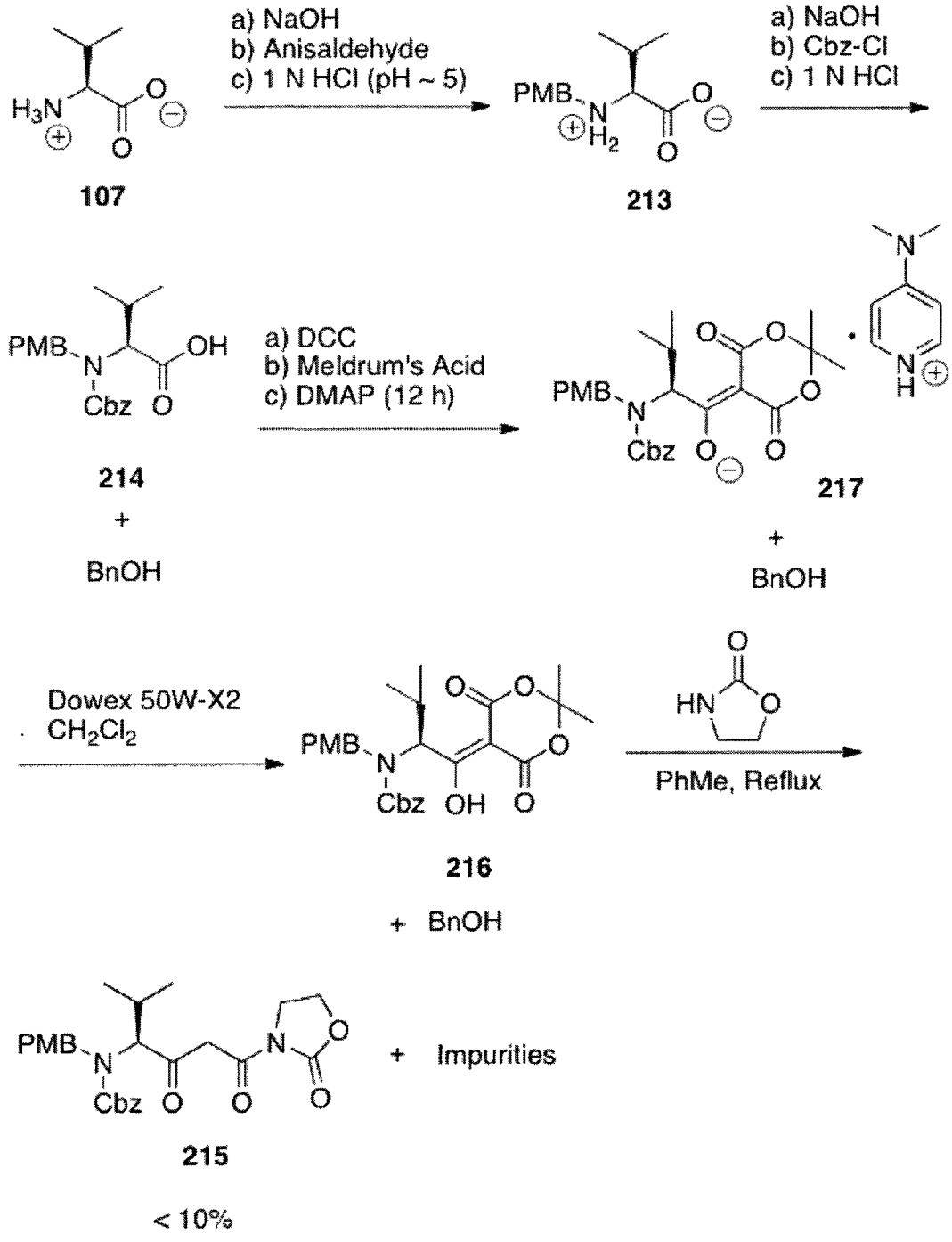


Scheme 75. Use of the Cbz-carbamate to form an amino acid derived bicyclic lactone

With successful optimization of the formation of the proline-derived β-keto imide (**202**), various amino acid derived β-keto imide analogs could be synthesized by application of the same approach. The next amino acid to be taken through to the Meldrum's acid coupling scheme was L-valine (**107**), which has a primary amine that required diprotection in order to prevent formation of tetramic acids. The use of *p*-methoxybenzyl (PMB) as a protecting group in the zinc homologation reactions has proven to be quite effective. A PMB group was incorporated via a reductive amination

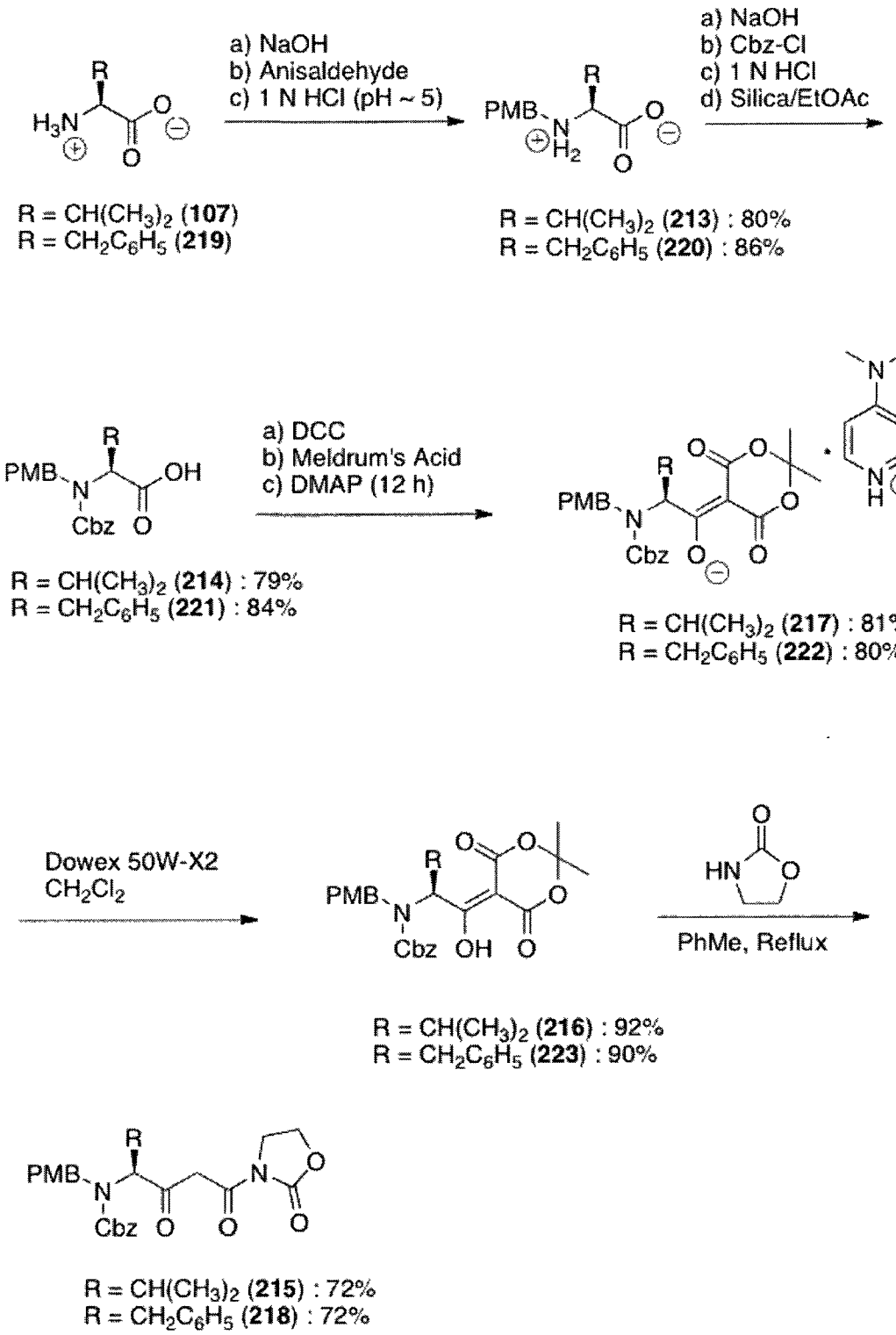
with anisaldehyde and L-valine (**107**). PMB-valine (**213**) was then subjected to sodium hydroxide and Cbz-Cl which afforded the diprotected amino acid (**214**) in an overall 91 % yield (**Scheme 76**).

When crude **214** was subjected to the Meldrum's acid coupling procedure followed by nucleophilic addition with 2-oxazolidone, the isolated yield of imide (**216**) was low and numerous by-products were observed via TLC (**Scheme 76**). When repeating the di-protection of L-valine (**107**) (**Scheme 76**), benzyl alcohol was observed as a byproduct. Alcohols and amines act as nucleophiles during the ring opening of Meldrum's acid adducts.[104] If benzyl alcohol were in solution with 2-oxazolidone during the reflux of **216** in toluene, this would help explain the presence of additional by-products.



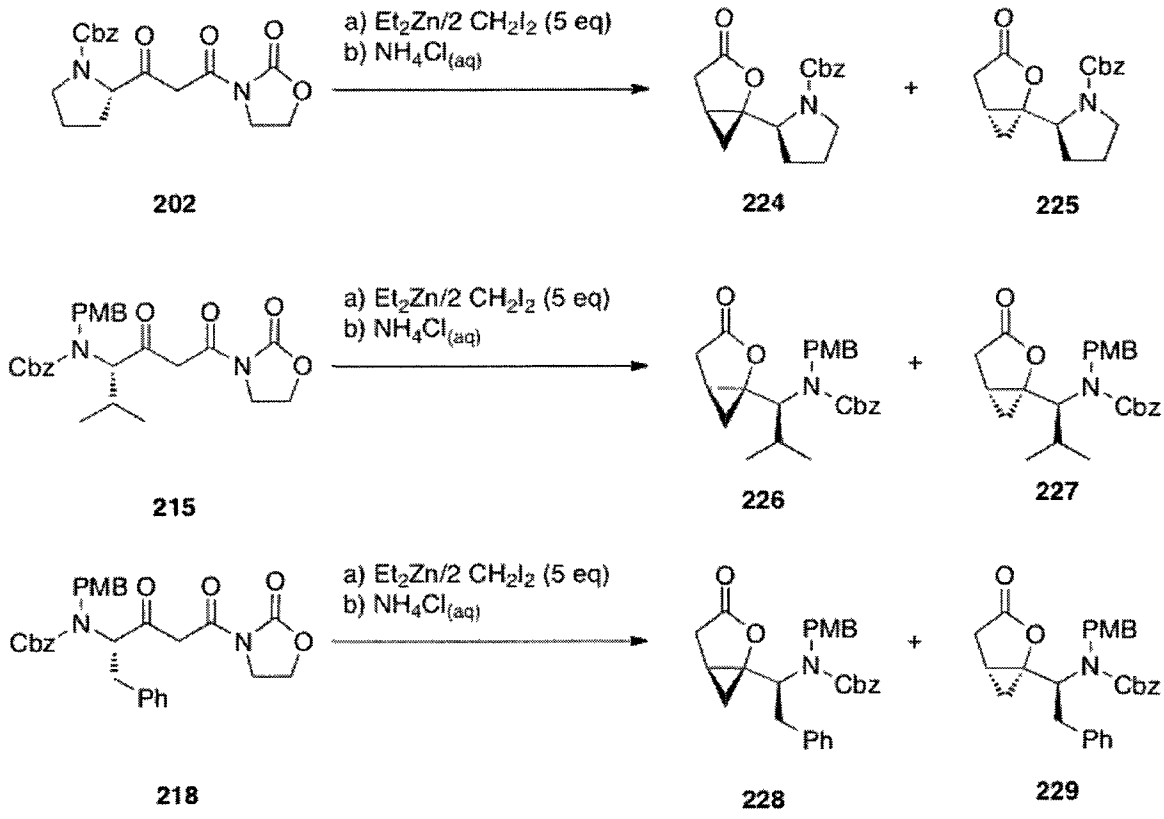
Scheme 76. Problematic synthesis of **215**

To remove the benzyl alcohol contaminat from the *N,N*-PMB-Cbz-valine (**214**), a short silica plug was employed to afford pure **214** in 79 % yield (**Scheme 77**). Exposure of **214** to the Meldrum's acid coupling reaction, was followed by and ring opening with 2-oxazolidone. Clean formation of the *N,N*-PMB-Cbz-valine β-keto imide (**216**) (**Scheme 77**) was observed in high yield. This procedure was repeated with phenylalanine to obtain the *N,N*-PMB-Cbz-phenylalanine β-keto imide (**218**) (**Scheme 77**).



Scheme 77. Clean synthesis of β-keto imides **215** and **218**

The three β-keto imides (**202**, **215**, and **218**) were subjected to the HCRL reaction and the bicyclic lactones (**224-229**) were isolated in good yields (**Scheme 78**). These bicyclic lactones are formed as mixtures of diastereomers. The determination of the cyclopropane diastereomeric ratio should be available from the ^{1}H NMR of the crude reaction mixture after the HCRL reaction. Unfortunately, analysis of the proline-derived bicyclic lactones **224** and **225** were complicated by rotomeric forms and by-products, therefore no definitive resonances could be identified for quantitatively assessing the diastereomeric ratio. This was also the case with the valine and phenylalanine adducts (**226-229**). The two diastereomers of the phenylalanine adduct (**228** and **229**) could be separated by column chromatography, which provided the two diastereomers in a 6:1 ratio.

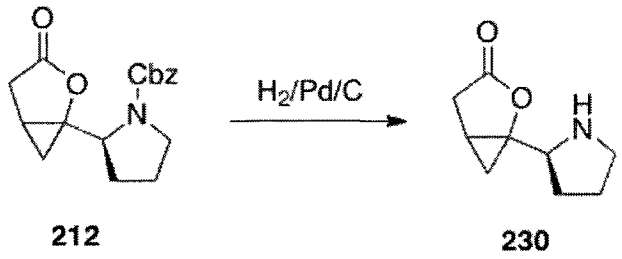


Scheme 78. HCRL on amino acid derived β-keto imides

Determination of the major bicyclic lactone

In an attempt to determine the major diastereomer isolated from the HCAL reaction many methods were utilized. The first was to subject the proline-derived lactone **212** to a hydrogenolysis reaction to remove the benzyl carboxy protecting group (**Scheme 79**). The removal took place in thirty minutes with hydrogen/palladium on carbon in a 94 % yield. After concentration the pyrrolidine lactone (**230**) was observed as an oily solid. When **230** was placed into a diffusion chamber (benzene/pentane) decomposition was

observed after twelve hours, presumably due to the free amine present within lactone **230**.

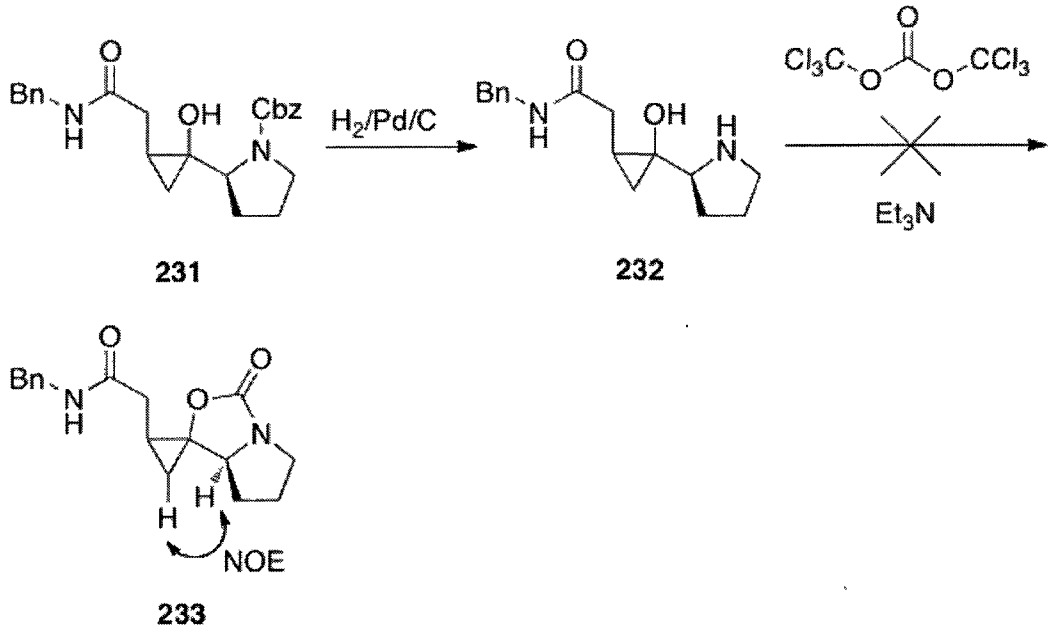


212 **230**

Scheme 79. Hydrogenolosis of bicyclic lactone **212**

With decomposition in a short period of time, formation of a single packed crystal was going to be complicated and demanding. The free amine was thought to contribute to the decomposition of the bicyclic lactone **230**. A hydrogenolysis of **212** performed in the presence of *p*-toluenesulfonic acid would trap the free amine as the ammonium salt. After the reaction was performed, decomposition of the cyclopropyl resonances in the crude ^{1}H NMR were observed and no product was formed.

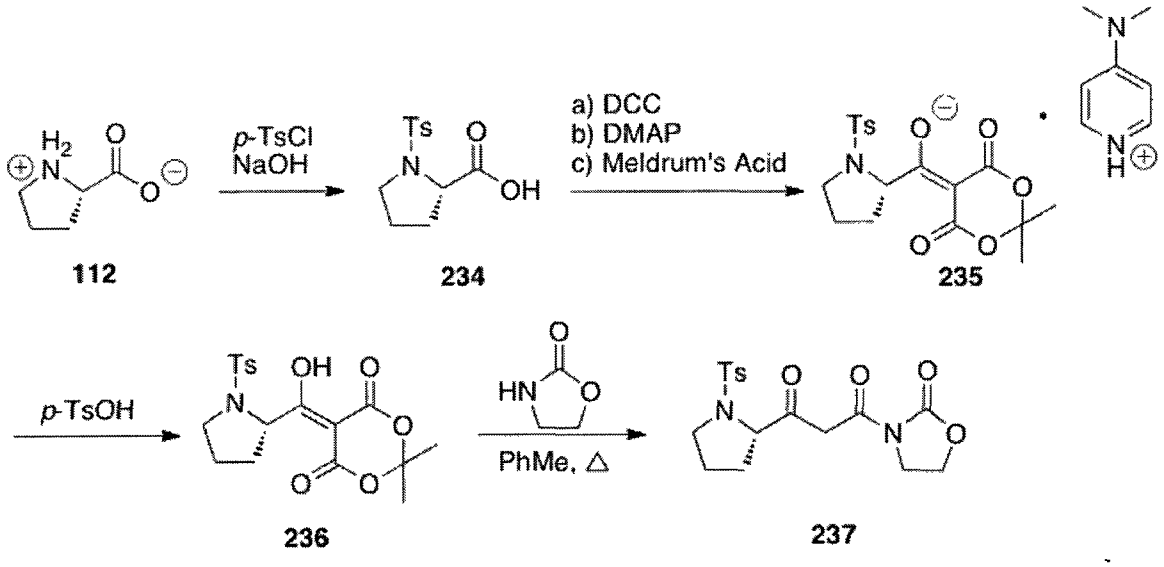
Deprotection of the benzyl carbamate on **231** followed by an intramolecular cyclization to afford oxazolidone **233** was thought to provide rigidity and allow for NOE studies (**Scheme 80**). After hydrogenolysis of **231**, triphosgene was used in an effort to form **233**. After a neutral work up decomposition of starting compound **232** was observed through ^{1}H NMR. This approach was then terminated due to the reactivity of triphosgene.



Scheme 80. Attempt at an oxazolidinone formation for NOE studies

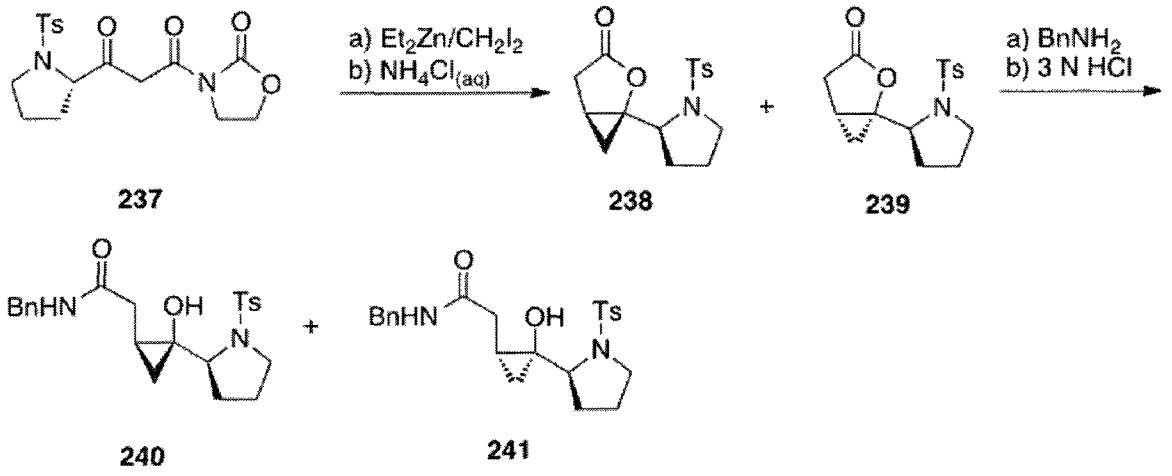
After deprotection of lactone **212**, the free amine was subjected to *p*-toluenesufonyl chloride in the presence of triethylamine. This again resulted in decomposition and complete loss of the pyrrolidine lactone **230**. Another strategy was to incorporate a sulfonamide functionality prior to formation of the β-keto imide and homologation. This was performed by protecting L-proline with *p*-toluenesufonyl chloride in aqueous sodium hydroxide as the sulfonamide (**234**).[123] Tosyl-proline (**234**) was then subjected to a coupling conditions to form an acylated Meldrum's acid adduct (**235**) as the DMAP salt. Removal of the DMAP salt to form the free acid (**236**) was done with dry *p*-toluenesulfonic acid. The free acid **236** and 2-oxazolidone were refluxed in

toluene to afford the sulfonamide-derived β-keto imide (**237**) in a 50% overall yield (**Scheme 81**).



Scheme 81. Formation of sulfonamide-derived β-keto imide **237**

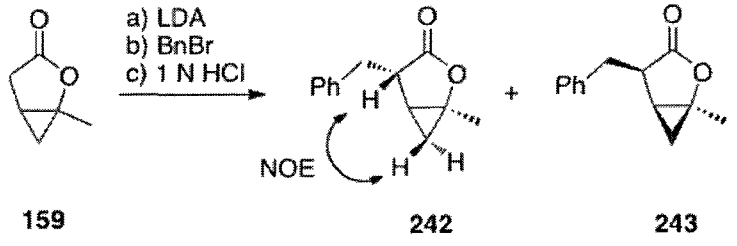
β-keto imide **237** was then subjected to the HCRL reaction conditions to obtain to bicyclic lactones **238** and **239** that coeluted together off of the column. The diastereomeric mixture was concentrated down to afford the lactones (**238** and **239**) as white solids (**Scheme 82**). Opening the lactones with neat benzylamine provided the *N*-tosylated cyclopropanols (**240** and **241**) in 90% yield (**Scheme 82**). The diastereomers were separated through flash chromatography to afford the minor diastereomer as a white solid and the major as a clear oil.



Scheme 82. Formation of bicyclic lactones **238** and **239** followed by ring opening

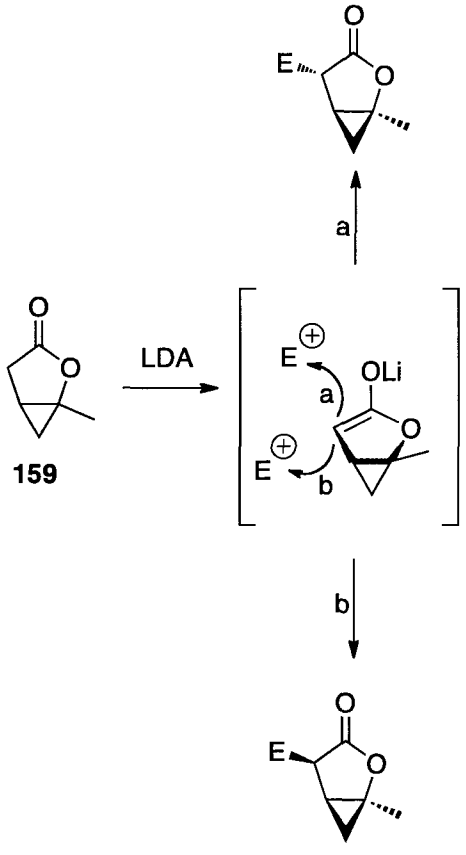
Alkylation and opening of bicyclic lactones

Functionalizing the α-carbon of bicyclic lactones would be necessary to demonstrate the ability to incorporate substituents that would mimic amino acid side chains in the peptide isostere. The lactone **159** provided a suitable template for incorporating the side chain by alkylation of an enoloate. Bicyclic lactone **159** was exposed to LDA and benzyl bromide as a test reaction (**Scheme 83**).



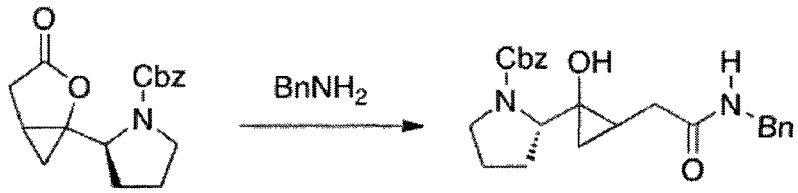
Scheme 83. Alkylation of **159**

Analysis of the ^{1}H NMR of the crude reaction mixture revealed that two diastereomers (**242** and **243**) were produced in a 5:1 ratio (**Scheme 83**). The major diastereomer was determined to be **242** through the use of NOE experiments (**Scheme 83**). Diastereomer **242** was formed by approach of the electrophile opposite to the sterically-encumbering cyclopropane fused to the lactone (**Scheme 84**).



Scheme 84. Cyclopropane influenced stereocontrol

The amino acid derived bicyclic lactones can be transformed into structures that may have utility as peptide isosteres. An efficient method for the opening of the lactones was through exposure to neat benzylamine. This procedure was mild and high yielding, and did not result in the decomposition of the hydroxy-cyclopropyl moiety (**Scheme 85**). With the ability to open the bicyclic lactones simply and efficiently, most primary and secondary amines could be incorporated as part of the amide functionality. Use of these amine residues could help establish a library of peptide isosteres that would help determine the optimal binding mode for a select aspartyl protease.



212 231

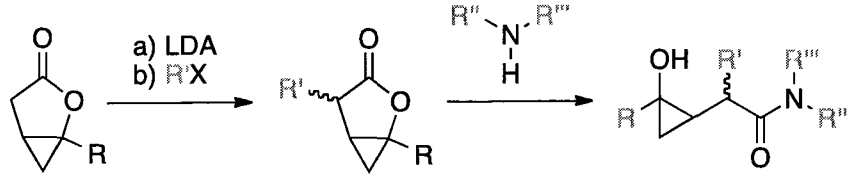
Scheme 85. Hydroxy-cyclopropyl isostere

Future Work

The hydroxy-cyclopropyl moiety provides structurally unique characteristics that may be useful in viral inhibition. One major limitation to many peptide amide isosteres is their ability to freely rotate, which is believed to compromise selectivity and binding. Also, the loss of hydrogen bond donor/acceptor interactions within the active site can

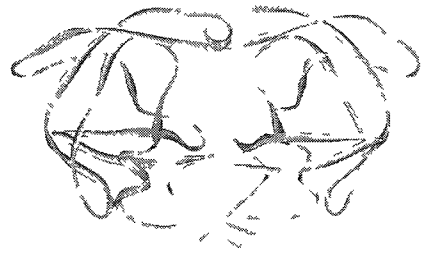
cause the peptide isosteres to exhibit a high K_i. Successful inhibition of HIV protease has been accomplished with only one of those features satisfied. For example, Indinavir (**132**) is a hydroxyethylene containing isostere, which functions as an effective inhibitor even though free rotation about the carbon-carbon bond is possible.[124] Use of the hydroxy-cyclopropyl motif embedded within a selective peptide could provide low K_i with the ability to easily modify any amino acid within the sequence of the peptide (**Scheme 86**).

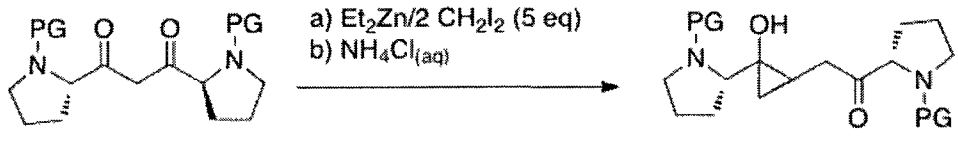
Chemical modification of a protease inhibitor is extremely important with respect to the viron HIV. The mutation of HIV's protease causes many of the pharmaceutical medications to become inactive and, therefore, of no use to the patient. Mutation of one amino acid within the viron's aspartyl protease can cause enough distortion within the binding site to make a therapeutic agent inactive. The ability to modify amino acid residues to include the hydroxy-cyclopropyl peptide isostere provides the opportunity to explore a family of potential protease inhibitors. There is the possibility of functionalizing the carbon adjacent to the cyclopropyl moiety allowing for the simple derivatization to satisfy different modes of binding within the protease's binding pocket (**Scheme 86**).



Scheme 86. Chemical modifications

Another tactic that is being pursued in the Zercher research group is to synthesize a symmetric amino acid derived β-diketone **244** and to subject it to the homologation-alkylation-cyclopropanation reaction (**Scheme 87**). β-Diketones have been shown to homologate and form cyclopropanol analogs.[106] Incorporation of symmetry within the scaffold of the HIV protease inhibitors has proven to be an effective approach due to the symmetric nature of the HIV protease (**Scheme 87**).[125] The homologation-alkylation-cyclopropanation reaction as performed on the amino acid-derived symmetric β-diketone would provide a one step method to form unusual cyclopropanol analogs (**245**).

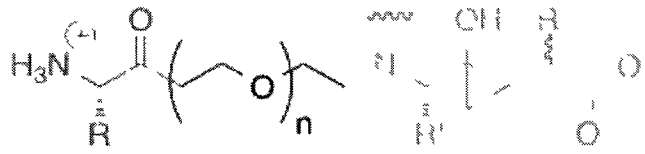




244 **245**

Scheme 87. HIV's symmetric aspartyl protease and a one step synthesis toward peptide isosteres

Another strategy that could be employed when opening the bicyclic lactone derivatives is the use of an amino acid residue. Nucleophilic addition of an amino acid to the bicyclic lactone would diversify the derivatization process and provide an expanded library of these novel isosteres. If a cyclopropyl isostere displays a reasonable efficacy (E_{max}), adding an amino acid tethered polyethylene glycol (PEG) unit to the amino terminous could aid in the allosteric modulation of an aspartyl protease. Using a PEGylated cyclopropanol isostere with high affinity to the known binding site in an aspartyl protease would probe the possible allosteric sites within the proximity to help establish a new tactic in aspartyl protease inhibition (**Scheme 88**).



Scheme 88. Allosteric modulation design

The use of the HCRL methodology with β-keto substrates provides the synthetic chemist with a plethora of routes to obtain potential peptide mimics. The ability to manipulate and derivatize a lead compound is a crucial element of designing pharmaceutical compounds. The HCRL methodology developed in the Zercher lab allows for the functionalization of all of the substituents attached to the hydroxy-cyclopropyl backbone.

CHAPTER IV

EXPERIMENTAL SECTION

Solvents

Anhydrous solvents were obtained from an Innovative Technology Inc. Solvent Delivery System prior to use.

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, phosphomolybdic acid stain, anisaldehyde stain, or an iodine chamber. 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 reported downfield relative to TMS, which was assigned 0.00 ppm for both ^{1}H and ^{13}C NMR analysis.

DETAILED EXPERIMENTAL SECTION

(2*S*,3*R*)-Methyl 5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carboxylate (72)

CAUTION! Neat diethylzinc will ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen. The reaction solvents must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

An oven-dried, 100-mL single-necked, round-bottomed flask equipped with a stir bar was charged with 30 mL of dry methylene chloride and capped with a septum. The solution was stirred under an inert atmosphere of nitrogen, which was provided through a needle inserted into the septum. The solution was cooled to 0°C (ice bath temperature) and neat diethylzinc (0.67 mL, 6.6 mmol) was added slowly by syringe over a period of 5 min.

Methylene iodide (0.53 mL, 6.6 mmol) was added by syringe dropwise. The mixture was allowed to stir for 10 min and methyl acetoacetate (0.32 mL, 3 mmol) was added in one portion by syringe. The β-keto ester was stirred in the carbenoid for 30 min, at which time butyraldehyde (0.27 mL, 3 mmol) was added by syringe. The reaction was allowed to proceed for 15 min and then quenched with a saturated solution of ammonium chloride and allowed to warm to room temperature by removal of the ice bath. The quenched reaction mixture was extracted with diethyl ether (3 x 30 mL). The ethereal extracts were dried over magnesium sulfate (*ca.* 10 g), filtered and evaporated affording **72** as a bright yellow oil. After column chromatography (hexane:ethyl acetate 1:15, R_f = 0.3) 0.45 g (75%) of (2*S*,3*R*)-methyl 5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carboxylate (**72**) was isolated as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (q, *J* = 5.6, 2H), 4.19 (ddd, , *J* = 11.5, 9.5, 3.1, 2H), 3.92 (m, 1H), 3.74 (s, 3 H), 3.70 (s, 3H), 2.5 (m, 3H), 2.09 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.44 (m, 7 H), 0.96 (t, *J* = 7.2, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.46, 176.81, 174.74, 173.97, 105.05, 105.00, 82.75, 82.66, 81.19, 81.16, 77.62, 77.30, 76.98, 71.47, 71.32, 52.76, 52.58, 52.26, 52.07, 49.09, 48.84, 48.73, 46.22, 42.81, 41.65, 41.53, 41.41, 40.21, 39.49, 38.01, 37.15, 27.88, 27.32, 26.59, 26.55, 19.35, 19.22, 18.90, 14.17, 14.08. IR (neat) ν 3345, 2900, 2255, 1701, 1423, 1333, 1202, 1195 cm^{-1}.

Methyl 5-allyl-tetrahydro-5-methyl-2-propylfuran-3-carboxylate (85 and 86)

An oven-dried, 50-mL, one-necked, round-bottomed flask equipped with a magnetic stiring bar was charged with dry methylene chloride (20 ml, 20 mL/mmol). The neck of

the round-bottomed was fitted with a septum and equipped with a gas inlet adapter attached to a nitrogen source. Methyl 3-hydroxy-2-(propyl-2-one)-hexanoate (**3**) (0.17g, 0.86 mmol) was added to the solution of methylene chloride via syringe. Allyl trimethylsilane (0.27 mL, 1.72 mmol) was added to the solution via syringe. This solution was then cooled down to -78°C with a dry ice acetone bath. Once the reaction reached -78 °C, $BF_3 \cdot Et_2O$ (0.324 mL, 2.58 mmol) drop wise to the solution and allowed to stir at -78 °C for 12 h. The solution was then allowed to warm to room temperature and was quenched with water (5 mL, 5mL/mmol), at which time the reaction mixture was transferred to a separatory funnel. The lower organic layer was withdrawn and placed in an Erlenmeyer flask. The aqueous washing was extracted with diethyl ether (3 x 30 mL) and the combined organic layers are dried over 20 g of anhydrous magnesium sulfate and filtered prior to concentration under reduced pressure. This gave 0.131 g. of **85** and **86**, in a 75.5% yield as a clear oil with a diastereomeric ratio of 2:1.5 determined from ^1H NMR of the crude reaction material. ^1H NMR (400 MHz, $CDCl_3$) δ: (**85**) 0.91 (t, 3 H, J = 7.3), 1.19 (s, 3 H), 1.62-1.30 (m, 2 H), 2.78 (q, 1 H, J = 9.1), 3.69 (s, 3 H), 4.05 (m, 1 H), 5.07 (m, 2 H), 5.82 (m, 1 H). (**86**) 0.918 (t, 3 H, J = 7.2), 1.26 (s, 3 H), 1.62-1.30 (m, 2 H), 2.70 (q, 2 H, J = 9.2), 3.68 (s, 3 H), 4.05 (m, 1H), 5.07 (m, 2 H), 5.82 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.07, 134.63, 134.56, 118.07, 118.01, 82.23, 81.12, 80.92, 80.85, 80.63, 80.44, 77.57, 77.25, 76.93, 52.06, 52.02, 50.20, 50.01, 49.78, 49.71, 49.65, 49.02, 48.28, 46.79, 45.74, 45.53, 44.95, 41.39, 40.97, 40.02, 37.86, 37.57, 37.45, 37.33, 29.08, 27.43, 26.84, 19.61, 19.52, 19.48, 19.14, 14.32. . IR (neat) ν 3114, 3100, 2998, 2870, 1738, 1278 cm^{-1}.

(2*S*,3*S*,5*S*)-Methyl 5-allyl-5-methyl-2-propyltetrahydrofuran-3-carboxylate (84)

An oven-dried, 50-mL, one-necked, round-bottomed flask equipped with a magnetic stiring bar was charged with dry methylene chloride (20 ml, 20 mL/mmol). The neck of the round-bottomed flask was fitted with a septum and equipped with a gas inlet adapter attached to a nitrogen source. Methyl 3-hydroxy-2-(propyl-2-one)-hexanoate (**82**) (0.17 g, 0.86 mmol) was added to the solution of methylene chloride via syringe. Allyl trimethylsilane (0.27 ml, 1.72 mmol) was added to the solution via syringe. This solution was then cooled down to -78°C with a dry ice acetone bath. Once the reaction reached -78 °C, $BF_3 \cdot Et_2O$ (0.324 mL, 2.58 mmol) was added drop wise to the solution and allowed to stir at -78 °C for 12 h. The solution was then allowed to warm to room temperature and was quenched with water (5 mL, 5 mL/mmol), at which time the reaction mixture was transferred to a separatory funnel. The lower organic layer was withdrawn and placed in an Erlenmeyer flask. The aqueous washing was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were dried over *ca.* 10 g of anhydrous magnesium sulfate and filtered prior to concentration under reduced pressure. The viscous yellow oil was subjected to column chromatography (hexane:ethylacetate 10:1, R_f = 0.6) and 0.145 g (79 %) of **84** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 – 5.62 (m, 1H), 5.11 – 4.89 (m, 2H), 4.19 – 3.98 (m, 1H), 3.61 (s, 3H), 3.21 – 3.07 (m, 1H), 2.16 (qd, J = 13.7, 7.3 Hz, 2H), 1.98 (dd, *J* = 13.0, 7.9 Hz, 2H), 1.50 – 1.32 (m, 2H), 1.30 (s, 4H), 1.01 – 0.64 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ:

173.49, 134.72, 117.96, 82.43, 79.18, 51.75, 48.33, 45.75, 38.95, 34.52, 27.38, 19.82, 14.25. IR (neat) ν 3014, 3001, 2988, 2846, 1730, 1223 cm^{-1}.

(2*S*,3*R*)-*tert*-butyl 3-hydroxy-2-(2-oxopropyl)hexanoate (87)

CAUTION! Neat diethylzinc will ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen. The reaction solvents must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

An oven-dried, 100-mL single-necked, round-bottomed flask equipped with a stir bar was charged with 30 mL of dry methylene chloride and capped with a septum. The solution was stirred under an inert atmosphere of nitrogen, which was provided through a needle inserted into the septum. The solution was cooled to 0°C (ice bath temperature) and neat diethylzinc (0.67 mL, 6.6 mmol) was added slowly by syringe over a period of 5 min. Methylene iodide (0.53 mL, 6.6 mmol) was added by syringe dropwise over 5 min. The mixture was allowed to stir for 10 min and *t*-butyl acetoacetate (0.50 mL, 3 mmol) was added in one portion by syringe. The β-keto ester was stirred in the carbenoid for 30 min, at which time butyraldehyde (0.27 mL, 3 mmol) was added by syringe. The reaction was allowed to proceed for 15 min and then quenched with a saturated solution of ammonium chloride and allowed to warm to room temperature by removal of the ice bath. The quenched reaction mixture was extracted with diethyl ether (3 x 30 mL). The ethereal extracts were dried over magnesium sulfate (*ca.* 10 g), filtered and evaporated affording 0.550 g (75 %) of (2*S*,3*R*)-*tert*-butyl 3-hydroxy-2-(2-oxopropyl)hexanoate in equilibrium with two closed hemiketals as a pale yellow oil after column chromatography

(hexane:ethyl acetate, 5:1, R_f = 0.3). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.15 (dd, *J* = 11.5, 6.3 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.81 (ddd, *J* = 12.3, 8.3, 4.2 Hz, 0.49H), 2.97 – 2.90 (m, 1H), 2.89 (d, *J* = 1.7 Hz, 1H), 2.85 – 2.76 (m, 1H), 2.67 – 2.60 (m, 1H), 2.60 – 2.50 (m, 1H), 2.28 – 2.10 (m, 3H), 2.09 – 1.97 (m, 2H), 1.65 – 1.50 (m, 3H), 1.46 (d, *J* = 4.2 Hz, 6H), 1.41 (s, 9H), 1.39 (d, *J* = 1.7 Hz, 9H), 1.86 (dd, *J* = 7.6, 4.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 207.56, 176.29, 173.52, 172.69, 105.06, 104.95, 82.68, 82.11, 81.49, 80.97, 71.60, 50.23, 50.00, 47.13, 42.75, 41.44, 40.57, 39.59, 38.21, 37.12, 30.35, 28.18, 28.09, 27.37, 26.29, 19.31, 19.17, 18.79, 14.19, 14.14. IR (neat) ν 3300, 2998, 2133, 1714, 1433, 1378, 1225, 1098 cm^{-1}.

3-(Trimethylsilyl)prop-2-yn-1-ol (93)

A 100-mL, round-bottomed flask, equipped with a magnetic stir bar and nitrogen inlet, was charged with diethyl ether (20 mL) and ethynyltrimethylsilane (2.12 mL, 15.0 mmol) and cooled to -78 °C in a dry ice/acetone bath. The solution was allowed to stir for 10 min at -78 °C then *n*-butyl lithium (4 mL, 2.5 M in hexanes, 10 mmol) was carefully syringed dropwise over 15 min into the flask. The reaction was allowed to warm to room temperature over a 30 min period. Paraformaldehyde (1.5 g) was cracked (60 °C) in a separate 20-mL round-bottomed flask and was bubbled into the reaction mixture. The reaction was allowed to stir for 30 min, at which time the reaction cooled to 0 °C and quenched with saturated ammonium chloride (10 mL). The solution was filtered and the aqueous layer was washed with ethyl acetate (3 x 10 mL). The combined organic layers were dried with magnesium sulfate (*ca.* 10 g) and concentrated in vacuo. The resulting

oil was distilled to obtain 1.67 g (87 %) of **93** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20 (d, J = 6.6 Hz, 2H), 0.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 104.00, 91.13, 51.91, -0.00. ^{13}C NMR (101 MHz, $CDCl_3$) δ 104.00, 91.29, 51.91, 0.00. IR (neat) ν 3601, 2888, 2755, 2225, 1200 cm^{-1}.

(*Z*)-2-((Dimethyl(phenyl)silyl)methylene)hexan-1-ol (95)

Dimethylsilyl choride (0.8 mL, 5 mmol) was stirred in a 100-mL, round-bottomed flask, equipped with a septum and a nitrogen inlet in THF (20 mL) and cooled in an ice bath. Lithium wire (0.104 g, 15 mmol) was added and stirred for 36 h. The formation of the silylcuprate was performed by cannulation of dimethylpenylsilyl lithium into a second round-bottomed flask containing THF (20mL) and dry copper cyanide (223.5 mg mL, 2.5 mmol) in an ice bath. This was stirred for 20 min and 1-hexyne (0.3 ml, 2.5 mmol) was then added and stirred for 20 min. Paraformaldehyde (1 g) in a 100-mL round-bottomed flask was then cracked via heating mantle, bubbled into the solution and allowed to stir for 1 h. The reaction was then quenched with saturated ammonium choride (10 mL) and filtered. The filtrate was extracted with diethyl ether (3 x 30 mL), the combined organic layers were dried over magnesium sulfate (*ca.* 10 g), filtered and concentrated under vacuum (25 mmHg) to give (*Z*)-2-((dimethyl(phenyl)silyl)methylene)hexan-1-ol as a yellow viscous oil. This was further purified by column chromatography (hexane:ethyl acetate, 15:1, R_f = 0.2) to give 0.341 (55 %) of **95** as a clear oil as a mixture of *E* and *Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67 – 7.47 (m, 2H), 7.42 – 7.32 (m, 3H), 5.57 (s, 1H), 4.00 (t, J = 8.4 Hz, 2H), 2.31 – 2.11 (m, 2H), 1.46 (ddd, J = 11.8, 8.4, 5.9 Hz,

2H), 1.34 (dq, J = 11.7, 7.0 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H), 0.38 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 162.93, 158.03, 142.18, 141.77, 135.67, 135.52, 135.45, 135.01, 134.97, 131.52, 131.48, 131.22, 130.92, 130.65, 129.95, 129.85, 129.77, 129.68, 124.73, 123.01, 117.33, 67.16, 66.96, 31.58, 31.13, 14.39, 14.27, 2.84, 2.70, 1.46, 1.44. IR (neat) ν 3598, 3014, 2859, 2822, 1628, 1228 cm^{-1}.

(*Z*)-2-((Dimethyl(phenyl)silyl)methylene)butan-1-ol (98)

Dimethylphenylsilyl choride (0.8 mL, 5 mmol) was stirred in a 100-mL round-bottomed flask equipped with a septum and a nitrogen inlet in THF (20 mL) and the flask lowered into an ice bath. Lithium wire (0.104 g, 15 mmol) was added and stirred for 36 h (dark red solution). The formation of the silylcuprate was performed by cannulation of dimethylpenylsilyl lithium into an ice cooled second 100 mL round-bottomed flask containing THF (20mL) and dry copper cyanide (223.5 mg, 2.5 mmol). The solution was stirred for 20 min and 1-butyne (collected in a test tube cooled in a dry ice/acetone bath) (0.2 mL, 2.5 mmol) was then added quickly and stirred for 20 min at 0 °C. Paraformaldehyde (1 g) in a separate 100-mL round-bottomed flask was then cracked via heating mantle, bubbled into the solution and allowed to stir for 1 h. The reaction was quenched with saturated ammonium chloride (10 mL) and filtered. The filtrate was extracted with diethyl ether (3 x 30 mL) and dried over magnesium sulfate. The solution was then filtered and concentrated under vacuum (30 °C, 25 mmHg) to give (*Z*)-2-((dimethyl(phenyl)silyl)methylene)butan-1-ol as a yellow viscous oil. This was further purified by column chromatography (hexane:ethyl acetate, 15:1, R_f = 0.1) to give 0.281 g

(51 %) of **98** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56 – 7.49 (m, 2H), 7.40 – 7.33 (m, 3H), 5.57 (t, J = 1.4 Hz, 1H), 4.02 (d, J = 6.0 Hz, 2H), 2.24 (qd, J = 7.4, 1.4, 2H), 1.08 (t, J = 7.4 Hz, 3H), 0.38 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.56, 140.78, 134.09, 129.49, 128.51, 123.34, 65.80, 30.18, 12.96, 0.01. IR (neat) ν 3522, 3021, 2891, 2827, 1677, 1272, 1229 cm^{-1}.

Ethyl 3-(dimethyl(phenyl)silyl)-4-methyleneoctanoate (101)

A flame-dried 10-mL microwave vessel was charged with montmorillonite KSF clay (0.05 g), dry dimethylformamide (2 mL), triethyl orthoacetate (1.28 mL, 7.02 mmol), and (*Z*)-2-((dimethyl(phenyl)silyl)methylene)hexan-1-ol (**95**) (0.248 g, 1.00 mmol). The vessel was capped and exposed to microwave irradiation (Power: 200 MHz, Temperature: 153 °C, Ramp: 5 min., Hold: 5 min). The reaction mixture was allowed to cool to room temperature and saturated ammonium chloride (30 mL) was added and the aqueous layer was extracted with diethyl ether (3 x 30 mL) and concentrated *in vacuo* (25 mmHg) to give a yellowish oil. This was then further purified via column chromatography (hexane:ethyl acetate, 20:1, R_f = 0.3) affording 0.300 g (98 %) of ethyl 3-(dimethyl (phenyl)silyl)-4-methylenehexanoate (**101**) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 – 7.33 (m, 2H), 7.30 – 7.16 (m, 3H), 4.63 (d, J = 1.1 Hz, 1H), 4.42 (s, 1H), 4.05 – 3.75 (m, 2H), 2.35 (ddd, J = 20.4, 15.8, 8.2 Hz, 2H), 2.19 – 2.03 (m, 1H), 1.77 – 1.65 (m, 2H), 1.38 – 1.25 (m, 1H), 1.24 – 1.11 (m, 3H), 1.07 (t, J = 7.1 Hz, 3H) 0.74 (t, J = 7.2 Hz, 3H), 0.25 (s, 3H), 0.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 178.26, 155.49, 142.32,

139.01, 134.23, 132.75, 111.69, 65.22, 43.03, 40.06, 36.89, 34.66, 27.58, 19.25, 19.01, 0.95, -0.01. IR (neat) ν 3590, 3096, 3091, 2987, 2859, 1740, 1463, 1105 cm^{-1}.

Ethyl 3-(dimethyl(phenyl)silyl)-4-methylenehexanoate (100)

A flame-dried, 10-mL microwave vessel was charged with montmorillonite KSF clay (0.05 g), dry dimethylformamide (2 mL), triethyl orthoacetate (2.2 mL, 1.69 mmol), and (*Z*)-2-((dimethyl(phenyl)silyl)methylene)butan-1-ol (**98**) (0.3732 g, 1.69 mmol). The vessel was sealed with a Teflon cap and exposed to microwave irradiation (Power: 200 MHz, Temperature: 153 °C, Ramp: 5 min., Hold: 5 min). The reaction was allowed to cool to room temperature and saturated ammonium chloride (30 mL) was added and the aqueous layer was extracted with diethyl ether (3 x 30 mL) and the organic extracts were concentrated *in vacuo* (25 mmHg) to affford a yellowish oil. The oil was further purified via column chromatography (hexane:ethyl acetate, 20:1, R_f = 0.3) yielding 0.486 g (99 %) of ethyl 3-(dimethyl(phenyl)silyl)-4-methylenehexanoate **100** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 – 7.46 (m, 2H), 7.41 – 7.31 (m, 3H), 4.75 (s, 1H), 4.52 (s, 1H), 4.03 (q, *J* = 7.1 Hz, 2H), 2.46 (ddd, *J* = 20.3, 15.9, 8.3 Hz, 2H), 2.25 – 2.16 (m, 1H), 1.86 (q, *J* = 7.3 Hz, 2H), 1.18 (dd, *J* = 9.1, 5.1, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.31 (s, 3H), 0.29 (s, 3H). ^{13}C (101 MHz, $CDCl_3$) δ: 178.45, 156.96, 142.41, 139.10, 134.67, 132.94, 111.01, 82.46, 82.14, 81.83, 65.35, 40.19, 37.08, 36.02, 19.34, 17.00, 1.06, -0.01. IR (neat) ν 3471, 3072, 3061, 2887, 2859, 1731, 1463, 1105, 1004, 996 cm^{-1}.

(2*S*,3*R*,5*S*)-Methyl-5-(2-(3-ethoxy-3-oxopropylidene)hexyl)-5-methyl-2-propyltetrahydrofuran-3-carboxylate (104)

An oven-dried, 20-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with dry methylene chloride (10 ml, 20 mL/mmol). The neck of the round-bottomed was fitted with a septum and equipped with a gas inlet adapter attached to a nitrogen source. Methyl 3-hydroxy-2-(propyl-2-one)-hexanoate (**81**) (0.10 g, 0.50 mmol) was added to the solution of methylene chloride via syringe. Ethyl 3-(dimethyl(phenyl)silyl)-4-methyleneoctanoate (**101**) (0.32 g, 1.00 mmol) was added to the solution via syringe. This solution was then cooled down to -78 °C with a dry ice acetone bath. Once the reaction is at -78 °C, addition of $SnBr_4$ (0.66 g, 1.50 mmol) was added in one portion to the solution and allowed to stir at -78 °C for 12 hours. The solution was then allowed to warm to room temperature and was quenched with water (5 mL, 5mL/mmol), at which time the reaction mixture was transferred to a separatory funnel. The lower organic layer was withdrawn and placed in an Erlenmeyer flask. The aqueous washing was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were dried over 10 g of anhydrous magnesium sulfate and filtered prior to concentration under reduced pressure to afford a yellow oil. After column chromatography (hexane:ethyl acetate 15:1, R_f = 0.2) 0.158g (43 %) of **104** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.29 (t, *J* = 7.2 Hz, 1H), 4.11 – 4.02 (m, 2H), 3.99 – 3.87 (m, 1H), 3.62 (s, 3H), 3.00 (d, J = 7.2 Hz, 2H), 2.66 (dd, *J* = 18.6, 9.5 Hz, 1H), 2.36 (dd, *J* = 15.0, 8.9 Hz, 1H), 2.21 – 2.02 (m, 4H), 2.01 – 1.82 (m, 1H), 1.60 – 1.34 (m, 3H), 1.31 – 1.22 (m, 5H), 1.21 – 1.15 (m, 4H), 1.09 (s, 2H), 0.89 – 0.77 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.96, 172.43, 140.87, 120.35, 82.95, 80.92, 60.61, 51.98, 49.76, 47.07, 42.81, 37.57, 33.84, 30.83, 30.60, 27.58, 22.97, 19.46, 14.38, 14.28, 14.20. IR (neat) ν 3011, 2998, 2911, 1745, 1733, 1028, 1011, 983, 958 cm^{-1}.

(*S*)-2-Amino-3-methylbutan-1-ol (108)

A 250-mL, three-necked, round-bottomed flask was equipped with a magnetic stir bar, a nitrogen inlet, condenser, and a pressure equalizing drop funnel was charged with L-valine (11.86 g, 0.10 mol) and tetrahydrofuran (100 mL). Boron trifluoroetherate (13.0 mL, 0.11 mol) was added drop wise over a 30 min period and the reaction was refluxed for 15 min via heating mantle. The reaction mixture was allowed to cool to room temperature and borane dimethylsulfide (11.0 mL, 0.12 mol) was added drop wise over a 1 h period. The reaction was then allowed to reflux for 12 h. Tetrahydrofuran/water (50 mL, 1/1) was added drop wise over 15 min, followed by the addition of sodium hydroxide (30.0 mL, 10 M) over a 15 min period. The solution was refluxed for an additional 2 h then cooled down and filtered through celite. The ethereal layer was evaporated via rotary evaporation, and the aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to give 8.97 g (87 %) of **108** as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 4.92 – 4.74 (m, 1H), 3.36 – 3.22 (m, 1H), 2.56 (ddd, J = 8.8, 6.4, 3.9 Hz, 1H), 1.66 – 1.49 (m, 1H), 1.23 – 0.56 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 64.23, 58.79, 31.28, 19.38, 18.70. IR (neat) ν 3610, 3500, 2987, 2930, 2614, 1477, 13,81, 1777, 1356, 1320, 1064, 990, 770 cm^{-1}.

(*S*)-4-Isopropyloxazolidin-2-one (106)

A dry 250-mL round-bottomed flask equipped with a Dean Stark trap was charged with potassium carbonate (0.667 g, 4.83 mmol), (S)-2-amino-3-methylbutan-1-ol (**108**) (4.801 g, 46.5 mmol), and diethyl carbonate (113 mL, 933 mmol). The mixture was lowered into an oil bath (135 °C). After 10 mL of ethanol was collected in the trap the flask was removed from the oil bath and cooled down to room temperature. Diethyl carbonate was removed in vacuo (5 mm Hg, 30 °C), at which time methylene chloride (60mL) was added. The solution was washed with 1M sodium hydroxide (2 x 20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo to afford a yellow oil. Hexanes (20 mL) were then added and stored at -5 °C for 12 h to produce 1.80 g (30 %) of (*S*)-4-isopropyloxazolidin-2-one (**106**) as white shards. MP = 67 – 70 °C (Lit. 65 – 68 °C)[126]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.00 (s, 1H), 4.45 (t, J = 8.6 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, 6.7 Hz, 1H), 0.97 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.8, 68.8, 58.5, 32.9, 18.2, 17.9. IR (neat) ν 3258, 3199, 2971, 2844, 1738, 1705, 1480, 1440, 1367, 1242 cm^{-1}.

(*S*)-1-(4-isopropyl-2-oxooxazolidin-3-yl)butane-1,3-dione (105)

A 50-mL round-bottomed flask equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with THF (10 mL) and (*S*)-4-isopropyloxazolidin-2-one (**106**) (0.13 g,

1.00 mmol) and cooled to -78 °C. To this solution *n*-butyl lithium (0.44 mL, 2.5 M, 1.10 mmol) was added dropwise over 15 min. The flask was allowed to warm to room temperature for 15 min and cooled back down to -78 °C. Diketene (0.10 mL, 1.10 mmol) was added dropwise over 5 min and allowed to stir for 30 min at -78 °C. Then the reaction was allowed to stir for 2 h at room temperature, after which the solution was quenched with saturated ammonium chloride (10 mL). The mixture was taken up in methylene chloride (50 mL) and washed with saturated sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo to give a brown viscous oil. After column chromatography (hexane:ethyl acetate, 1:1, R_f= 0.8) 0.089 g (42 %) of compound **105** was obtained as a light yellow solid. MP = 54 – 55 °C (Lit. 53 – 55 °C)[127]. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ: 4.51 – 4.43 (m, 1H), 4.38 – 4.19 (m, 2H), 4.14 – 3.92 (m, 2H), 2.36 – 2.21 (m, 1H), 2.10 – 1.98 (s, 3H), 1.04 – 0.82 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) *keto and enol tautomers* δ: 201.19, 166.56, 154.51, 89.99, 63.83, 63.56, 63.45, 63.21, 60.58, 59.49, 58.60, 58.20, 51.68, 30.27, 29.33, 28.94, 28.50, 18.20, 18.12, 14.94, 14.88, 14.71, 14.44, 14.40. IR (neat) ν 2936, 2899, 1722, 1712, 1569, 1432, 1351, 1311, 1129, 1061, 901, 883 cm^{-1}.

(4*S*)-3-((2*S*,3*S*)-5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carbonyl)-4-isopropyloxazolidin-2-one (110)

CAUTION! Neat diethylzinc will ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen. The reaction solvents must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

A 100-mL round-bottomed flask equipped with a septum, mechanical stir bar, and a nitrogen inlet was charged with methylene chloride (30 mL) and cooled to 0 °C. Diethyl zinc (0.56 mL, 5.4 mmol) was added and methylene iodide (0.44 mL, 5.4 mmol) was added dropwise over 5 min. This was allowed to react for 15 min, at which time (*S*)-1-(4-isopropyl-2-oxooxazolidin-3-yl)butane-1,3-dione (**105**) (0.384 g, 1.801 mmol) in methylene chloride (5 mL) was quickly added. The solution was allowed to stir for 0.5 h, after which butyraldehyde (0.2 ml, 2.16 mmol) was added and allowed to stir for 15 min. This was then quenched with saturated ammonium chloride (20 mL). The organic layer was extracted with methylene chloride (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, and concentrated in vacuo to yield a yellow oil. The oil was further purified by column chromatography (hexane:ethyl acetate, 15:1, R_f = 0.5) to give 0.367 g (68 %) of (4*S*)-3-(5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carbonyl)-4-isopropyloxazolidin-2-one **110** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.53 (td, *J* = 7.6, 5.1 Hz, 1H), 4.47 – 4.38 (m, 1H), 4.34 – 4.16 (m, 2H), 3.87 – 3.70 (m, 0.5H), 3.57 – 3.31 (m, 1H), 2.52 – 2.23 (m, 2H), 2.18 – 1.99 (m, 1H), 1.78 – 1.28 (m, 16H), 1.03 – 0.80 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 201.34, 166.58, 105.26, 105.08, 82.77, 81.50, 77.66, 77.34, 77.03, 63.83, 63.61, 63.45, 59.24, 58.92, 58.85, 58.54, 51.64, 47.64, 47.41, 43.92, 42.45, 41.69, 37.94, 37.88, 30.24, 29.10, 28.53, 28.46, 26.96, 26.88, 19.39, 19.35,

19.00, 18.89, 18.15, 18.07, 14.85, 14.67, 14.49, 14.17, 14.11. IR (neat) ν 3249, 2943, 2231, 1711, 1429, 1325, 1255, 1195, 1090, 985 cm^{-1}.

(*S*)-3-((2*S*,3*S*,5*S*)-5-allyl-5-methyl-2-propyltetrahydrofuran-3-carbonyl)-4-isopropyloxazolidin-2-one (109)

An oven dried, 50mL, one neck, round-bottom flask equipped with a magnetic stiring bar was charged with dry methylene chloride (20ml, 20mL/mmol). The neck of the round bottom was fitted with a septum and equipped with a gas inlet adapter attached to a nitrogen source. Addition of (4*S*)-3-((2*S*,3*S*)-5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carbonyl)-4-isopropyloxazolidin-2-one (**110**) (0.1223 g, 0.410 mmol) was added to the solution of methylene chloride via syringe. Allyl trimethylsilane (0.13 ml, 0.82 mmol) was added to the solution via syringe. This solution was then cooled down to -78°C with a dry ice acetone bath. Once the reaction is at -78 °C, addition of $BF_3 \cdot Et_2O$ (0.0.15 mL, 1.23 mmol) drop wise to the solution and allowed to stir at -78 °C for 12 hours. The solution was then allowed to warm to room temperature and was quenched with water (5 mL, 5mL/mmol), at which time the reaction mixture was transferred to a separatory funnel. The lower organic layer was withdrawn and placed in an Erlenmeyer flask. The aqueous washing was extracted with diethyl ether (3 x 30 mL) and the combined organic layers are dried over 10 g of anhydrous magnesium sulfate and filtered prior to concentration under reduced pressure to give 0.114 g (86 %) of **109** as a clear viscous oil. ^1H NMR (400 MHz, $CDCl_3$) δ: 5.92 – 5.75 (m, 1H), 5.18 – 4.99 (m, 2H), 4.49 – 4.39 (m, 1H), 4.33 – 4.22 (m, 3H), 4.14 – 4.00 (m, 1H), 2.47 – 2.07 (m, 5H),

2.06 – 1.89 (m, 1H), 1.85 – 1.46 (m, 3H), 1.34 – 1.23 (m, 3H), 0.94 – 0.87 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.80, 172.50, 153.86, 134.69, 118.20, 82.67, 81.01, 63.30, 58.73, 48.23, 45.95, 41.98, 37.19, 35.31, 29.02, 27.43, 19.98, 18.18, 14.77. IR (neat) ν 3201, 2921, 2211, 1702, 1399, 1322, 1201, 1149, 1008, 927 cm^{-1}.

Ethyl-4-(((2*R*,4*S*,5*S*)-4-((*S*)-4-isopropyl-2-oxooxazolidine-3-carbonyl)-2-methyl-5-propyltetrahydrofuran-2-yl)methyl)hex-3-enoate (111)

An oven-dried, 50-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar was charged with dry methylene chloride (20 ml, 20 mL/mmol). The neck of the round bottom was fitted with a septum and a needle attached to a nitrogen source. Addition of (4*S*)-3-((2*S*,3*S*)-5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-yl)-4-isopropyloxazolidin-2-one **110** (0.277 g, 0.410 mmol) was added to the solution of methylene chloride via syringe. Ethyl 3-(dimethyl(phenyl)silyl)-4-methylenehexanoate (**100**) (0.277 g, 0.94 mmol) was suspended in methylene chloride (3 mL) was added to the solution via syringe. This solution was then cooled down to -78 °C through use of a dry ice/acetone bath. Once the reaction was at -78 °C, addition of tin (IV) bromide (0.627 g, 1.410 mmol) was added in one portion to the solution and the solution was allowed to stir at -78 °C for 12 h. The reaction was then allowed to warm to room temperature and was quenched with water (5 mL, 5mL/mmol), at which time the reaction mixture was transferred to a separatory funnel. The lower organic layer was withdrawn and placed in an Erlenmeyer flask. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over 10 g of anhydrous magnesium

sulfate and filtered prior to concentration under reduced pressure to give a yellow oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.2) 0.154 (86 %) of **111** was isolated as a clear viscous oil as a mixture of *E* and *Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.34 (dd, J = 16.1, 8.8 Hz, 1H), 4.44 (dt, J = 8.3, 3.5 Hz, 1H), 4.28 (ddd, J = 15.6, 8.6, 5.2 Hz, 3H), 4.18 – 4.08 (m, 3H), 4.04 – 3.94 (m, 1H), 3.09 (t, J = 7.2 Hz, 3H), 2.47 – 2.31 (m, 3H), 2.18 (ddd, J = 13.5, 10.6, 6.6 Hz, 3H), 1.82 (dd, J = 12.3, 9.1 Hz, 1H), 1.71 – 1.34 (m, 7H), 1.30 – 1.21 (m, 10H), 0.99 – 0.86 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 120.08, 83.52, 81.03, 63.25, 60.64, 58.76, 48.61, 47.87, 42.91, 37.23, 33.73, 28.59, 26.95, 24.42, 19.66, 18.18, 14.79, 14.41, 14.37, 13.12. IR (neat) ν 3022, 3010, 2961, 2899, 1784, 1257, 1198, 942 cm^{-1}.

(*S*)-pyrrolidin-2-ylmethanol (113)

A 250-mL, three-necked round-bottomed flask equipped with a magnetic stir bar, a nitrogen inlet, condenser, and a pressure equalizing drop funnel was charged with L-proline (11.62 g, 0.10 mol) and tetrahydrofuran (100 mL). Boron trifluoroetherate (13.0 mL, 0.11 mol) was added dropwise over a 30 min period and the reaction was refluxed for 15 min. The reaction mixture was cooled to room temperature and boran dimethylsulfide (11.0 mL, 0.12 mol) was added dropwise over a 1 h period after which time the reaction was refluxed for 12 h. Tetrahydrofuran/water (50 mL, 1/1) was added dropwise over 15 min, followed by the addition of sodium hydroxide (30.0 mL, 10 M) over a 15 min period. The reaction was refluxed for an additional 2 h, then cooled down in an ice bath and filtered through celite. The ethereal component of the mixture was

evaporated via rotary evaporation, and the aqueous layer was extracted with ethyl acetate (3 x 40 mL). The combined organic layers were dried with sodium sulfate and concentrated in vacuo to give 7.89 g (78 %) of **113** as a clear oil. Carried on without NMR analysis.

(*S*)-2-(hydroxymethyl)pyrrolidine-1-carbaldehyde (114)

A 250-mL round-bottomed flask containing (*R*)-pyrrolidin-2-ylmethanol **113** (10.216 g, 0.101 mol) equipped with a pressure equalizing drop funnel and a magnetic stir bar was cooled down to 0 °C. Ethyl formate (10.6 mL, 0.131 mol) was added over 20 min and stirred for 30 min at 0 °C to give a green colored solution. Excess ethyl formate was evaporated in vacuo (10 mmHg, 30 °C). The reaction was then taken up in dichloromethane (60 mL) and dried by stirring with sodium carbonate for 30 min. The drying agent was filtered off and the final product was concentrated in vacuo to yield 11.34 g (87 %) of (*R*)-2-(hydroxymethyl)pyrrolidine-1-carbaldehyde **114** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotomeric form* δ: 8.28 (s, 1H), 4.17 – 4.02 (m, 2H), 3.78 – 3.31 (m, 3H), 2.22 – 1.75 (m, 2H), 1.72 – 1.49 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.12, 162.09, 66.79, 65.16, 60.46, 59.14, 47.87, 43.87, 28.61, 27.48, 24.18, 22.96. IR (neat) ν 3540, 2983, 1703, 1251, 1014, 1009, 942, 841 cm^{-1}.

(*S*)-2-(methoxymethyl)pyrrolidine (116)

A 100-mL round-bottomed flask equipped with a magnetic stir bar and septum was charged with water (15 mL), (*R*)-2-(methoxymethyl)pyrrolidine-1-carbaldehyde **115**

(2.184 g, 0.0169 mol), and potassium hydroxide (3.033 g, 0.054 mol) stirred under a blanket of nitrogen for 12 h. Saturated potassium carbonate (10 mL) caused the reaction to precipitate the potassium salts, which were then filtered away. The filtrate was then washed with ether (3 x 30 mL), dried with sodium sulfate and concentrated in vacuo to give 1.79 g (92 %) of **116** as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.36 (s, 3H), 3.35 – 3.32 (m, 1H), 3.30 – 3.24 (m, 3H), 2.99 – 2.96 (m, 1H), 2.92 – 2.83 (m, 1H), 1.85 – 1.80 (m, 1H), 1.76 – 1.68 (m, 2H), 1.44 – 1.35 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 76.60, 59.19, 57.95, 46.72, 28.11, 25.54 cm^{-1}.

L-Proline methylester hydrochloride salt (118 HCl)

A 500-mL round-bottomed flask equipped with a pressure-equalizing droping funnel, magnetic stir bar, and a calcium chloride drying tube was charged with L-proline (11.51 g, 100 mmol) in methanol (100 mL) and then lowered into an ice bath. Thionyl chloride (8.0 mL, 110 mmol) was added to the pressure-equalizing droping funnel and added slowly to the flask over 0.5 h. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The solvent was removed under vacuum (25 mmHg) and then dried further on a high vacuum pump (1 mmHg). This procedure provided 15.73 g (95 %) of L-proline methyl ester hydrochloride salt (**118 HCl**). ^{1}H NMR (400 MHz, D_2O) δ 4.37 (t, J = 8.0 Hz, 1H), 3.72 (s, 3H), 3.40-3.22 (m, 2H), 2.32 (ddd, J = 15.2, 13.5, 6.8 Hz, 1H), 2.05 (tt, J = 15.5, 7.9 Hz, 1H), 1.99-1.89 (m, 2H). ^{13}C NMR (101 MHz, D_2O) δ 170.59, 59.66, 53.91, 46.71, 28.21, 23.42. IR (neat) ν 3330, 3022, 2993, 2974, 1783, 1104, 1048, 974 cm^{-1}.

L-Proline methylester (118)

L-Proline methylester hydrochloride salt **(118 HCl)** (10 g, 77.4 mmol) was dissolved in saturated sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 x 30 mL) to afford 6.89 g (69 %) of **118** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (dd, J = 8.6, 5.7 Hz, 1 H), 3.74 (s, 3H), 3.11 – 3.06 (m, 1H), 2.96 – 2.91 (m, 1H), 2.26 – 2.10 (m, 3H), 1.90 – 1.82 (m, 1H), 1.81 – 1.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 176.00, 59.74, 52.32, 47.12, 30.41, 25.69. IR (neat) ν 3250, 3199, 2981, 2849, 1738, 1110, 1022, 839 cm^{-1}.

(*S*)-Methyl 1-(3-oxobutanoyl)pyrrolidine-2-carboxylate (119)

Diketene acetone adduct # (0.13 mL, 1.00 mmol) was mixed with proline methyl ester (**118**) (0.39 g, 1.00 mmol) in a 10 mL pyrex microwave vessel sealed with a Teflon cap. The solution was subjected to microwave irradiation (Time: 2 min, Power: 200 Watt, Temperature: 178 °C). The resulting brown solution was taken up in ethyl acetate (30 mL) and washed with water (10 mL), HCl (1 M, 10 mL), and brine (10 mL). The organic solution was dried with sodium sulfate and concentrated in vacuo. After column chromatography (hexane:ethyl acetate 1:8, R_f = 0.6) 0.043 g (20 %) **119** was obtained as a clear, viscous oil as a mixture of keto and enol forms, with the appearance of amide rotomeric forms. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ: 4.56 – 4.49 (m, 1H), 3.74 (s, 3H), 3.67 – 3.53 (m, 2H), 3.44 – 3.33 (m, 2H), 2.31 (s, 3H), 2.25 – 2.16 (m, 2H), 2.04 – 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) *keto and enol tautomers* δ: 202.06,

172.38, 165.30, 88.60, 77.34, 77.02, 76.70, 59.89, 58.80, 58.06, 52.28, 51.39, 51.06, 47.64, 46.53, 31.22, 30.09, 29.29, 24.75, 24.45, 22.63, 21.77. IR (neat) ν 2913, 2822, 1704, 1700, 1569, 1399, 1345, 1303, 1109, 1027, 984, 881 cm^{-1}.

Methyl-1-((2*R*,3*S*,5*S*)-5-hydroxy-5-methyl-2-propyltetrahydrofuran-3-carbonyl) pyrrolidine-2-carboxylate (120)

CAUTION! Neat diethylzinc will ignite on exposure to air and reacts violently with water. It must be handled and reacted under nitrogen. The reaction solvents must be dried and distilled prior to use and all glassware and syringes must be thoroughly dried.

A 100-mL round-bottomed flask equipped with a septum, mechanical stir bar, and a nitrogen inlet was charged with methylene chloride (50 mL) and cooled to 0 °C. Diethyl zinc (0.92 mL, 8.82 mmol) was added and methylene iodide (0.73 mL, 8.82 mmol) was added dropwise over 5 min. These reagents were allowed to react for 15 min at which time (*S*)-methyl 1-(3-oxobutanoyl)pyrrolidine-2-carboxylate (**119**) (0.627 g, 2.94 mmol) in methyene chloride (5mL) was added in one portion. The reaction was allowed to stir for 0.5 h, at which time butyraldehyde (0.32 ml, 3.53 mmol) was added and the solution was allowed to stir for 15 min. The reaction was quenched with saturated ammonium chloride (20 mL). The biphasic solution was extracted with methylene chloride (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo to yield a yellow oil. The oil was further purified by column chromatography (hexane:ethyl acetate, 15:1, R*f* = 0.4) to give 0.634 g (72 %) of **120** as a clear oily-solid. The product exists as a mixture of open chain and hemi-ketal forms as well as rotomeric

forms. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.75 (s, 1H), 6.56 (s, 3H), 6.48 (s, 1H), 4.54 (dd, J = 8.7, 4.1 Hz, 3H), 4.63 – 4.42 (m, 6H), 4.37 – 4.18 (m, 5H), 3.87 – 3.53 (m, 6H), 3.18 – 3.07 (m, 3H), 3.06 – 2.97 (m, 3H), 2.31 – 2.17 (m, 7H), 2.17 – 1.88 (m, 30H), 1.70 – 1.56 (m, 8H), 1.55 – 1.30 (m, 26H), 1.02 – 0.79 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.23, 175.63, 173.97, 172.22, 105.00, 104.91, 104.81, 83.68, 81.88, 81.60, 77.64, 77.32, 77.00, 71.31, 60.53, 60.18, 59.28, 59.11, 58.92, 53.05, 52.54, 52.39, 48.36, 48.21, 48.01, 47.81, 47.66, 47.52, 47.38, 47.21, 43.53, 43.26, 42.24, 41.74, 40.98, 39.02, 38.83, 36.40, 31.57, 30.18, 29.34, 29.26, 27.47, 25.88, 25.56, 25.05, 24.97, 24.84, 22.79, 21.20, 19.42, 19.22, 19.11, 18.96, 14.36, 14.23. IR (neat) ν 3449, 2991, 2159, 1759, 1700, 1498, 1398, 1222, 1110 cm^{-1}.

(*S*)-Methyl-1-((2*R*,3*S*,5*S*)-5-allyl-5-methyl-2-propyltetrahydrofuran-3-carbonyl) pyrrolidine-2-carboxylate (121)

To a solution of the γ-lactol (**120**) (0.093 g, 0.310 mmol) in dry methylene chloride (10 mL) was added allyltrimethylsilane (0.10 mL, 0.620 mmol) and the solution was cooled to -78 °C. To this solution was added dry $SnBr_4$ (0.299 g, 0.682 mmol) in one portion and the solution stirred at -78 °C for 12 h. The reaction was quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with methylene chloride (3 x 10 mL) and dried over magnesium sulfate and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate, 5:1, R_f = 0.3) 0.067 g (67 %) of **121** was isolated as a clear oil. Compound **121** exists in two rotomeric forms. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotamer* δ: 5.92 – 5.75 (m, 1H), 5.15

– 5.01 (m, 2H), 4.49 – 4.40 (m, 1H), 4.34 – 4.24 (m, 1H), 4.17 – 4.02 (m, 1H), 3.71 (s, 3H), 3.61 – 3.50 (m, 1H), 2.93 – 2.70 (m, 1H), 2.27 – 2.14 (m, 4H), 2.05 – 1.89 (m, 1H), 1.84 – 1.48 (m, 6H), 1.37 – 1.22 (m, 3H), 0.95 – 0.88 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.77, 171.84, 153.86, 134.72, 117.97, 82.00, 81.89, 81.38, 81.09, 59.06, 52.33, 49.45, 49.26, 49.01, 47.29, 46.87, 45.06, 44.01, 42.00, 37.06, 36.90, 29.36, 27.68, 26.88, 25.01, 19.46, 17.98, 14.81, 14.54. IR (neat) ν 3099, 3072, 2907, 2144, 1751, 1692, 1459, 1341, 1288, 1109, 1016, 975, 841 cm^{-1}.

(*S*)-methyl-1-((2*R*,3*S*,5*S*)-5-allyl-5-methyl-2-propyltetrahydrofuran-3-carbonyl) pyrrolidine-2-carboxylate (122)

A 50-mL round-bottomed flask was charged with γ-lactol **120** (0.093 g, 0.310 mmol) in dry methylene chloride (10 mL) ethyl 3-(dimethyl(phenyl)silyl)-4-methylenehexanoate (**100**) (0.180 g, 0.620 mmol) was added in one portion and the solution was cooled to -78 °C. To this solution was added dry $SnBr_4$ (0.299 g, 0.682 mmol) in one portion and the solution was stirred at -78 °C for 12 h. The reaction was quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 5:1, R_f = 0.2) 0.100 g (37 %) of **122** was isolated as a clear oil and exists in two rotomeric forms. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.41 – 5.26 (m, 1H), 4.18 – 4.07 (m, 2H), 3.58 – 3.43 (m, 2H), 3.40 – 3.29 (m, 2H), 3.08 (d, J = 7.1 Hz, 1H), 2.31 – 1.82 (m, 9H), 1.59 – 1.37 (m, 4H), 1.36 – 1.21 (m, 9H), 1.05 – 0.82

(m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.26, 171.39, 142.87, 119.40, 83.03, 81.50, 72.47, 59.93, 59.14, 56.81, 49.80, 47.76, 46.32, 45.53, 41.54, 41.19, 37.28, 33.73, 30.28, 27.66, 24.37, 19.70, 14.55, 13.02. IR (neat) ν 3011, 2965, 2111, 1759, 1685, 1471, 1342, 1299, 1123, 1009, 948, 871 cm^{-1}.

(4*S*)-3-(1-Hydroxy-2-(2-oxopropyl)cyclopropyl)-4-isopropyloxazolidin-2-one (139)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, nitrogen inlet, and septum, was charged with methylene chloride (30.0 mL) and placed in an ice bath (0 °C). Diethylzinc (0.5 mL, 5.0 mmol) was added to the flask and allowed to stir for 15 min. Methylene iodide (0.4 mL, 5.0 mmol) was added drop-wise over 5 min and allowed to stir for 15 min at 0 °C. To the milky white solution (*S*)-1-(4-isopropyl-2-oxooxazolidin-3-yl)butane-1,3-dione (**105**) (0.21 g, 1.00 mmol) in methylene chloride (5.0 mL) was added in one portion. The reaction was stirred for 1 h at 0 °C and quenched with saturated ammonium chloride (15.0 mL) and the aqueous layer was washed with methylene chloride (3 x 10 mL), dried with magnesium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a viscous yellow oil. After column chromatography (hexanes:ethylacetate 5:1, R_f = 0.1) 0.053 g (22 %) of **139** was isolated as a viscous clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 – 4.40 (m, 1H), 4.24 – 4.02 (m, 2H), 4.02 – 3.81 (m, 1H), 2.72 (ddd, J = 26.2, 18.2, 6.7 Hz, 2H), 2.44 – 2.24 (m, 1H), 2.22 (d, J = 13.2 Hz, 2H), 1.46 (tt, J = 10.3, 6.7 Hz, 1H), 1.35 (dd, J = 10.1, 5.8 Hz, 1H), 1.23 (dd, J = 16.7, 9.6 Hz, 1H), 1.06 – 0.72 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.42, 158.24, 64.58,

63.64, 60.72, 42.07, 30.18, 29.26, 22.11, 19.62, 18.20, 14.50. IR (neat) ν 3622, 2851, 2772, 1722, 1678, 1222, 1105, 880, 792 cm^{-1}.

(*S*)-4-Isopropyl-3-((1*S*,3*R*,5*R*)-3-methyl-2-oxabicyclo[3.1.0]hexan-1-yl)oxazolidin-2-one (140)

A 25-mL round-bottomed flask, equipped with a septum, nitrogen inlet, and a magnetic stir bar, was charged with methylene chloride (10 mL) and cyclopropanol **139** (0.04 g, 0.18 mmol). The solution was cooled to -78 °C and triethylsilane (0.06 mL, 0.35 mmol) was added in one portion. This was followed by the addition of boron trifluoride etherate (0.04 mL, 0.35 mmol) and the reaction was allowed to stir for 12 h. The reaction was quenched with saturated sodium bicarbonate (10 mL) and the aqueous was layer was extracted with methylene chloride (3 x 5 mL), the combined organic layers were dried with sodium sulfate (3 g) and concentrated in vacuo to afford a yellow oil. Title compound **140** was separated via flash chromatography (hexane:ethyl acetate 5:1, R_f = 0.2) to obtain 0.024 g (60 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 – 4.71 (m, 1H), 4.26 – 4.18 (m, 1H), 4.06 – 3.99 (m, 2H), 2.67 – 2.54 (m, 1H), 2.28 (dtd, *J* = 13.9, 6.9, 3.1 Hz, 1H), 2.09 – 2.00 (m, 1H), 1.44 (ddd, *J* = 12.7, 8.9, 2.0 Hz, 1H), 1.34 (ddd, *J* = 9.6, 5.6, 0.6 Hz, 1H), 1.14 (d, *J* = 6.2 Hz, 3H), 1.05 (t, *J* = 5.5 Hz, 1H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.69, 84.26, 76.17, 62.77, 60.66, 38.80, 28.99, 27.78, 23.17, 21.87, 18.28, 14.20. IR (neat) ν 2980, 2877, 1723, 1105, 1098, 922, 781 cm^{-1}.

Methyl 2-(2-methyl-2-((trimethylsilyl)oxy)cyclopropyl)acetate (145)

A 100-mL, round-bottomed flask equipped with a magnetic stir bar, nitrogen inlet, and septum was charged with methylene chloride (30.0 mL) and cooled to 0 °C in an ice bath. Diethylzinc (0.5 mL, 5.0 mmol) was added to the flask and allowed to stir for 15 min. Methylene iodide (0.4 mL, 5.0 mmol) was added drop-wise over 5 min and allowed to stir for 15 min at 0 °C. Methyl acetoacetate (0.1 mL, 1 mmol) and trimethylsilyl chloride (0.2 mL, 1.5 mmol) were added to the milky white solution respectively. This mixture was stirred for 12 h at 24 °C and quenched with saturated ammonium chloride (15.0 mL), the aqueous layer was washed with methylene chloride (3 x 10 mL), dried with magnesium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a viscous yellow oil. After column chromatography (hexanes:ethylacetate 15:1, R_f = 0.1) 0.041 g (19 %) of **145** was isolated as a viscous clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 3H), 2.39 (dt, J = 16.6, 8.3 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.26 (s, 3H), 0.83 – 0.74 (m, 1H), 0.54 (dd, J = 9.3, 5.7 Hz, 1H), 0.31 (t, J = 5.9 Hz, 1H), 0.05 – -0.03 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 54.74, 50.24, 40.64, 31.87, 24.74, 18.32, 0.00. IR (neat) ν 2956, 2943, 2877, 1749, 1234, 1185, 849, 766 cm^{-1}.

Methyl pivaloylacetate (154)

Into a three-necked, round-bottomed flask, equipped with a pressure-equalizing dropping funnel, stir bar, condenser, and a nitrogen inlet, a solution of pinacolone (1.2 mL, 10 mmol) in dry dioxane (15 mL) was added drop-wise over 3 h to a stirred solution of prewashed (hexanes: 3 x 10 mL) sodium hydride dispersion (0.842 g, 20 mmol), dimethyl

carbonate (8 mL, 95.0 mmol), and dioxane (20 mL) at an oil bath temperature of 85 °C. After the release of hydrogen gas (~ 30 min) the reaction was allowed to reflux for an additional 2 h. The solution was then cooled to room temperature and neutralized with acetic acid (pH ~ 7). The solution was extracted with diethyl ether (3 x 30 mL), the combined organic layers dried with magnesium sulfate (*ca.* 20 g), and concentrated in vacuo. The resulting oil was distilled (91 - 95 °C) under reduced pressure (20 mmHg) to give 1.20 g (76 %) of **154** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 3.73 (s, 3H), 3.57 (s, 2H), 1.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.23, 168.40, 85.41, 52.45, 51.30, 44.99, 43.91, 36.79, 27.89, 27.81, 27.65, 26.27, 26.08. IR (neat) ν 3201, 3004, 2774, 1791, 1772, 1703, 1195, 1108, 951, 831 cm^{-1}.

Methyl 2-(2-(*tert*-butyl)-2-((trimethylsilyl)oxy)cyclopropyl)acetate (156)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, nitrogen inlet, and septum, was charged with methylene chloride (30 mL) and placed in an ice bath (0 °C). Diethylzinc (0.5 mL, 5.0 mmol) was added to the flask and allowed to stir for 15 min. Methylene iodide (0.4 mL, 5.0 mmol) was added dropwise over 5 min and allowed to stir for 15 min at 0 °C. Methyl pivaloylacetate **154** (0.1 mL, 1 mmol) and trimethylsilyl chloride (0.2 mL, 1.5 mmol) were added to the milky white solution. This mixture was stirred for 12 h at 24 °C and quenched with saturated ammonium chloride (15.0 mL), the aqueous layer was washed with methylene chloride (3 x 10 mL), the combined organic layers were dried with magnesium sulfate (*ca.* 10 g), filtered, and concentrated in vacuo to give a viscous yellow oil. After column chromatography (hexanes:ethylacetate 15:1,

R_f = 0.2) 0.062 (24 %) of **156** was isolated as a viscous clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.49 – 2.30 (m, 2H), 1.14 (tt, *J* = 11.0, 4.1 Hz, 1H), 0.94 (dd, *J* = 12.2, 5.8 Hz, 1H), 0.87 (s, 9H), 0.37 (t, *J* = 6.4 Hz, 1H), 0.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.44, 66.65, 51.58, 35.01, 33.05, 26.97, 15.76, 14.47, 1.99. IR (neat) ν 2984, 2779, 1743, 1299, 1183, 1021, 836, 760 cm^{-1}.

(*E*)-Methyl 6,6-dimethyl-5-oxohept-2-enoate (157)

A 50-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with THF (15 mL) and cooled to -78 °C. Diisopropylamine (0.3 mL, 1.91 mmol) was added followed by drop-wise addition of *n*-butyllithium (0.8 mL, 2.5 M, 1.91 mmol) and the solution stirred for 20 min. To this solution **156** (0.494 g, 1.91 mmol) in THF (5 mL) was added and the solution was allowed to warm to room temperature. Iodine (0.58 g, 2.29 mmol) in THF (5 mL) was added to a second 50 mL round-bottomed flask and this solution was lowed to -78 °C. The first round-bottomed flask was transferred by cannula to the iodine in THF solution and the reaction was allowed to warm to room temperature. Once at room temperature the reaction was quenched with concentrated hydrochloric acid (0.3 mL) and water (5 mL). The aqueous layer was extacted with diethyl ether (3 x 20 mL) and the ethereal washes were washed with saturated sodium thiosulfate (2 x 5 mL). The combined organic layers were dried with magnesium sulfate (*ca.* 10g) and concentrated in vacuo to give 0.260 g (74 %) of **157** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 6.84 (m, 1H), 5.93 – 5.75 (m, 1H), 3.65 (s, 3H), 3.38 (d, *J* = 1.5 Hz, 1H), 3.36 (d, *J* = 1.2 Hz, 1H), 1.10 (m, 9H). ^{13}C

NMR (101 MHz, $CDCl_3$) δ 211.68, 166.39, 141.92, 124.08, 51.67, 44.70, 39.63, 26.33. IR (neat) ν 2955, 2900, 2818, 1723, 1737, 1221, 892, 739, 663 cm^{-1}.

1-Methyl-2-oxabicyclo[3.1.0]hexan-3-one (159)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (20 mL) and **145** (0.577 g, 2.23 mmol) and lowered into a dry ice/acetone bath. Triethylsilane (0.7 mL, 4.46 mmol) was added followed by boron trifluoride etherate (0.6 mL, 4.46 mmol) and allowed to stir for 12 h. The reaction was then quenched with saturated ammonium chloride (10 mL) and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried with sodium sulfate (*ca.* 15 g) and concentrated in vacuo to afford a red viscous oil. After column chromatography (hexanes:ethyl acetate 15:1, R_f = 0.1) 0.218 g (87 %) of **159** was isolated as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.97 – 2.88 (m, 1H), 2.58 – 2.50 (m, 1H), 1.66 (s, 3H), 1.53 – 1.47 (m, 1H), 0.93 – 0.87 (m, 1H), 0.64 (dd, *J* = 7.0, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.68, 65.03, 34.66, 20.20, 18.57, 15.76. IR (neat) ν 3620, 2990, 2911, 2029, 1770, 1486, 1163, 983, 873, 801 cm^{-1}.

***N*-Benzyl-2-(2-hydroxy-2-methylcyclopropyl)acetamide (160)**

A 10-mL round-bottomed flask, equipped with a septum, nitrogen inlet, and a magnetic stir bar, was charged with **159** (0.384 g, 3.42 mmol) and benzylamine (1.9 mL, 17.1 mmol) and stirred at room temperature for 3 d. Ethyl acetate (30 mL) was added and the solution was washed with 3 N hydrochloric acid (3 x 15 mL), the combined organic

layers were dried with sodium sulfate (*ca.* 15 g) and concentrated in vacuo to give a yellow oil. After column chromatography (hexanes:ethyl acetate 1:1, R_f = 0.25) 0.689 g (92 %) of **160** was isolated as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.17 (m, 5H), 6.34 (s, 1H), 4.56 – 4.32 (m, 2H), 3.86 (s, 1H), 2.59 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.26 (dd, *J* = 14.8, 10.6 Hz, 1H), 1.40 (s, 3H), 0.88 (dddd, *J* = 10.6, 9.1, 5.8, 4.7 Hz, 1H), 0.71 (dd, *J* = 9.0, 5.5 Hz, 1H), 0.52 (t, *J* = 5.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.85, 138.34, 128.94, 127.91, 127.74, 54.43, 43.88, 36.99, 26.01, 22.04, 21.22. IR (neat) ν 3499, 3200, 2993, 2811, 1672, 1559, 1222, 954 cm^{-1}.

5-(1-Hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (162)

A 250-mL round-bottomed flask, equipped with a pressure-equalizing addition funnel with septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (30 mL) and Meldrum's acid (8.1 g, 56.2 mmol). The solution was cooled to 0 °C and pyridine (11.4 mL, 140.6 mmol) was added dropwise over 30 min. Acetyl chloride (3.96 mL, 56.2 mmol) in methylene chloride (20 mL) was added to the addition funnel and added over 2 h. The solution was allowed to warm to room temperature and stir for 12 h. The reaction was diluted with methylene chloride (30 mL), poured over crushed ice and 2 N hydrochloric acid (30 mL). The aqueous phase was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with 2 N hydrochloric acid (2 x 30 mL), brine (20 mL), dried with magnesium sulfate (*ca.* 30 g) and concentrated in vacuo to yield 8.16 g (78 %) of **162** as a light brown solid. MP = 81 – 83 °C (Lit. 82 – 85 °C)[128]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 3H), 1.74 (s, 6H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 194.83, 170.41, 160.68, 105.14, 92.06, 27.36, 27.07, 23.73. IR (neat) ν 3372, 2954, 2766, 1750, 1722, 1245, 1110, 912, 766 cm^{-1}.

1-(2-Oxo-oxazolidin-3-yl)butane-1,3-dione (164)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and condenser with a calcium sulfate drying tube, was charged with toluene (40 mL), acylated Meldrum's acid (**162**) (2.36 g, 13 mmol), and 2-oxazolidone (0.871 g, 10 mmol) and refluxed for 2 h. The solution was then concentrated in vacuo and diluted with ethyl acetate (50 mL). The ethyl acetate was washed with water (20 mL), brine (20 mL), dried with magnesium sulfate (*ca.* 15 g) and concentrated in vacuo to give a bright orange solid. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.6) 1.60 g (72 %) of **164** was isolated in as a light yellow solid. MP = 53 – 55 °C (Lit. 61 -63 °C)[129]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (t, J = 8.1 Hz, 2H), 4.11 – 4.02 (m, 4H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.10, 166.66, 153.94, 62.48, 51.21, 42.36, 30.31. IR (neat) ν 3001, 2904, 2855, 1741, 1700, 1525, 1477, 1422, 1396, 1362, 1014, 962, 880 cm^{-1}.

(*S*)-2-Amino-3-phenylpropan-1-ol (168)

A 3-necked round-bottomed flask, equipped with a mechanical stir rod, condenser, and a nitrogen inlet, was charged with THF (250 mL). The flask was then lowered into an ice bath and lithium aluminum hydride (5.90 g, 156.0 mmol) was added slowly over 10 min. The solution was then refluxed for 15 min then the heating mantle was removed and the solution was allowed to cool to room temperature. Once the solution was at room

tempurature L-phenylalanine (16.519 g, 100 mmol) was added slowly to maintain a gentle reflux. After all of the L-phenylalanine was added the reaction was refluxed for 1 h. The reaction was allowed to cool to room temperature and the excess lithium aluminum hydride was quenched with potassium hydroxide (2.800 g, 12 mL water) through a pressure-equilizing drop funnel. After the addition was complete the solution was refluxed for 15 min and filtered through a Büchner funnel and concentrated in vacuo affording 14.36 g (95 %) of (*S*)-2-amino-3-phenylpropan-1-ol (**168**) as a clear, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.08 (m, 5H), 3.64 (dd, J = 10.6, 3.9 Hz, 1H), 3.38 (dd, J = 10.6, 7.2 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.80 (dd, J = 13.4, 5.2 Hz, 1H), 2.53 (dd, J = 13.5, 8.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.91, 129.42, 128.79, 126.63, 66.64, 54.38, 41.24. IR (neat) ν 3365, 3299, 3122, 3110, 2941, 2919, 2876, 1606, 1494, 1090, 994, 964, 704 cm^{-1}.

Ethyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (106a')

A 250-mL round-bottomed flask equipped with a septum and a magnetic stir bar was charged with water (35 mL), **168** (3.02 g, 20.0 mmol), sodium bicarbonate (8.4 g, 100 mmol), ethyl chloroformate (2.0 mL, 21.0 mmol) and stirred for 1.5 h. The solution was extracted with ethyl acetate (3 x 25 mL) and the organic layer was washed with brine (15 mL), dried with sodium sulfate, filtered, and concentrated in vacuo to afford 4.11 g (92 %) **106a'** as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.07 (m, 5H), 5.09 (s, 1H), 4.22 – 4.01 (m, 2H), 3.92 (s, 1H), 3.72 – 3.43 (m, 2H), 2.91 - 2.76 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.04, 137.96, 129.50, 128.77,

126.77, 64.10, 61.20, 54.22, 37.58, 14.77. IR (neat) ν 3310, 3102, 3001, 2911, 1701, 1129, 1009, 991, 710 cm^{-1}.

(*S*)-4-Benzyloxazolidin-2-one (106a)

A 100-mL round-bottomed flask, equipped with a gas inlet adapter, was charged with **106a'** (4.465 g, 20.0 mmol) and potassium carbonate (0.138 g, 1.0 mmol). The pressure was lowered in the flask to 40 mmHg using a vacuum pump. The flask was then placed in a 125 °C oil bath and maintained at this temperature for 1.5 h. The reaction was then allowed to warm to room temperature and the pressure was released. The mixture was diluted with dichloromethane and washed with 1 N HCl (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried with magnesium sulfate (*ca.* 5 g) and concentrated in vacuo to afford 3.66 g (82 %) of **106a** as a light yellow solid. MP = 86 - 88 °C (Lit. 89 °C)[130]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.10 (m, 5H), 6.05 (s, 1H), 4.42 (t, J = 8.1 Hz, 1H), 4.16 – 4.05 (m, 2H), 2.88 (qd, J = 13.6, 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.80, 136.16, 129.26, 129.20, 127.44, 69.80, 54.01, 41.61. IR (KBr disc) ν 3274, 3055, 2946, 2925, 1766, 1710, 1324, 1096, 1022, 943, 777 cm^{-1}.

(*S*)-1-(4-Benzyl-2-oxooxazolidin-3-yl)butane-1,3-dione (169)

A 250-mL round-bottomed flask, equipped with a magnetic stir bar and reflux condenser, was charged with toluene (100 mL), acyl Meldrum's acid (**162**) (11.76 g, 62.2 mmol), and **106a** (8.80 g, 49.8 mmol). The condenser was equipped with a calcium chloride drying tube and the solution was refluxed for 2 h. The reaction was then cooled to room

temperature, washed with water (2 x 30 mL), dried with sodium sulfate (*ca.* 20 g), and concentrated in vacuo. The resulting orange solid was recrystallized from diethyl ether to afford 10.80 g (83 %) of **169** as a light yellow solid. MP = 98 - 99 °C (Lit. 98 – 99 °C)[90]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.16 (m, 5H), 4.76 – 4.67 (m, 1H), 4.25 – 4.14 (m, 2H), 4.06 (s, 2H), 3.36 (dd, J = 13.5, 3.4 Hz, 1H), 2.84 – 2.78 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.22, 166.62, 153.93, 135.36, 129.68, 129.17, 127.55, 66.61, 55.14, 51.58, 37.84, 30.37, 25.23. IR (neat) ν 3321, 3102, 3002, 2986, 2911, 1725, 1699, 1645, 1294, 1109, 1005, 923, 800, 722 cm^{-1}.

2-(2-Hydroxy-2-methylcyclopropyl)-*N*-((*R*)-1-phenylethyl)acetamide (171 and 172)

A 100-mL round-bottomed flask, equipped with a septum and a magnetic stir bar, was charged with **159** (0.112 g, 1.00 mmol) and (*R*)-1-phenylethanamine (6 mL, 47.0 mmol) and stirred at room temperature for 3 d. The reaction was then diluted with ethyl acetate (25 mL) and washed with 3 N hydrochloric acid (3 x 10 mL), dried with sodium sulfate (*ca.* 10 g), and concentrated in vacuo to yield 0.208 g (89 %) of **171** and **172** as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 6.49 – 6.42 (m, 1H), 5.16 – 5.05 (m, 1H), 4.01 – 3.97 (m, 1H), 2.62 – 2.53 (m, 1H), 2.25 – 2.16 (m, 1H), 1.50 – 1.46 (m, 3H), 1.40 – 1.37 (m, 3H), 0.89 – 0.81 (m, 1H), 0.72 – 0.67 (m, 1H), 0.52 – 0.48 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.08, 143.47, 128.87, 127.54, 126.26, 54.39, 49.00, 37.15, 26.00, 22.25, 22.08, 21.21 cm^{-1}.

5-(1-Hydroxypropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (174)

A 250-mL round-bottomed flask, equipped with a pressure-equalizing addition funnel with septum, magnetic stirbar, and a nitrogen inlet, was charged with methylene chloride (30 mL) and Meldrum's acid (**161**) (3.00 g, 20.8 mmol). The solution was cooled to 0 °C and pyridine (3.4 mL, 41.9 mmol) was added dropwise over 30 min. Propionyl chloride (1.8 mL, 20.8 mmol) in methylene chloride (10 mL) was added to the addition funnel and added to the solution over 2 h. The solution was allowed to warm to room temperature and stir for 12 h. The reaction was then diluted with methylene chloride (30 mL) and poured over crushed ice and 2 N hydrochloric acid (15 mL). The aqueous phase was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with 2 N hydrochloric acid (2 x 15 mL), brine (10 mL), dried with magnesium sulfate (*ca.* 20 g), and concentrated in vacuo to yield **174** as a light yellow solid. The product was recrystallized from diethyl ether to give 3.41 g (82 %) of compound **174** as a white solid. MP = 43 - 47 °C (Lit. 48 – 49 °C)[131]. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 3.01 (q, J = 7.4 Hz, 2H), 1.64 (s, 6H), 1.15 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.00, 170.74, 104.94, 91.07, 29.57, 26.88, 9.81. IR (neat) ν 3002, 2983, 2931, 1799, 1754, 1456, 1423, 1300, 1230, 1167, 1085, 979, 932, 839 cm^{-1}.

1-(2-Oxooxazolidin-3-yl)pentane-1,3-dione (173)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and condenser with a calcium sulfate drying tube, was charged with toluene (40 mL), acylated Meldrum's acid **174** (2.56 g, 12.8 mmol), and 2-oxazolidone (1.11 g, 12.8 mmol) and refluxed for 4 h. The solution was then concentrated in vacuo and diluted with ethyl acetate (50 mL). The

ethyl acetate was washed with water (20 mL), brine (20 mL), dried with magnesium sulfate (*ca.* 20 g) and concentrated in vacuo to give a bright orange solid. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.6) 1.71 g (72 %) of **173** was isolated as a light yellow solid. MP = 59 – 61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 4.58 – 4.30 (m, 2H), 4.23 – 3.92 (m, 4H), 2.59 (qd, *J* = 7.3, 2.6 Hz, 2H), 1.10 (td, *J* = 7.3, 2.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.97, 166.95, 153.94, 62.47, 50.16, 42.40, 36.36, 7.69. IR (neat) ν 3024, 2974, 2888, 1750, 1705, 1519, 1427, 1401, 1345, 1011, 901, 880 cm^{-1}.

3-Acetyloxazolidin-2-one (177)

A dry 25-mL, 2-necked round-bottomed flask, equipped with a glass stopper, magnetic stir bar, and a condenser with a calcium chloride drying tube, was charged with acetyl chloride (4.9 mL, 69.0 mmol) and 2-oxazolidone (2.0 g, 23.0 mmol). The solution was cooled in an ice bath and pyridine (1.9 mL, 23 mmol) was added over a 1 h period. Once all of the pyridine was added, the reaction was gently refluxed for 10 h. The reaction was cooled down and diluted with methylene chloride (100 mL) and washed with 5 % hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried with magnesium sulfate (*ca.* 15 g) and concentrated in vacuo. The solid was washed with diethyl ether and dried to afford 2.33 g (90%) of **177** as a light yellow solid. MP = 64 – 65 °C (Lit. 63 – 64 °C)[132]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (t, J = 8.1 Hz, 2H), 4.13 – 3.97 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.68, 153.93, 62.17, 42.57, 23.45 cm^{-1}.

4,4-Dimethyl-1-(2-oxooxazolidin-3-yl)pentane-1,3-dione (175)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and a nitrogen inlet, was charged with THF (50 mL) and cooled in an ice bath. Diisopropylamine (0.6 mL, 4.0 mmol) was added followed by dropwise addition of *n*-butyllithium (1.5 mL, 2.6 M, 4.0 mmol) and allowed to warm to room temperature. Then the solution was cooled to -78 °C followed by the addition of acyl oxazolidinone (**177**) (0.516 g, 4.0 mmol) in THF (10 mL) over a 1 h perioid. After which, pivaloyl chloride (0.241 g, 2.0 mmol) was added to the solution and stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL) and the reaction was concentrated to half of the volume under reduced pressure (25 mmHg, 30 °C). The aqueous layer was extracted with methylene chloride (3 x 25 mL), the combined organic layers were dried with magnesium sulfate (*ca.* 10 g) and concentrated in vacuo to give a viscous yellow oil. After column chromatography (hexane:ethyl acetate 10:1, $R_f = 0.2$) 0.401 g (47 %) of **175** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 4.46 – 4.37 (m, 2H), 4.16 (s, 2H), 4.10 – 4.00 (m, 2H), 1.17 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.45, 167.94, 153.81, 85.63, 77.59, 77.27, 76.96, 62.38, 62.11, 45.70, 44.65, 42.47, 42.31, 27.74, 26.73. IR (neat) ν 3000, 2905, 2783, 1764, 1721, 1525, 1437, 1417, 1384, 1291, 1012, 962, 880 cm^{-1}.

1-(2-oxooxazolidin-3-yl)-3-phenylpropane-1,3-dione (176)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and a nitrogen inlet, was charged with THF (50 mL) and cooled in an ice bath. Diisopropylamine (0.6 mL, 4.0 mmol) was added followed by dropwise addition of *n*-butyllithium (1.5 mL, 2.6 M, 4.0 mmol) and allowed to warm to room temperature. Then the solution was cooled to -78 °C followed by the addition of acyl oxazolidinone (**177**) (0.516 g, 4.0 mmol) in THF (10 mL) over a 1 h perioid. After which, benzoyl chloride (0.28 g, 2.0 mmol) was added to the solution and stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL) and the reaction was concentrated to half of the volume under reduced pressure (25 mmHg, 30 °C). The aqueous layer was extracted with methylene chloride (3 x 25 mL), the combined organic layers were dried with magnesium sulfate (*ca.* 10 g) and concentrated in vacuo to give a viscous yellow oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.2) 0.438 g (47 %) of **176** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 8.00 – 7.85 (m, 2H), 7.64 – 7.55 (m, 1), 7.55 – 7.38 (m, 2H), 4.62 (s, 2H), 4.47 (t, *J* = 8.1 Hz, 2H), 4.14 (t, *J* = 8.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.51, 174.99, 171.11, 167.48, 153.94, 136.07, 133.98, 132.15, 128.99, 128.46, 126.79, 87.05, 62.53, 62.26, 53.76, 47.09, 42.50, 34.05. IR (neat) ν 3022, 2955, 2701, 1756, 1700, 1529, 1517, 1400, 1390, 1239, 1005, 930, 897 cm^{-1}.

1-Ethyl-2-oxabicyclo[3.1.0]hexan-3-one (178)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (40 mL) and cooled in an ice bath. Diethylzinc (1.0 mL, 10 mmol) was added to the flask and stirred for 10 min at which

time methylene iodide (1.6 mL, 20 mmol) was added dropwise over 5 min. The reaction was allowed to stir for 20 min followed by addition of β-keto imide **173** (0.37 g, 2 mmol). The mixture was allowed to stir for 24 h at room temperature and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried with sodium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.2) 0.106 g (42 %) **178** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (ddd, *J* = 18.8, 6.8, 0.9 Hz, 1H), 2.55 (d, *J* = 18.8 Hz, 1H), 2.00 – 1.78 (m, 2H), 1.50 (dddd, *J* = 8.8, 6.8, 4.9, 0.7 Hz, 1H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.92 (ddd, *J* = 8.8, 7.0, 1.0 Hz, 1H), 0.63 (dd, *J* = 7.0, 4.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.79, 69.79, 34.63, 25.56, 18.97, 14.47, 10.29. IR (neat) ν 2958, 2884, 1722, 1462, 1294, 1171, 921, 900, 884, 728 cm^{-1}.

1-(*tert*-Butyl)-2-oxabicyclo[3.1.0]hexan-3-one (179)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (40 mL) and cooled in an ice bath. Diethylzinc (1.0 mL, 10 mmol) was added to the flask and stirred for 10 min at which time methylene iodide (1.6 mL, 20 mmol) was added dropwise over 5 min. The reaction was allowed to stir for 20 min followed by addition of β-keto imide **175** (0.43 g, 2 mmol). The mixture was allowed to stir for 24 h at room temperature and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL),

dried with sodium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.2) 0.163 g (53 %) of compound **179** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (dd, *J* = 18.8, 6.6 Hz, 1H), 2.57 (d, *J* = 18.8 Hz, 1H), 1.59 (dddd, *J* = 9.0, 6.6, 5.0, 0.7 Hz, 1H), 1.11 (ddd, *J* = 9.0, 7.1, 0.9 Hz, 1H), 1.00 (s, 9H), 0.50 (dd, *J* = 7.1, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.72, 76.28, 34.58, 31.70, 26.38, 16.44, 12.72. IR (neat) ν 2911, 2760, 1739, 1349, 1254, 1041, 997, 934, 809, 779 cm^{-1}.

1-phenyl-2-oxabicyclo[3.1.0]hexan-3-one (180)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (40 mL) and cooled in an ice bath. Diethylzinc (1.0 mL, 10 mmol) was added to the flask and stirred for 10 min at which time methylene iodide (1.6 mL, 20 mmol) was added dropwise over 5 min. The reaction was allowed to stir for 20 min followed by addition of β-keto imide **176** (0.47 g, 2 mmol). The mixture was allowed to stir for 24 h at room temperature and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried with sodium sulfate (*ca.* 5 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.2) 0.146 g (42 %) compound **180** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 7.33 – 7.24 (m, 3H), 3.07 (dd, *J* = 18.8, 6.8 Hz, 1H), 2.71 (d, *J* = 18.8 Hz, 1H), 1.98 (dt, *J* = 8.9, 6.1 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.14 (dd, *J* = 7.3, 5.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.04, 136.95, 128.82, 127.84, 124.67, 68.53, 34.44, 22.80, 19.88. IR (neat) ν 2984, 2778, 1722, 1301, 1253, 1032, 997, 909, 811, 702 cm^{-1}.

1,3-Diphenylpropane-1,3-dione (191)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and a nitrogen inlet, was charged with THF (50 mL) and cooled in an ice bath. Diisopropylamine (0.6 mL, 4.0 mmol) was added followed by drop-wise addition of *n*-butyllithium (1.5 mL, 2.6 M, 4.0 mmol), after which the solution was allowed to warm to room temperature. Then the solution was cooled to -78 °C followed by the addition of acetophenone (0.481 g, 4.0 mmol) in THF (10 mL) over a 1 h perioid. Benzoyl chloride (0.2 mL, 2.0 mmol) was then added to the solution, which was stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL) and the reaction was concentrated to half of the volume under reduced pressure (25 mmHg, 30 °C). The solution was extracted with methylene chloride (3 x 25 mL) and the combined organic layers were dried with magnesium sulfate (*ca.* 10 g) and concentrated in vacuo to give a bright yellow solid. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.1) 0.439 g (49 %) of **191** was isolated as a white solid. MP = 77 – 79 °C (Lit. 79 °C)[133]. ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.98 (d, J = 7.8 Hz, 4H), 7.57 – 7.51 (m, 2H), 7.47 (t, J = 7.4 Hz, 4H), 6.85 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.98, 135.76, 132.70, 128.92, 127.41, 93.38. IR (neat) ν 3066, 3048, 1963, 1900, 1810, 1603, 1561, 1029, 1001, 964, 506 cm^{-1}.

2-((1*R*,2*R*)-2-Hydroxy-2-phenylcyclopropyl)-1-phenylethanone (192)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (40 mL) and cooled in an ice bath. Diethylzinc (1.0 mL, 10 mmol) was added to the flask and stirred for 10 min, at which time methylene iodide (1.6 mL, 20 mmol) was added drop-wise over 5 min. The reaction was allowed to stir for 20 min followed by addition of dibenzoylmethane (**191**) (0.45 g, 2 mmol). The mixture was allowed to stir for 24 h at room temperature and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried with sodium sulfate (*ca.* 10 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.1) 0.262 g (52 %) of **192** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.96 (m, 2H), 7.66 – 7.14 (m, 8H), 3.69 (dd, *J* = 17.1, 5.2 Hz, 1H), 3.18 (s, 1H), 3.01 (dd, *J* = 17.2, 8.9 Hz, 1H), 1.55 (tdd, *J* = 9.0, 6.7, 5.2 Hz, 1H), 1.34 (dd, *J* = 9.5, 5.8 Hz, 1H), 1.08 – 1.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.41, 144.68, 136.93, 133.62, 128.91, 128.60, 128.52, 126.86, 125.36, 59.03, 37.99, 23.70, 22.58. IR (neat) ν 3302, 3009, 2911, 1733, 1608, 1109,1004, 992, 821 cm^{-1}.

192(D)

A 50-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with D_2O (10 mL) and sodium methoxide (0.019 g, 0.35 mmol) followed by addition of **192** (0.22 g, 0.87 mmol) in D_2O (5 mL). The reaction was

allowed to stir at room temperature for 5 h, at which time ethyl acetate (10 mL) and 1 N HCl (5mL) were added. The organic phase was separated, washed with water (10 mL), brine (10 mL), dried with sodium sulfate (*ca.* 10 g), and concentrated in vacuo to afford 0.199 g of **192(D)** as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 7.86 (m, 4H), 7.62 – 7.38 (m, 6H), 4.33 – 3.93 (m, 1H), 3.73 (t, J = 6.7 Hz, 1H), 3.08 (dd, J = 12.3, 6.8 Hz, 1H), 2.14 (s, 1H), 1.38 – 1.12 (m, 1H), 1.00 – 0.76 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.21, 137.03, 133.31, 128.83, 128.73, 128.55, 128.50, 128.29, 53.70, 37.70, 37.54, 37.35, 37.19, 37.01, 36.82, 29.93, 23.48, 18.63, 18.43, 18.23. IR (neat) ν 3122, 3001, 2930, 2899, 1701, 1661, 1199, 1009, 905, 821 cm^{-1}.

(*S*)-1-(4-Benzyl-2-oxooxazolidin-3-yl)-4,4-dimethylpentane-1,3-dione (194)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and a nitrogen inlet, was charged with THF (50 mL) and cooled in an ice bath. Diisopropylamine (0.6 mL, 4.0 mmol) was added followed by dropwise addition of *n*-butyllithium (1.5 mL, 2.6 M, 4.0 mmol) and the solution allowed to warm to room temperature. The solution was cooled to -78 °C followed by the addition of acyl oxazolidone (**177**) (0.876 g, 4.0 mmol) in THF (10 mL) over a 1 h perioid. Pivaloyl chloride (0.241 g, 2.0 mmol) was then added to the solution and stirred for 12 h. The reaction was quenched with saturated ammonium chloride (20 mL) and the mixture was concentrated to half of the volume under reduced pressure (25 mmHg, 30 °C). The solution was extracted with methylene chloride (3 x 25 mL), the combined organic layers were dried with magnesium sulfate (*ca.* 10 g) and concentrated in vacuo to give a viscous yellow oil. After column

chromatography (hexane:ethyl acetate 10:1, R_f = 0.3) 0.461 g (38 %) of **194** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 7.29 (ddd, *J* = 15.6, 12.9, 6.9 Hz, 5H), 4.73 (ddd, *J* = 13.5, 7.1, 3.3 Hz, 1H), 4.31 – 4.01 (m, 4H), 3.43 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.79 (dd, *J* = 13.5, 10.0 Hz, 1H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.57, 167.88, 153.77, 135.56, 129.66, 129.17, 127.51, 66.50, 55.34, 46.04, 44.71, 37.95, 27.79, 26.77. IR (neat) ν 3321, 3001, 2974, 2944, 1722, 1701, 1190, 1009, 1000, 918, 782 cm^{-1}.

(*S*)-4-Benzyl-3-((1*S*,2*S*)-2-(3,3-dimethyl-2-oxobutyl)-1-((trimethylsilyl)oxy) cyclopropyl)oxazolidin-2-one (193)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (40 mL) and cooled in an ice bath. Diethylzinc (1.0 mL, 10.0 mmol) was added to the flask and stirred for 10 min at which time methylene iodide (1.6 mL, 20.0 mmol) was added dropwise over 5 min. The reaction was allowed to stir for 20 min followed by addition of β-keto imide **194** (0.61 g, 2.0 mmol) and trimethylsilyl chloride (0.3 mL, 2.2 mmol). The mixture was allowed to stir for 24 h at room temperature and quenched with saturated ammonium chloride (20 mL). The aqueous layer was extracted with methylene chloride (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried with sodium sulfate (*ca.* 10 g), filtered, and concentrated in vacuo to give a yellow viscous oil. After column chromatography (hexane:ethyl acetate 10:1, R_f = 0.4) 0.315 g (39 %) of compound **193** was isolated as an oily clear solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz,

3H), 7.36 (dd, J = 10.3, 4.8 Hz, 2H), 4.31 (ddd, J = 11.5, 8.0, 3.9 Hz, 1H), 4.08 – 3.91 (m, 2H), 3.44 (dd, J = 13.0, 3.6 Hz, 1H), 2.76 (dd, J = 18.5, 3.3 Hz, 1H), 2.61 (d, J = 9.9 Hz, 1H), 1.60 (dd, J = 10.2, 6.5 Hz, 1H), 1.18 (s, 9H), 0.92 (t, J = 6.4 Hz, 1H), 0.51 (dd, J = 7.2, 5.1 Hz, 1H), 0.21 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.25, 172.56, 153.77, 135.50, 129.68, 129.14, 127.51, 66.44, 55.30, 53.67, 44.17, 37.98, 30.91, 29.97, 26.84. IR (neat) ν 3321, 3199, 2900, 2298, 1782, 1701, 1300, 1127, 734 cm^{-1}.

2-(2-(*tert*-Butyl)-2-hydroxycyclopropyl)-*N*-((*R*)-1-phenylethyl)acetamide (199 and 200)

A 100-mL round-bottomed flask, equipped with a septum and a magnetic stir bar, was charged with bicyclic lactone **179** (0.154 g, 1.00 mmol) and (*R*)-1-phenylethanamine (6 mL, 47.0 mmol) and stirred at room temperature for 3 d. The reaction solution was then diluted with ethyl acetate (25 mL) and washed with 3 N hydrochloric acid (3 x 10 mL), dried with sodium sulfate (*ca.* 5 g), and concentrated in vacuo to yield 0.242 g (88 %) of **199** and **200** as a light yellow oil. ^{1}H NMR analysis used for diastereoselectivity.

(*S*)-1-((Benzyloxy)carbonyl)pyrrolidine-2-carboxylic acid (201)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and a septum, was charged with water (50 mL), sodium hydroxide (1.6 g, 40 mmol), and L-proline (2.32, 20 mmol) in the indicated order. The mixture was cooled in an ice bath and Cbz-Cl (3.5 mL, 25 mmol) was added over a 0.5 h period. The reaction was allowed to stir vigorously for 4 h and then poured into a separatory funnel. The un-reacted Cbz-Cl was extracted with

diethyl ether (3 x 20 mL). The aqueous phase was acidified to pH ~ 2 and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried with sodium sulfate (*ca.* 20 g) and concentrated in vacuo to afford 5.23 g (84 %) **201** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotameric form* δ 9.02 (s, 1H), 7.57 – 7.12 (m, 5H), 5.34 – 5.02 (m, 2H), 4.51 – 4.31 (m, 1H), 3.65-3.44 (m, 2H), 2.38 – 1.75 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.41, 176.57, 156.08, 154.64, 136.69, 136.50, 128.95, 128.74, 128.63, 128.37, 128.18, 128.12, 127.89, 127.26, 67.77, 67.37, 59.52, 58.85, 47.16, 46.89, 31.13, 29.55, 24.53, 23.69. IR (neat) ν 3411, 3011, 2991, 1688, 1005, 981, 881, 770 cm^{-1}.

(*S*)-Benzyl 2-(3-oxo-3-(2-oxooxazolidin-3-yl)propanoyl)pyrrolidine-1-carboxylate (202)

A dry, 250-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with THF (100 mL) and placed in an ice bath. A separate 250-mL round-bottomed flask equipped with a magnetic stir bar, septum, and a nitrogen inlet was charged with THF (50 mL), Cbz-proline **201** (1.71 g, 6.85 mmol), and carbonyl diimidizole (1.22 g, 7.54 mmol). Diisopropylamine (3.8 mL, 27.4 mmol) was added to the first round-bottomed flask followed by *n*-butyllithium (11.0 mL, 2.5 M, 6.85 mmol) and the solution was allowed to stir at 0 °C for 10 min, at which time the flask was placed in a dry ice/acetone bath. To this flask, acyl oxazolidone **177** (3.54 g, 6.85 mmol) in THF (20 mL) was slowly added via a syringe pump over a 1 h period. This solution was then allowed to warm to room temperature and the second round-bottomed flask was placed into a dry ice/acetone. The contents of the first flask was added to the second flask via

cannula and the resulting solution was allowed to stir for 2 h at -78 °C. The reaction was allowed to warm to room temperature and quenched with 1 N HCl (20 mL). The reaction mixture was then concentrated to half of its volume and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried with sodium sulfate (*ca.* 20 g) and concentrated in vacuo to afford a yellow oil. After column chromatography (hexanes:ethyl acetate 5:1, R_f = 0.1) 0.790 g (32 %) of compound **202** was isolated as a clear viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.15 (m, 5H), 5.22 – 5.05 (m, 2H), 4.54 – 4.35 (m, 3H), 4.31 – 4.13 (m, 2H), 4.12 – 3.96 (m, 2H), 3.68 – 3.43 (m, 2H), 2.33 – 1.82 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.18, 203.10, 166.49, 166.27, 155.28, 153.72, 136.61, 128.56, 128.51, 128.22, 127.86, 67.39, 67.18, 65.28, 65.07, 62.29, 62.27, 48.02, 47.38, 47.35, 46.86, 42.27, 29.61, 28.44, 24.39, 23.55. IR (neat) ν 3321, 3001, 2974, 2944, 1722, 1701, 1190, 1009, 1000, 918, 782 cm^{-1}.

(*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid (204)

A 250-mL round-bottomed flask, equipped with a magnetic stir bar and a nitrogen inlet, was charged with dioxane (40 mL), water (40 mL), sodium hydroxide (0.8 g, 20 mmol), and L-proline (2.32 g, 20 mmol) in the indicated order. This solution was stirred for 15 min and then cooled in an ice bath. Di-*tert*-butyl dicarbonate (4.8 g, 22 mmol) was added and the mixture was stirred for 12 h, then the solution was washed with diethyl ether (3 x 20 mL). The aqueous layer was then acidified to pH ~ 3 and extracted with ethyl acetate (3 x 30 mL). The organic layer was dried with magnesium sulfate (*ca.* 20 g), and

concentrated in vacuo to afford 3.14 g (73 %) of **204** as a white solid. MP = 133 – 136 °C (Lit. 133 – 136 °C)[134]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 4.39 – 4.22 (m, 1H), 3.62 – 3.33 (m, 2H), 2.36 – 2.18 (m, 1H), 2.16 – 2.02 (m, 1H), 2.02 – 1.83 (m, 2H), 1.70 – 1.17 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.64, 175.69, 156.01, 153.96, 81.12, 80.38, 59.03, 58.96, 46.92, 46.35, 30.84, 28.94, 28.93, 28.40, 28.27, 24.31, 23.65. IR (neat) ν 3309, 3005, 2901, 2880, 1700, 1632, 1007, 991, 829 cm^{-1}.

(*S*)-*tert*-Butyl-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl) pyrrolidine-1-carboxylate DMAP salt (206)

A 100-mL round-bottomed flask, equipped with a septum, maganetic stir bar, and a nitrogen inlet, was charged with methylene chloride (10 mL) and lowered into an ice bath. Boc-proline **(204)** (1.04 g, 4.86 mmol) in methylene chloride (5 mL) was added followed by dicyclohexylcarbodiimide (1.00 g, 4.86 mmol), Meldrum's acid (0.70 g, 4.86 mmol), and *N, N*-dimethyl aminopyridine (0.59 g, 4.86 mmol) in the indicated order. The solution was allowed to stir at room temperature for 12 h, at which time the dicyclohexylurea was removed by filtration and the filtrate was concentrated in vacuo to afford 1.93 g (86 %) of **206** as a white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 – 8.17 (m, 2H), 6.90 – 6.45 (m, 2H), 5.69 – 5.34 (m, 1H), 3.80 – 3.36 (m, 2H), 3.21 (s, 6H), 2.68 – 2.22 (m, 1H), 2.02 – 1.87 (m, 1H), 1.82 – 1.72 (m, 2H), 1.70 – 1.34 (m, 9H), 1.29 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.31, 166.50, 157.16, 155.40, 141.68, 106.54, 101.16, 87.10, 78.57, 64.54, 47.44, 40.15, 31.66, 28.91, 28.61, 26.59, 26.50, 23.23. IR (neat) ν 3201, 3019, 2900, 2811, 1770, 1633, 1142, 910, 729 cm^{-1}.

(*S*)-*tert*-butyl-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl) pyrrolidine-1-carboxylate (207)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (10 mL), (*S*)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl)pyrrolidine-1-carboxylate DMAP salt **206** (0.46 g, 1 mmol), and anhydrous Dowex 50W-X2 (1.5 g) ion exchange resin. The solution was stirred for 20 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give 0.314 g (92 %) of **207** as a yellow, viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (dd, J = 9.0, 4.5 Hz, 1H), 3.64 – 3.48 (m, 2H), 2.64 – 2.48 (m, 1H), 2.12 – 1.83 (m, 4H), 1.74 (dd, J = 8.2, 4.0 Hz, 6H), 1.48 – 1.36 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.65, 197.81, 170.92, 159.98, 154.39, 153.60, 105.67, 105.55, 90.63, 89.90, 80.26, 80.15, 59.45, 59.34, 47.58, 47.31, 36.38, 32.57, 31.62, 28.64, 28.51, 27.82, 27.28, 26.90, 26.67, 26.15, 24.78, 24.59, 23.84. IR (neat) ν 3211, 3033, 2900, 1722, 1630, 1002, 981, 810 cm^{-1}.

(*S*)-*tert*-Butyl 2-(3-oxo-3-(2-oxooxazolidin-3-yl)propanoyl)pyrrolidine-1-carboxylate (208)

A 100-mL round-bottomed flask, equipped with a condenser fitted with a drying tube and a magnetic stir bar, was charged with toluene (20 mL), 2-oxazolidone (0.09 g, 1.00 mmol), and (*S*)-*tert*-butyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy) methyl)pyrrolidine-1-carboxylate **207** (0.34 g, 1.00 mmol) and refluxed for 5 h. The

reaction was then allowed to cool to room temperature and the mixture was washed with water (10 mL), brine (10 mL), and the organic layer was dried with sodium sulfate (*ca.* 10 g) and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.3) 0.267 g (82 %) of compound **208** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 – 6.21 (m, 1H), 4.56 – 4.31 (m, 2H), 4.34 – 4.01 (m, 4H), 3.68 – 3.35 (m, 2H), 2.32 – 2.09 (m, 2H), 2.09 – 1.81 (m, 2H), 1.76 – 1.10 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.84, 166.83, 154.05, 153.83, 80.98, 80.25, 80.11, 65.65, 65.06, 62.45, 47.99, 47.18, 47.09, 46.98, 46.86, 42.46, 29.80, 28.60, 28.44, 24.60, 23.94. IR (neat) ν 3299, 3110, 3007, 2901, 1702, 1609, 1114, 991, 880 cm^{-1}.

(*S*)-Benzyl-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl) pyrrolidine-1-carboxylate DMAP salt (210)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (10 mL) and lowered into an ice bath. Cbz-proline **112** (1.21 g, 4.86 mmol) in methylene chloride (5 mL) was added followed by dicyclohexylcarbodiimide (1.00 g, 4.86 mmol), Meldrum's acid (0.70 g, 4.86 mmol), and *N, N*-dimethyl aminopyridine (0.59 g, 4.86 mmol) in the indicated order. This solution was allowed to stir at room temperature for 12 h, at which time the dicyclohexylurea was filtered off and the solution was concentrated in vacuo to afford 1.95 g (81 %) of **210** as a white oily solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.02 (m, 2H), 7.42 – 6.99 (m, 5H), 6.56 (dd, J = 5.9, 1.5 Hz, 2H), 5.60 (dd, J = 8.9, 3.3 Hz, 1H),

5.37 – 4.84 (m, 4H), 3.77 – 3.40 (m, 2H), 3.20 - 3.12 (m, 6H), 2.61 – 2.10 (m, 1H), 2.08 – 1.80 (m, 3H), 1.75 – 1.55 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.45, 166.45, 157.09, 155.60, 141.27, 137.46, 128.58, 128.32, 127.93, 127.60, 127.54, 127.36, 127.31, 127.17, 106.47, 101.24, 87.35, 66.15, 64.56, 48.08, 40.12, 31.83, 27.77, 26.59, 26.56, 26.46, 23.14. IR (neat) ν 3211, 3000, 2929, 2901, 1711, 1605, 1105, 940, 710 cm^{-1}.

(*S*)-Benzyl-2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl) pyrrolidine-1-carboxylate (211)

A 100-mL round-botttomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (10 mL), (*S*)-benzyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl)pyrrolidine-1-carboxylate DMAP salt **210** (0.49 g, 1.00 mmol), and anhydrous Dowex 50W-X2 (1.5 g) ion exchange resin. This solution was stirred for 20 min. The resin was removed by filtration and the filtrate concentrated in vacuo to give 0.338 g (90 %) of **211** as a yellow, viscous oil. ^1H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 7.46 – 7.23 (m, 5H), 5.63 - 5.56 (m, 1H), 5.33 – 4.85 (m, 2H), 3.79 – 3.56 (m, 2H), 2.12 – 1.89 (m, 4H), 1.80 - 1.66 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.88, 196.51, 170.47, 162.85, 159.82, 154.69, 153.96, 136.55, 136.24, 128.57, 128.53, 128.47, 128.41, 128.32, 128.23, 128.14, 128.11, 128.07, 127.97, 127.88, 127.80, 127.76, 106.26, 105.62, 105.40, 90.86, 90.29, 67.31, 67.14, 59.51, 58.94, 47.78, 47.28, 36.19, 32.32, 31.34, 27.64, 27.17, 27.03, 26.00, 24.49, 23.68. IR (neat) ν 3300, 3211, 3002, 2991, 2971, 1701, 1682, 1102, 991, 837 cm^{-1}.

(*S*)-Benzyl 2-(3-oxo-3-(2-oxooxazolidin-3-yl)propanoyl)pyrrolidine-1-carboxylate (202)

A 100-mL round-bottomed flask, equipped with a condenser fitted with a drying tube (cacium sulfate) and a magnetic stir bar, was charged with toluene (20 mL), 2-oxazolidone (0.09 g, 1.00 mmol), and (*S*)-benzyl 2-((2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)(hydroxy)methyl)pyrrolidine-1-carboxylate **211** (0.38 g, 1.00 mmol) and refluxed for 5 h. The reaction was then allowed to cool to room temperature and the toluene mixture was washed with water (10 mL) and brine (10 mL). The organic layer was dried with sodium sulfate (*ca.* 10 g) and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.3) 0.281 g (78 %) of compound **202** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.18 (m, 5H), 5.31 – 5.01 (m, 2H), 4.60 – 4.37 (m, 3H), 4.27 – 4.12 (m, 2H), 4.10 – 3.97 (m, 2H), 3.64 – 3.44 (m, 2H), 2.35 – 1.79 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.88, 196.51, 170.47, 162.85, 159.82, 154.69, 153.96, 136.55, 136.24, 128.57, 128.53, 128.47, 128.41, 128.32, 128.23, 128.14, 128.11, 128.07, 127.97, 127.88, 127.80, 127.76, 106.26, 105.62, 105.40, 90.86, 90.29, 67.31, 67.14, 59.51, 58.94, 47.78, 47.28, 36.19, 32.32, 31.34, 27.64, 27.17, 27.03, 26.00, 24.49, 23.68. IR (neat) ν 3321, 3001, 2974, 2944, 1722, 1701, 1190, 1009, 1000, 918, 782 cm^{-1}.

(2*S*)-Benzyl 2-(3-oxo-2-oxabicyclo[3.1.0]hexan-1-yl)pyrrolidine-1-carboxylate (212)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged methylene chloride (30 mL) and cooled in an ice bath.

Diethylzinc (0.5 mL, 5.00 mmol) was added and allowed to stir at 0 °C for 5 min. Methylene iodide (0.8 mL, 10.0 mmol) was added to the flask dropwise over 5 min and the solution was allowed to stir for 20 min. β-Keto imide **202** (0.36 g, 1.00 mmol) in methylene chloride (5 mL) was then syringed into the milky white mixture and allowed to stir at room temperature for 24 h. The reaction was then cooled down in an ice bath and saturated ammonium chloride (20 mL) was added slowly. The organic phase was separated, washed with water (10 mL), brine (10 mL), dried with sodium sulfate (*ca.* 10 g), and concentrated in vacuo to obtain a viscous, yellow oil. After column chromatography (hexane:ethyl acetate 5:1) two diastereomers were separated. Major: (Hexane:ethyl acetate 1:1, R_f = 0.5) 0.096 g (32 %) of **212** as a clear oil. Minor: (Hexane:ethyl acetate 1:1, R_f = 0.4) 0.067 g (22 %) of **212** as a clear oil. ***Major diastereomer*:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.41 – 4.83 (m, 2H), 3.75 (d, *J* = 7.3 Hz, 1H), 3.51 (s, 2H), 3.14 – 2.68 (m, 1H), 2.61 – 2.38 (m, 1H), 2.33 – 2.00 (m, 3H), 1.98 – 1.72 (m, 1H), 0.99 (t, *J* = 7.8 Hz, 1H), 0.61 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.81, 155.60, 137.01, 128.88, 128.72, 128.15, 127.76, 70.05, 67.39, 66.97, 59.97, 58.84, 48.01, 47.60, 34.01, 33.69, 30.68, 29.69, 24.24, 23.42, 17.68, 17.16, 16.78. IR (neat) ν 3002, 2981, 2881, 1701, 1119, 990, 877 cm^{-1}.

(*S*)-2-(((Benzyloxy)carbonyl)(4-methoxybenzyl)amino)-3-methylbutanoic acid (214)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and septum, was charged with water (50 mL), sodium hydroxide (1.6 g, 40.0 mmol), and PMB-valine **213** (4.75, 20 mmol) in the indicated order. The mixture was cooled in an ice bath and Cbz-

Cl (3.5 mL, 25 mmol) was added over a 0.5 h period. The reaction was allowed to stir vigorously for 4 h and then poured into a separatory funnel. The un-reacted Cbz-Cl was extracted with diethyl ether (3 x 20 mL). The aqueous phase was acidified to pH ~ 2 (3 N HCl) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried with sodium sulfate (*ca.* 25 g) and concentrated in vacuo to afford 5.87 g (79 %) of **214** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.79 – 6.53 (m, 9H), 5.39 – 5.01 (m, 2H), 4.27 (d, J = 71.2 Hz, 1H), 4.02 – 3.47 (m, 2H), 2.22 (s, 1H), 1.31 – 0.55 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.44, 155.40, 135.07, 129.93, 128.75, 128.68, 127.66, 127.51, 127.43, 127.40, 127.34, 127.22, 127.10, 126.24, 112.67, 112.58, 109.31, 109.22, 66.17, 65.37, 57.83, 54.29, 54.16, 34.05, 33.98, 30.01, 19.97, 17.96, 16.31. IR (neat) ν 3401, 3119, 2991, 2899, 1659, 1200, 1008, 980, 770 cm^{-1}.

(*S*)-Benzyl-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-methylbutan-2-yl)(4-methoxybenzyl)carbamate DMAP salt (217)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet was charged with methylene chloride (10 mL) and cooled in an ice bath. *N,N*-PMB-Cbz-Valine (**214**) (1.81 g, 4.86 mmol) in methylene chloride (5 mL) was added followed by dicyclohexylcarbodiimide (1.00 g, 4.86 mmol), Meldrum's acid (0.70 g, 4.86 mmol), and *N, N*-dimethyl aminopyridine (0.59 g, 4.86 mmol) in the indicated order. This solution was allowed to stir at room temperature for 12 h, at which time the dicyclohexylurea was removed by filtration. The solution was concentrated in vacuo to afford 2.44 g (81 %) of compound **217** as a white oily solid. The product was carried on

to the next step without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 7.1 Hz, 2H), 7.47 – 6.90 (m, 9H), 6.65 (d, J = 11.6 Hz, 2H), 5.20 – 4.99 (m, 2H), 4.62 – 4.20 (m, 2H), 3.74 – 3.62 (m, 3H), 3.08 (s, 6H), 2.32 (qd, J = 13.2, 6.6 Hz, 1H), 1.64 (s, 6H), 0.91 - 0.67 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.38, 167.58, 158.62, 156.57, 156.36, 142.00, 136.32, 135.43, 129.62, 113.51, 106.78, 103.13, 67.48, 66.46, 64.81, 55.65, 55.15, 55.13, 39.69, 34.90, 33.85, 28.08, 26.28, 26.21, 25.41, 25.04, 24.61, 18.93. IR (neat) ν 3329, 3019, 2993, 2834, 1722, 1700, 1603, 1189, 1006, 925, 729 cm^{-1}.

(*S*)-benzyl (1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-methylbutan-2-yl)(4-methoxybenzyl)carbamate (216)

A 100-mL round-botttomed, flask equipped with a magnetic stir bar, septum, and a nitrogen inlet was charged with methylene chloride (10 mL), (*S*)-benzyl (1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-methylbutan-2-yl)(4-methoxybenzyl)carbamate DMAP salt (**217**) (0.62 g, 1 mmol), and anhydrous Dowex 50W-X2 (1.5 g) ion exchange resin. The solution was stirred for 20 min, then filtered and concentrated in vacuo to give 0.458 g (92 %) of compound **216** as a yellow, viscous oil. Compound **216** was carried along without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 6.56 (m, 9H), 6.02 (d, J = 10.4 Hz, 1H), 5.21 (dt, J = 31.0, 9.9 Hz, 2H), 4.69 – 4.26 (m, 2H), 3.86 – 3.53 (m, 3H), 2.34 – 2.01 (m, 1H), 1.88 – 1.48 (m, 6H), 1.23 – 0.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.30, 163.07, 158.80, 136.57, 130.76, 129.88, 129.57, 128.80, 113.84, 106.48, 105.17, 67.45, 55.45, 36.64, 31.87, 28.22, 27.84,

27.22, 27.09, 26.61, 19.90, 19.06, 17.48. IR (neat) ν 3314, 3091, 2900, 2805, 1730, 1692, 1301, 1108, 1005, 921, 888, 729 cm^{-1}.

(*S*)-Benzyl 4-methoxybenzyl(2-methyl-4,6-dioxo-6-(2-oxooxazolidin-3-yl)hexan-3-yl) carbamate (215)

A 100-mL round-bottomed flask, equipped with a condenser fitted with a drying tube, and a magnetic stir bar, was charged with toluene (20 mL), 2-oxazolidone (0.09 g, 1.00 mmol), and (*S*)-benzyl (1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-methylbutan-2-yl)(4-methoxybenzyl)carbamate (**216**) (0.50 g, 1.00 mmol). The solution was heated to reflux for 5 h. The reaction was allowed to cool to room temperature and the toluene solution was washed with water (10 mL) and brine (10 mL). The organic layer was dried with sodium sulfate (*ca.* 20 g) and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.3) 0.347 g (72 %) of compound **215** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer* δ 7.57 – 6.57 (m, 9H), 5.43 – 5.03 (m, 2H), 4.82 (d, *J* = 14.4 Hz, 1H), 4.52 (dd, *J* = 25.4, 17.5 Hz, 1H), 4.38 – 4.08 (m, 4H), 4.05 – 3.85 (m, 3H), 3.76 (s, 3H), 3.54 (d, *J* = 16.8 Hz, 1H), 3.28 (d, *J* = 16.7 Hz, 1H), 2.49 – 2.34 (m, 1H), 0.96 (dd, *J* = 11.3, 6.5 Hz, 3H), 0.77 (dd, *J* = 21.6, 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.19, 200.01, 177.97, 170.79, 170.60, 166.97, 166.91, 159.45, 159.26, 156.67, 156.39, 153.69, 153.64, 136.41, 136.12, 131.04, 130.39, 129.58, 129.47, 128.77, 128.72, 128.44, 128.40,

128.37, 114.18, 114.04, 113.66, 70.91, 70.35, 68.16, 68.12, 62.41, 62.20, 55.43, 50.12, 48.65, 47.97, 42.54, 42.31, 42.22, 27.29, 27.18, 26.66, 23.40, 21.55, 20.84, 19.10. IR (neat) ν 3203, 3009, 2931, 2870, 1790, 1702, 1629, 1104, 1003, 930, 901, 832 cm^{-1}.

(*S*)-Benzyl-(3,5-dioxo-5-(2-oxooxazolidin-3-yl)-1-phenylpentan-2-yl)(4-methoxybenzyl)carbamate (221)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar and septum was charged with water (50 mL), sodium hydroxide (1.6 g, 40 mmol), and PMB-phenylalanine (**220**) (7.71 g, 20 mmol) in the indicated order. The mixture was cooled in an ice bath and Cbz-Cl (3.5 mL, 25 mmol) was added over a 0.5 h period. The reaction was allowed to stir for 4 h and then the solution was poured into a separatory funnel. The un-reacted Cbz-Cl was extracted with diethyl ether (3 x 20 mL). The aqueous phase was acidified to pH ~ 2 (3 N HCl) and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried with sodium sulfate (*ca.* 30 g) and concentrated in vacuo to afford 7.05 g (84 %) of **221** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotameric form* δ 7.40 – 7.10 (m, 14H), 5.33 – 5.06 (m, 2H), 4.80 – 4.37 (m, 2H), 3.76 (s, 3H), 3.70 – 3.56 (m, 1H), 3.34 – 3.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.43, 175.55, 159.20, 156.48, 156.04, 137.82, 136.49, 135.71, 130.37, 129.67, 129.57, 129.47, 128.90, 128.76, 128.54, 128.45, 128.39, 128.33, 128.20, 127.45, 126.89, 114.02, 68.13, 67.92, 67.35, 62.06, 60.61, 55.46, 54.81, 52.17, 37.96, 36.47, 35.28. IR (neat) ν 3309, 3011, 2922, 2881, 1711, 1633, 1110, 1000, 933, 782 cm^{-1}.

(*S*)-Benzyl-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-phenylpropan-2-yl)(4-methoxybenzyl)carbamate DMAP salt (222)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (10 mL) and cooled in an ice bath. *N,N*-PMB-Cbz-Phenylalanine (**221**) (2.03 g, 4.86 mmol) in methylene chloride (5 mL) was added followed by dicyclohexyl carbodiimide (1.00 g, 4.86 mmol), Meldrum's acid (0.70 g, 4.86 mmol), and *N, N*-dimethylaminopyridine (0.59 g, 4.86 mmol) in the indicated order. The solution was allowed to stir at room temperature for 12 h, at which time the dicyclohexylurea was removed by filtration. The filtrate was concentrated in vacuo to afford 2.60 g (80 %) of **222** as a yellow oily solid. Compound **222** was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer and rotomer* δ 8.13 (dd, *J* = 5.7, 1.5 Hz, 2H), 7.83 – 6.60 (m, 9H), 6.52 (d, *J* = 1.5 Hz, 2H), 5.36 – 4.90 (m, 2H), 4.75 – 4.04 (m, 2H), 3.89 – 3.66 (m, 2H), 3.51 – 3.23 (m, 2H), 3.10 (s, 6H), 1.79 – 1.64 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.09, 194.84, 170.58, 167.02, 166.66, 166.42, 165.34, 156.30, 143.61, 130.33, 129.62, 129.49, 129.23, 128.95, 128.72, 128.64, 128.45, 128.25, 128.14, 127.85, 127.61, 127.24, 125.88, 113.80, 113.54, 106.64, 101.24, 87.59, 67.13, 67.01, 55.96, 55.39, 39.86, 35.14, 34.15, 33.58, 27.15, 26.62, 26.48, 26.32, 25.87, 25.66, 25.48, 25.22, 24.90, 24.43. IR (neat) ν 3356, 3119, 3009, 2922, 2900, 1739, 1700, 1109, 1018, 892, 754 cm^{-1}.

(*S*)-Benzyl-(1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-phenylpropan-2-yl)(4-methoxybenzyl)carbamate (223)

A 100-mL round-botttomed, flask equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (10 mL), (*S*)-benzyl (1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-phenylpropan-2-yl)(4-methoxybenzyl)carbamate DMAP salt (**222**) (0.67 g, 1.00 mmol), and anhydrous Dowex 50W-X2 (1.5 g) ion exchange resin. The solution was stirred for 20 min. The resin was removed by filtration and the filtrate was concentrated in vacuo to give 0.491 g (90 %) of **223** as a yellow, viscous oil. Compound **223** was carried on without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) *major tautomer and rotomer* δ 7.55 – 6.48 (m, 14H), 5.37 – 4.94 (m, 4H), 4.69 - 4.51 (m, 1H), 3.76 (s, 3H), 3.41 - 2.78 (m, 2H), 1.96 – 1.36 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.44, 170.86, 159.81, 158.96, 136.43, 135.58, 129.58, 129.46, 128.97, 128.76, 128.69, 128.63, 128.47, 128.31, 127.57, 126.99, 114.53, 113.96, 105.33, 67.38, 55.45, 38.96, 27.84, 27.10, 26.80. IR (neat) ν 3398, 3002, 2991, 2983, 1798, 1708, 1679, 1102, 981, 770 cm^{-1}.

(*S*)-Benzyl-(3,5-dioxo-5-(2-oxooxazolidin-3-yl)-1-phenylpentan-2-yl)(4-methoxybenzyl)carbamate (218)

A 100-mL round-bottomed flask, equipped with a condenser fitted with a drying tube (calcium sulfate) and a magnetic stir bar, was charged with toluene (20 mL), 2-oxazolidone (0.09 g, 1.00 mmol), and (*S*)-benzyl (1-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-1-hydroxy-3-phenylpropan-2-yl)(4-methoxybenzyl)carbamate (**223**)

(0.55 g, 1.00 mmol). The solution was refluxed for 5 h. The reaction was allowed to cool to room temperature and the toluene was washed with water (10 mL) and brine (10 mL). The organic layer was dried with sodium sulfate (*ca.* 10 g) and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.3) 0.382 g (72 %) of compound **218** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 6.56 (m, 14H), 5.52 – 4.99 (m, 2H), 4.62 (dd, *J* = 75.0, 14.9 Hz, 1H), 4.43 – 4.26 (m, 2H), 3.98 – 3.83 (m, 2H), 3.75 (s, 3H), 3.53 (dd, *J* = 41.1, 16.7 Hz, 1H), 3.41 – 3.21 (m, 2H), 3.16 – 2.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.37, 200.20, 167.17, 166.96, 159.44, 159.32, 155.92, 155.77, 153.74, 153.62, 138.41, 138.14, 136.52, 135.88, 130.91, 130.43, 129.56, 129.49, 129.24, 129.10, 129.00, 128.87, 128.74, 128.66, 128.57, 128.39, 128.27, 126.85, 126.73, 114.26, 114.18, 68.31, 68.25, 68.06, 67.86, 62.44, 55.47, 52.87, 52.26, 47.12, 46.90, 42.30, 34.87, 33.74. IR (neat) ν 3229, 3100, 2998, 1781, 1704, 1683, 1109, 1006, 996, 701 cm^{-1}.

Benzyl-4-methoxybenzyl((1*S*)-2-methyl-1-(3-oxo-2-oxabicyclo[3.1.0]hexan-1-yl) propyl)carbamate (226 and 227)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (30 mL) and cooled in an ice bath. Diethylzinc (0.5 mL, 5.00 mmol) was added and the solution was allowed to stir at 0 °C for 5 min. Methylene iodide (0.8 mL, 10.0 mmol) was added to the flask drop-wise over 5 min and the reaction allowed to stir for 20 min. β-Keto imide **215** (0.48 g, 1.00 mmol) in methylene chloride (5 mL) was then added by syringe in one portion to the milky

white mixture. The solution was allowed to stir at room temperature for 24 h. After the reaction was cooled down in an ice bath, saturated ammonium chloride (20 mL) was added slowly. The organic phase was separated, washed with water (10 mL) and brine (10 mL), dried with sodium sulfate (*ca.* 10 g), and concentrated in vacuo to obtain a viscous, yellow oil. After column chromatography (hexane:ethyl acetate 5:1) two diastereomers were separated.

Major: (hexane:ethyl acetate 1:1, R_f = 0.5) 0.123 g (29 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotomeric form* δ 7.50 – 6.57 (m, 9H), 5.40 – 5.07 (m, 2H), 4.82 (d, *J* = 16.4 Hz, 1H), 4.14 (d, *J* = 16.4 Hz, 1H), 3.84 (d, *J* = 11.0 Hz, 1H), 3.79 (s, 3H), 2.57-2.40 (m, 1H), 2.02 (d, *J* = 17.7 Hz, 1H), 1.63 (s, 1H), 1.49 - 1.33 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.12 (dd, *J* = 14.3, 7.9 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 2H), 0.63 (dd, *J* = 6.6, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.89, 158.89, 157.72, 136.53, 130.58, 129.19, 128.79, 128.68, 128.58, 128.48, 128.34, 114.06, 68.82, 67.83, 64.84, 55.55, 45.88, 33.50, 29.03, 24.50, 20.29, 20.03, 13.81. IR (neat) ν 3092, 2901, 2883, 1709, 1123, 1085, 934, 769 cm^{-1}.

Minor: (hexane:ethyl acetate 1:1, R_f = 0.4) 0.085 g (20 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) *major rotomeric form* δ 7.55 – 7.17 (m, 7H), 6.83 - 6.73 (m, 3H), 5.33 – 5.07 (m, 2H), 4.53 (q, *J* = 15.6 Hz, 2H), 3.76 (s, 3H), 2.95 – 2.67 (m, 1H), 2.51 - 2.42 (m, 1H), 2.23 (tt, *J* = 12.3, 6.2 Hz, 1H), 1.21 – 1.08 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.83 - 0.73 (m, 1H), 0.36 - 0.27 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.42, 158.69, 157.61, 136.75, 136.60, 131.15, 130.00, 129.28, 128.76, 128.68, 128.63, 128.58, 128.34, 128.22, 128.18, 114.06, 113.58, 68.98, 68.82, 67.83, 67.75, 66.20, 64.84,

55.54, 55.44, 46.96, 45.88, 33.50, 33.31, 29.03, 28.21, 24.50, 20.30, 20.17, 20.05, 19.92, 19.71, 19.56, 18.26, 13.81. IR (neat) ν 3009, 2909, 2899, 1722, 1359, 1099, 992, 747 cm^{-1}.

Benzyl-4-methoxybenzyl((1*S*)-1-(3-oxo-2-oxabicyclo[3.1.0]hexan-1-yl)-2-phenylethyl)carbamate (228 and 229)

A 100-mL round-bottomed flask equipped with a magnetic stir bar, septum, and a nitrogen inlet was charged with methylene chloride (30 mL) and lowered into an ice bath. Diethylzinc (0.5 mL, 5.00 mmol) was added and the solution was allowed to stir at 0 °C for 5 min. Methylene iodide (0.8 mL, 10.0 mmol) was added to the flask dropwise over 5 min and the solution was allowed to stir for 20 min. β-Keto imide **218** (0.47 g, 1.00 mmol) in methylene chloride (5 mL) was then added by syringe into the milky white mixture and allowed to stir at room temperature for 24 h. The reaction was cooled down in an ice bath and saturated ammonium chloride (20 mL) was added slowly. The organic phase was separated, washed with water (10 mL) and brine (10 mL), dried with sodium sulfate, and concentrated in vacuo to obtain a viscous, yellow oil. After column chromatography (Hexane:ethyl acetate 5:1) two diastereomers were separated.

Major: (Hexane:ethyl acetate 1:1, R_f = 0.5) 0.146 g (31 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 6.63 (m, 14H), 5.21 - 4.97 (m, 2H), 4.54 – 4.33 (m, 2H), 3.78 (s, 3H), 3.27 (dd, *J* = 13.4, 9.1 Hz, 1H), 3.12 (dd, *J* = 12.9, 7.5 Hz, 1H), 2.21 – 1.93 (m, 1H), 1.88 – 1.62 (m, 1H), 1.34 – 1.16 (m, 1H), 0.65 (t, *J* = 7.8 Hz, 1H), 0.42 - 0.26 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.75, 158.88, 157.03, 137.62, 136.54, 130.64, 129.56,

128.67, 128.57, 128.19, 126.82, 114.06, 69.05, 67.68, 60.06, 55.55, 46.75, 36.73, 33.62, 22.39, 14.13. IR (neat) ν 3019, 2980, 2835, 1719, 1333, 1009, 901, 832 cm^{-1}.

Minor: (Hexane:ethyl acetate 1:1, R_f = 0.4) 0.104 g (22 %) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) *major rotomeric form* δ 7.52 – 6.66 (m, 14H), 5.25 – 5.05 (m, 2H), 4.69 (q, *J* = 16.6 Hz, 2H), 4.53 (t, *J* = 8.4 Hz, 1H), 3.78 (s, 3H), 3.09 – 2.89 (m, 2H), 2.08 (d, *J* = 18.7 Hz, 1H), 1.81 (dd, *J* = 18.9, 6.1 Hz, 1H), 1.12 – 0.64 (m, 2H), 0.26 – 0.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.90, 158.73, 156.96, 137.58, 136.54, 131.43, 129.44, 129.27, 128.89, 128.68, 128.54, 128.38, 128.26, 128.16, 126.97, 113.80, 68.09, 67.79, 61.75, 55.47, 47.09, 36.54, 33.08, 19.02, 17.98. IR (neat) ν 3063, 2992, 2849, 1731, 1394, 1006, 943, 928 cm^{-1}.

(2*S*)-benzyl 2-(2-(2-(benzylamino)-2-oxoethyl)-1-hydroxycyclopropyl)pyrrolidine-1-carboxylate (230)

A 100-mL round-bottomed flask, equipped with a septum and a magnetic stir bar, was charged with bicyclic lactone **212** (0.301 g, 1.00 mmol) and benzylamine (6 mL, 54.9 mmol) and stirred at room temperature for 3 d. The reaction solution was then diluted with ethyl acetate (25 mL) and washed with 3 N hydrochloric acid (3 x 10 mL), dried with sodium sulfate (*ca.* 5 g), and concentrated in vacuo to yield 0.359 g (88 %) of **230** as a light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.02 (m, 10H), 5.17 – 4.87 (m, 2H), 4.64 – 4.24 (m, 2H), 3.75 – 3.25 (m, 3H), 2.65 (dd, *J* = 15.4, 3.9 Hz, 1H), 2.27 (dd, *J* = 15.2, 11.1 Hz, 1H), 2.08 – 1.81 (m, 3H), 1.74 (dt, *J* = 12.5, 6.5 Hz, 1H), 1.56 – 1.36 (m, 1H), 0.72 (dd, *J* = 9.4, 5.9 Hz, 1H), 0.49 (t, *J* = 6.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$)

δ 173.64, 156.61, 138.83, 136.88, 128.81, 128.68, 128.17, 127.86, 127.74, 127.47, 67.05, 65.02, 59.90, 48.14, 43.52, 36.66, 29.20, 24.44, 21.89, 17.19. IR (neat) ν 3277, 3113, 3001, 2940, 1733, 1300, 1021, 991 cm^{-1}.

(*S*)-1-tosylpyrrolidine-2-carboxylic acid (234)

A 250-mL round bottomed flask, equipped with a septum and a magnetic stir bar, was charged with L-proline (5.76 g, 50 mmol) and 2M sodium hydroxide (50 mL, 100 mmol) and cooled in an ice bath. *p*-Toluenesulfonyl chloride (9.53 g, 50 mmol) in diethyl ether (20 mL) was added dropwise to the solution over 4 h. The ethereal solution was then separated and the aqueous solution was acidified to pH ~2 with 3N hydrochloric acid. The aqueous layer was extracted with ethylacetate (3 x 30 mL), dried with magnesium sulfate (*ca.* 15 g), and concentrated in vacuo to afford 12.52 g (93 %) of **234** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.47 – 7.19 (m, 2H), 4.41 – 4.11 (m, 1H), 3.58 – 3.35 (m, 1H), 3.21 (dd, J = 16.6, 7.2 Hz, 1H), 2.38 (s, 3H), 2.16 – 1.86 (m, 3H), 1.78 – 1.53 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.63, 144.25, 134.59, 130.07, 127.70, 60.56, 48.93, 31.02, 24.85, 21.75. IR (neat) ν 3544, 3214, 2982, 2880, 2642, 1730, 1597, 1491, 1012, 818, 703 cm^{-1}.

(*S*)-5-(hydroxy(1-tosylpyrrolidin-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione DMAP salt (235)

A 100-mL round-bottomed flask, equipped with a septum, magnetic stir bar, and a nitrogen inlet, was charged with methylene chloride (10 mL) and cooled in an ice bath. Compound **234** (1.31 g, 4.86 mmol) in methylene chloride (5 mL) was added followed by dicyclohexyl carbodiimide (1.00 g, 4.86 mmol), Meldrum's acid (0.70 g, 4.86 mmol), and *N, N*-dimethylaminopyridine (0.59 g, 4.86 mmol) in the indicated order. The solution was allowed to stir at room temperature for 12 h, at which time the dicyclohexylurea was removed by filtration. The filtrate was concentrated in vacuo to afford 2.01 g (80 %) of **235** as a yellow oily solid. Compound **235** was carried on without further purification and directly subjected to acidification without spectroscopic analysis.

(*S*)-5-(hydroxy(1-tosylpyrrolidin-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (236)

A 100-mL round-botttomed, flask equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (10 mL), (*S*)-5-(hydroxy(1-tosylpyrrolidin-2-yl)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione DMAP salt (**235**) (0.67 g, 1.00 mmol), and anhydrous Dowex 50W-X2 (1.5 g) ion exchange resin. The solution was stirred for 20 min. The resin was removed by filtration and the filtrate was concentrated in vacuo to give 0.356 (90 %) of **236** as a yellow, viscous oil. Compound **236** was carried on without further purification and directly subjected to ring opening.

(*S*)-1-(2-oxooxazolidin-3-yl)-3-(1-tosylpyrrolidin-2-yl)propane-1,3-dione (237)

A 100-mL round-bottomed flask, equipped with a condenser fitted with a drying tube (calcium sulfate) and a magnetic stir bar, was charged with toluene (20 mL), 2-oxazolidone (0.09 g, 1.00 mmol), and (*S*)-5-(hydroxy(1-tosylpyrrolidin-2-yl) methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**236**) (0.381 g, 1.00 mmol). The solution was refluxed for 5 h. The reaction was allowed to cool to room temperature and the toluene was washed with water (10 mL) and brine (10 mL). The organic layer was dried with sodium sulfate (*ca.* 10 g) and concentrated in vacuo to afford a yellow, viscous oil. After column chromatography (hexane:ethyl acetate 1:1, R_f = 0.3) 0.270 g (71 %) of compound **237** was isolated as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 13.4, 8.2 Hz, 2H), 7.33 (dd, *J* = 16.4, 9.4 Hz, 2H), 4.62 – 4.32 (m, 4H), 4.16 (dt, *J* = 7.3, 3.6 Hz, 1H), 4.13 – 4.02 (m, 2H), 3.61 – 3.43 (m, 1H), 3.33 – 3.18 (m, 1H), 2.44 (s, 3H), 2.30 – 2.16 (m, 1H), 1.98 – 1.81 (m, 1H), 1.76 – 1.59 (m, 1H), 1.58 - 1.50 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.21, 167.06, 154.02, 144.44, 133.58, 130.17, 129.99, 127.92, 67.49, 62.58, 49.72, 48.19, 42.52, 29.14, 24.77, 21.78. IR (neat) ν 3532, 3290, 2977, 2809, 2691, 1722, 1701, 1555, 1489, 1071, 883, 729 cm^{-1}.

1-((*S*)-1-tosylpyrrolidin-2-yl)-2-oxabicyclo[3.1.0]hexan-3-one (238) and (239)

A 100-mL round-bottomed flask, equipped with a magnetic stir bar, septum, and a nitrogen inlet, was charged with methylene chloride (30 mL) and cooled in an ice bath. Diethylzinc (0.5 mL, 5.00 mmol) was added and the solution was allowed to stir at 0 °C for 5 min. Methylene iodide (0.8 mL, 10.0 mmol) was added to the flask drop-wise over 5 min and the reaction allowed to stir for 20 min. β-Keto imide **238** (0.28 g, 1.00 mmol)

in methylene chloride (5 mL) was then added by syringe in one portion to the milky white mixture. The solution was allowed to stir at room temperature for 24 h. After the reaction was cooled down in an ice bath, saturated ammonium chloride (20 mL) was added slowly. The organic phase was separated, washed with water (10 mL) and brine (10 mL), dried with sodium sulfate (*ca.* 10 g), and concentrated in vacuo to obtain a viscous, yellow oil. After column chromatography (hexane:ethyl acetate 5:1, R_f = 0.2) 0.189 g (59 %) of **238** and **239** co-eluted together off of the column as a white solid. MP = 149 – 151 °C.

Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.64 (dd, *J* = 8.7, 3.3 Hz, 1H), 3.53 - 3.47 (m, 1H), 3.38 – 3.29 (m, 1H), 2.73 (dd, *J* = 18.7, 6.8 Hz, 1H), 2.47 (d, *J* = 19.5 Hz, 1H), 2.44 (s, 3H), 2.19 – 1.92 (m, 2H), 1.88 - 1.77 (m, 1H), 1.68 – 1.55 (m, 2H), 1.16 – 1.11 (m, 1H), 0.69 (dd, *J* = 6.7, 4.9 Hz, 1H).

Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 4.18 – 4.09 (m, 1H), 3.43 – 3.14 (m, 2H), 2.98 (dd, *J* = 19.0, 7.0 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.44 (s, 3H), 2.18 – 1.94 (m, 2H), 1.85 – 1.82 (m, 2H), 1.65 – 1.58 (m, 1H), 1.30 – 1.25 (m, 1H), 0.64 (dd, *J* = 7.0, 5.3 Hz, 1H).

Major and Minor: ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.39, 144.15, 143.93, 135.56, 130.08, 127.80, 127.41, 70.73, 70.13, 61.74, 59.75, 50.19, 49.73, 34.09, 33.98, 30.20, 30.04, 24.72, 24.50, 21.75, 18.63, 17.42, 16.38, 13.82. IR (neat) ν 3109, 3001, 2919, 2771, 2589, 1709, 1681, 1459, 1306, 1001, 845, 701 cm^{-1}.

(1*S*,4*S*,5*S*)-4-benzyl-1-methyl-2-oxabicyclo[3.1.0]hexan-3-one (242)

A 250-mL, round-bottomed flask, equipped with a nitrogen inlet, septum, and a magnetic stir bar, was charged with dry THF (60 mL) and *n*-butyllithium (1.6 mL, 2.5 M, 3.97 mmol) and the solution was cooled to 0 °C. Diisopropylamine (0.56 mL, 3.97 mmol) was added dropwise over 10 min, after which the reaction was stirred for 0.5 h at room temperature (23 °C). The round-bottomed flask was cooled to -78 °C in a dry ice/acetone bath and bicyclic lactone **159** (0.40 g, 3.61 mmol) in dry THF (10 mL) was added over a 45 min period via syringe pump. The reaction was allowed to warm to room temperature, at which point it was allowed to stir for 30 min. The solution was then cooled to -78 °C in a dry ice/acetone bath and benzyl bromide (0.47 mL, 3.61 mmol) was added in one portion. The reaction was allowed to warm to room temperature and stir for 60 min. The reaction was quenched with 1 N HCl (30 mL), and the biphasic solution was reduced to half its volume via rotary evaporation. This solution was extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were dried with magnesium sulfate and concentrated in vacuo to afford a viscous yellow oil. The major diastereomer (1*S*,4*S*, 5*S*)-4-benzyl-1-methyl-2-oxabicyclo[3.1.0]hexan-3-one (**242**) was isolated as a clear oil via column chromatography (hexane:ethyl acetate 5:1, R_f = 0.5) to give 0.328 g (45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.17 (m, 3H), 3.12 (dd, *J* = 13.6, 4.7 Hz, 1H), 3.01 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.93 (dd, *J* = 7.3, 4.7 Hz, 1H), 1.39 – 1.15 (m, 4H), 0.81 (dd, *J* = 8.9, 7.0 Hz, 1H), 0.63 (dd, *J* = 7.0, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.79, 137.73, 129.44, 128.83, 127.13, 64.40, 48.05, 37.97, 20.18, 20.13, 18.20. IR (neat) ν 3014, 2991, 2871, 1703, 1638, 1148, 1092, 8821, 765 cm^{-1}.

REFERENCES

1. Mastrolorenzo, A.; Rusconi, S.; Scozzafava, A; Barbaro, G.; Supuran, C. T., "Inhibitors of HIV-1 protease current stage of the art 10 years after their introduction. From antiretroviral drugs to antifungal, antibacterial, and antitumor agents based on aspartic protease inhibitors". *Curr. Med. Chem*, **2007**, *14*, 2734-2748.
2. Langmuir, I., "Isomorphism, isosterism, and covalence". *J. Am. Chem. Soc.* **1919**, *41*, 1543-1559.
3. Patani, G. A.; LaVoie, E. J., "Bioisosterism: A rational approach in drug design". *Chem. Rev.* **1996**, *96*, 3147-3176.
4. Clavel, F.; Mammano, F., "Role of Gag in HIV resistance to protease inhibitors". *Viruses* **2010**, *2*, 1411-1426.
5. Harbeson, S. L.; Rich, D. H., "Inhibition of aminopeptidases by peptides containing ketomethylene and hydroxyethylene amide bond replacements". *J. Med. Chem.* **1989**, *32*, 1378-1392.

6. Hoffman, R. V.; Kim, H. O., "A simple synthetic approach to Cbz-Phe-psi(CH_2) Gly-Pro-OMe and related peptide isosteres". *Tetrahedron Lett.* **1992**, *33*, 3579-3582.

7. Ballini, R.; Bosica, G.; Gigli, F., "α-Nitrocycloalkanones as a new source for the one-pot synthesis of functionalized 1,4-diketones, γ-oxoaldehydes, γ-ketoesters, and methyl ω-oxoalkanoates". *Tetrahedron* **1998**, *54*, 7573-7580.

8. Lygo, B.; Rudd, C. N., "Synthesis of Xaa-Gly-Xaa' ketomethylene tripeptide isosteres incorporating phenylalanine, tyrosine, and valine units". *Tetrahedron Lett.* **1995**, *36*, 3577-3580.

9. Miyakoshi, T. "Preparation and reactions of 4-oxocarbonyl compounds. A review". *Org. Prep. Proc. Int.* **1989**, *21*, 659.

10. Nagata, W.; Yoshioka, M., "Hydrocyanation of unsaturated carbonyls". *Org. React.* **1977**, 25, 255.

11. Bieraugel, H.; Akkerman, J. M.; Lapierre Armond, J. C.; Padit, U. K., "Specific insertion of carbenes into carbon-carbon bonds". *Tetrahedron Lett.* **1974**, 2817-2820.

12. Saigo, K.; Kurihara, H.; Miura, H.; Hongu, A.; Kubota, N.; Nohira, H. "Conversion of 1.3-dicarbonyls to 1,4 dicarbonyls". *Synth. Commun.* **1984**, 787-796.

13. Saigo, K.; Yamashita, T.; Hongu, A.; Hasegawa, M. "The double Simmons-Smith reactions via silatropies". *Synth. Commun.* **1985**, 715-721.

14. Dowd, P.; Choi, S.-C. "A new tributyltin hydride-based rearrangement of bromomethyl.beta.-keto esters. A synthetically useful ring expansion to .gamma.-keto esters". *J. Am. Chem. Soc.* **1987**, *109*, 3493-3494.

15. Dowd, P.; Choi, S.-C. "Free radical ring expansion by three and four carbons". *J. Am. Chem. Soc.* **1987**, *109*, 6548-6549.

16. Dowd, P.; Choi, S.-C. "Novel free radical ring-expansion reactions". *Tetrahedron* **1989**, *45*, 77-90.

17. Dowd, P.; Choi, S.-C. "Free radical ring-expansion leading to novel six- and seven-membered heterocycles". *Tetrahedron Lett.* **1989**, *30*, 6129-6132.

18. Reissig, H.-U., "Donor-acceptor-substituted cyclopropanes: versatile building blocks in organic synthesis". *Top. Curr. Chem.* **1988**, *144*, 73.

19. Brogan, J. B.; Zercher, C. K., "Zinc-mediated conversion of beta-keto esters to gamma-keto esters". *J. Org. Chem.* **1997**, *62*, 6444-6446.

20. Furukawa, J.; Kawabata, N.; Nishimura, J., "Novel route to cyclopropanes from olefins". *Tetrahedron Lett.* **1966**, 3353-3354.

21. Hilgenkamp, R.; Zercher, C. K., "Zinc carbenoid-mediated chain extension of β-keto amides". *Tetrahedron.* **2001**, *57*, 8793-8800.

22. Verbicky, C. A.; Zercher, C. K., "Zinc mediated-chain extension of β-keto phosphonates". *J. Org. Chem.* **2000**, *65*, 5615-5622.

23. Lin, W. Ph. D. Dissertation. University of New Hampshire, **2006**.

24. Henderson, T. J. M.S. Thesis. University of New Hampshire. **2009**.

25. Sadlowski, C. B.S. Thesis. University of New Hampshire. **2007**.

26. Eger, W. A.; Zercher, C. K.; Williams, C. M., "A mechanistic investigation into the zinc carbenoid-mediated homologation reaction by DFT methods: Is a classical donor-acceptor cyclopropane involved?". *J. Org. Chem.* **2010**, *75*, 7322 – 7331.

27. Reformatsky, S., "Neue synthese zweiatomiger einbasischer sauren aus den ketonen". *Chem. Ber.* **1887**, *20*, 1210-1211.

28. Aiken, K. Ph. D. Dissertation. University of New Hampshire. **2005**.

29. Reformatskii S. *J. Russ. Phys. Chem. Soc.* **1890**, *22*, 44.

30. Ocampo, R.; Dolbier, W. R. "The Reformatsky reaction in organic synthesis. Recent advances". *Tetrahedron* **2004**, *42*, 9325 – 9374.

31. Heathcock, C. H. *Asymm. Synth.* **1984**, *3*, 111.

32. Tagliavini, E.; Trombini, C. *Advances in Carbanion Chemistry: Stereoselective Synthesis based Zinc and Boron Enolates*, **1996**, *2*, 111.

33. Andres, J.; Martinez, M.; Pedrosa, R.; Perez-Encabo, A. *Synthesis*, **1996**, 1070.

34. Hilgenkamp, R. A.; Zercher, C. K., "Tandem chain extension-homoenolate formation: The formation of alpha-methylated-gamma-keto esters." *Org. Lett.* **2001**, *3*, 3037-3040.

35. Jacobine, A. Unpublished Results, University of New Hampshire.

36. Lai, S-J. M.S. Thesis, University of New Hampshire.

37. Hanson, K. BS Thesis, University of New Hampshire.

38. Hilgenkamp, R. A., M. S. Thesis, University of New Hampshire.

39. Ronsheim, M. D.; Zercher, C. K. "Zinc carbenoid-mediated chain extension: Prepatation of α,β-unsaturated-Y-keto esters and amides. *J. Org. Chem.* **2003**, *68 (11)*, 4535.

40. Hilgenkamp, R.; Zercher, C. K. "Tandem chain extension-homoenolate formation: The formation of a α-methylated-γ-keto esters". *Org. Lett.* **2001**, *3(19)*, 3037-3040.

41. Pu, Q-L. Unpublished Results, University of New Hampshire.

42. Morrison, J. D. Eds *Asymmetric Synth.* **1984**; *3*, 111.

43. Zimmerman, H. E.; Traxler, M. D., " The stereochemistry of the Ivanov and Reformatsky reactions". *J. Am. Chem. Soc.* **1956**, *79*, 1920-1923.

44. Rathke, M. W.; Weipert, P., "*Preparation of organozinc reagents*". **1991**, *1*, 212-229.

45. Dewar, M. J. S.; Merz, K. M., Jr., "The Reformatsky reaction". *J. Am. Chem. Soc.* **1987**, *109*, 6553-6554.

46. Lai, S.; Zercher, C. K.; Jasinski, J. P.; Reid, S. N.; Staples, R. J. "Tandem chain extension-aldol reaction: *syn*-selectivity with a zinc enolate". *Org. Lett.* **2001**, *3 (26)*, 4169.

47. Lin, W.; Tryder, N.; Su, F.; Zercher, C. K.; Jasinski, J .P.;Butcher, R. J. "Stereocontrolled Formation of Ketomethylene Isosteres through Tandem Chain Extension Reactions". *J. Org. Chem.* **2006**, *71*, 8140-8145.

48. Heathcock, C. H.; Danda, H., "Reversal of stereochemistry in the aldol reactions of a chiral boron enolate". *J. Org. Chem.* **1990**, *55*, 173-181.

49. Jacobine, A. M.; Lin, W.; Walls, B.; Zercher, C. K., "Formation of γ-lactones through CAN-mediated oxidative cleavage of hemiketals". IJ. Org. Chem. **2008**, *73*, 7409-7412.

50. Amador, M.; Ariza, X.; Garcia, J., "A versatile stereoselective approach to paraconic acids". *Heterocycles* **2006**, *67*, 705-720.

51. Mazzone, J. R. Unpublished results. University of New Hampshire.

52. Ronsheim, M. D.; Zercher, C. K., "Ring expansion of β-keto lactones with zinc carbenoid: synthesis of (+)-patulolide A and (±)-patulolide B". *J. Org. Chem.* **2003**, *68*, 1878-1885.

53. Filipeanu, C. M.; Brailoie, E.; Costuleanu A.; Toma, C. P.; Branisteanu, D. D., "Vasorelaxant properties of brefeldin A in rat aorta". *Eur. J. Pharmacol.* **1997**, *332*, 71-76.

54. Lin, W.; Zercher, C. K., "Formal synthesis of (+)-Brefeldin A: application of a zinc-mediated ring expansion". *J. Org. Chem.* **2007**, *72*, 4390-4395.

55. Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S., "Asymmetric total synthesis of (+)-Brefeldin A from (S)-lactate by triple chirality transfer process and nitrile oxide cycloaddition". *J. Org. Chem.* **2002**, *67*, 764 – 771.

56. Fattorusso, E; Faulkner, D. J., "Activity against *Plasmodium falciparum* of cycloperoxide compounds obtained from the sponge *Plakortis simplex*". *J. Antimicrob. Chemother.* **2002**, *50*, 883.

57. Higgs, M. D., "Plakortin, an antibiotic from plakortis halichondrioides". *J. Org. Chem.*, **1978**, *43*, 3454.

58. Pettit, G. R.; Parapini, S.; Campagnuolo, C., "Antineoplastic agents. 535. Isolation and structure of plakorstatins 1 and 2 from the indo-pacific sponge *Plakortis nigra*". *J. Nat. Prod.*, **2004**, *67*, 1611.

59. John, J. P.; Jost, J.; Novikov, A. V.; "Synthesis of Plakortethers F and G". *J. Org. Chem.* **2009**, *74*, 6083-6091.

60. Henderson, Tim. B. S. Thesis. University of New Hampshire.

61. Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J., "Conversion of lactones into ethers". *J. Org. Chem.* **1981**, *46*, 2417.

62. Reissig, H-U.; Bruckner, C.; Holzinger, H. "Diastereoselective syntheses of highly substituted methyl tetrahydrofuran-3-carboxylates by reaction of .gamma.-lactols with silylated nucleophiles". *J. Org. Chem.* **1988**, *53*, 2450-2456.

63. Woerpel, K. A.; Larson, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M., "Stereoselective C-glycosilation reactions of ribose derivatives: electronic effects of five-membered ring oxocarbenium ions". *J. Am. Chem. Soc.* **2005**, *127*, 10879-10884.

64. Matteson, D. S., "Recent advances in asymmetric synthesiswith boronic esters". *Pure & Appl. Chem.* **1991**, *63*, 339 – 344.

65. Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A., "Scope and stereochemical course of the (trimethylsilyl)cyclopentene annulation". *Tetrahedron* **1983**, *39*, 935-947.

66. Westmijze, H.; Kleijn, H.; Vermeer, P., "Organocopper synthesis of 1-alkenylsilanes and 1,3-alkadienylsilanes from ethynylsilanes". *J. Organometallic Chem* **1984**, *276*, 317-323.

67. Armarego, W. L.; Chai, C. L. "Purification of laboratory chemicals". **2003**, 416.

68. Chen, H. M.; Oliver, J. P., "Silylcupration of acetylenes". *J. Organometallic Chem.* **1986**, *316*, 255-260.

69. Sharma, S.; Oehlschlager, A. C. "Synthetic and mechanistic implications of ligand mixing in higher-order mixed (trialkylsilyl)cuprates and (trialkylstannyl) cuprates". *J. Org. Chem.* **1991**, *56*, 770-776.

70. Fleming, I.; Landais, Y.; Raithby, P. R. "The stereochemistry of the silylcupration of allenes". *J. Chem. Soc., Perkin Trans 1* **1991**, 715-719.

71. Fleming, I.; Newton, T. W.; Roessler, F. "The silylcupration of acetylenes. A synthesis of vinylsilanes". *J. Chem. Soc., Perkin Trans 1* **1981**, 2527-2532.

72. Johnson, W. S.; Werthemann, L., Bartlett, W. R.; Brocksom, T. J.; Faulkner, J.; Petersen, M., "Simple stereoselective version of the Claisen rearrangement leading to trans-trisubstituted olefinic bonds. Synthesis of squalene". *J. Am. Chem. Soc.* **1970**, *92*, 741-743.

73. Hayes, B. L., "Recent advances in microwave-assisted synthesis". *Aldrichimica Acta* **2004**, *37*, 66-77.

74. Jones, G. B.; Huber, R. S.; Chau, S., "The Claisen rearrangement in synthesis: acceleration of the Johnson orthoester protocol en route to bicyclic lactions". *Tetrahedron* **1992**, *49*, 369-380.

75. Enders, D.; Fey, P.; Kipphardt, H., "(*S*)-(-)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (*R*)-(-)-1-amino-2-methoxymethylpyrrolidine (RAMP), versatile chiral auxillaries". *Org. Syn* **1993**, *65*, 173.

76. Clemens, R. J.; Hyatt, J. A., "Acetoacylation with 2,2,6-trimethyl-4H-1,3-doxin-4-one: a convenient alternative to diketene". *J. Org. Chem.* **1985**, *50*, 2431-2435.

77. Baker, S. J.; Goldsmith, P. J.; Hancox, T. C.; Pegg, N. A.; Price, S.; Shuttleworth, S. J.; Sohal, S., "Preparation of thienopyrimidine derivatives as PI3 kinase inhibitors". PCT Int. Appl. **2007**, 169.

78. Georg, G. I.; White, J. M.; Tunoori, A. R. "A novel and expeditious reduction of tertiary amides to aldehydes using $Cp_2Zr(H)Cl$". *J. Am. Chem. Soc.* **2000**, *122*, 11995-11996.

79. Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333-340.

80. Erker, G.; Schlund, R.; Krueger, C., "Studies on hydrometalation reactions: an improved hydrozirconation reagent and the structure of a $(MeCp)_2ZrCl$(alkenyl) carbonylation product". *Organometallics* **1989**, *8*, 2349-2355.

81. Kath, J. C.; DiRico, A. P.; Gladue, R. P.; Martin, W. H.; McElroy, E. B.; Stock, I. A.; Tylaska, L. A., "The discovery of structurally novel CCR1 antagonists derived from a hydroxyethlene peptide isostere template". *Bioorg. Med. Chem Lett.* **2004**, *14*, 2163 – 2167.

82. Garbe, D.; Sieber, S. A.; Bandur, N. G.; Koert, U.; Marahiel, M. A., "Enzyme cyclisation of peptidomimetics with incorporated (*E*)-alkene dipeptide". *ChemBioChem* **2004**, *5*, 1000 – 1003.

83. Wipf, P.; Xiao, J., "Convergent approach to (*E*)-alkene and cyclopropane peptide isosteres". *Org. Lett.* **2005**, *7*, 103 – 106.

84. Greenea, W. C.; Debyserb, Z.; Ikedac, Y. Freedd, E. O.; Stephenes, E. "Novel Targets for HIV therapy". *Antivir. Res.* **2008**, *80*, 251 – 265.

85. Markowitz, M.; Nguyen, B. Y.; Gotuzzo, E.; Mendo, F.; Crumpacker, C. S. "Rapid and antiretroviral effect of the HIV-1 integrase inhibitor Raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: resicts of a 48-week controlled study". *J. Acquir. Immune Defic. Syndr.* **2007**, *46*, 125-133.

86. Martin, S. F.; Dorsey, G. O.; Gane, T.; Hillier, M. C.; Kessler, H.; Baur, M.; Mathä, B.; Erickson, J. W.; Bhat, T. N.; Munshi, S.; Gulnick, S. V.; Topol, I. A., "Cyclopropane-derived peptidomimetics. Design, synthesis, evaluation, and structure of novel HIV-1 protease inhibitors". *J. Med. Chem.* **1998**, *41*, 1581 – 1597.

87. Radi, M.; Maga, G.; Alongi, M.; Bellucci, L.; Tafi, A.; Giorgi, G.; Dumas, P.; Botta, M. "Discovery of chiral cyclopropyl dihydro-alkylthio-benzyl-oxopyrimidine derivatives as potent HIV-1 reverse transcriptase inhibitors with high activity against clinically relevant mutants". *J. Med. Chem.* **2009**, *52*, 840-851.

88. Drew, M. G. B.; Gorsuch, S.; Mann, J.; Yoshida, S. "Novel peptide isosteres that were designed to inhibit the binding of the HIV surface glycoprotein (gp120) to the T cell surface glycoprotein CD4". *J. Chem. Soc., Perkins Trans. 1*, **1998**, 1627-1636.

89. Chen, C-A.; Sieburth, S. McN.; Glekas, A.; Hewitt, G. W.; Trainor, G. L.; Erickson-Viitanen, S.; Garber, S. S.; Cordova, B.; Jeffry, S.; Klabe, R. M. "Drug design with a new transition state analog of the hydrated carbonyl: silicon-based inhibitors of the HIV protease". *Chemistry and biology*, **2001**, *12*, 1161-1166.

90. Lin, W.; Tyrder, N.; Su, F.; Zercher, C. K. "Stereocontrolled formation of ketomethylene isosteres through tandem chain extension reactions". *J. Org. Chem.*, **2006**, *71*, 8140-8145.

91. Vuligonda, V.; Lin, Y.; Roshantha, A. S. "Synthesis of highly potent RXR-specific retinoids: The use of a cyclopropyl group as a double bond isostere". *Bioorg. Med. Chem Lett.* **1996**, *6*, 213-218.

92. Gupta, S.; Payne, J. W., "Evaluation of the conformational propensities of peptide isosteres as a basis for selecting bioactive pseudopeptides". *J. Peptide Res.* **2001**, *58*, 546-561.

93. Mathivet, P.; Bernasconi, R.; De Barry, J. "Binding characteristics of γ-hydroxybutyrateas a weak but selective $GABA_B$ receptor agonist". *Eur. J. Pharmacol.* **1997**, *321*, 67-75.

94. Fuller, D. E.; Hornfeldt, C. S. "From club drug to orphan drug: sodium oxybate (Xyrem) for the treatment of cataplexy". *Pharmacotherapy* **2003**, *23*, 1205-1209.

95. Seamans, J. K.; Gorelova, N.; Durstewitz, D.; Yang, C. R. "Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons". *J. Neuroscience* **2001**, *21*, 3628-3638.

96. Barnard, E. A.; Skolnick, P.; Olsen, R. W.; Mohler, H.; Sieghart, W., Biggop, G.; Braestrup, C.; Bateson, A.N.; Langer, A. N. " Subtypes of γ-aminobutyric acid A receptors: Classification on the basis of subunit and receptor function". *Pharmacol. Rev.* **1998**, *50*, 291-313.

97. Young, R.; Glennon, R. A. "Stimulus properties of benzodiazepines: correlations with binding affinities, therapeutic potency, and structure acitivity relationships (SAR)". *Psychopharmacology* **1987**, *93*, 529-533.

98. Snead, O. C. "Evidence for a G protein-coupled γ-hydroxybutyric receptor". *J Neurochem.* **2000**, *75*, 1986-1996.

99. Wellendorph P.; Hog, S.; Greenwood, J. R.; Nielsen, B.; Clausen R. P. "Novel cyclic γ-hydroxybutrate (GHB) analogs with high affinity and stereoselectivity of binding to GHB sites in rat brain". *J. Pharmacol. Exp. Ther.* **2005**, *315*, 346-351.

100. Saigo, K.; Kurihara, H.; Miura, H.; Hongu, A.; Kubota, N.; Nohira, H. "Conversion of 1.3-dicarbonyls to 1,4 dicarbonyls". *Synth. Commun.* **1984**, 787-796.

101. Deseke, E.; Hoyer, W.; Winterfeldt, E. "Chemical differentiation of enantiotopic groups: diastereoselective opening of a prochiral dilactone". *Tetrahedron* **1996**, *52*, 14577-14598.

102.Campbell, A. D.; Shaw, D. R. D. " A direct method for the preparation of some α-chlorocarboxylic esters, and notes on other α-halo carboxylic esters". *J. Chem. Soc.* **1952**, 5042-5043.

103.Brueckner, C.; Holzinger, H.; Reissig, H. U. "Diastereoselective synthesis of highly substituted methyl tetrahydrofuran-3-carboxylates by reaction of γ-lactols with silated nucleophiles". *J. Org. Chem.* **1988**, *53*, 2450-2456.

104.Chen, B-C. "Meldrum's acid in organic synthesis". *Heterocycles* **1991**, *32*, 529-597.

105.Meerwein, H., Schmidt, R. "Ein neues Verfahren zur redukttion von aldehyden und ketonen". *Justus Liebigs Annalen der Chemie* **1925**, 221-238.

106.Xue, S.; Li, L. Z.; Liu, Y. K.; Guo, Q. X. "Zinc-mediated chain extensions of 1,3-diketones to 1,4-diketones and diastereoselective synthesis of trans-1,2-disubstituted cyclopropanols". *J. Org. Chem.* **2006**, *71*, 215-218.

107.Yang, Y.; Lorenz, J. C.; Shi, Y. "Exploring new species for cyclopropanation". *Tet. Lett.* **1998**, *39*, 8621-8624.

108.Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. "Reduction of α-amino acids". *Org. Syn.* **1990**, *7*, 530.

109.Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. "Reduction of α-amino acids: L-valinol". *Org. Syn.* **1990**, *7*, 530.

110.Cotarca, L.; Heiner, E. *Phosgenations – A handbook,* **2003**, 202-203.

111.Wu, Y.; Shen, X. "A high-yielding low-cost facile synthesis of 2-oxazolidinones chiral auxiliaries". *Tetrahedron: Asymmetry* **2000**, *11*, 4359-4363.

112.Xue, S.; Li, L-Z.; Guo, Q-X., "Zinc mediated chain extention of 1,3-diketones to 1,4-diketones and diastereoselective synthesis of trans-1,2-disubstituted cyclopropanols". *J. Org. Chem.* **2006**, *71*, 215-218.

113.Mower, M. Unpublished results. University of New Hampshire.

114.Mazzone, J. Unpublished results. University of New Hampshire.

115.Jacobine, A. Ph. D. Dissertation. University of New Hampshire.

116.Jouin, P.; Nisato, D., "Stereospecific synthesis of N-protected statine and its analogues via chiral tetramic acid". *J. Chem. Soc. Perkin Trans. 1* **1987**, 1177-1182.

117.Schobert, R., "Domino synthesis of tetronic and tetramic acids". *Naturwissenschaften* **2007**, *94*, 1-11.

118.Li, B.; Franck, R. W., "Facile synthesis of *N*-protected γ-and δ-amino-β-keto esters". *Bioorg. Med. Chem. Lett.* **1999**, 2629-2634.

119.Houghton, R.; Lapham, D. J., "A modified preparation of β-keto esters". *Synthesis* **1982**, 451-452.

120.Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M."*N*-hydroxysuccinimide esters in peptide synthesis". *J. Am. Chem. Soc.* **1963**, *85*, 3039.

121.Raillard, S. P.; Chen, W.; Sullivan, E.; Bajjalieh, W.; Bhandari, A.; Baer, T. A., "Preparation and improved stability of *N*-Boc-α-amino-5-acyl Meldrum's acids, a versatile class of building blocks for combitorial chemisty". *J. Comb. Chem.* **2002**, *4*, 470-474.

122.Green T. W.; Wuts P. G. M., *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, **1999**, 518-525, 736-739.

123.Han, J.; Wang, R.; Zhou, Y.F., "Simple derivatives of natural amino acids as chiral ligands in the catalytic asymmetric addition of phenylacetylene to aldehydes". *Eur. J. Org. Chem.* **2005**, *5*, 934 – 938.

124.Sauna, Z. E.; Smith, M. M.; Marianna, M.; Kerr, K. M.; Ambudkar, S. V. "The mechanism of action of multidrug-resistance-linked P-glycoprotein". *J. Bioenergetics and Biomembranes* **2001**, *33*, 481-491.

125.Benedetti, F.; Miertus, S.; Norbedo, S. "C_2 –symetric Val-Val dipeptide isosteres *via* diethylaluminium azide ring opening of epoxyalcohols". *Croatica Chemica Acta* **2001**, *4*, 763-777.

126.Guillaume, B.; Laure, J.; Motherwell, W. B.; Sheppard, T. D.; Cladingboel, D. E., "Asymmetric synthesis of amlnocyclopropanes and N-cyclopropylamino alcohols through direct amidocyclopropanation of alkenes using chiral organozinc carbenoids". *Euro. J. Org. Chem.* **2009**, *10*, 1532 – 1548.

127.Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A., "Electrochemically-initiated Michael addition of chiral acetoacetic derivatives to methyl vinyl ketone: stereocontrolled construction of quaternary carbon center". *Tet. Asymm.* **2002**, *13*, 2311 – 2316.

128.Sato, M.; Ogasawara, H.; Kato, T., "The synthesis of β-keto lactones via cyclization of β-keto ester dianions or the cyclization of Meldrum's acid derivatives". *Chem. Pharm. Bull.* **1984**, *32*, 2602 – 2608.

129.Palombi, L.; Feroci, M.; Orsini, M.; Inesi, A., "Electrochemically-initiated Michael addition of chiral acetoacetic derivatives to methyl vinyl ketone: stereocontrolled construction of quaternary carbon centers". *Tet. Asymmetry* **2002**, *13*, 2311 – 2316.

130.Merlo, A. A.; Fernandes, M. S., "An Efficient Strategy for the Synthesis of Chiral Liquid Crystals Using Evans' Methodology". *Syn. Comm.* **2003**, *33*, 1167 – 1178.

131.Soerensen, U. K.; Falch, E.; Krogsgaard-Larsen, P., "A Novel Route to 5-Substituted 3-Isoxazolols. Cyclization of N,O-DiBoc β-Keto Hydroxamic Acids Synthesized via Acyl Meldrum's Acids". *JOC* **2000**, *65*, 1003 – 1007.

132.Mundy, B. P.; Kim, Y. "A Novel Synthesis of 2-Substituted Oxazolines". *J. Het. Chem.* **1982**, *19*, 1221 – 1222.

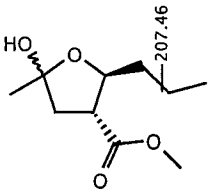
133.Turanova, O. A.; Turanov, A. N.; Lapaev, D. V.; Gnezdilov, O. I.; Lobkov, S. V.; Galyametdinov, Y. G., "The First Mesogenic Derivative of Boron Difluoride β-Diketonate". *Russ. J. Gen. Chem.* **2006**, *76*, 730 – 732.

134.Kelleher, F.; Sinead, K.; Watts, J.; Mckee, V., "Structure-reactivity relationships of l-proline derived spirolactams and α-methyl prolinamide organocatalysts in the asymmetric Michael addition reaction of aldehydes to nitroolefins". *Tetrahedron* **2010**, *66*, 3525 – 3536.

OH
O
O
O

74

1.14
1.17
0.84
3.00
0.26
0.88
0.84
1.80
1.55
0.69
1.79
1.20
2.20
3.55
6.26
5.31
0.48
6.78
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



74

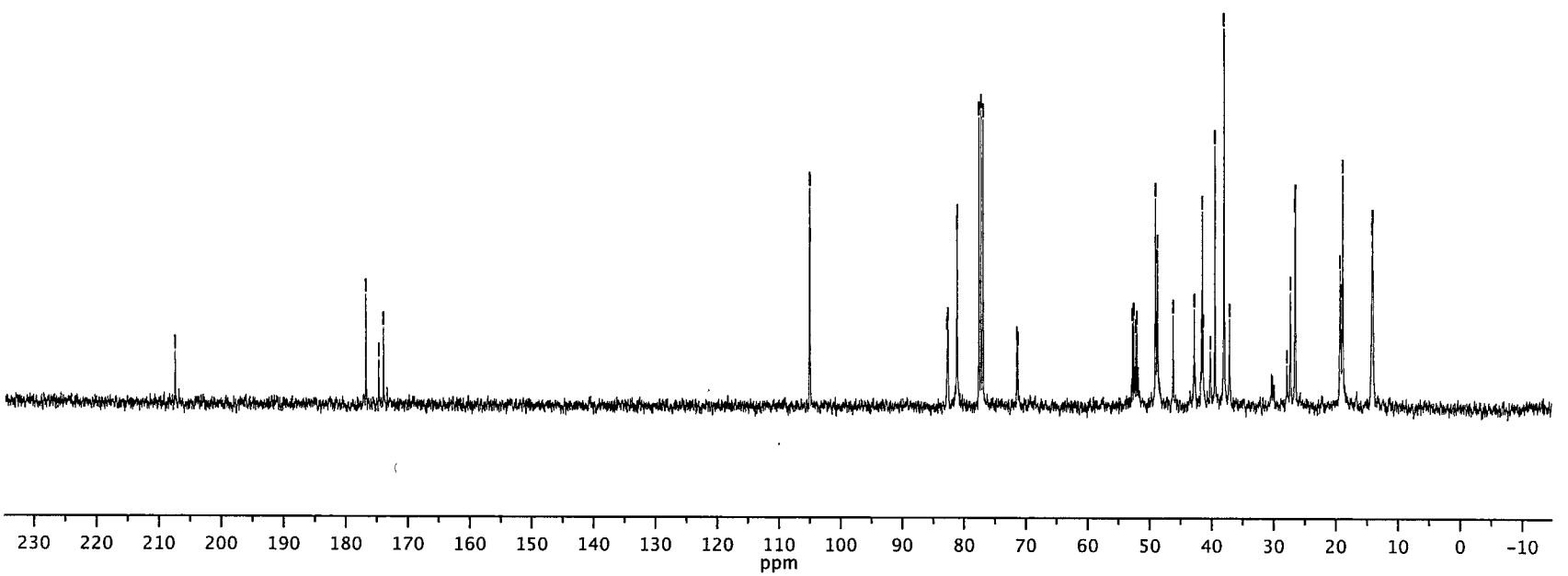
176.81
174.74
173.97

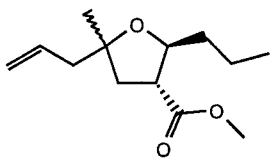
105.05
105.00

82.75
82.66
81.19
81.16
77.62
77.30
76.98
71.47
71.32

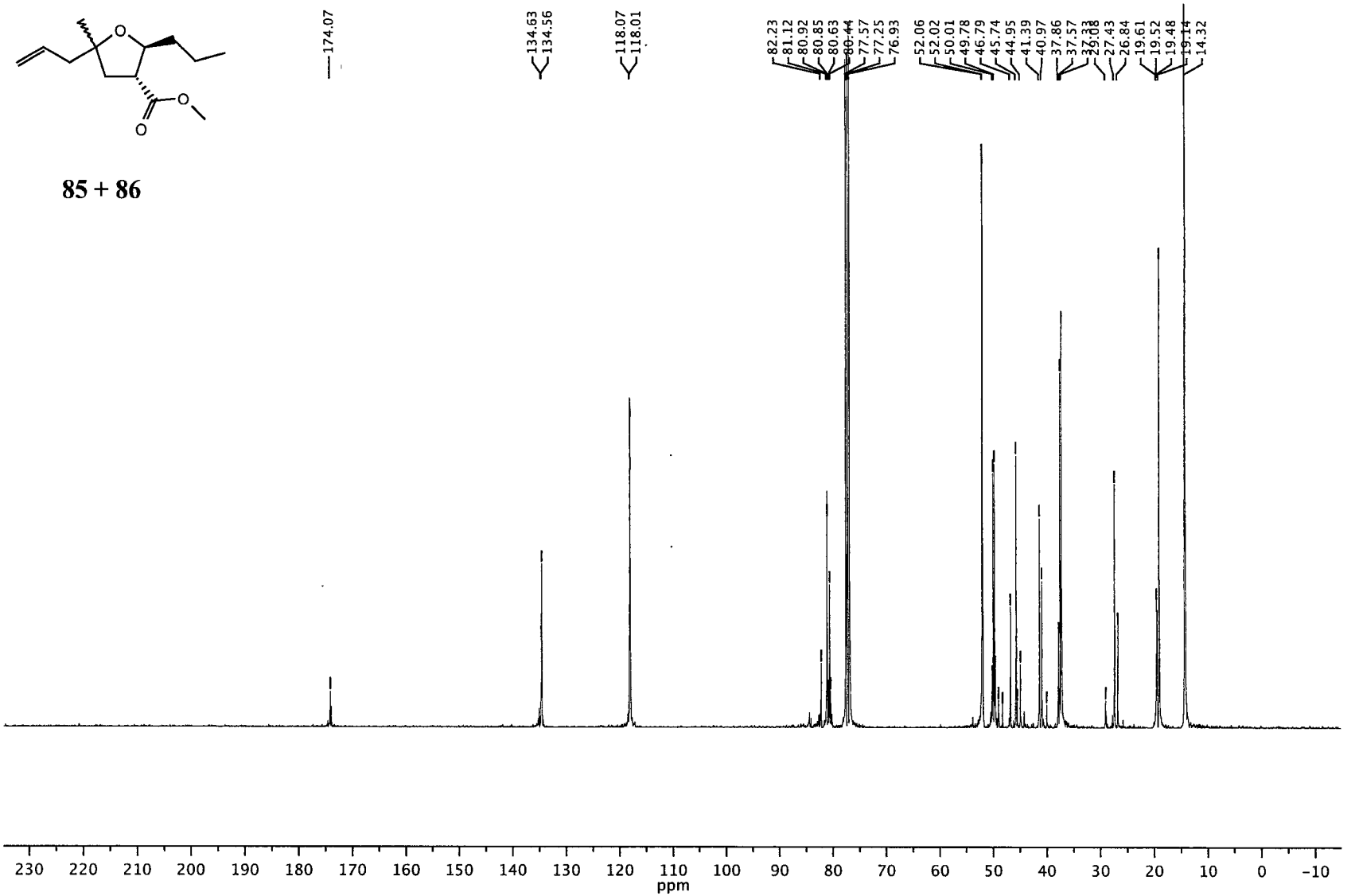
52.76
52.58
49.09
48.84
48.73
46.22
42.81
41.53
39.49
38.01
37.15

27.32
26.59
26.55
19.33
19.22
18.90
14.17
14.08

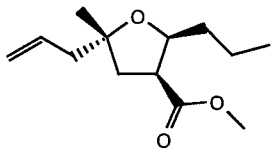




85 + 86

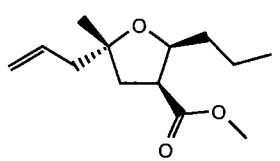

174.07
134.63
134.56
118.07
118.01
82.23
81.12
80.92
80.85
80.63
80.44
77.57
77.25
76.93
52.06
52.02
50.01
49.78
46.79
45.74
44.95
41.39
40.97
37.86
37.57
27.43
26.84
19.61
19.52
19.48
19.14
14.32
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

85 + 86



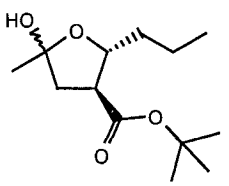
84

1.00
1.95
1.05
2.74
0.95
1.84
1.97
1.76
3.64
2.87
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm



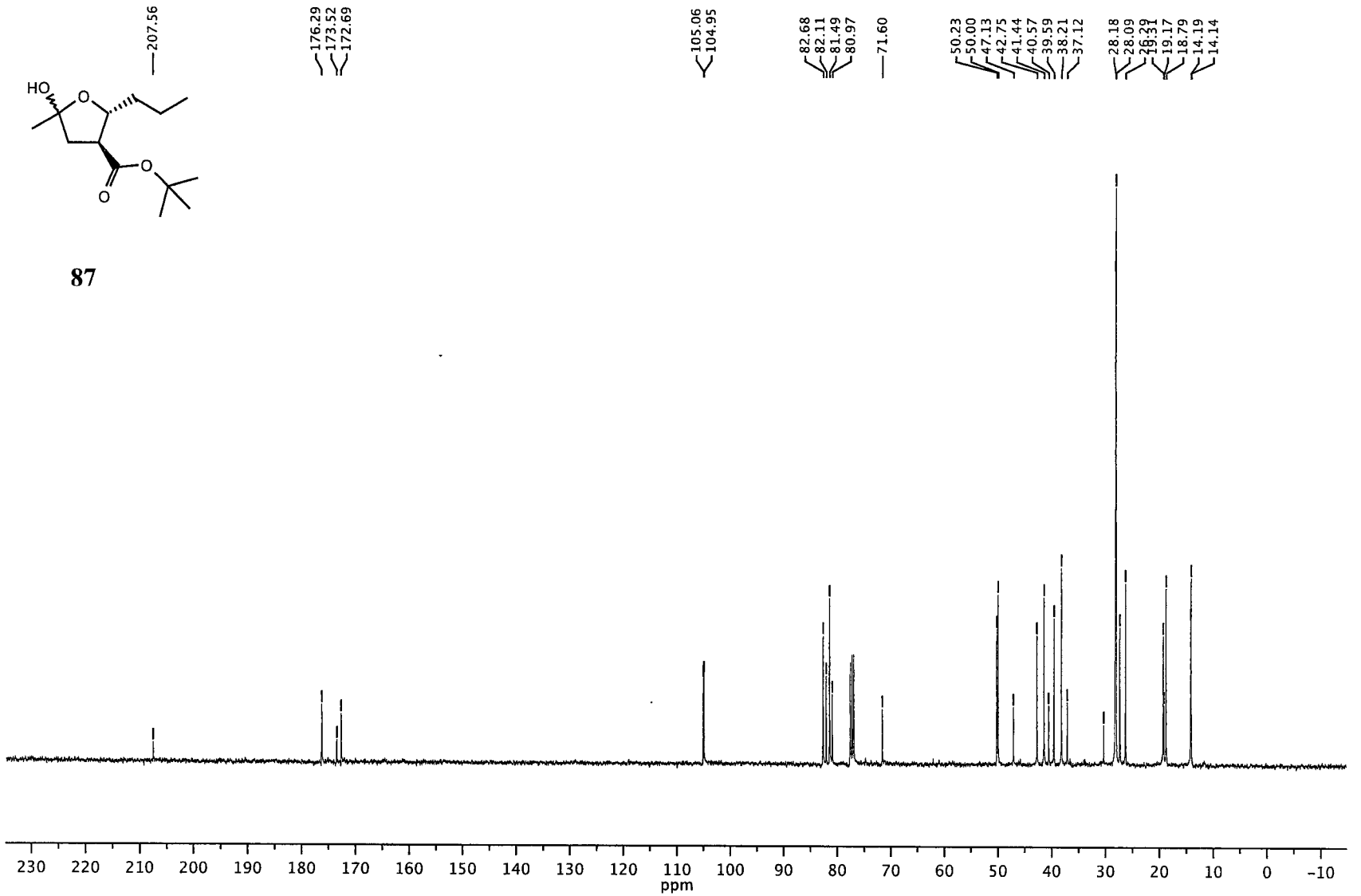
84

173.49
134.72
117.96
82.43
79.18
77.58
77.26
76.94
51.75
48.33
45.75
38.95
34.52
27.38
19.82
14.25
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


HO
O
O
O

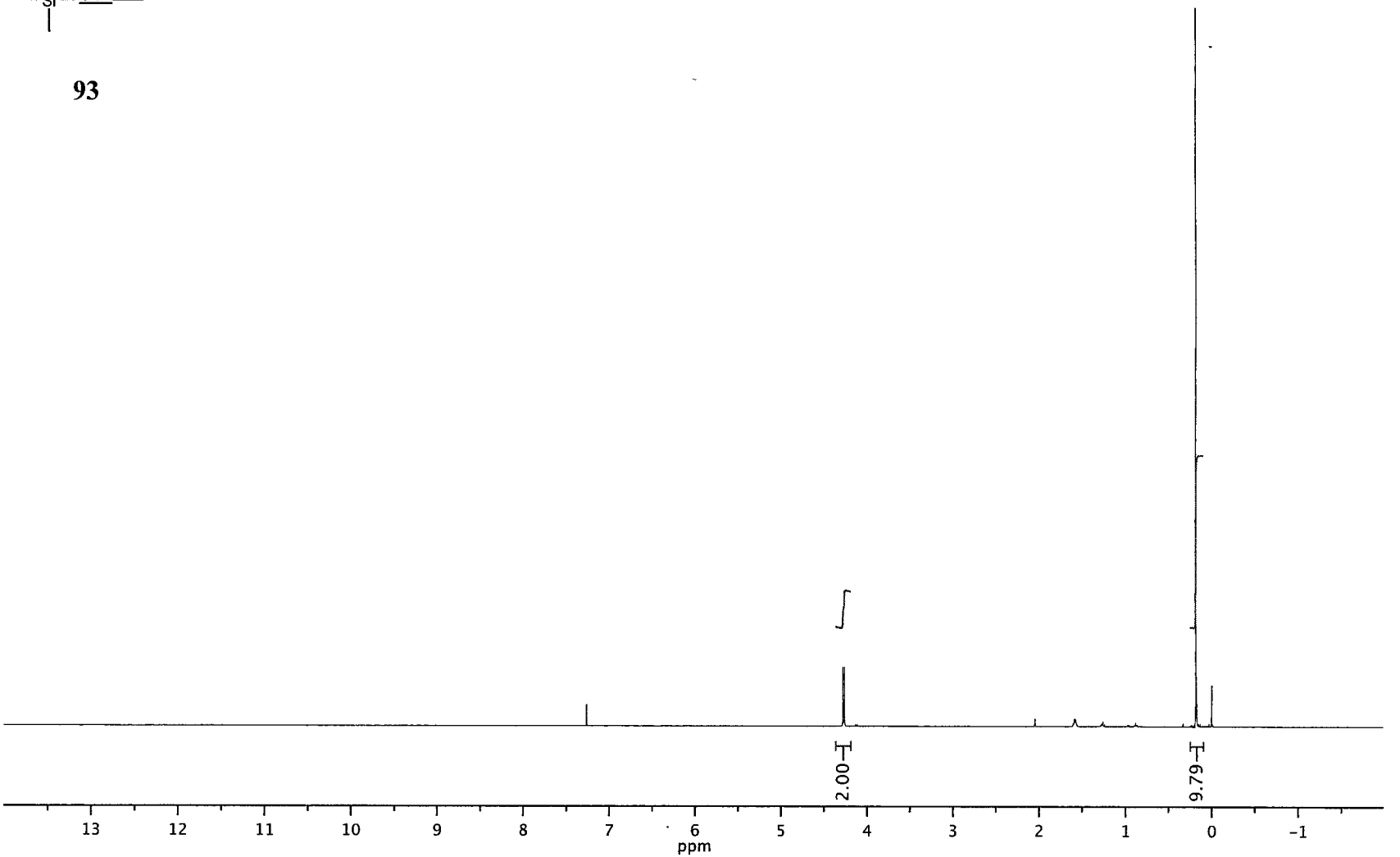
87

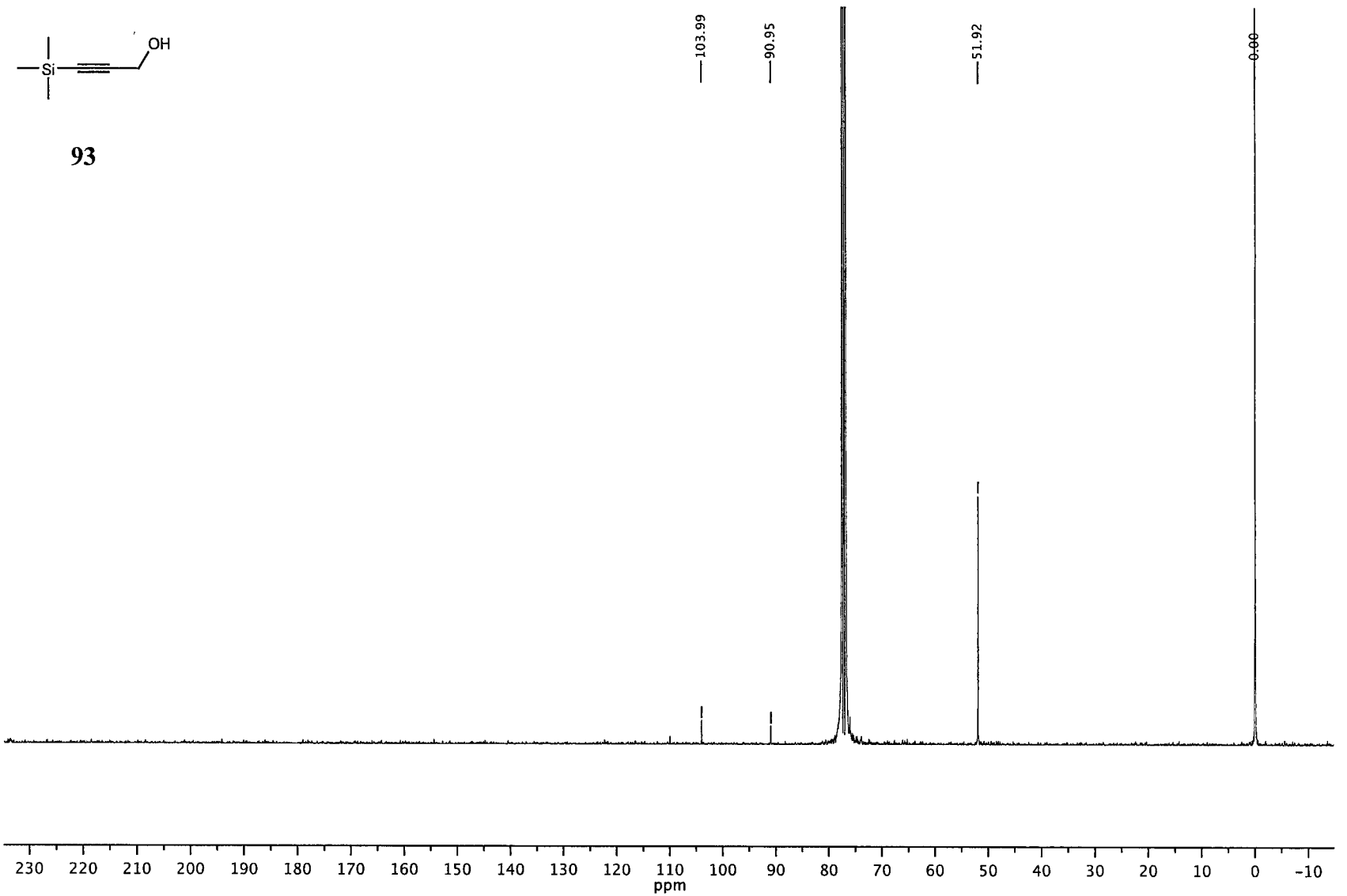
1.00
0.76
0.45
1.61
0.80
1.06
0.53
1.24
1.85
1.86
2.79
5.52
22.17
6.16
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


207.56
176.29
173.52
172.69
105.06
104.95
82.68
82.11
81.49
80.97
71.60
50.23
50.00
47.13
42.75
41.44
40.57
39.59
38.21
37.12
28.18
28.09
26.29
19.31
19.17
18.79
14.19
14.14
HO
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

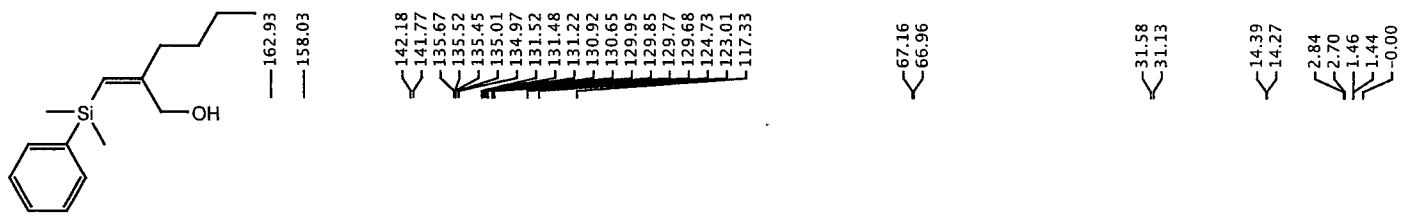
87

93

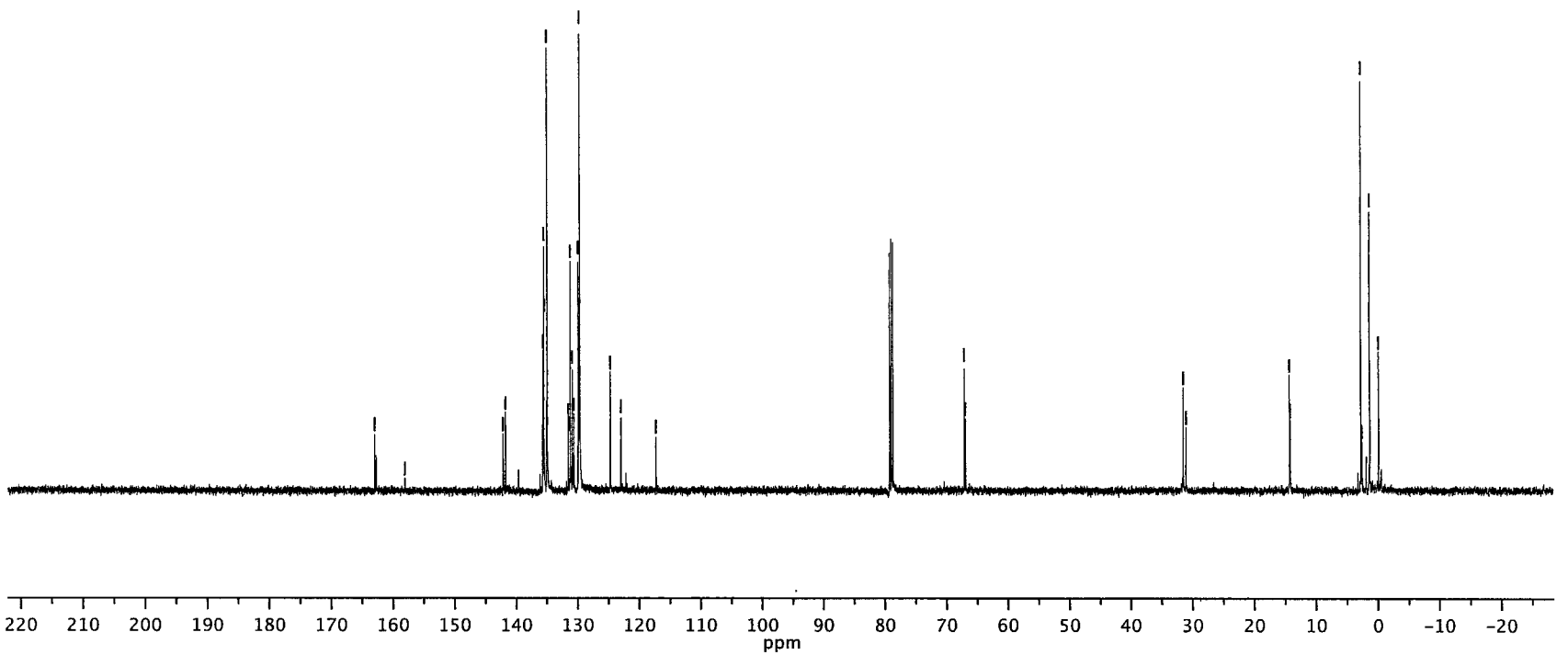


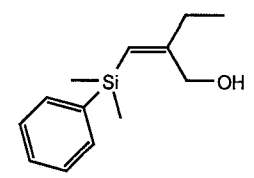

OH
Si
93
103.99
90.95
51.92
0.00
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

95


Si
OH
162.93
158.03
142.18
141.77
135.67
135.52
135.45
135.01
134.97
131.52
131.48
131.22
130.92
130.65
129.95
129.85
129.77
129.68
124.73
123.01
117.33
67.16
66.96
31.58
31.13
14.39
14.27
2.84
2.70
1.46
1.44
-0.00

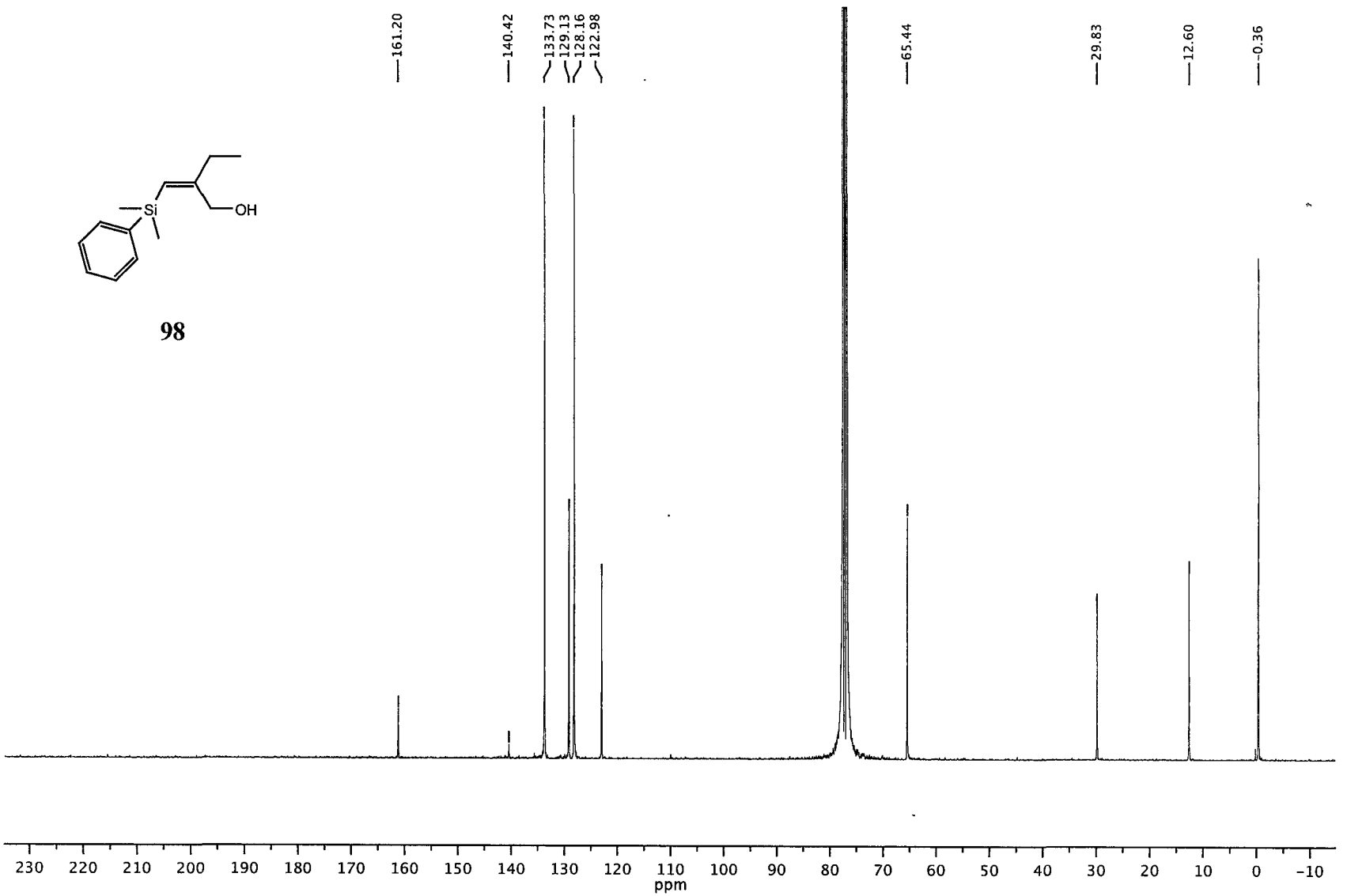
95


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

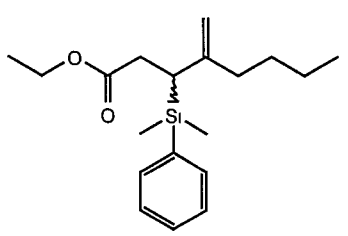

Si
OH

98

1.74
2.58
1.00
1.81
1.81
2.51
5.28
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

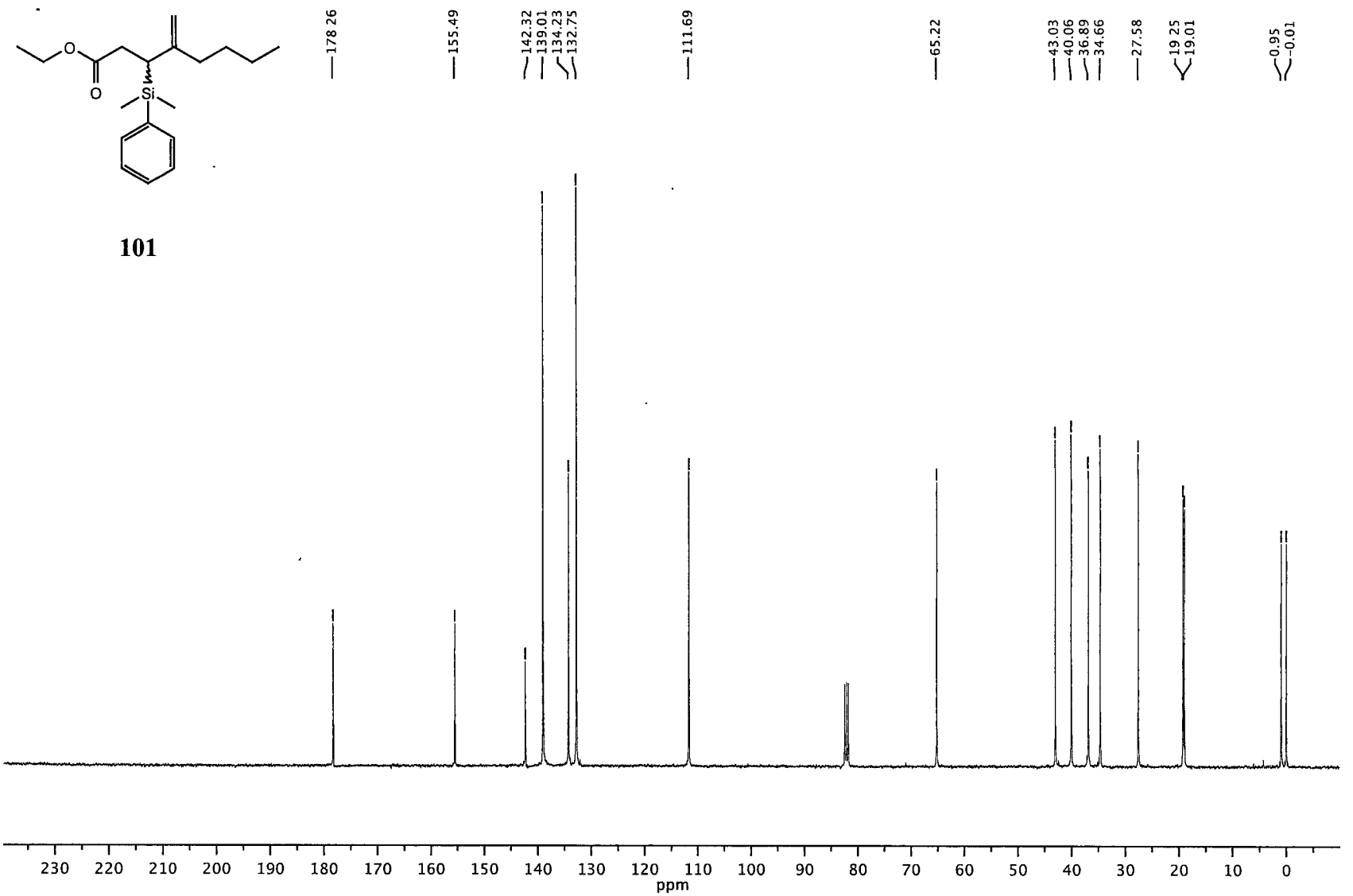

161.20
140.42
133.73
129.13
128.16
122.98
65.44
29.83
12.60
-0.36
Si
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

98

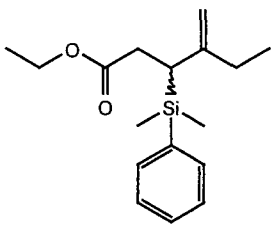


101

2.00
2.94
1.03
1.06
1.97
2.05
1.02
2.03
0.91
2.43
3.63
3.01
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

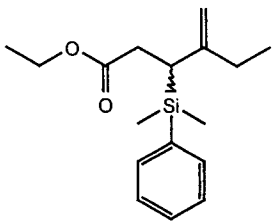

O
O
Si
178.26
155.49
142.32
139.01
134.23
132.75
111.69
65.22
43.03
40.06
36.89
34.66
27.58
19.25
19.01
0.95
-0.01
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

101



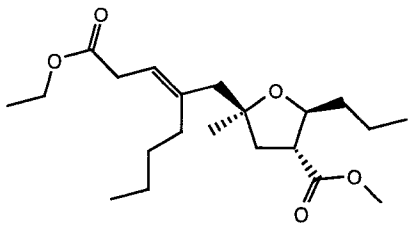
100

1.49
2.77
0.65
0.68
1.30
2.05
1.35
2.66
2.13
5.81
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

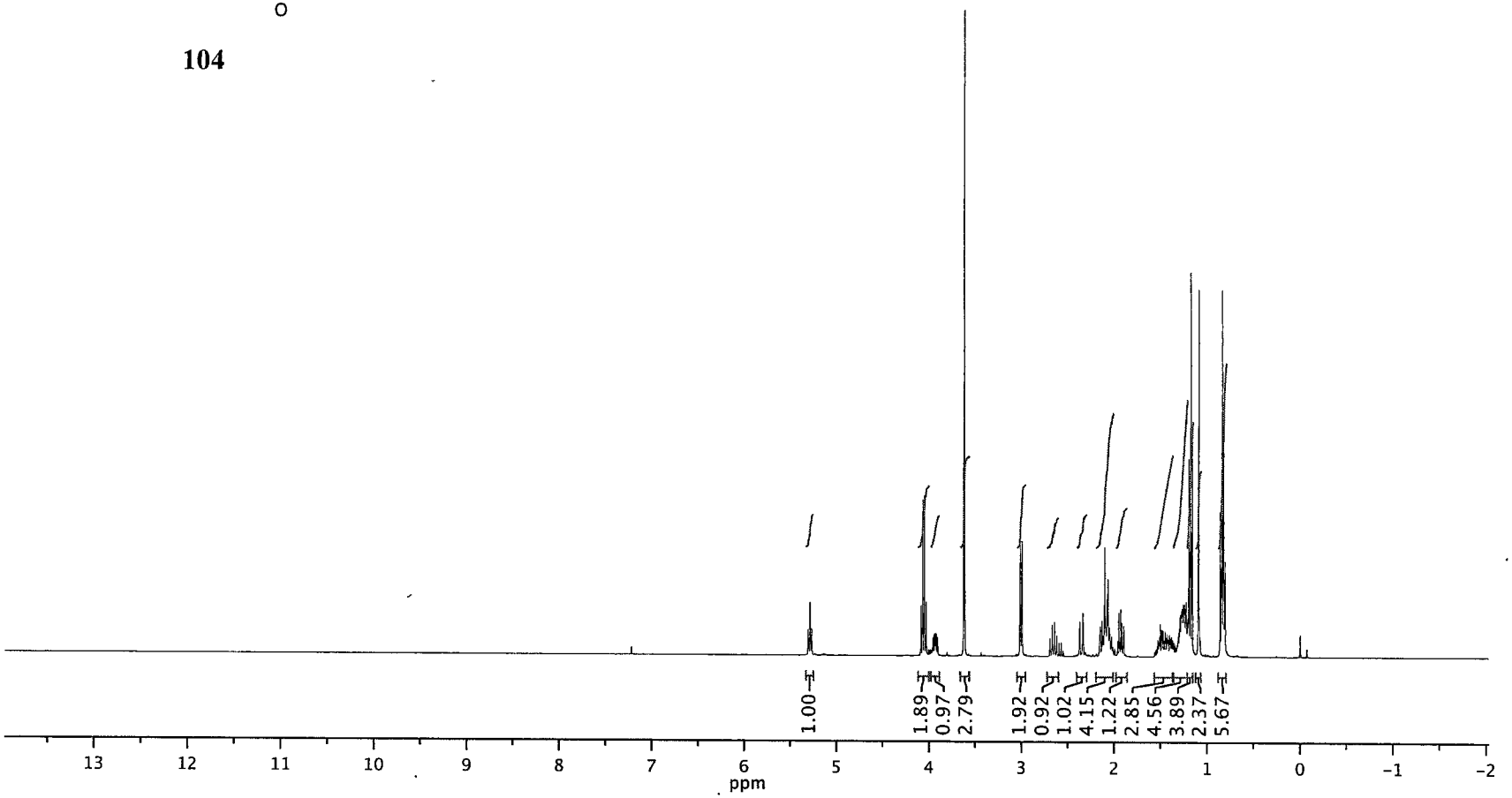


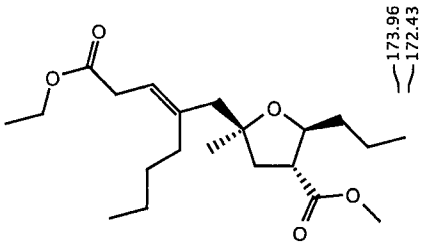
100

173.58
152.09
137.53
134.23
133.71
129.79
129.45
128.07
127.98
106.13
60.48
35.31
32.21
31.15
14.47
12.12
-3.81
-4.88
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



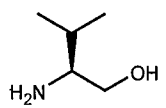
104


1.00
1.89
0.97
2.79
1.92
0.92
1.02
4.15
1.22
2.85
4.56
3.89
2.37
5.67
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
ppm

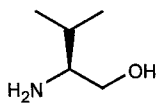


104

173.96
172.43
140.87
120.35
82.95
80.92
60.61
51.98
49.76
47.07
42.81
37.57
33.84
30.83
30.60
27.58
22.97
19.46
14.38
14.28
14.20
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

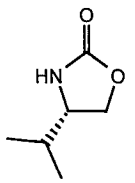


108

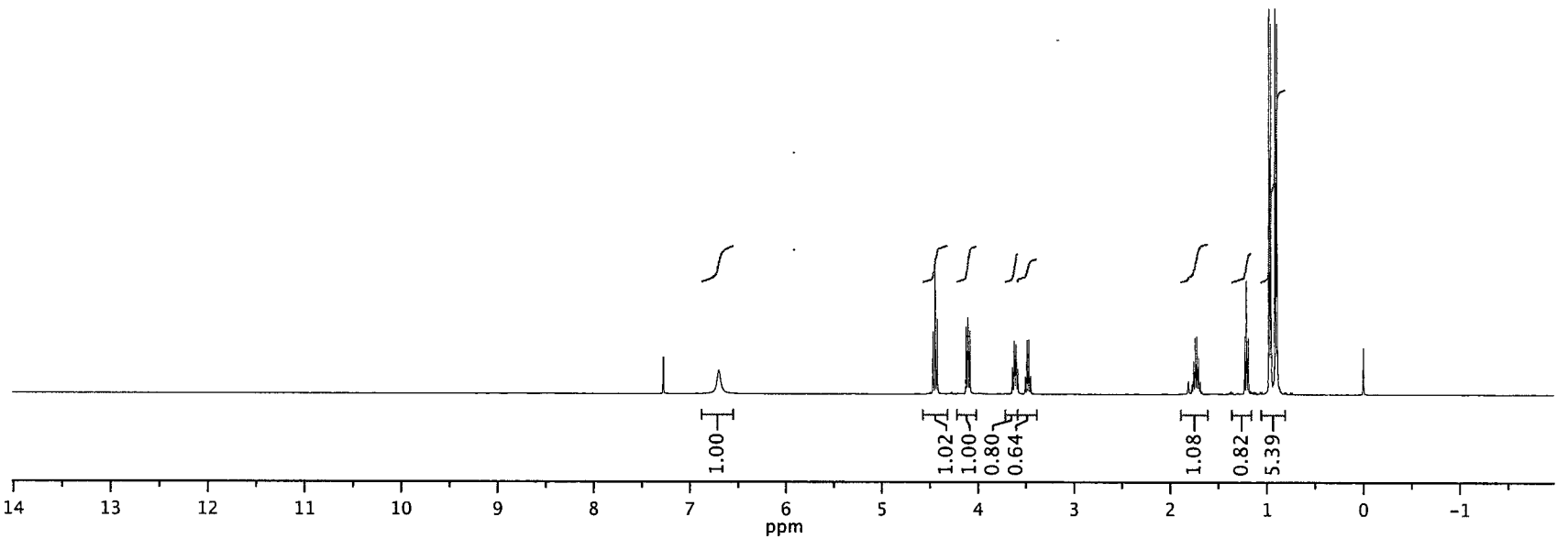

OH
H_2N

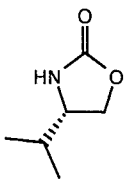
108

64.23
58.79
31.28
19.38
18.70
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
HN
O

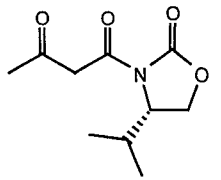
106


1.00
1.02
1.00
0.80
0.64
1.08
0.82
5.39
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

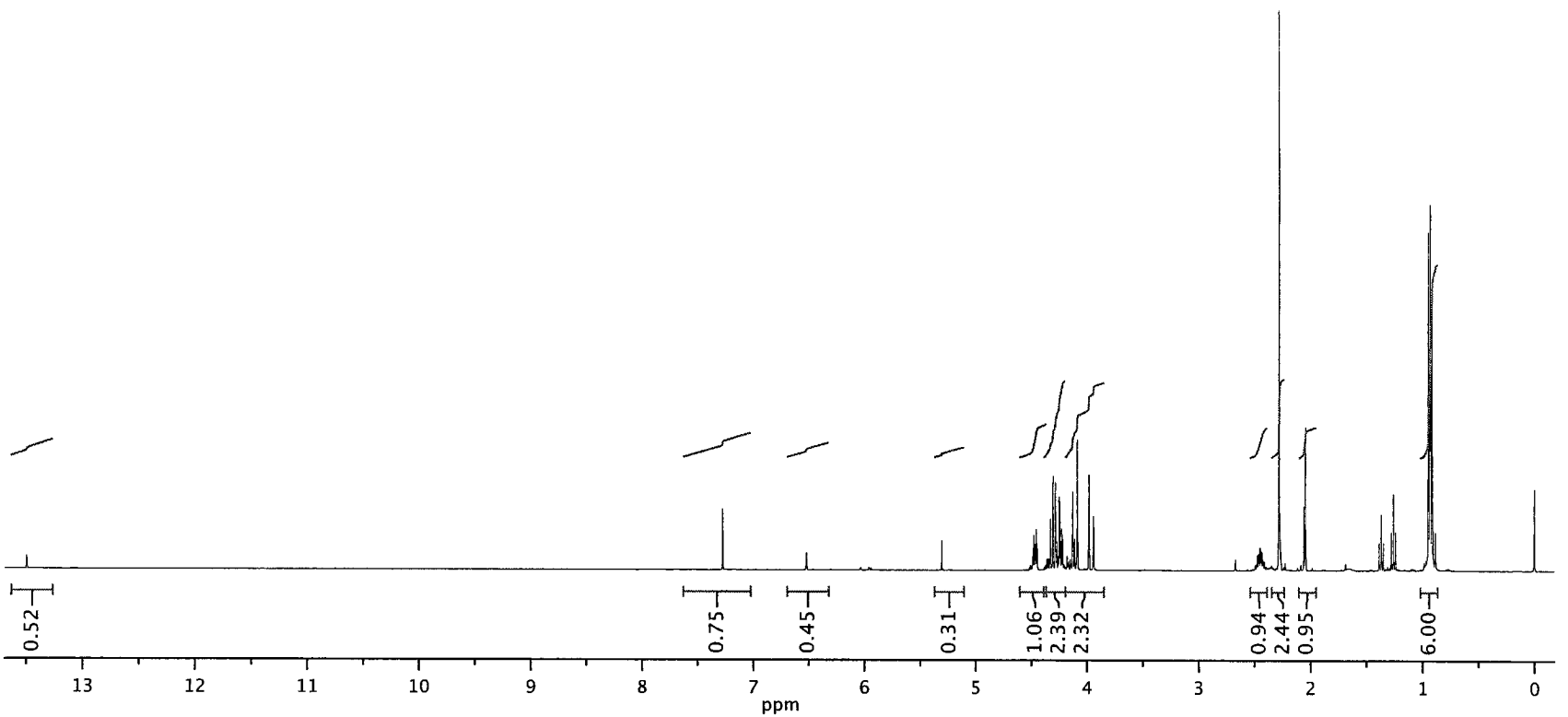

O
HN
O

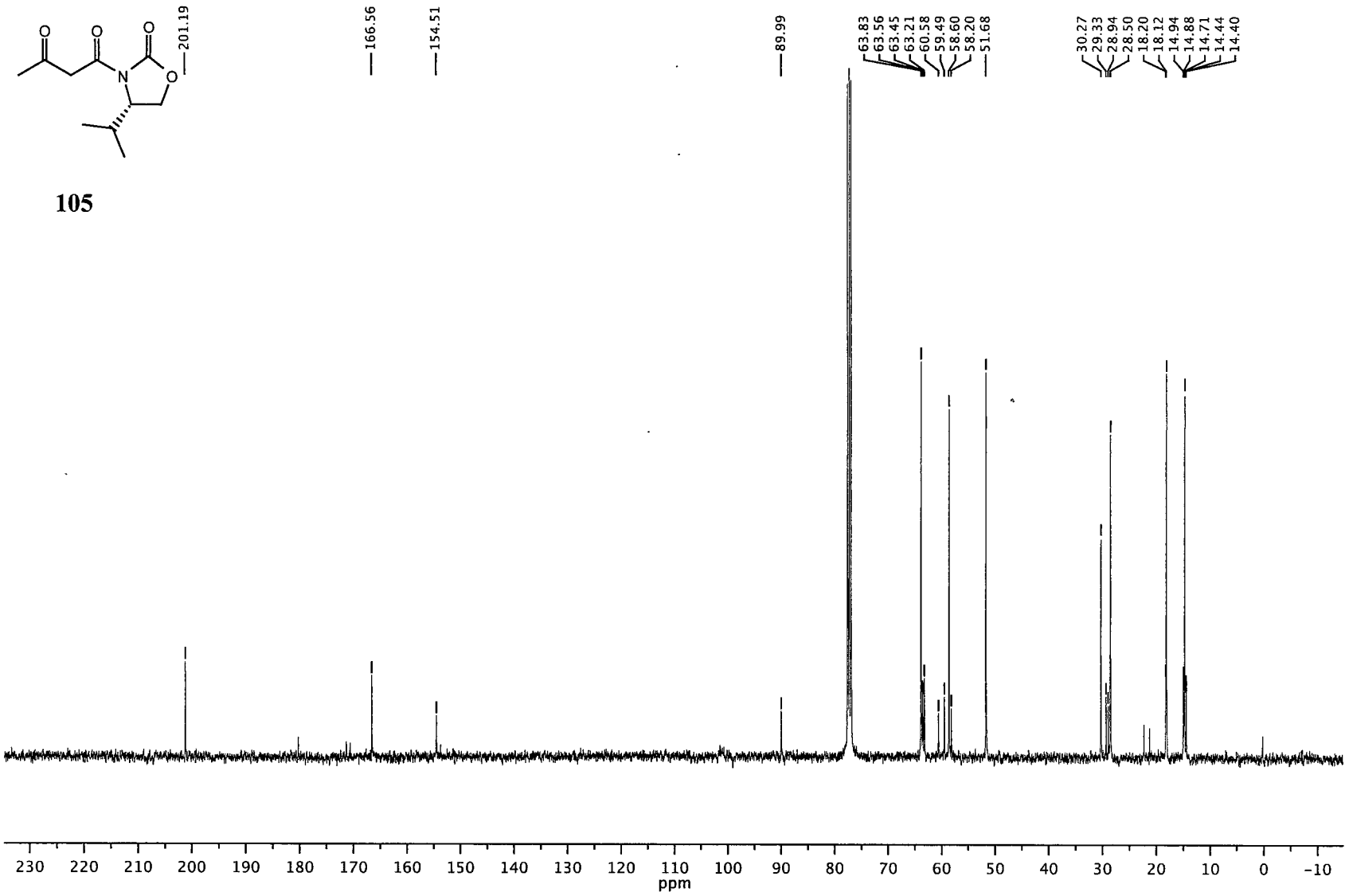
106

160.63
68.85
66.06
58.60
32.92
18.23
17.87
15.49
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

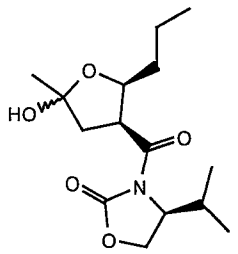


105

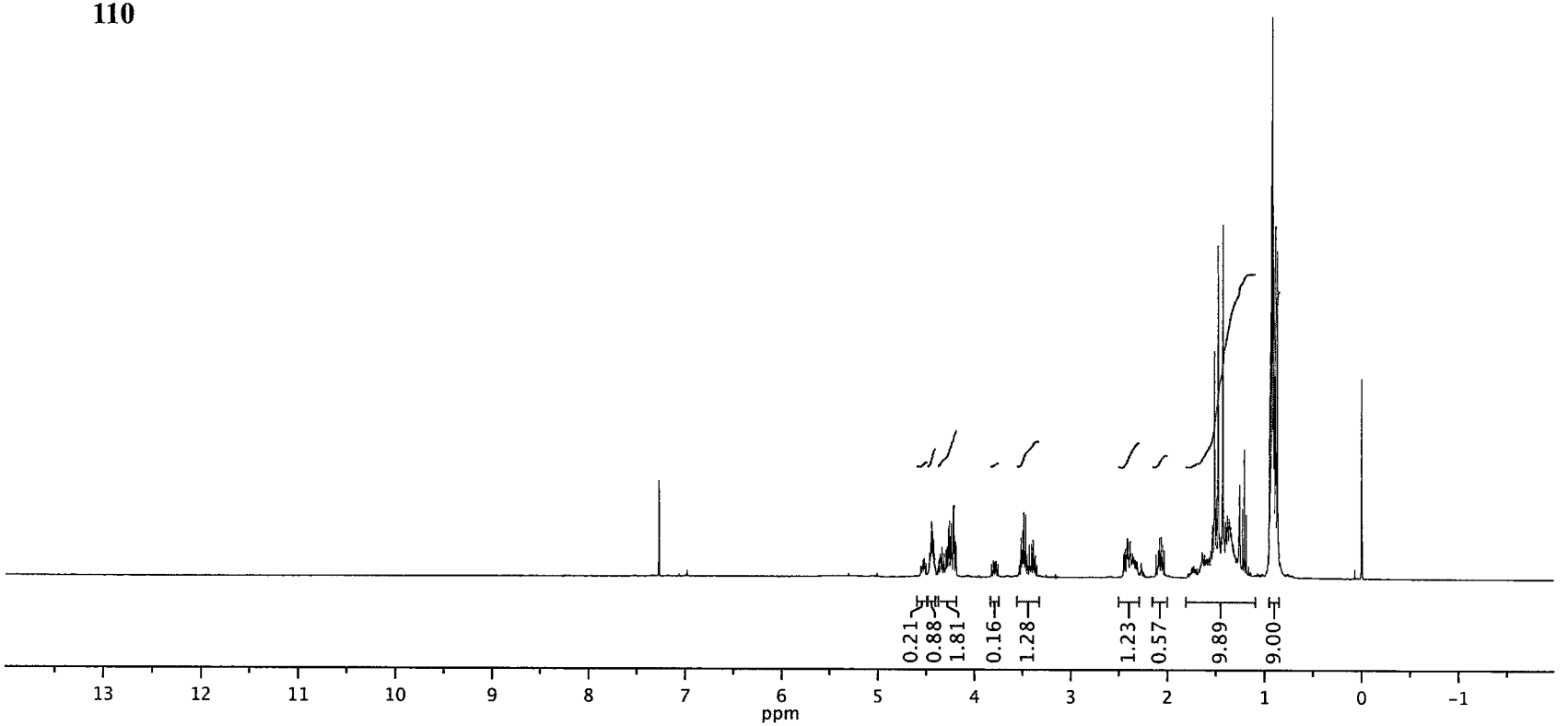

0.52
0.75
0.45
0.31
1.06
2.39
2.32
0.94
2.44
0.95
6.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

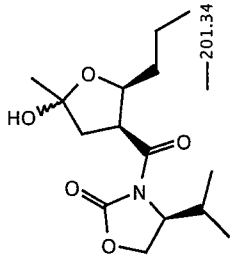

201.19
166.56
154.51
89.99
63.83
63.56
63.45
63.21
60.58
59.49
58.60
58.20
51.68
30.27
29.33
28.94
28.50
18.20
18.12
14.94
14.88
14.71
14.44
14.40
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

105


HO
O
O
O
N
O

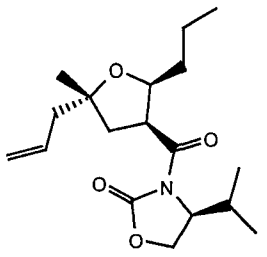
110


0.21
0.88
1.81
0.16
1.28
1.23
0.57
9.89
9.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


HO
O
O
O
N
O
O

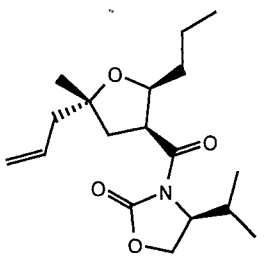
110

201.34
166.58
105.26
105.08
82.77
81.50
77.66
77.34
77.03
63.83
63.61
63.45
58.92
58.85
58.54
51.64
47.64
47.41
42.45
41.69
37.94
37.88
30.24
28.46
26.96
19.39
19.35
19.00
18.89
18.15
18.07
14.85
14.67
14.49
14.17
14.11
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



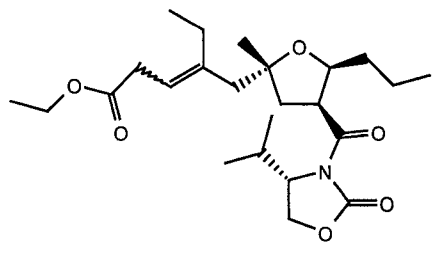
109

1.00
2.03
1.23
2.57
0.85
4.55
0.95
3.04
3.33
9.14
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

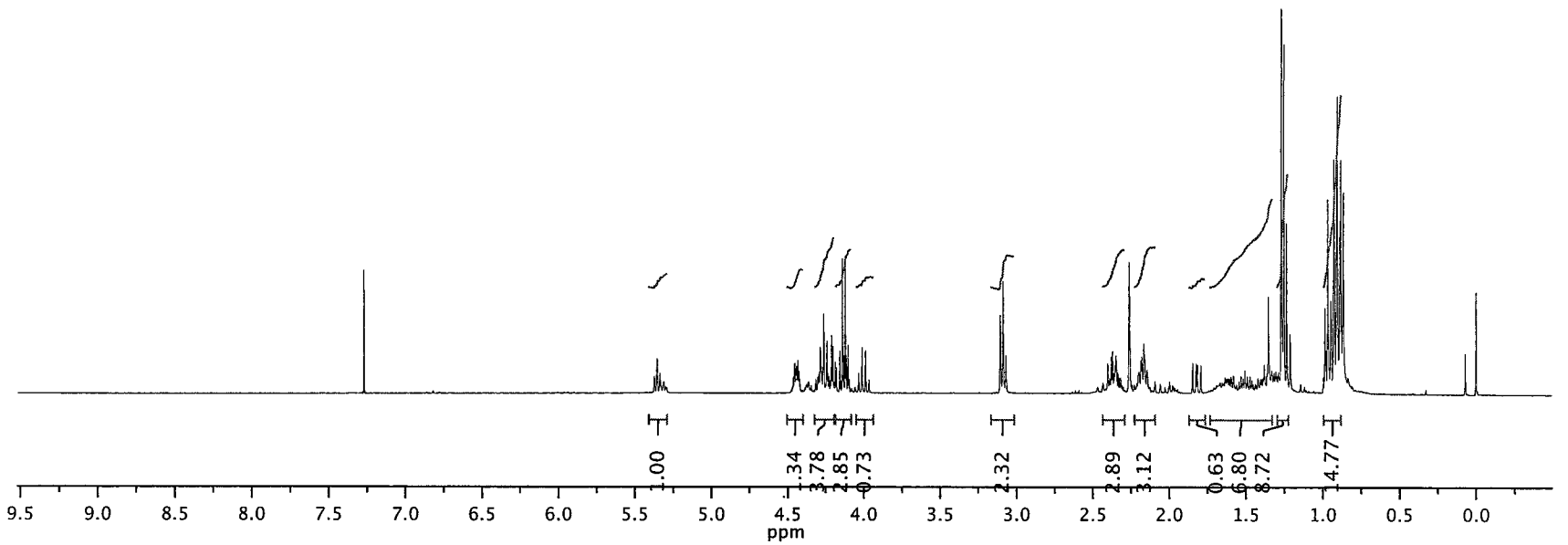


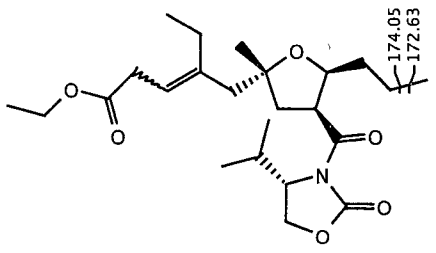
109

173.80
172.50
153.86
134.69
118.20
82.67
81.01
78.84
63.30
58.73
48.23
45.95
41.98
37.19
35.31
29.02
27.43
19.98
18.18
14.77
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



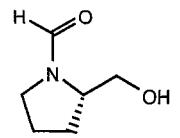
111


1.00
1.34
3.78
2.85
0.73
2.32
2.89
3.12
0.63
6.80
8.72
4.77
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

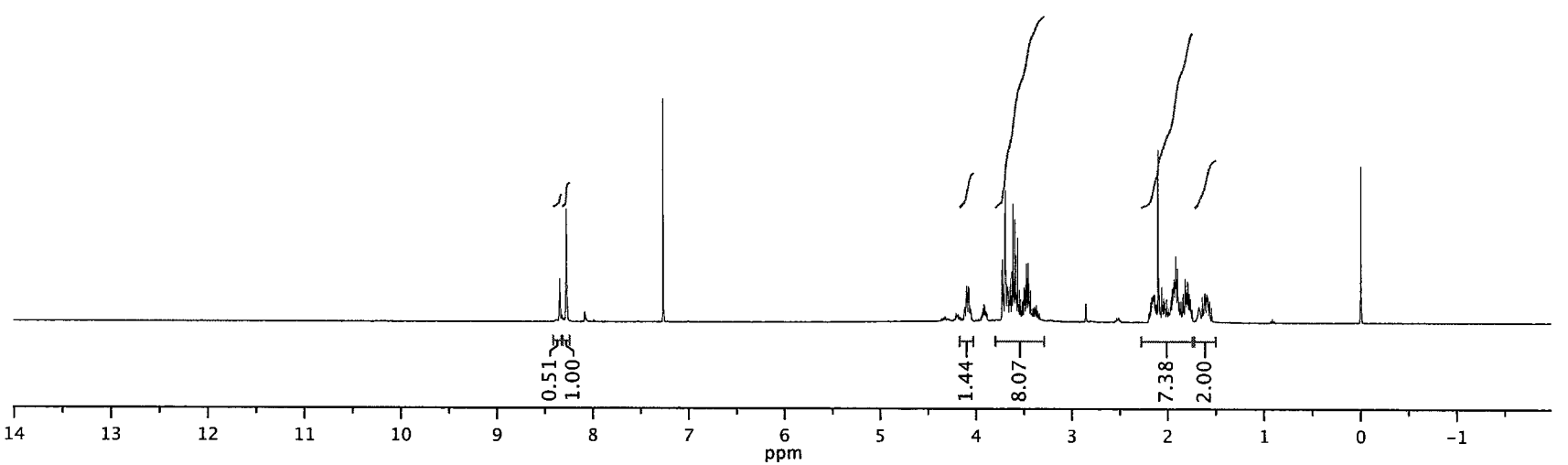


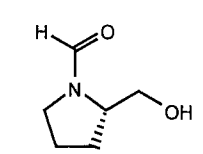
111

174.05
172.63
153.80
142.90
142.24
120.08
83.52
81.03
63.25
60.64
58.76
48.61
47.87
42.91
37.23
33.73
28.59
26.95
24.42
19.66
18.18
14.79
14.41
14.37
13.12
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



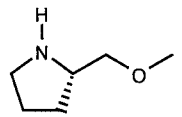
114



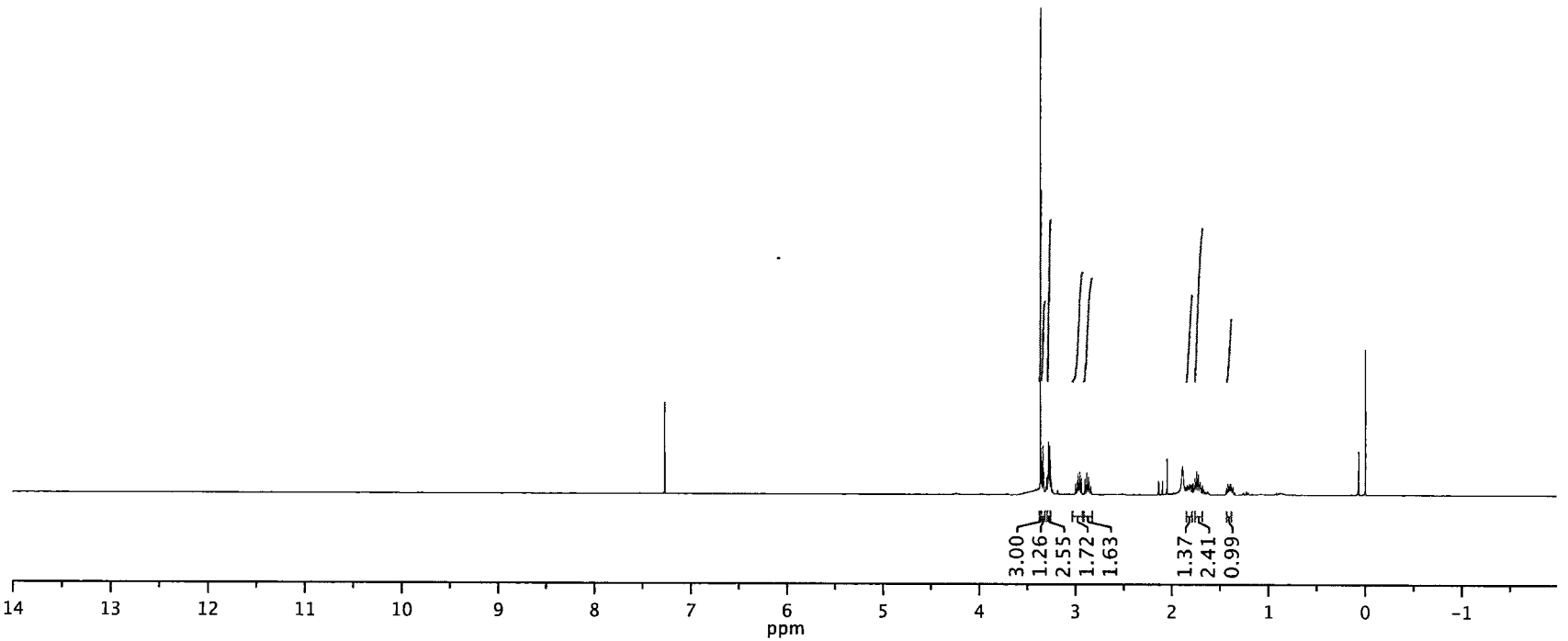

H
O
N
OH

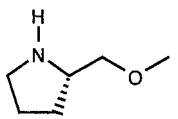
114

163.12
162.09
66.79
65.16
60.46
59.14
47.87
43.87
28.61
27.48
24.18
22.96
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



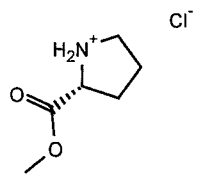
116



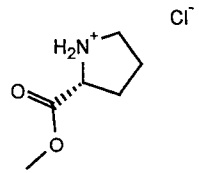


116

76.60
59.19
57.95
46.72
28.11
25.54
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

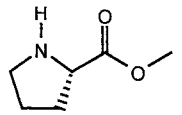


118HCl

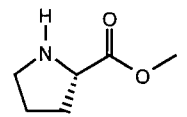

Cl⁻
H2N+
O
O
O

118HCl

170.59
59.66
53.91
46.42
28.21
23.42
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

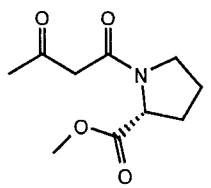


118



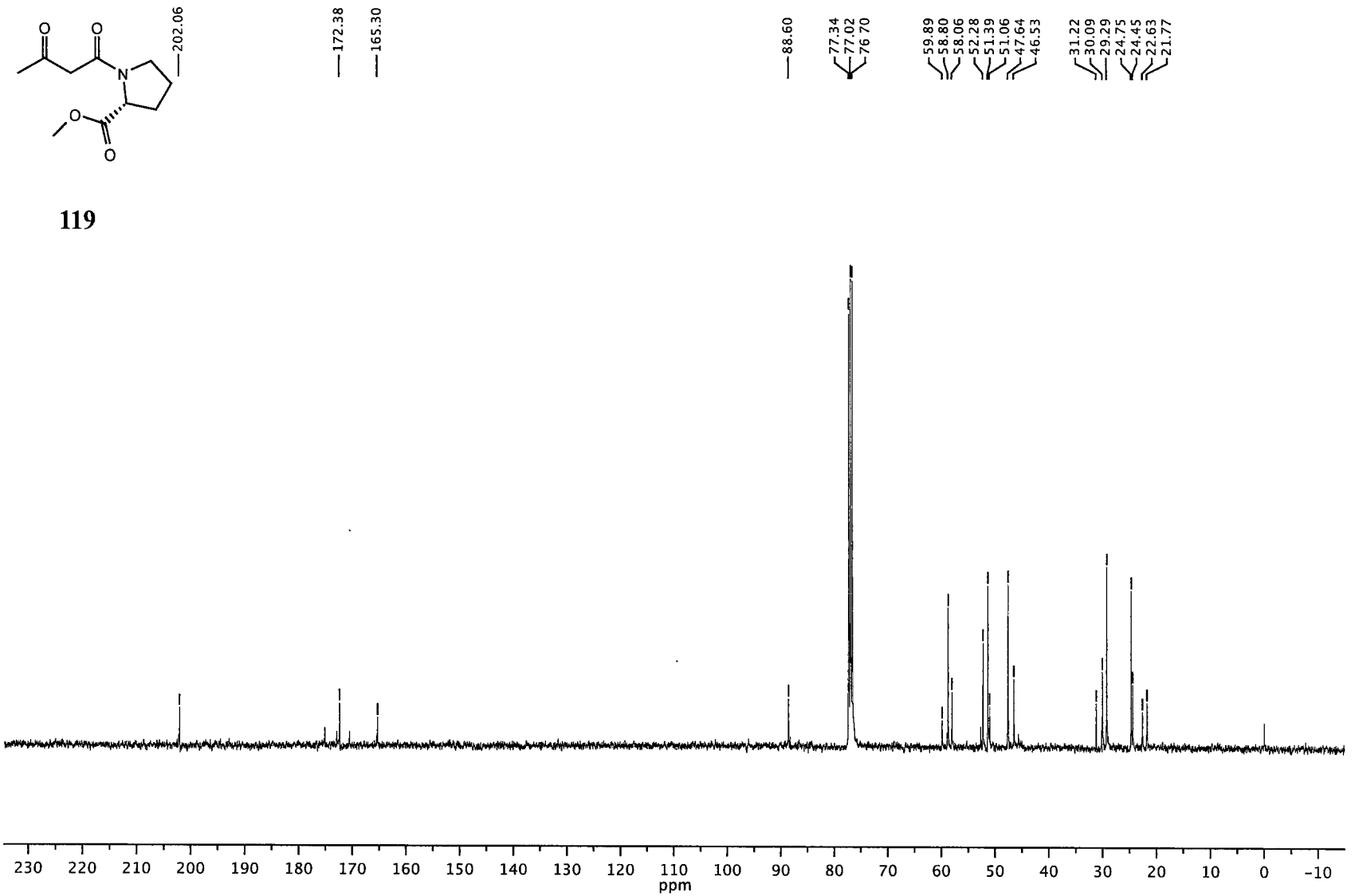
118

176.00
59.74
52.32
47.12
30.41
25.69
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

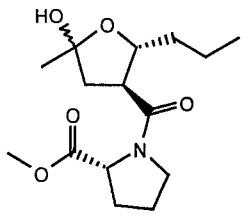


119

0.14
1.26
0.92
1.12
3.00
2.06
3.69
2.80
1.95
6.49
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

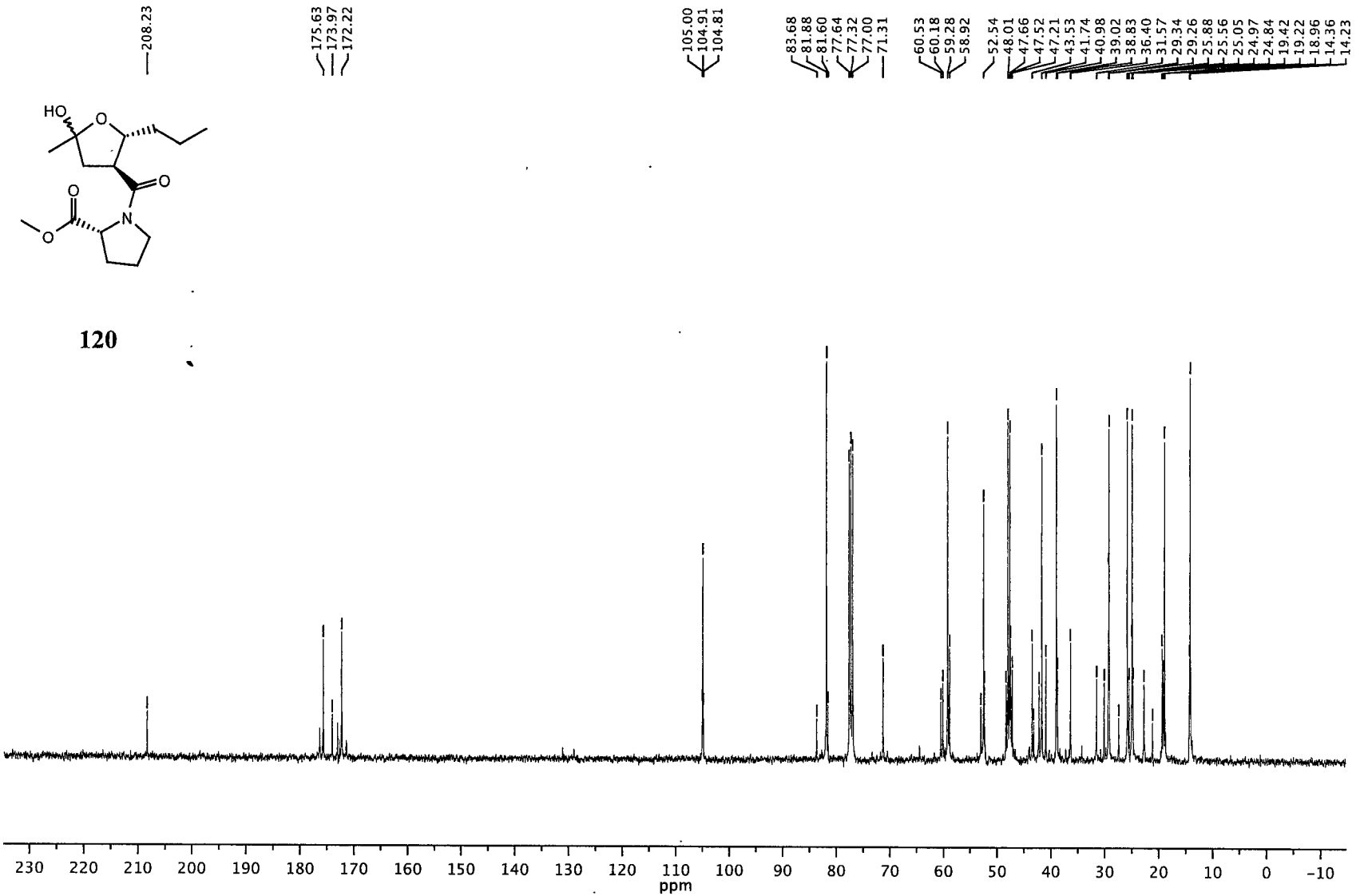

202.06
172.38
165.30
88.60
77.34
77.02
76.70
59.89
58.80
58.06
52.28
51.39
51.06
47.64
46.53
31.22
30.09
29.29
24.75
24.45
22.63
21.77
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

119

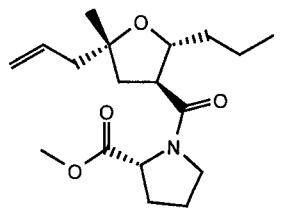

HO
O
O
O
O
N

120

1.00
0.86
1.38
1.36
8.12
0.95
1.14
0.87
2.17
11.25
11.81
6.54
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

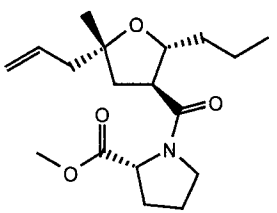

208.23
175.63
173.97
172.22
105.00
104.91
104.81
83.68
81.88
81.60
77.64
77.32
77.00
71.31
60.53
60.18
59.28
58.92
52.54
48.01
47.66
47.52
47.21
43.53
41.74
40.98
39.02
38.83
36.40
31.57
29.34
29.26
25.88
25.56
25.05
24.97
24.84
19.42
19.22
18.96
14.36
14.23
HO
O
O
O
O
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

120



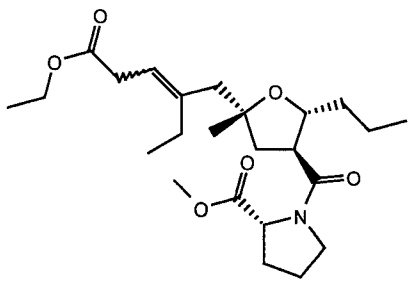
121

2.27
2.14
1.00
1.16
1.02
1.04
3.10
1.01
1.14
7.29
6.45
2.96
3.73
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

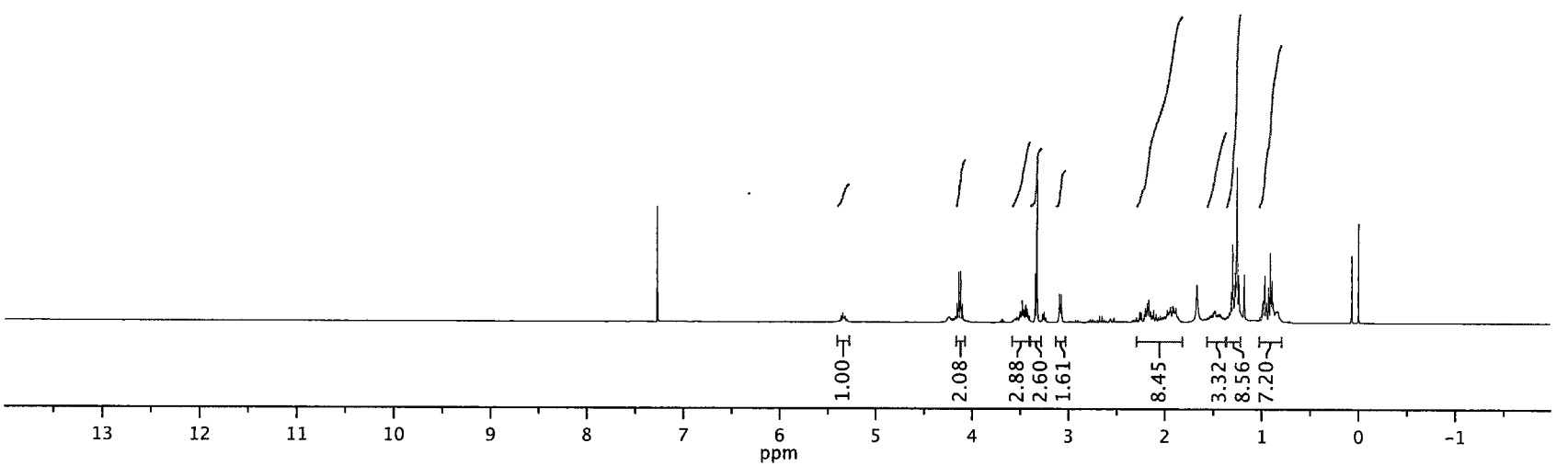


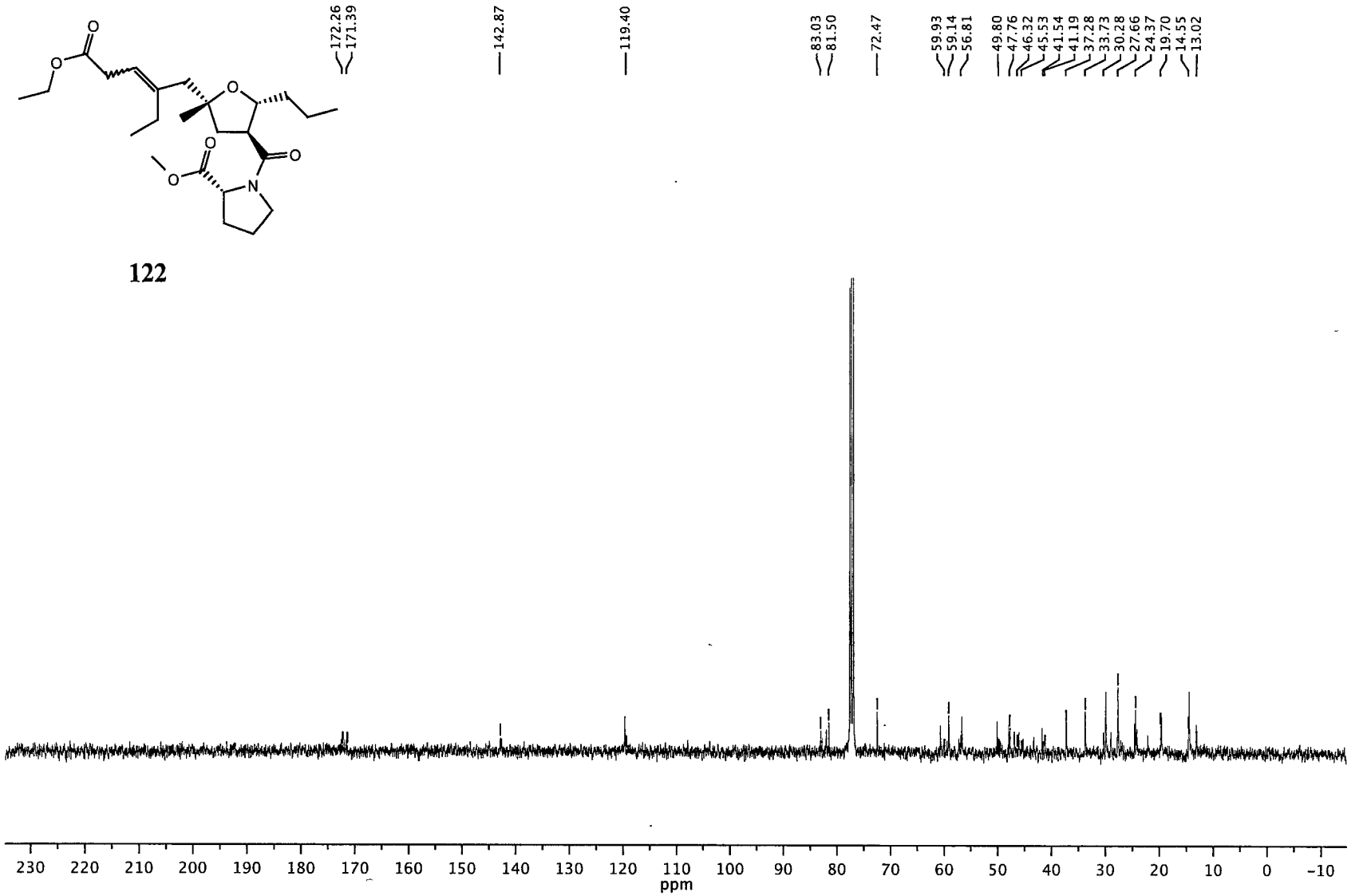
121

172.77
171.84
134.72
117.97
82.51
82.00
81.89
81.38
81.09
59.06
52.33
49.01
47.29
44.01
42.53
42.00
37.13
27.68
27.57
26.88
25.01
20.88
19.46
19.36
17.98
14.81
14.54
14.49
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

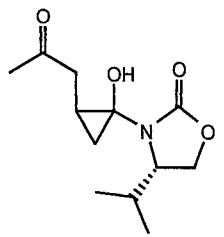


122

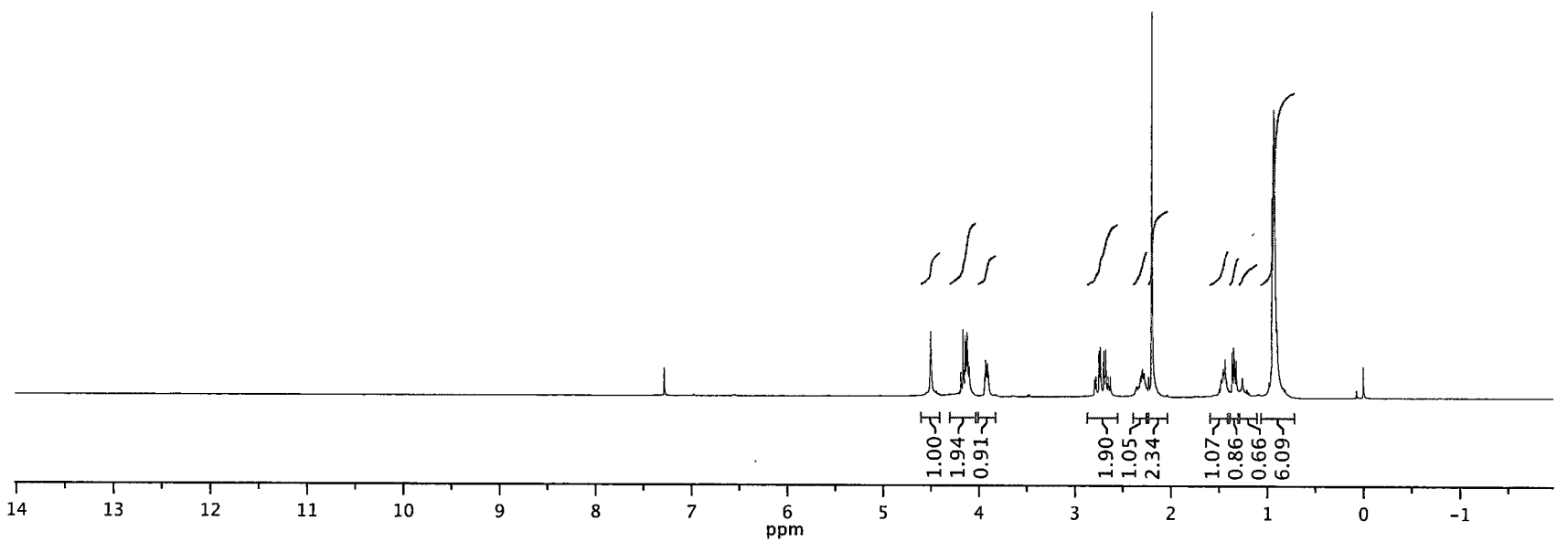


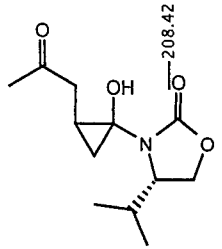

172.26
171.39
142.87
119.40
83.03
81.50
72.47
59.93
59.14
56.81
49.80
47.76
46.32
45.53
41.54
41.19
37.28
33.73
30.28
27.66
24.37
19.70
14.55
13.02
O
O
O
O
O
O
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

122


O
OH
O
N
O

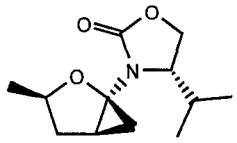
139


1.00
1.94
0.91
1.90
1.05
2.34
1.07
0.86
0.66
6.09
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


O
OH
208.42
O
N
O

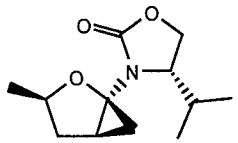
139

158.24
77.58
77.26
76.94
64.58
63.64
60.72
42.07
30.18
29.26
22.11
19.62
18.20
14.50
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



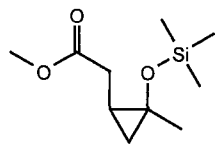
140

1.00
1.14
2.00
1.13
1.13
1.01
1.09
0.97
3.05
0.97
6.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

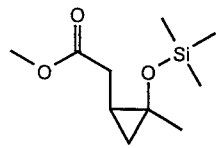


140

158.69
84.26
76.17
62.77
60.66
38.80
28.99
27.78
23.17
21.87
18.28
14.20
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

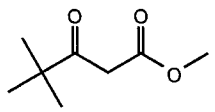


145

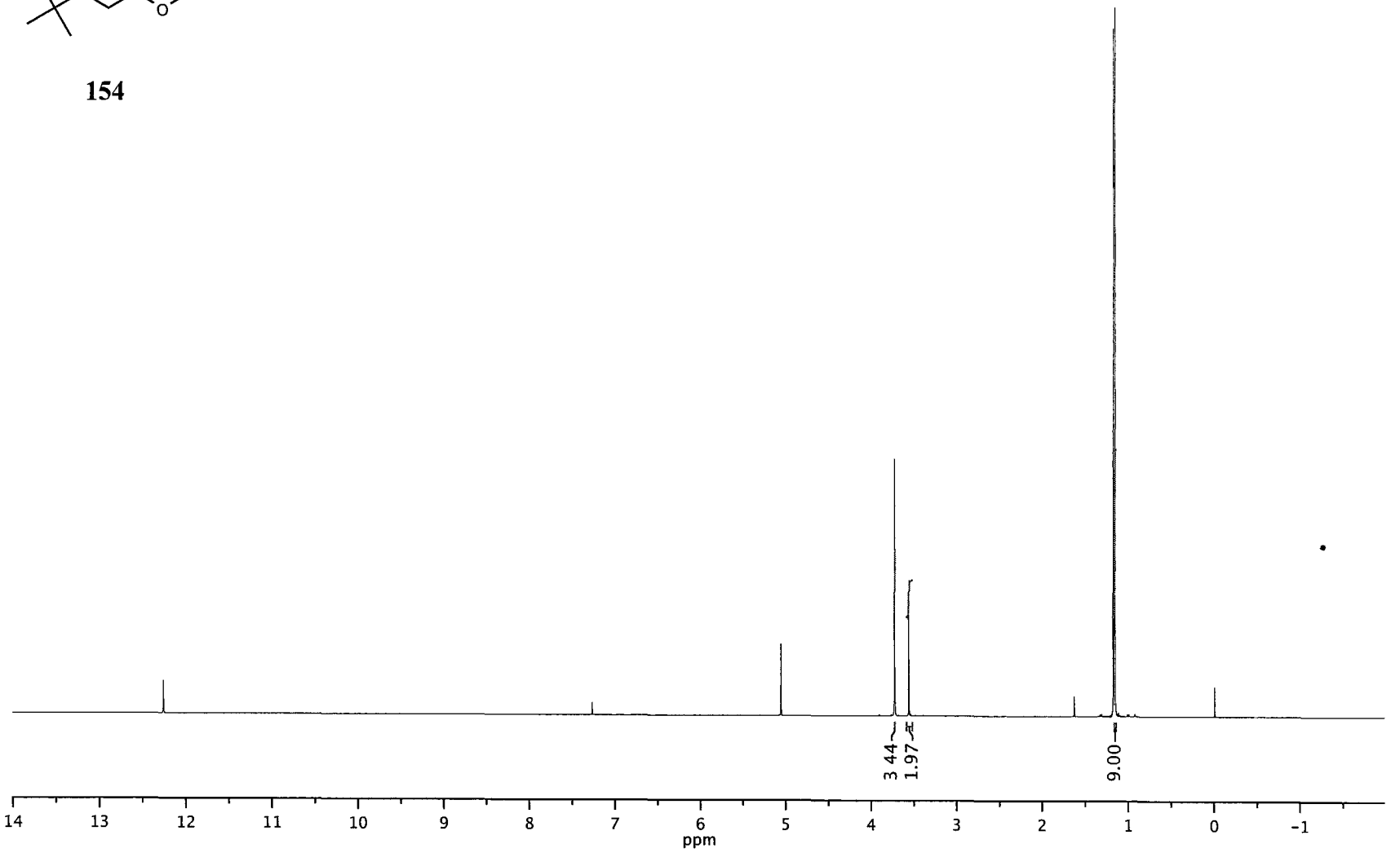


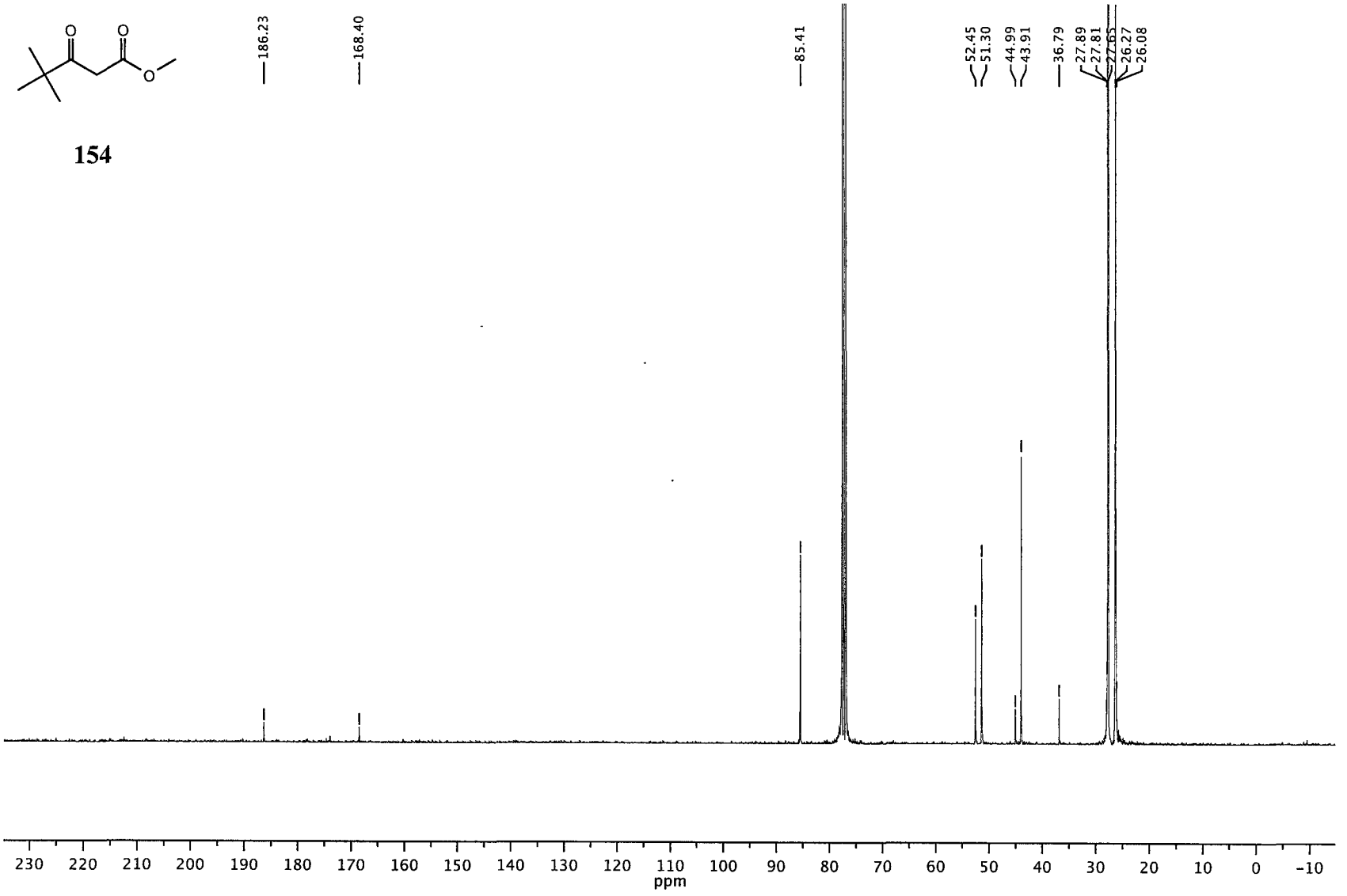
145

172.93
54.74
50.24
40.64
31.87
24.74
18.32
0.00
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

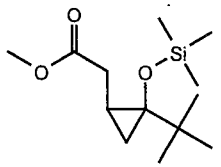


154

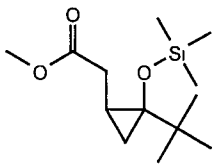



186.23
168.40
85.41
52.45
51.30
44.99
43.91
36.79
27.89
27.81
27.65
26.27
26.08
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

154

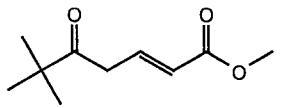


156

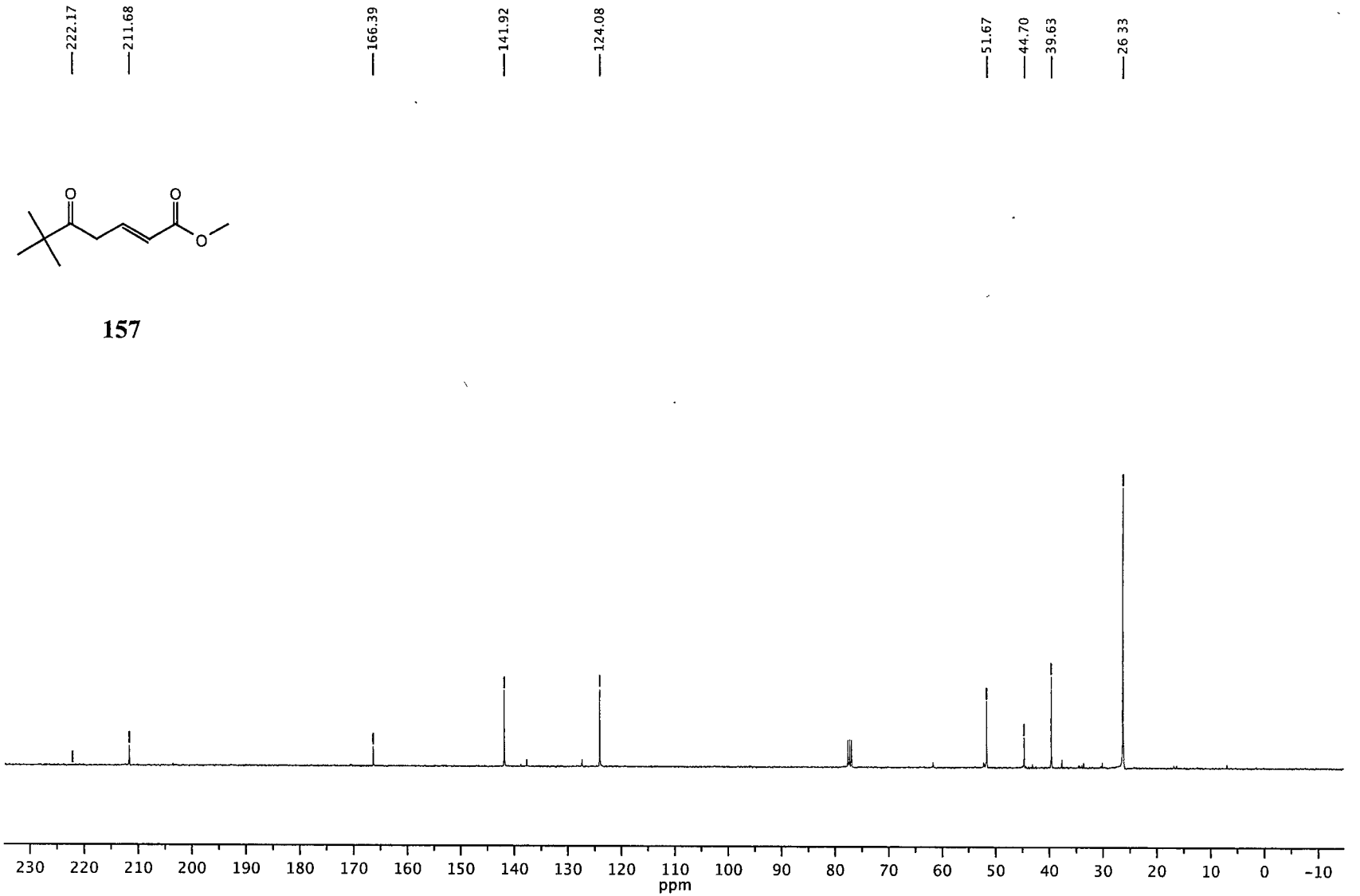


156

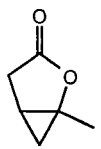
174.44
66.65
51.58
35.01
33.05
26.97
15.76
14.47
1.99
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



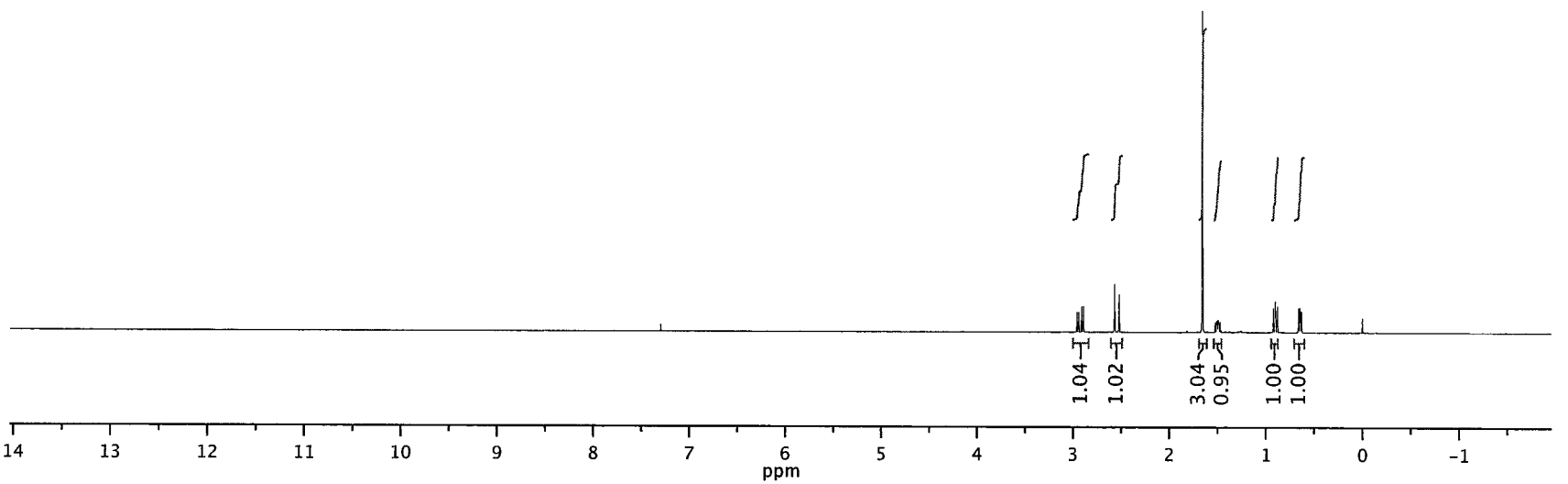
157

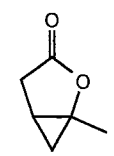

222.17
211.68
166.39
141.92
124.08
51.67
44.70
39.63
26 33
O
O
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

157



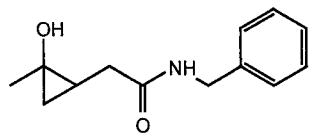
159



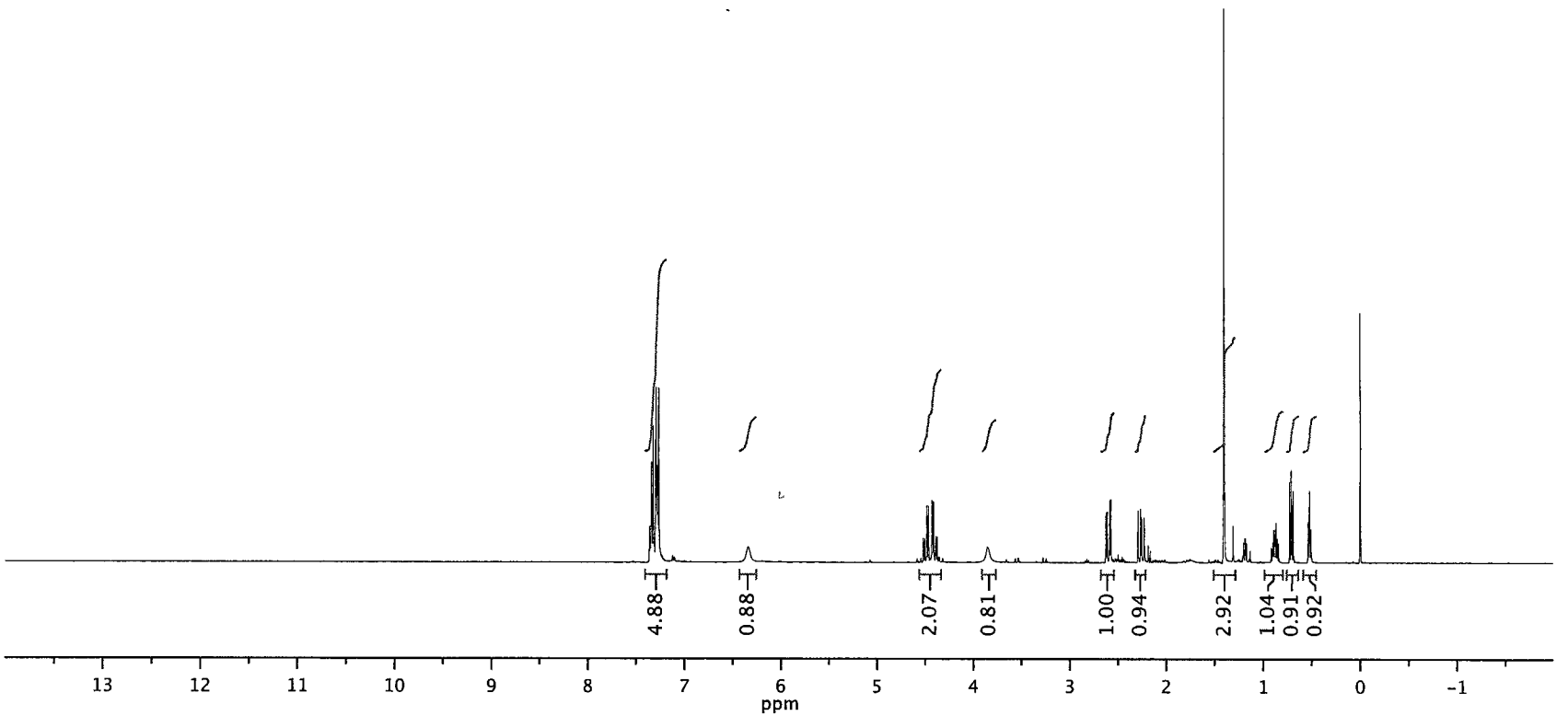


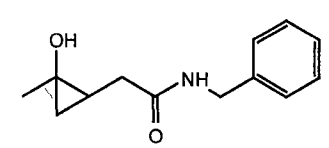
159

176.68
65.03
34.66
20.20
18.57
15.76
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


OH
NH
O

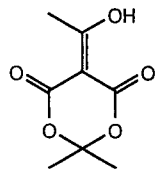
160


4.88
0.88
2.07
0.81
1.00
0.94
2.92
1.04
0.91
0.92
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

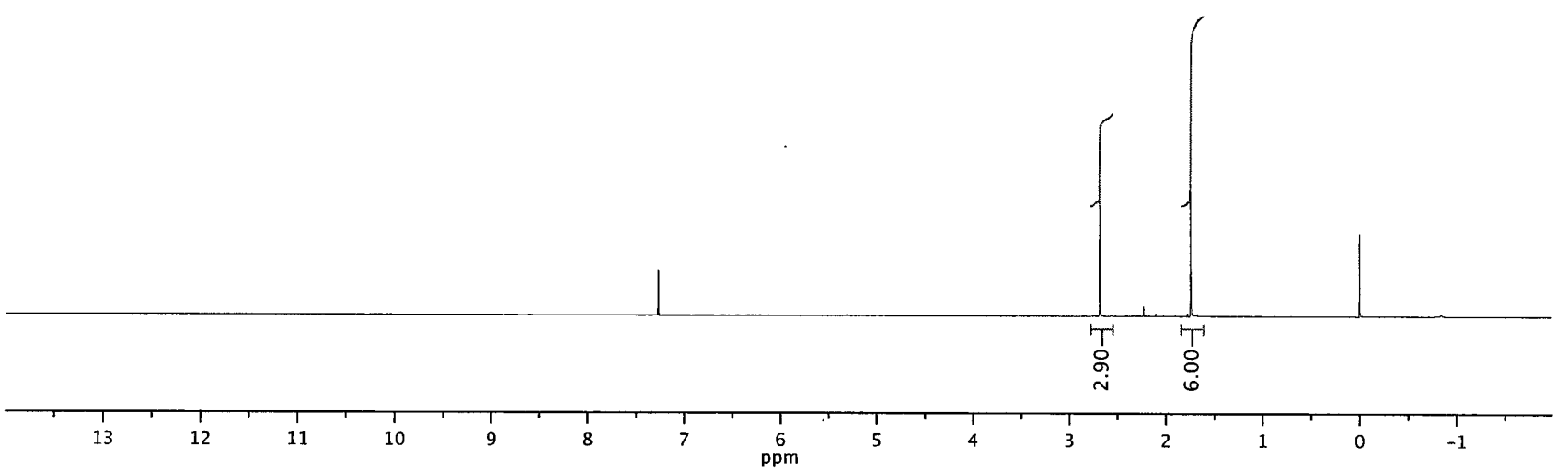

OH
NH
O

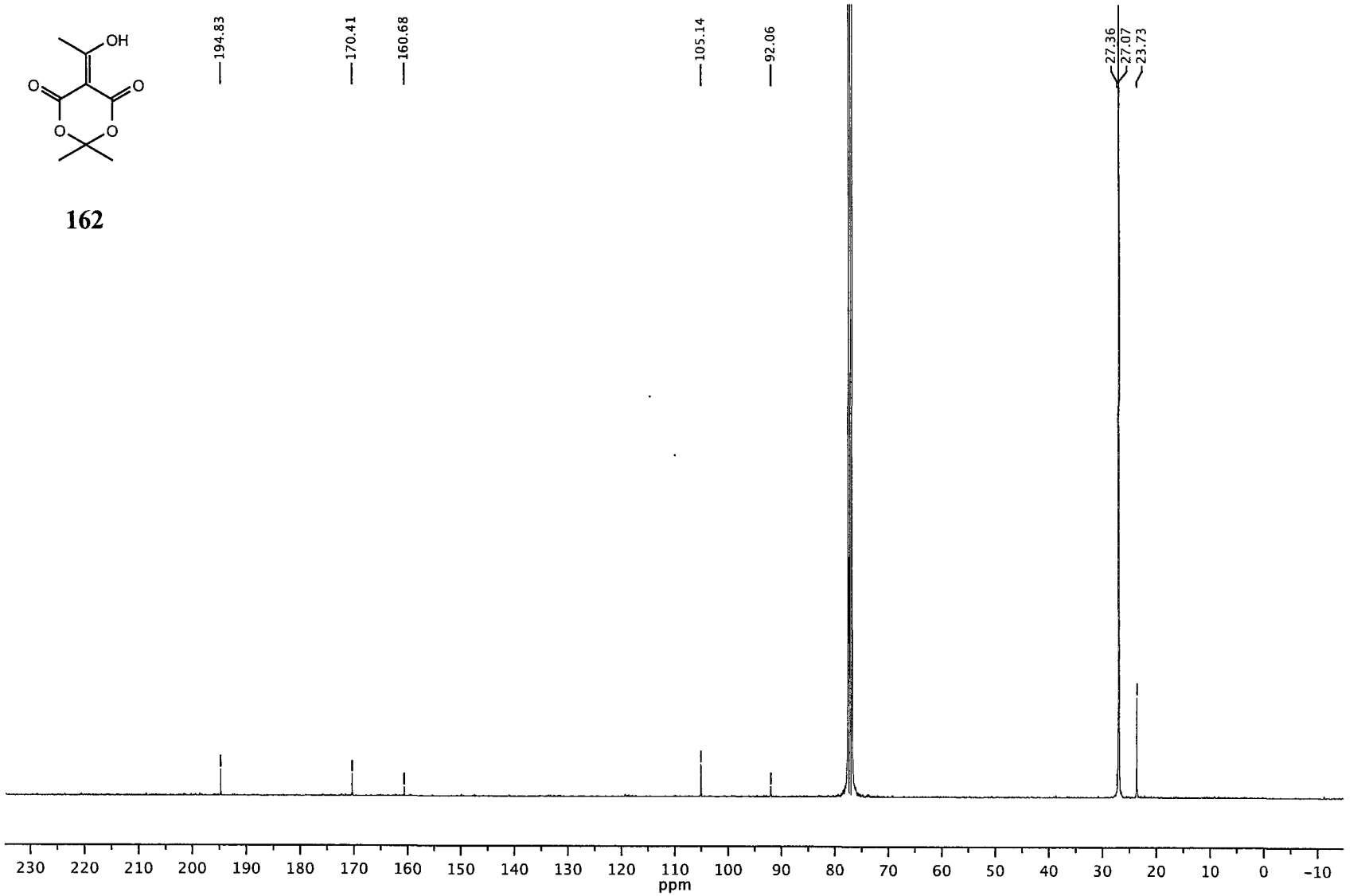
160

173.85
138.34
128.94
127.91
127.74
54.43
43.88
36.99
26.01
22.04
21.22
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

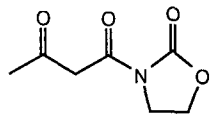


162

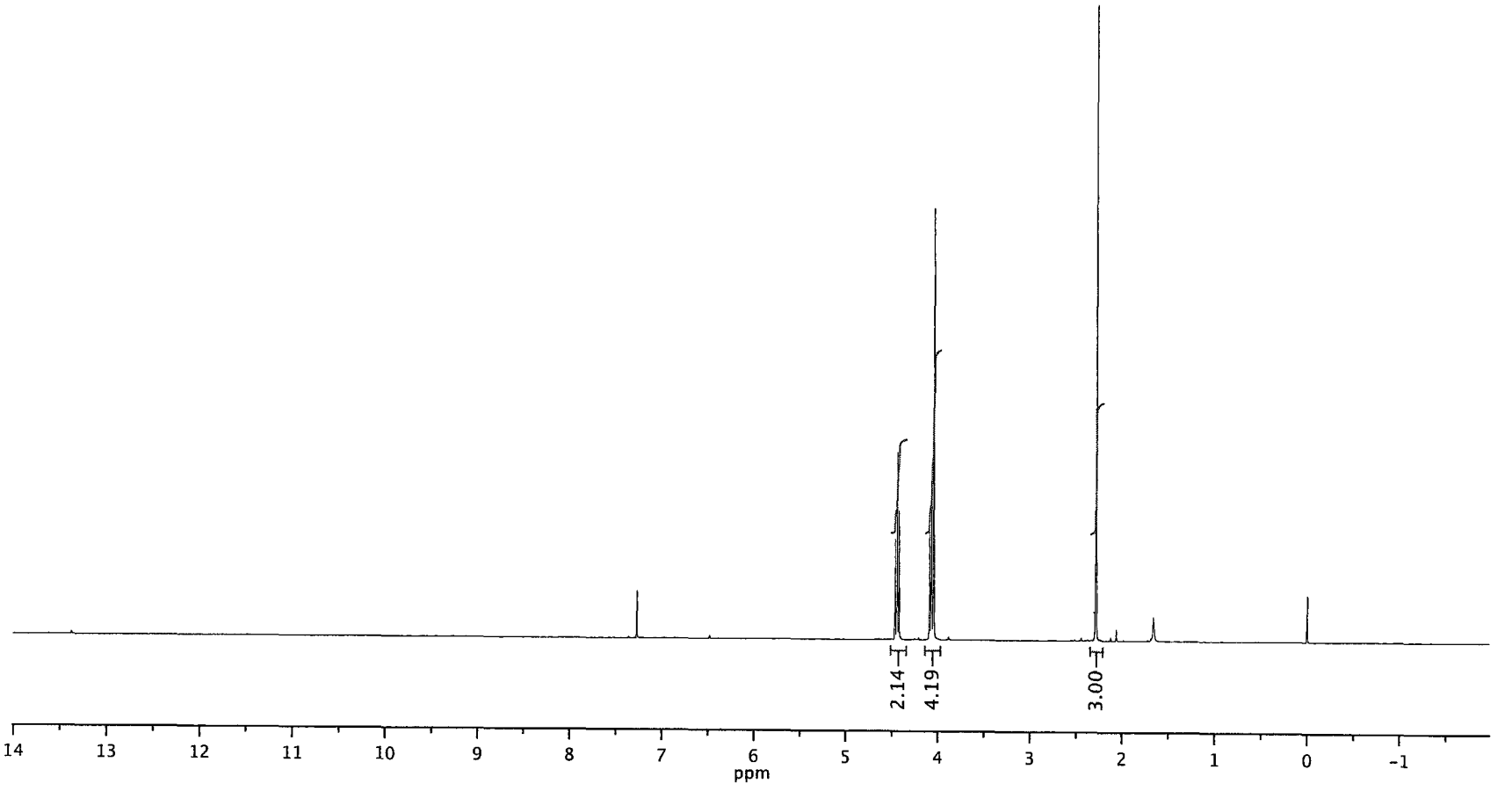


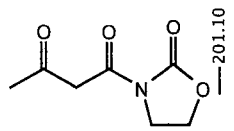

OH
O
O
O
O
194.83
170.41
160.68
105.14
92.06
27.36
27.07
23.73
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

162



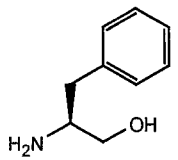
164



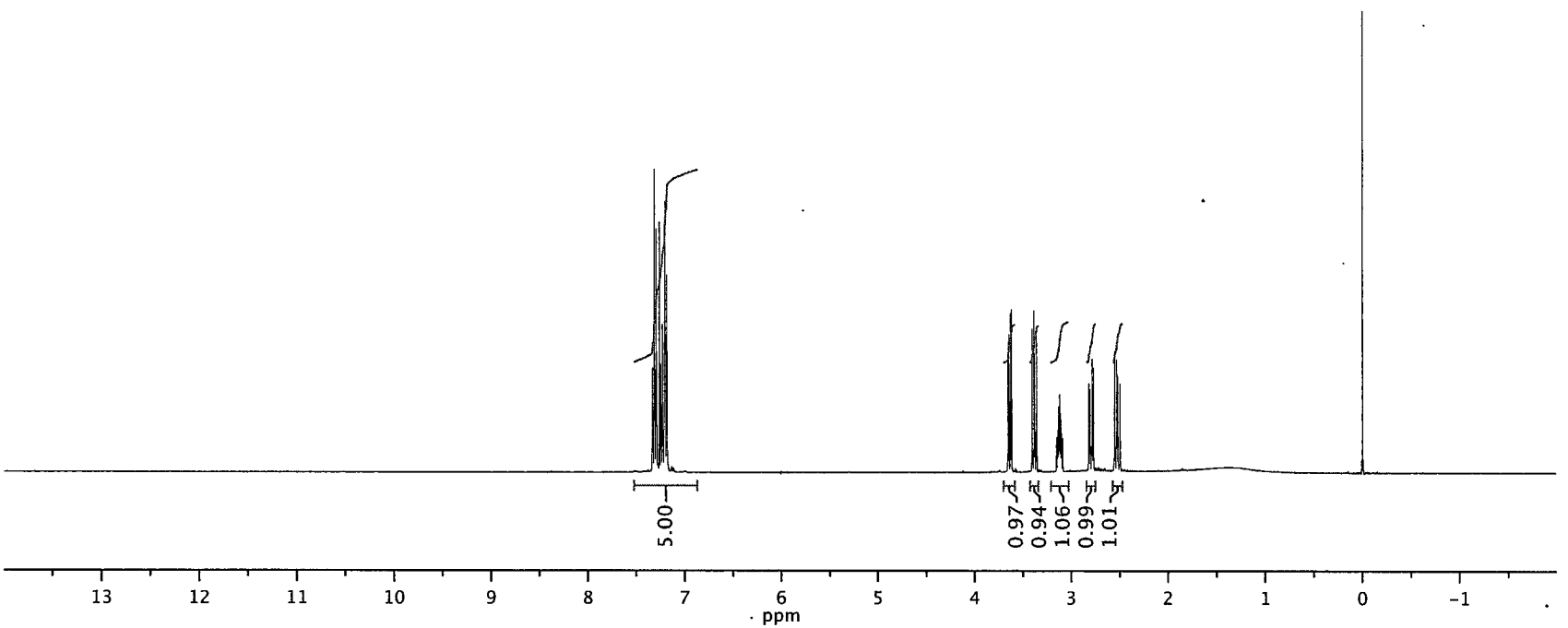

O
O
O
N
O
201.10

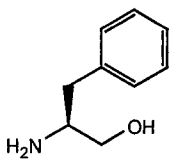
164

166.66
153.94
62.48
51.21
42.36
30.31
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



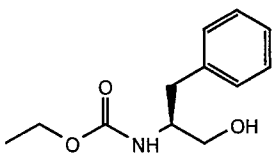
168



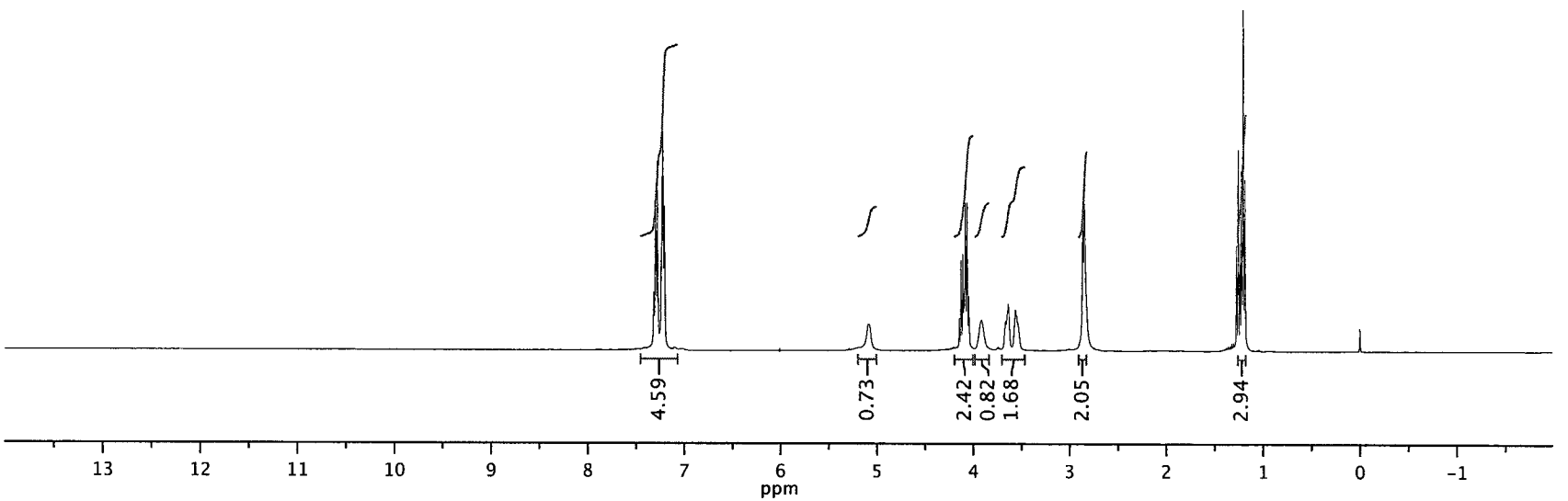

H2N
OH

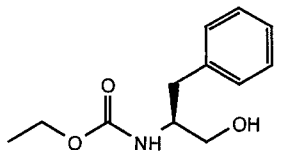
168

138.91
129.42
128.79
126.63
66.64
54.38
41.24
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



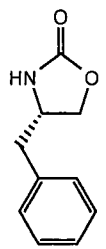
106a'



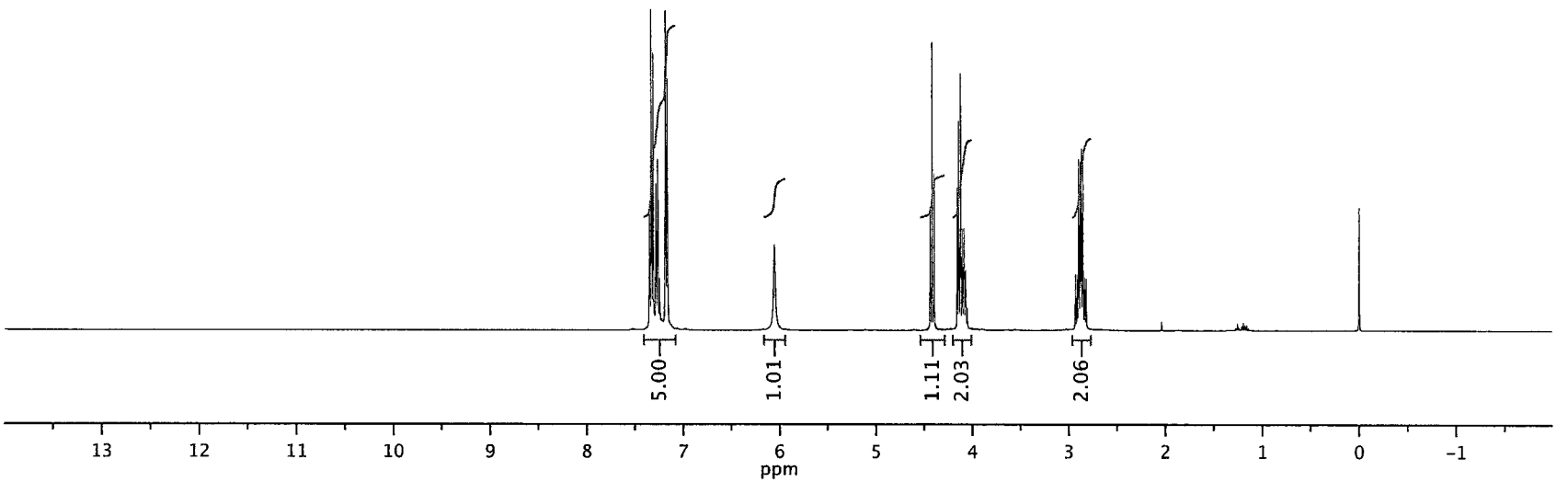

O
O
NH
OH

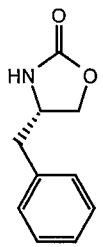
106a'

157.04
137.96
129.50
128.77
126.77
64.10
61.20
60.67
54.22
37.58
14.77
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



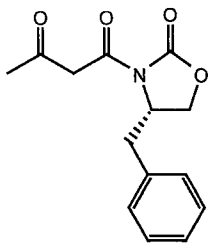
106a



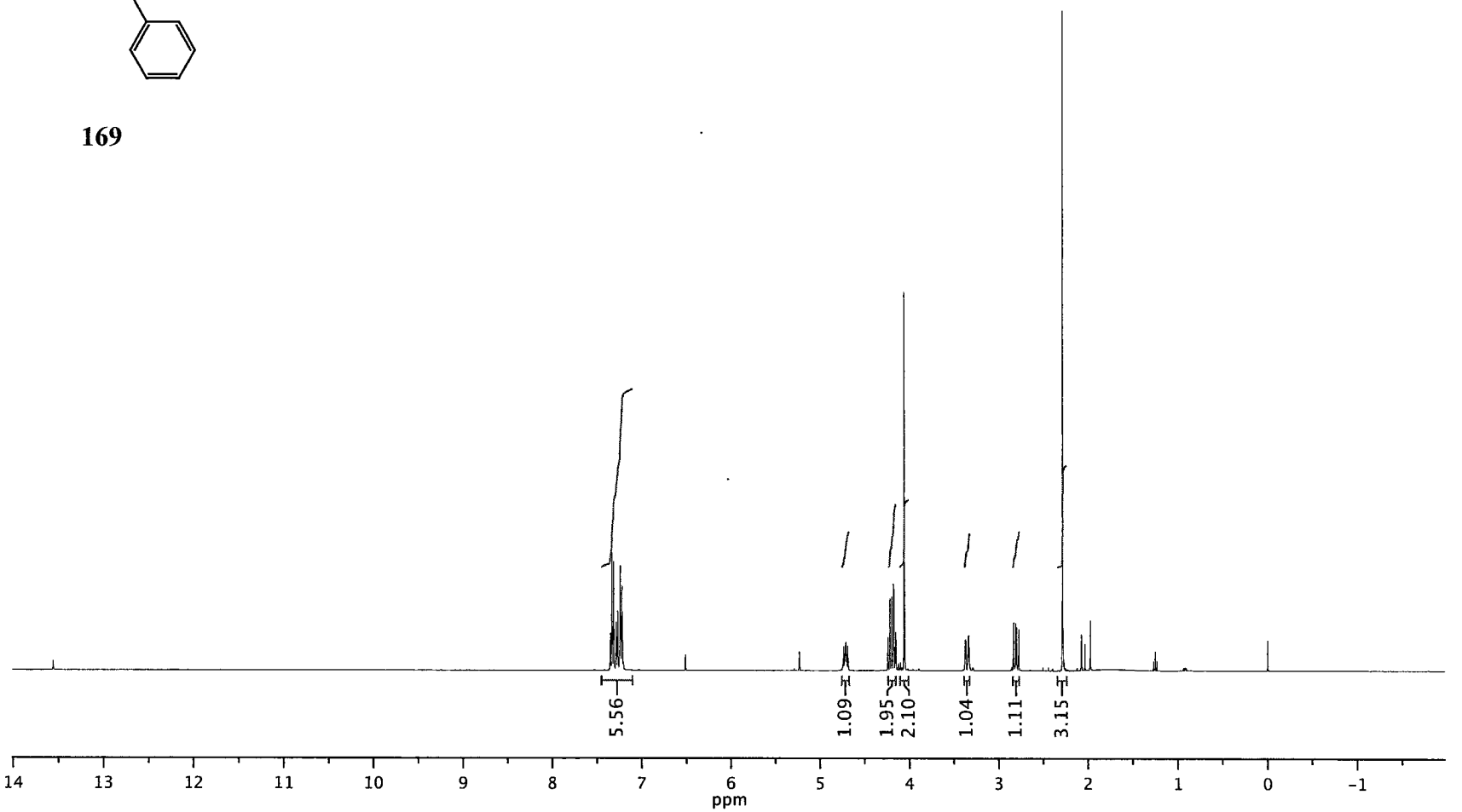

O
HN
O

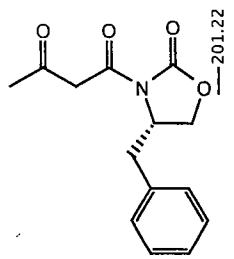
106a

159.80
136.16
129.26
129.20
127.44
69.80
54.01
41.61
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



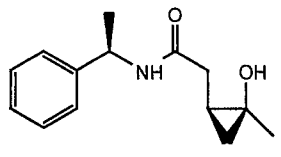
169



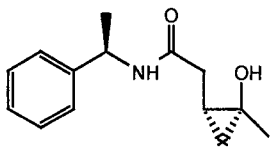


169

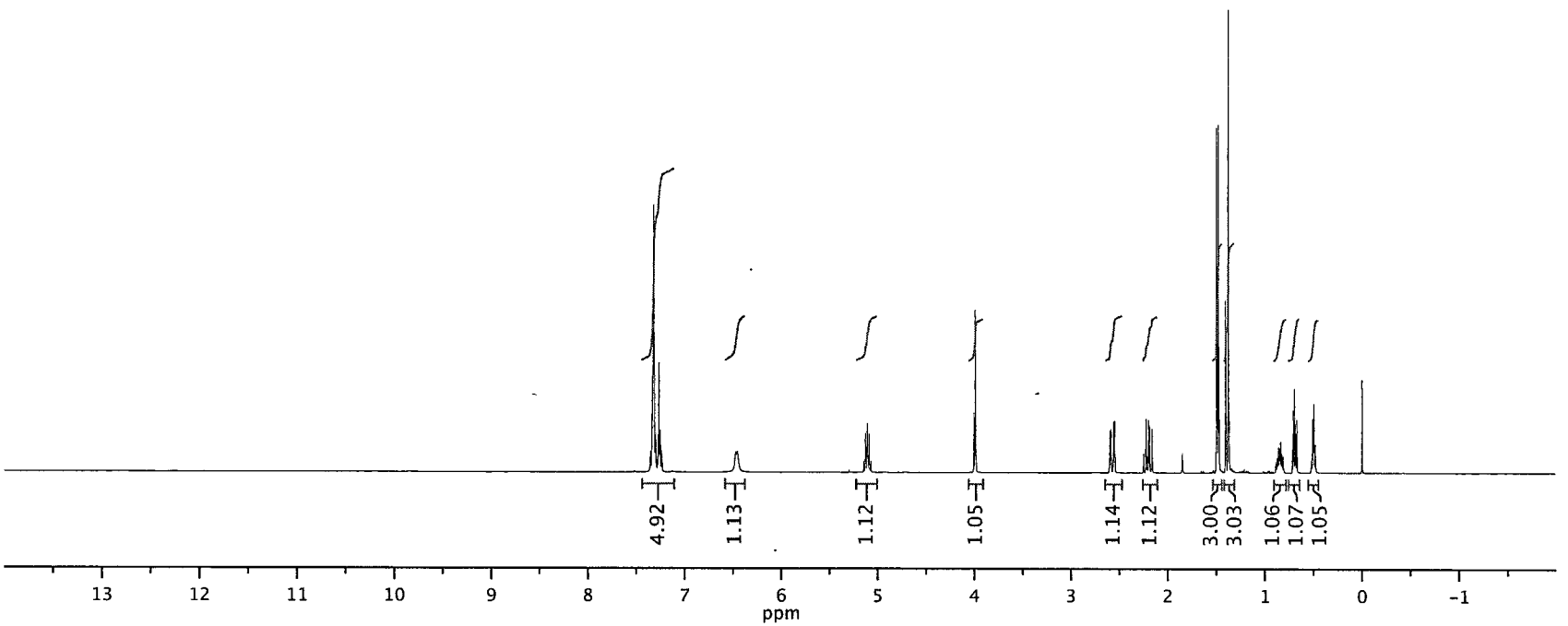
201.22
166.62
153.93
135.36
129.68
129.17
127.55
66.61
55.14
51.58
37.84
30.37
25.23
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

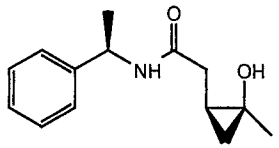

O
NH
OH

171

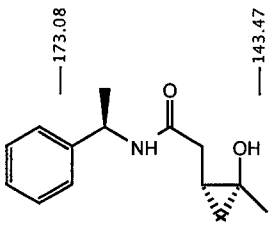

O
NH
OH

172


4.92
1.13
1.12
1.05
1.14
1.12
3.00
3.03
1.06
1.07
1.05
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

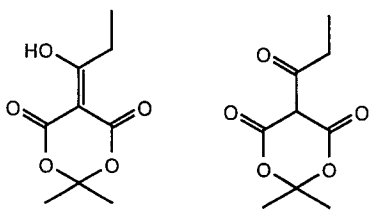

NH
O
OH

171

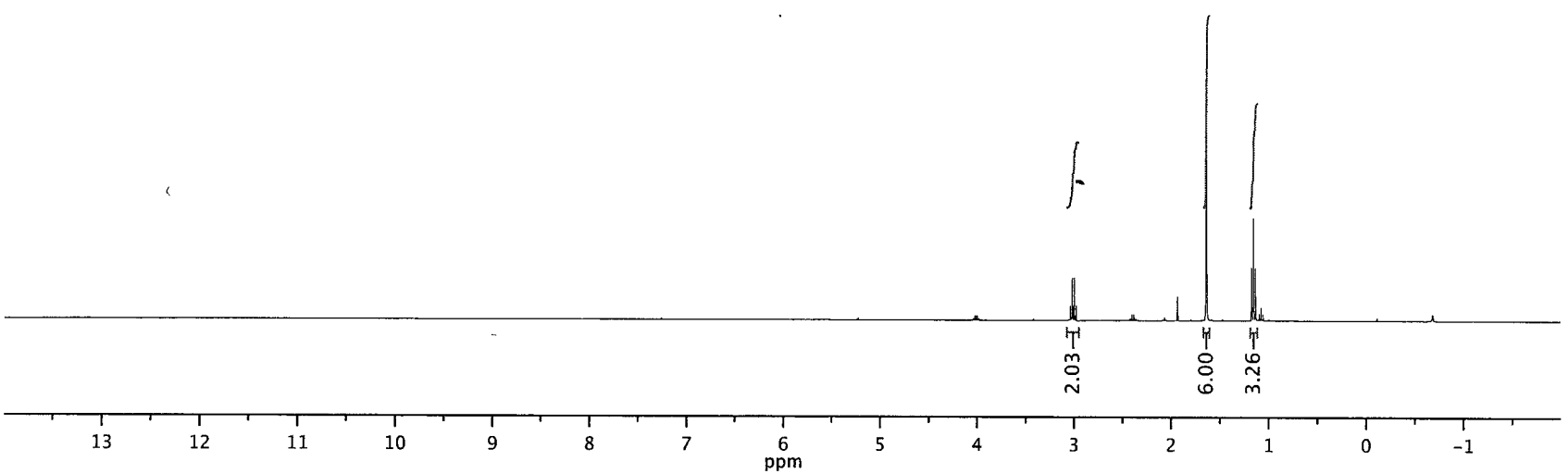

NH
O
OH

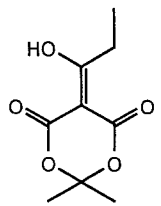
172

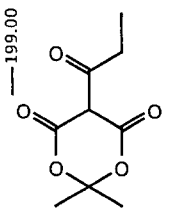
173.08
143.47
128.87
127.54
126.26
54.39
49.00
37.15
26.00
22.25
22.08
21.21
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



174

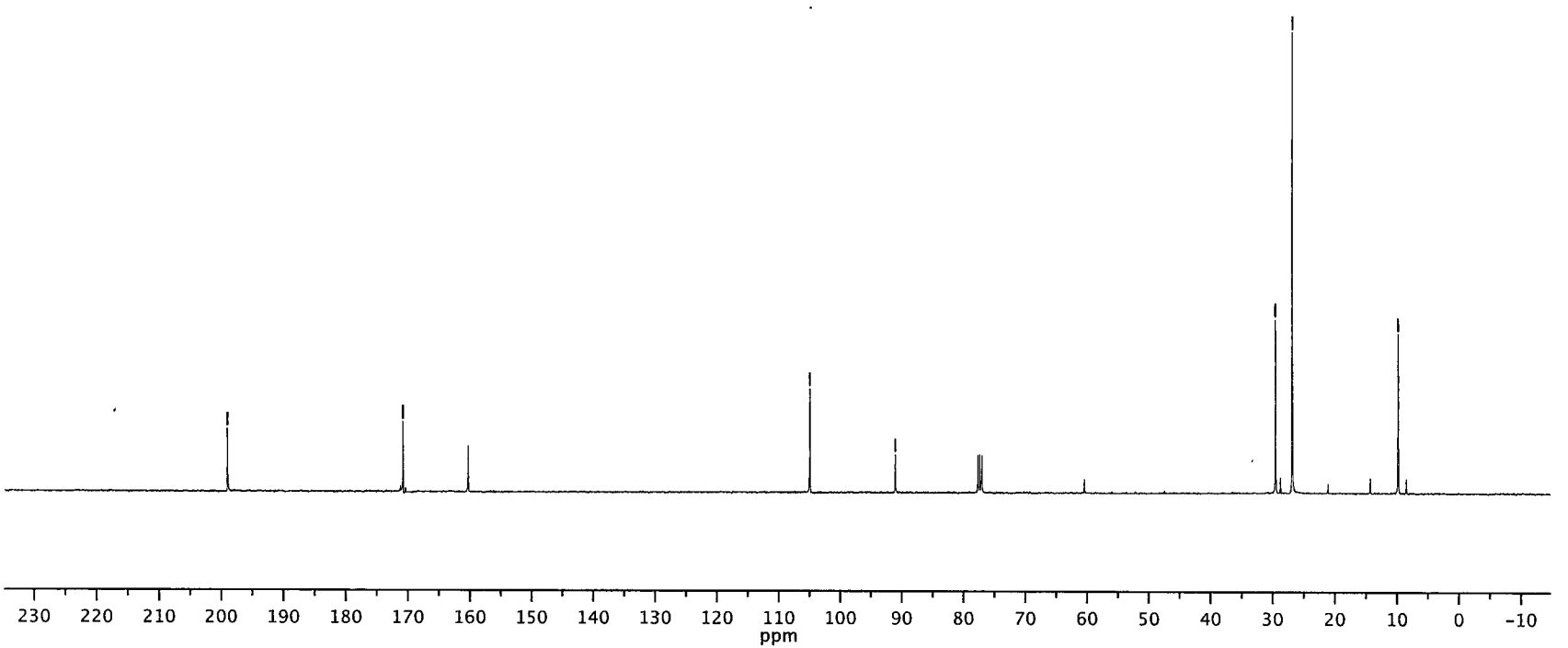


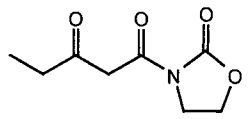

HO
O
O
O
O


199.00
170.74
O
O
O
O

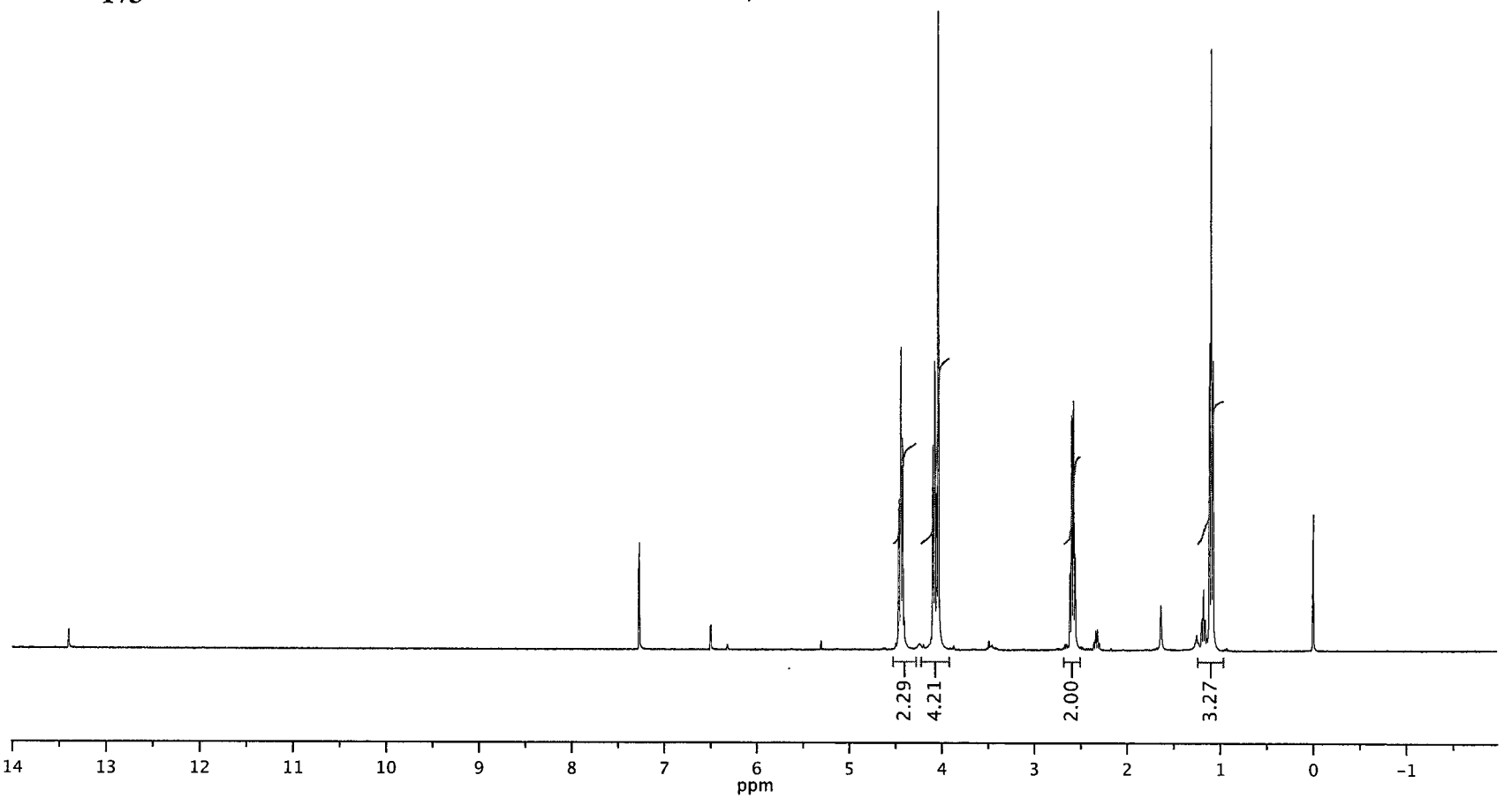
174

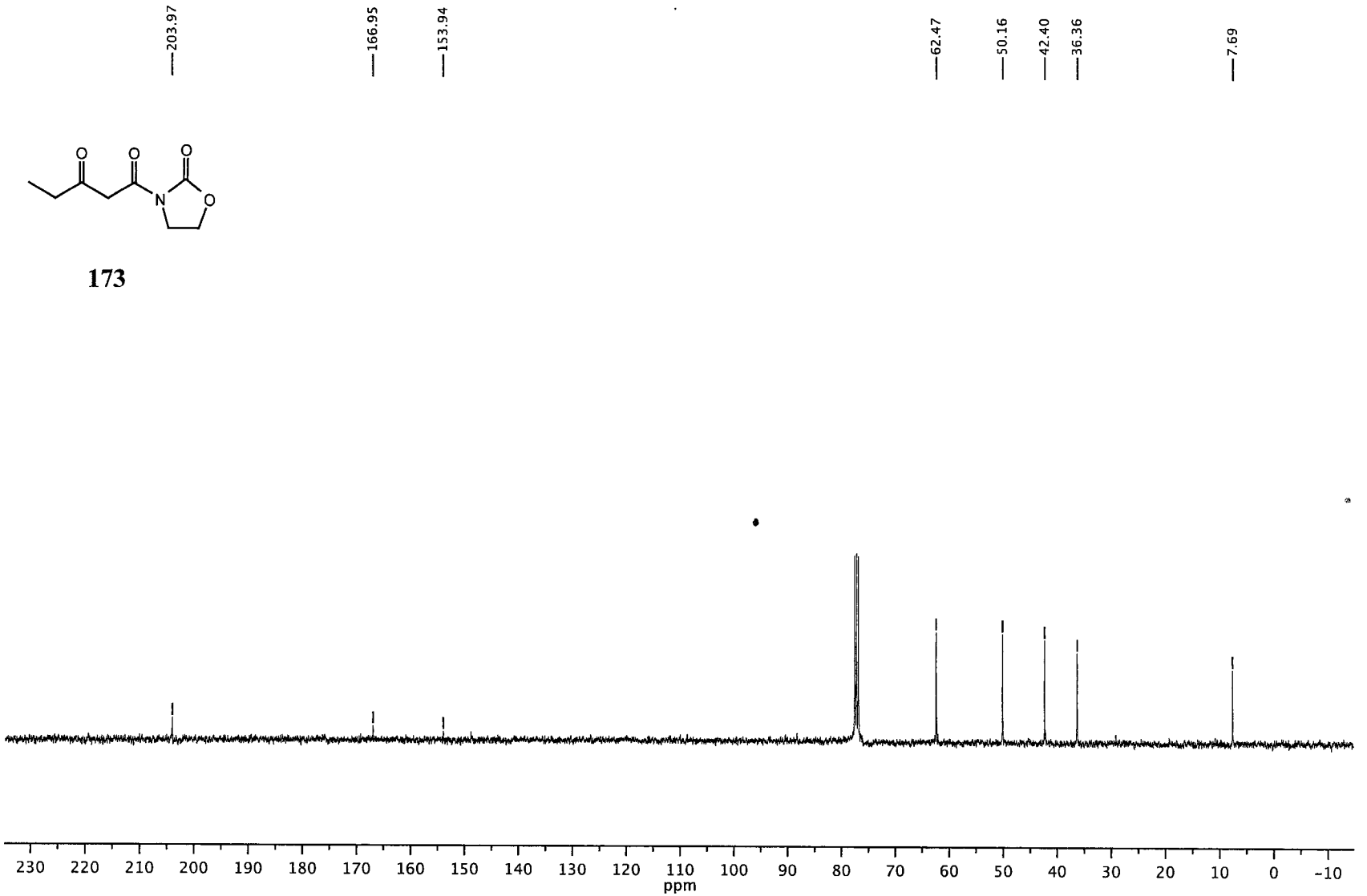

104.94
91.07
29.57
26.88
9.81


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

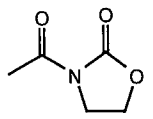


173

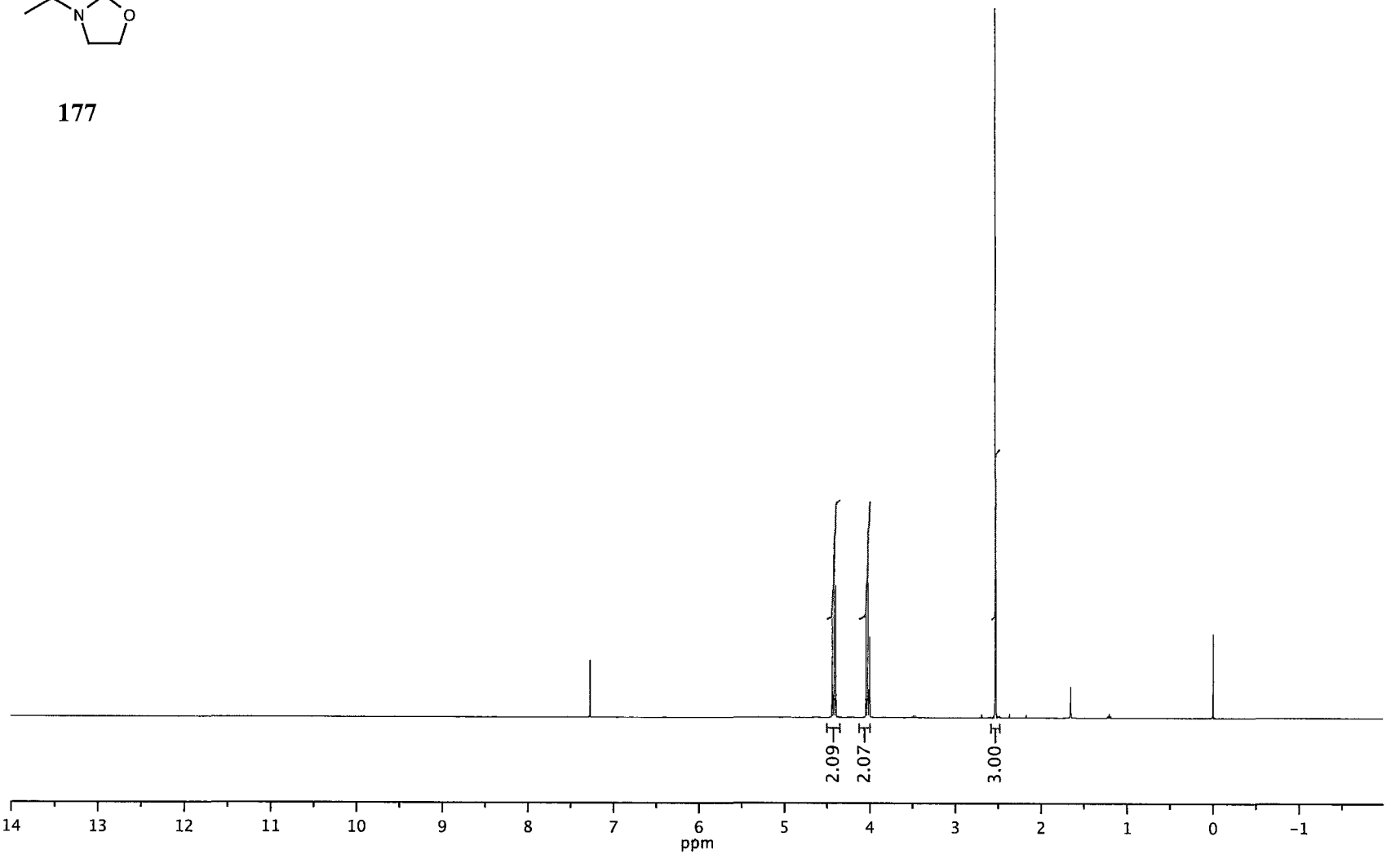


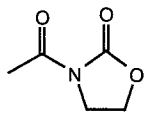

203.97
166.95
153.94
62.47
50.16
42.40
36.36
7.69
O
O
O
N
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

173



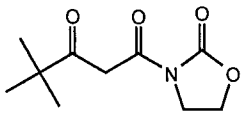
177



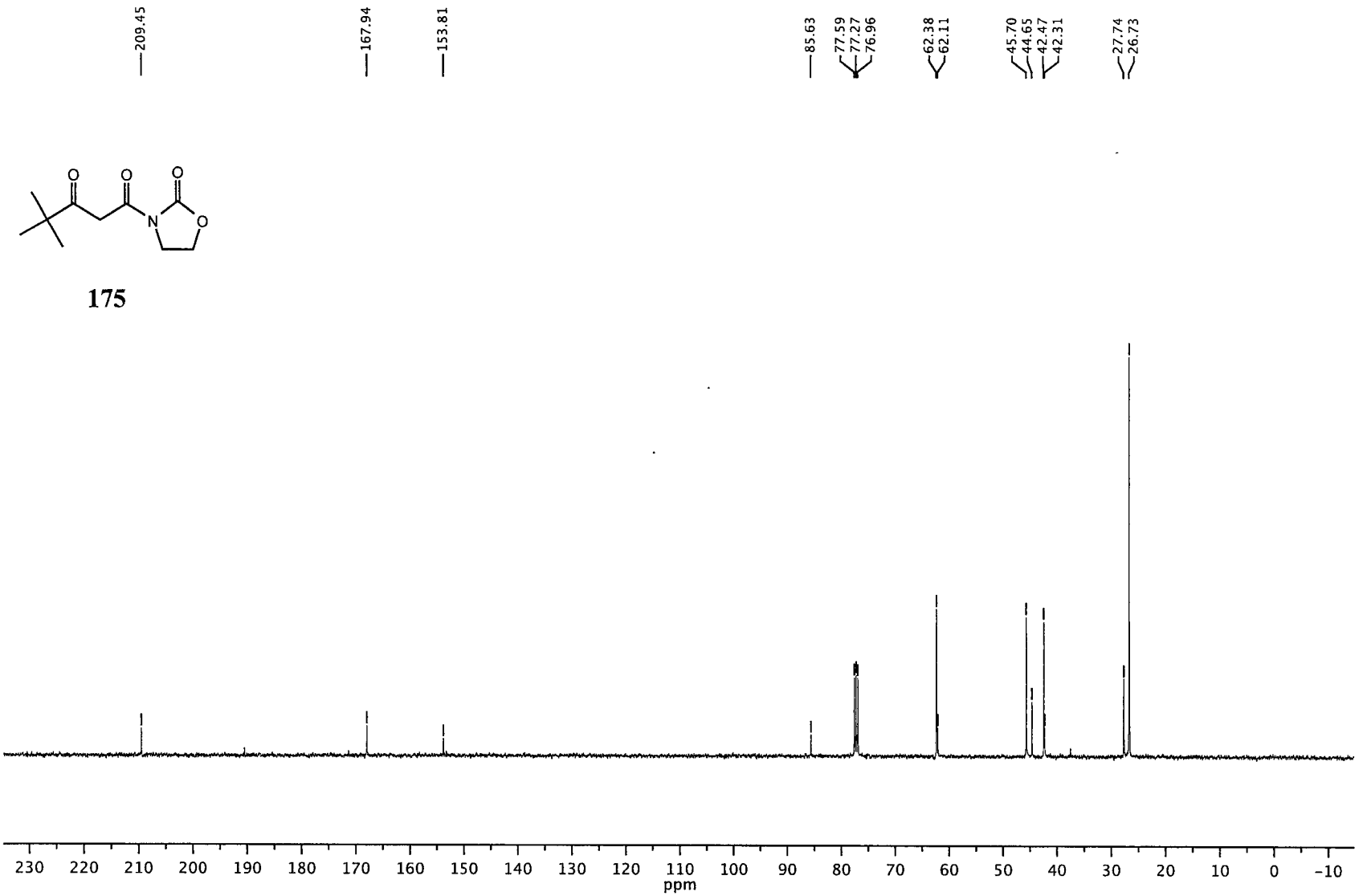


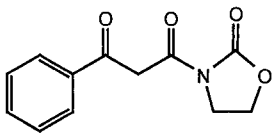
177

170.68
153.93
62.17
42.57
23.45
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

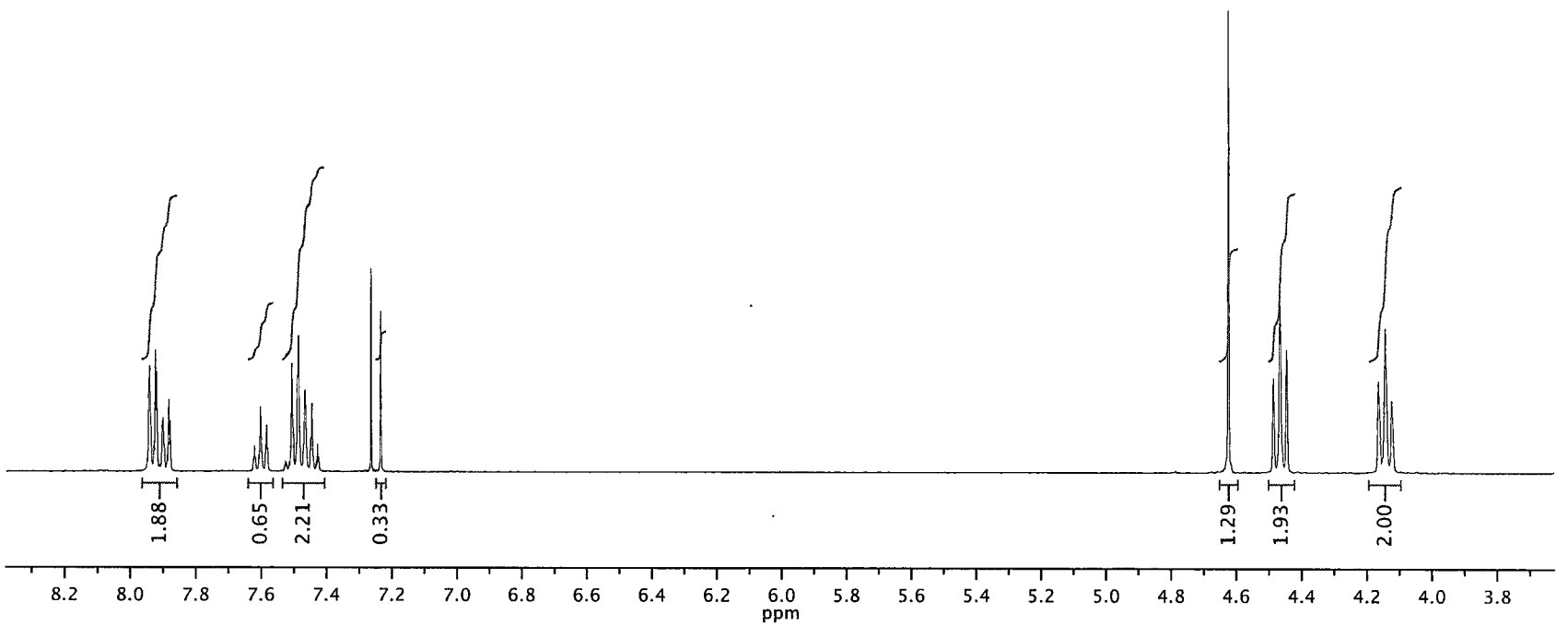


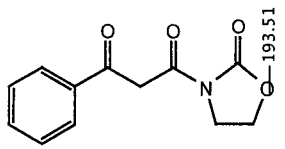
175


209.45
167.94
153.81
85.63
77.59
77.27
76.96
62.38
62.11
45.70
44.65
42.47
42.31
27.74
26.73
O
O
O
N
O
175
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



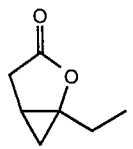
176


1.88
0.65
2.21
0.33
1.29
1.93
2.00
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
ppm



176

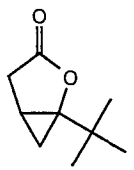
193.51
174.99
171.11
167.48
153.94
136.07
133.98
132.15
128.99
128.85
128.46
126.79
87.05
62.53
62.26
53.76
47.09
42.50
42.38
34.05
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm



178

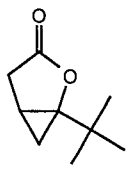
178

17773.84
7016.18
3479.70
2567.49
1905.49
1454.01
1034.09
ppm
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



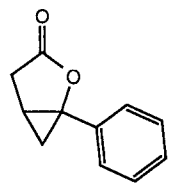
179

2.89
2.87
2.84
2.82
2.60
2.55
1.61
1.60
1.58
1.58
1.11
1.11
1.09
1.02
0.51
0.50
0.49
1.00
0.99
0.93
1.03
8.99
0.96
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

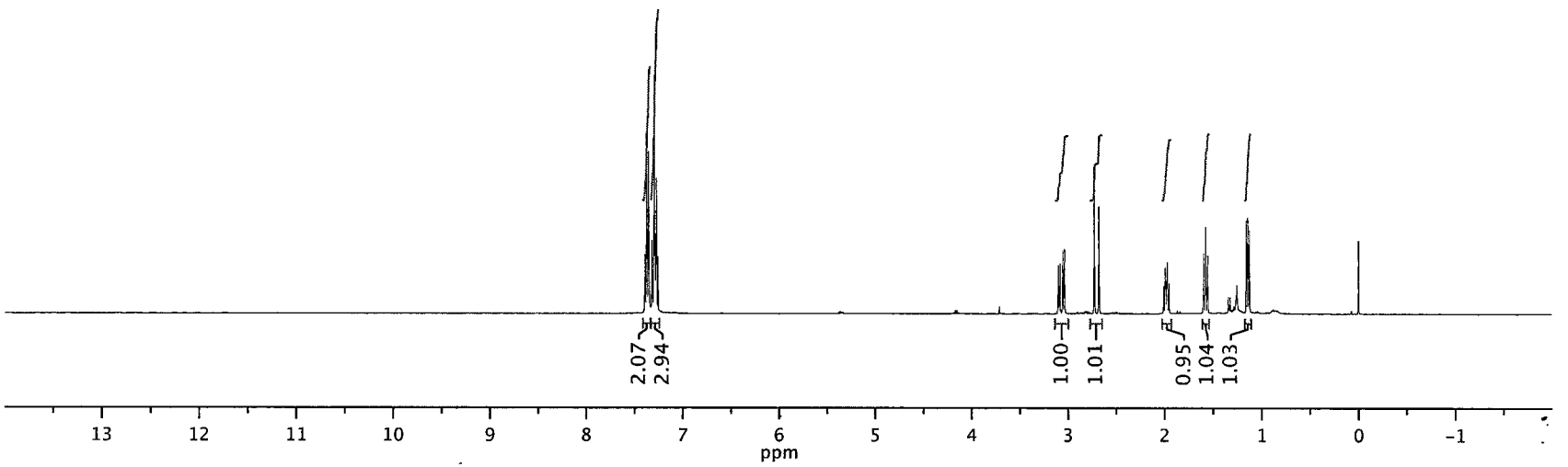


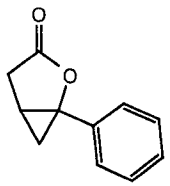
179

176.72
76.28
34.58
31.70
26.38
16.44
12.72
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



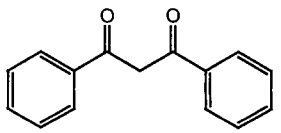
180





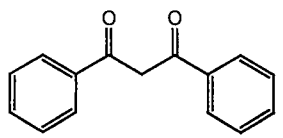
180

176.04
136.95
128.82
127.84
124.67
68.53
34.44
22.80
19.88
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



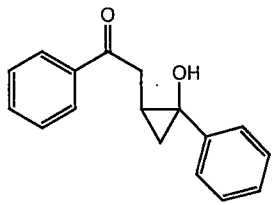
191

7.99
7.97
7.49
7.47
7.45
6.85
3.79
1.86
3.70
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

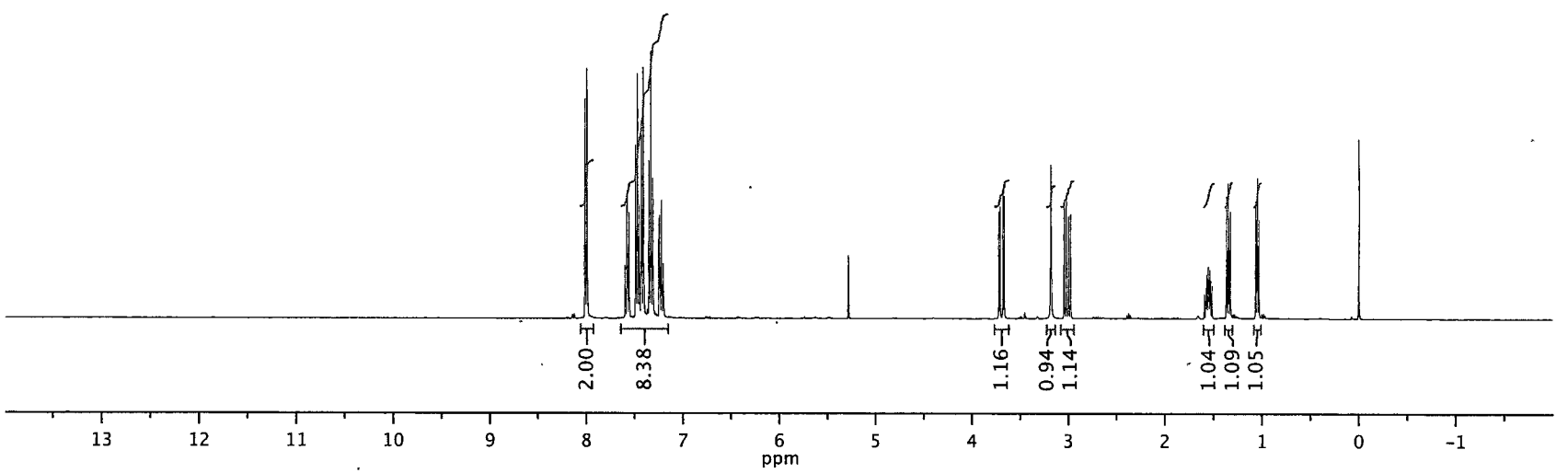


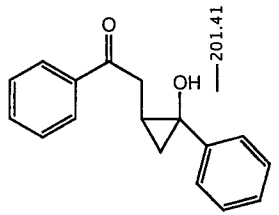
191

185.98
135.76
132.70
128.92
127.41
93.38
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



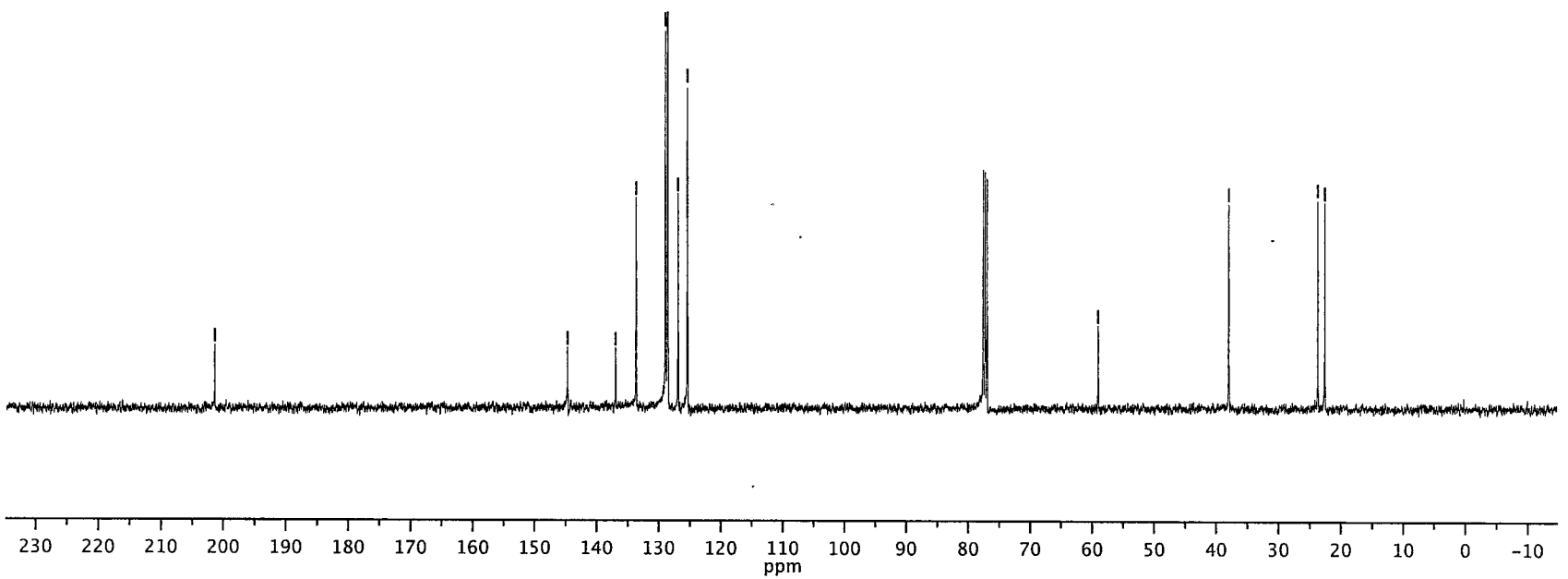
192

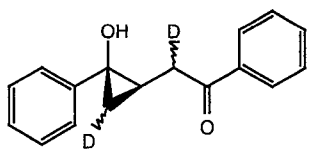



O
OH
201.41

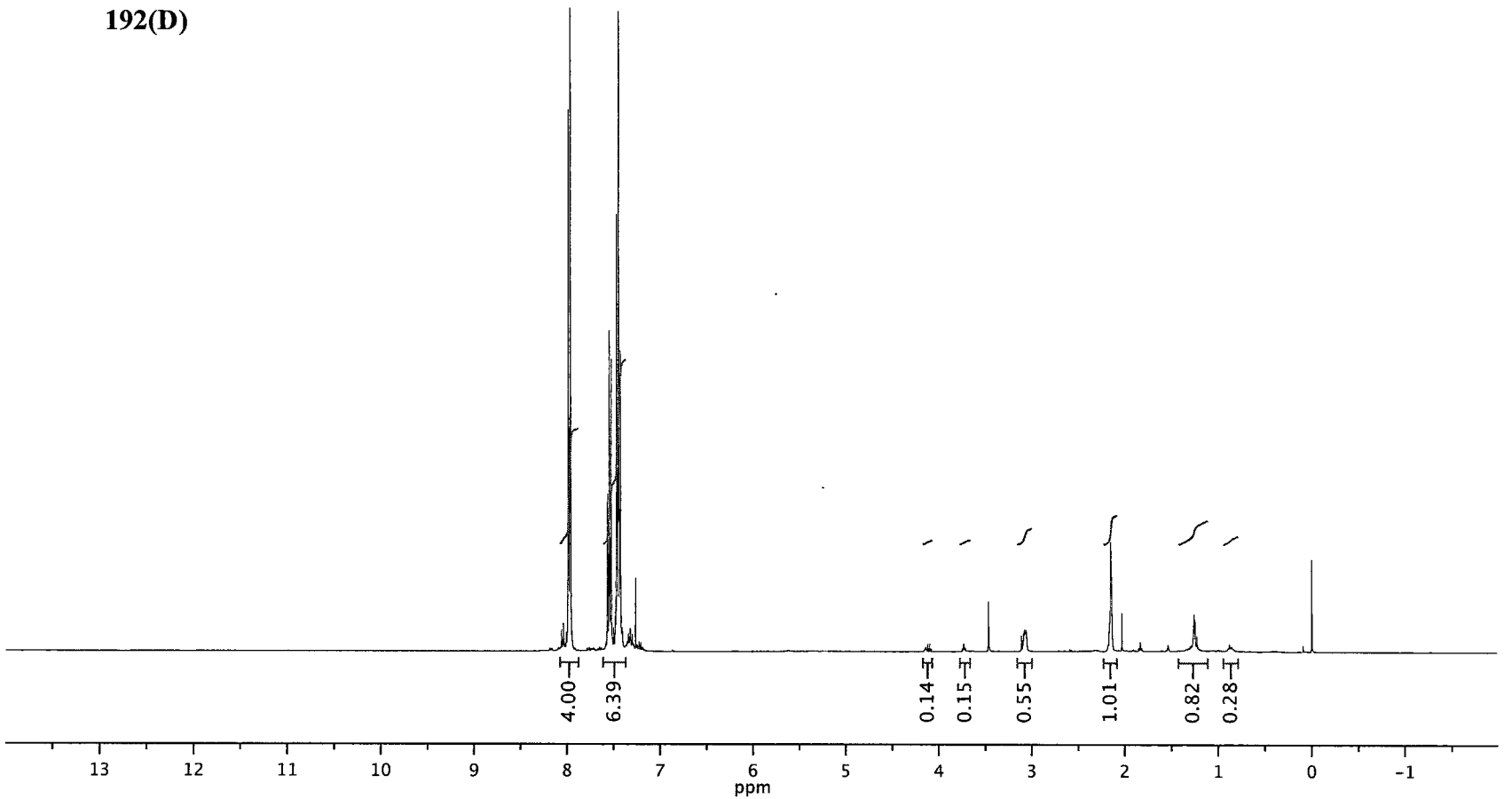
192

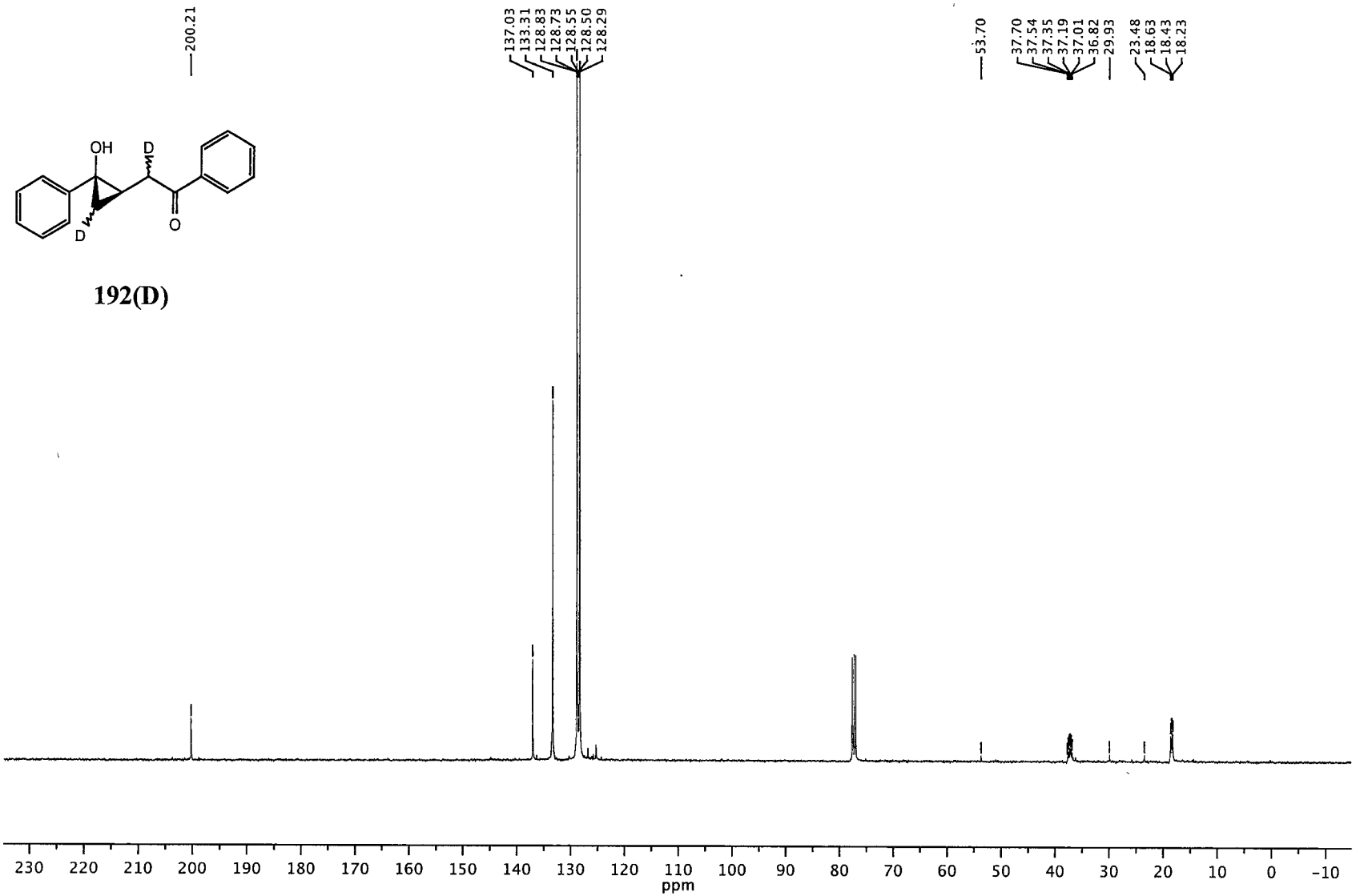

144.68
136.93
133.62
128.91
128.60
128.52
126.86
125.36
59.03
37.99
23.70
22.58


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

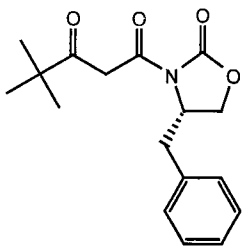

OH
D
D
O

192(D)

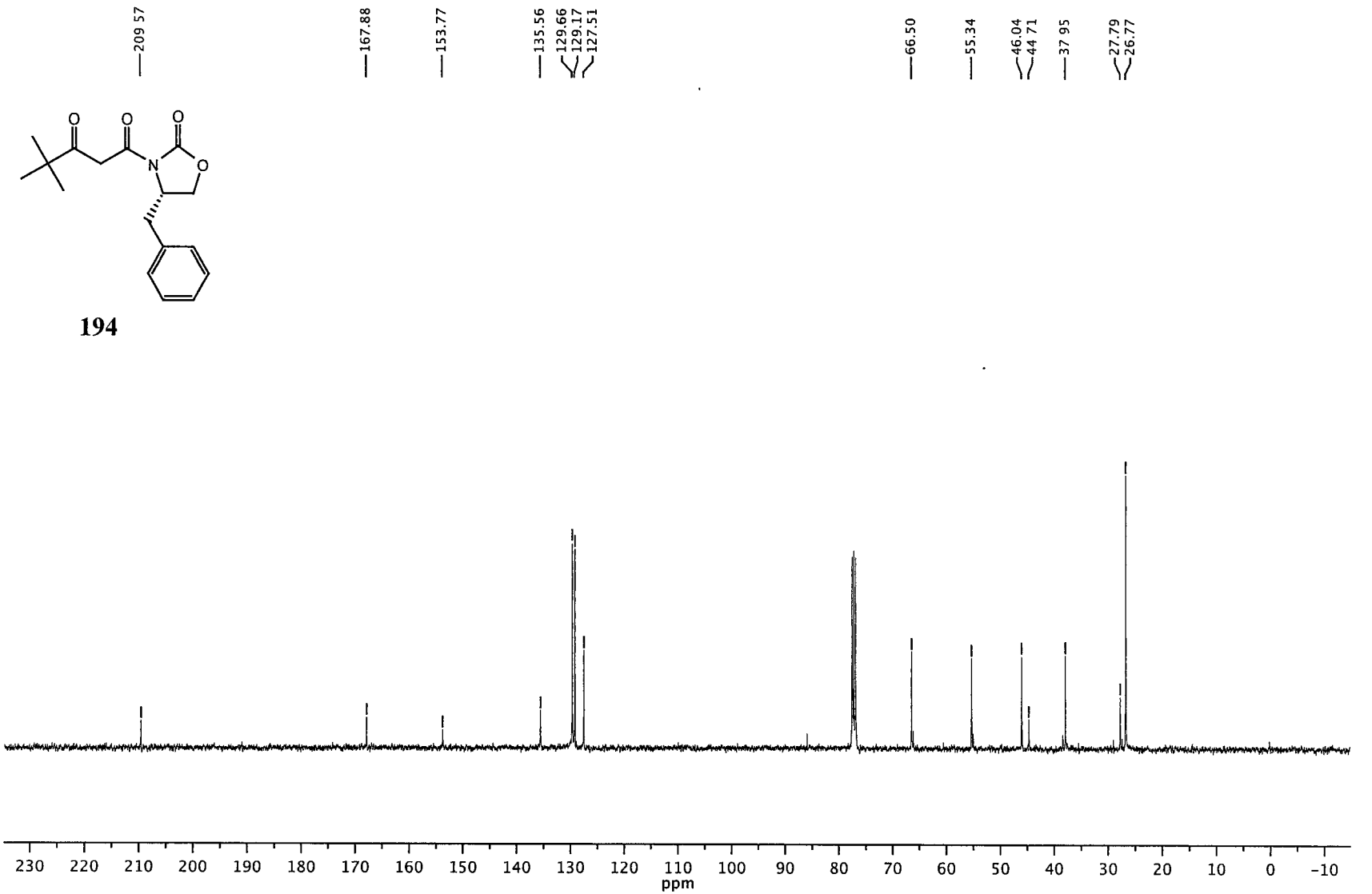

4.00
6.39
0.14
0.15
0.55
1.01
0.82
0.28
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


200.21
137.03
133.31
128.83
128.73
128.55
128.50
128.29
53.70
37.70
37.54
37.35
37.19
37.01
36.82
29.93
23.48
18.63
18.43
18.23
OH
D
D
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

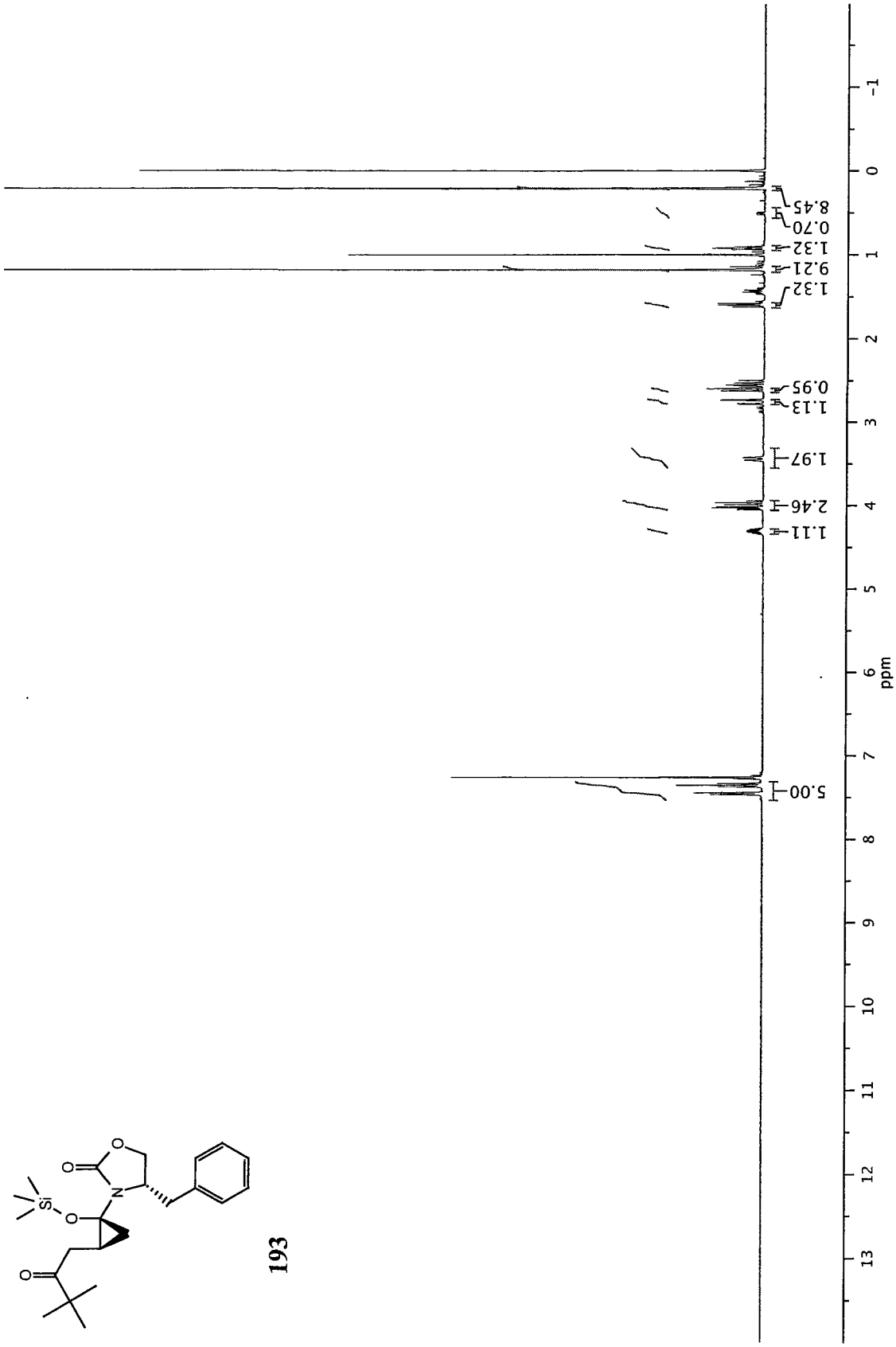
192(D)



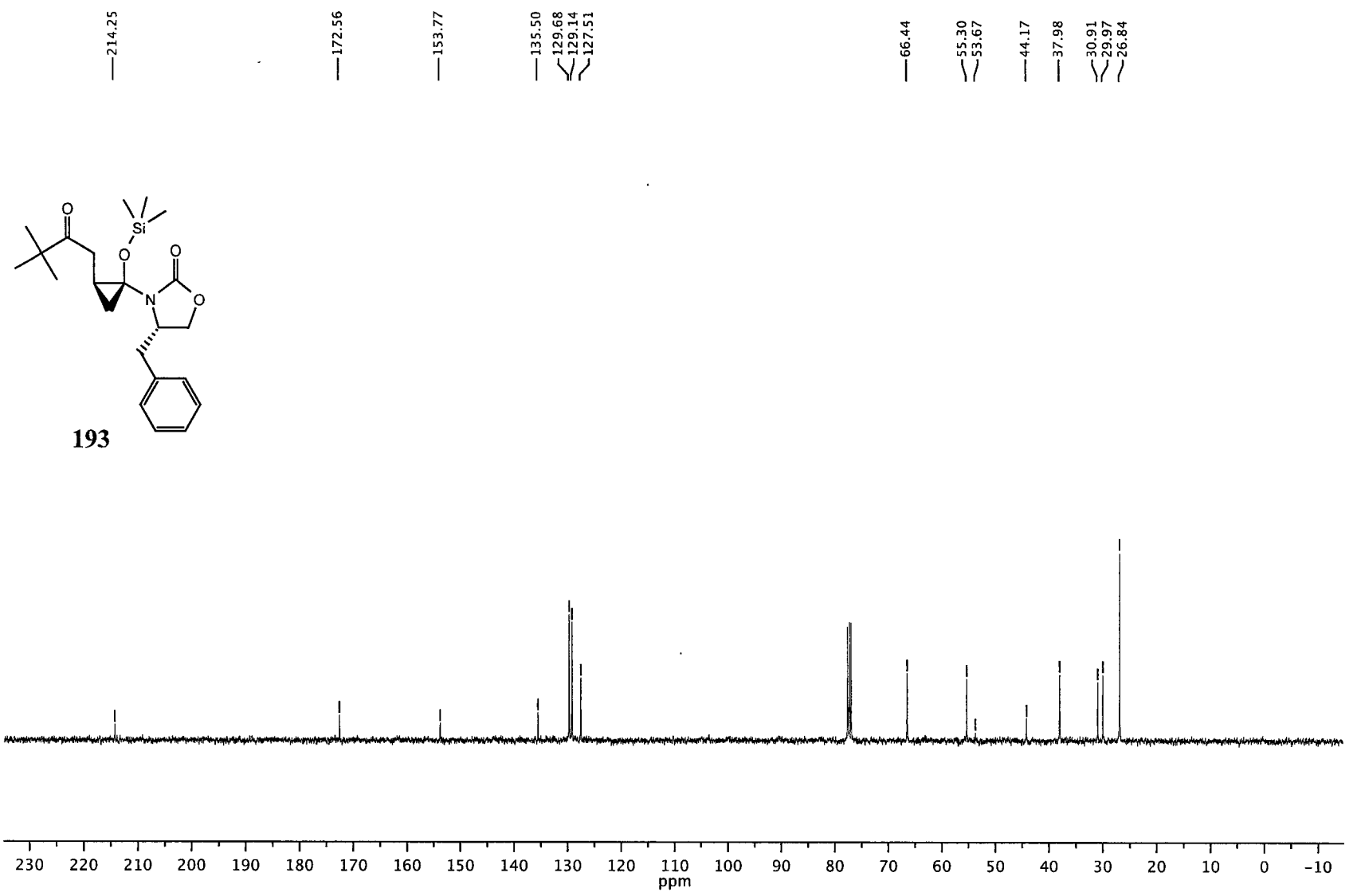
194


209 57
167.88
153.77
135.56
129.66
129.17
127.51
66.50
55.34
46.04
44 71
37 95
27.79
26.77
O
O
O
N
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

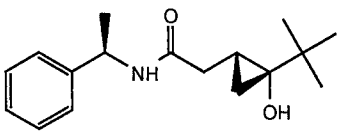
194



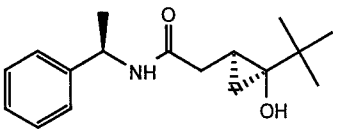
193


214.25
172.56
153.77
135.50
129.68
129.14
127.51
66.44
55.30
53.67
44.17
37.98
30.91
29.97
26.84
O
Si
O
O
N
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

193

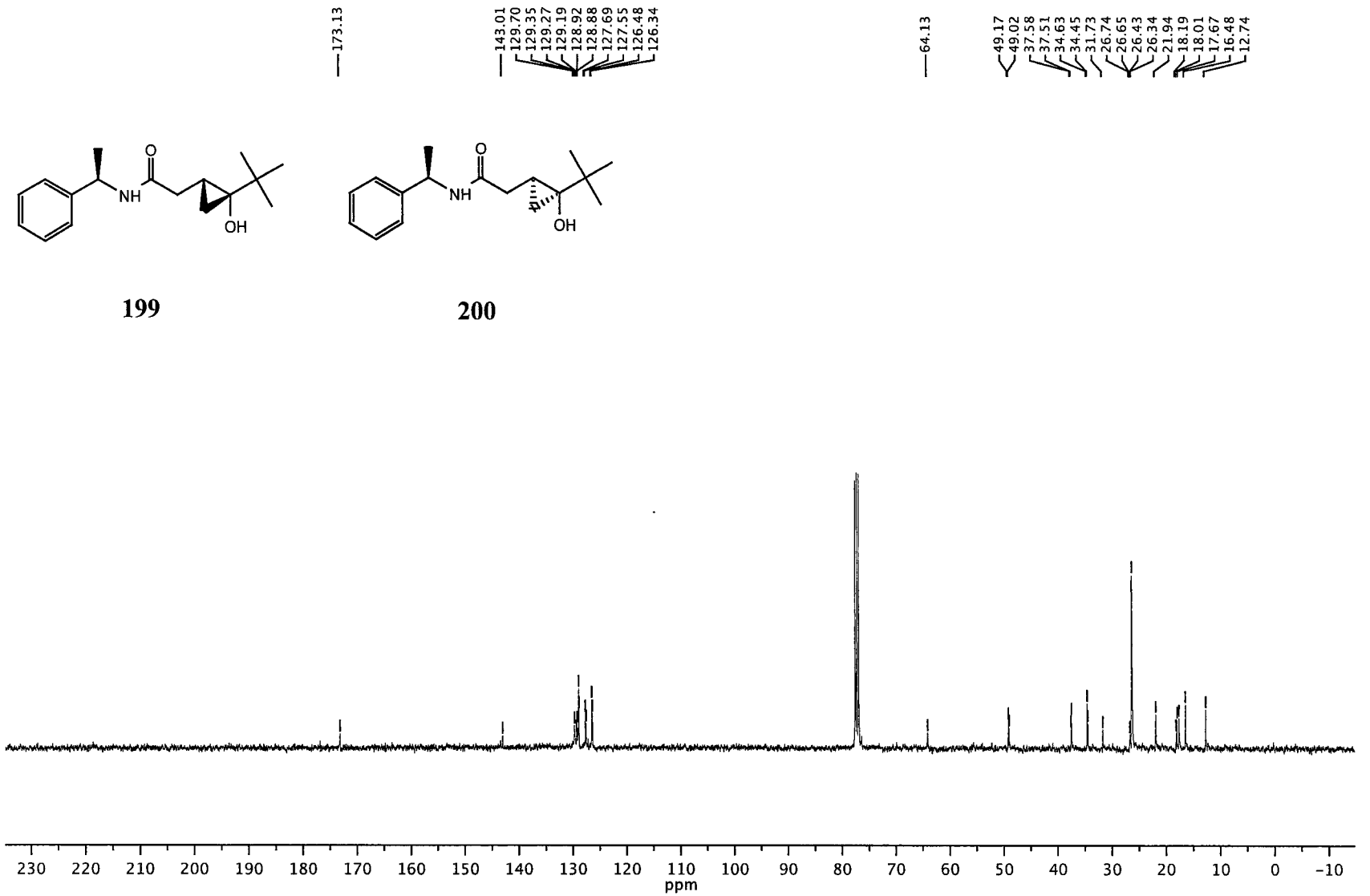

NH
O
OH

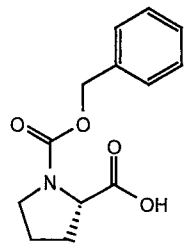
199


NH
O
OH

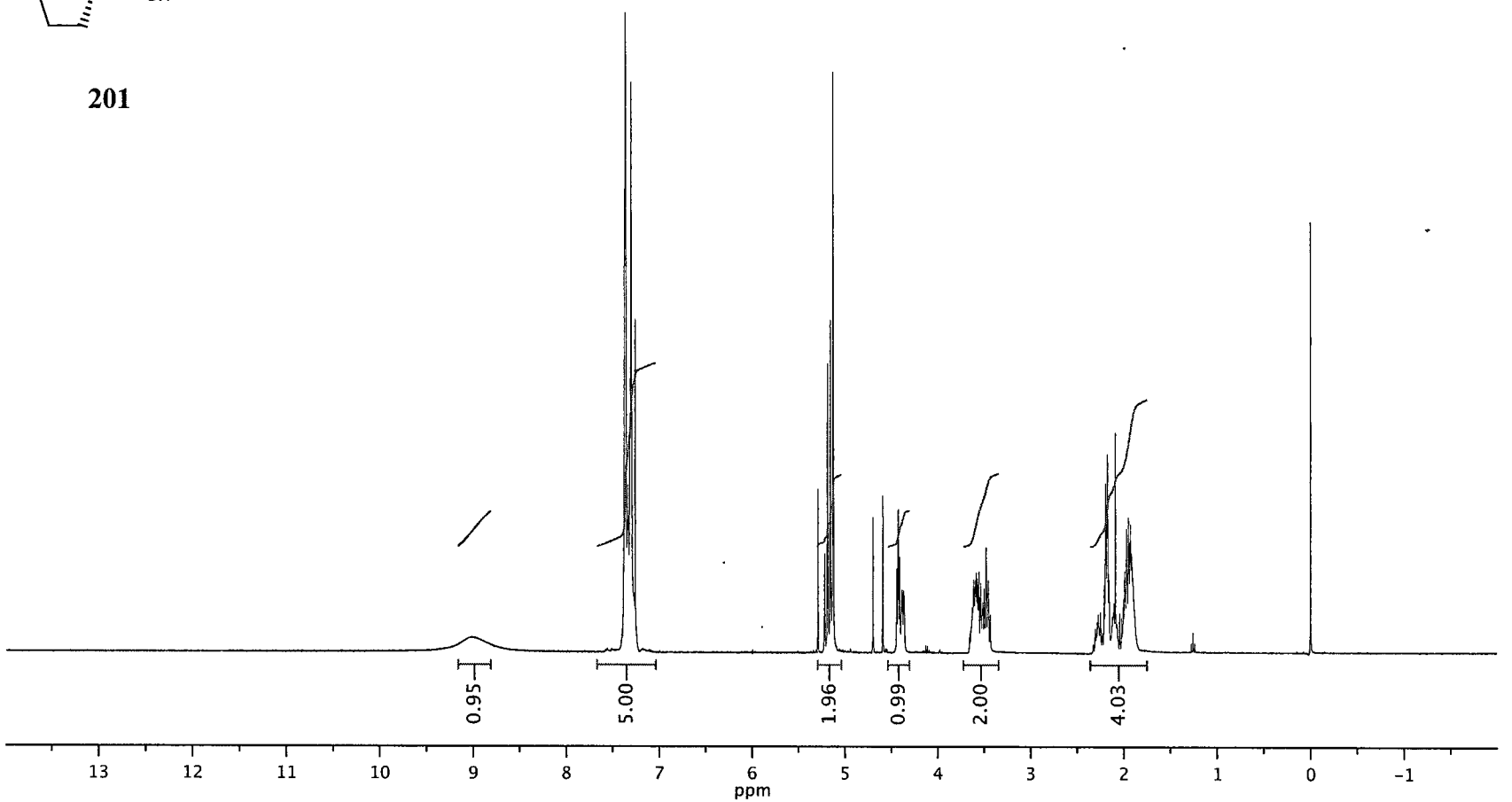
200

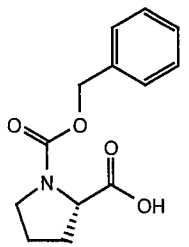
5.00
1.02
1.19
1.44
1.00
0.80
2.12
1.32
1.24
5.13
5.19
0.66
0.63
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


173.13
143.01
129.70
129.35
129.27
129.19
128.92
128.88
127.69
127.55
126.48
126.34
64.13
49.17
49.02
37.58
37.51
34.63
34.45
31.73
26.74
26.65
26.43
26.34
21.94
18.19
18.01
17.67
16.48
12.74
NH
O
OH
199
200
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



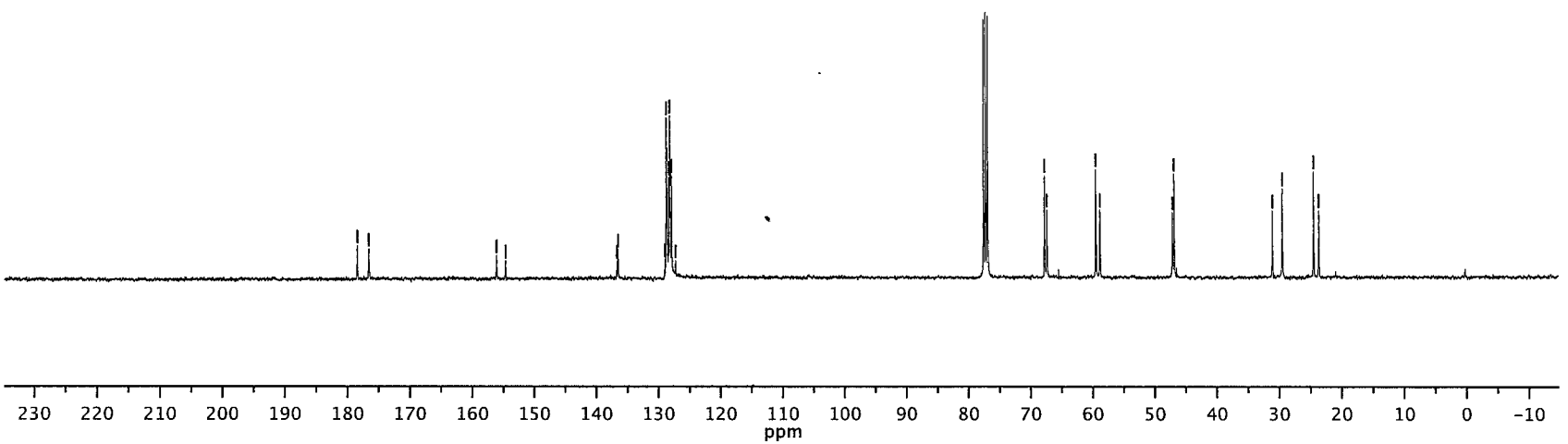
201

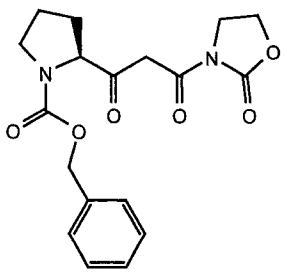




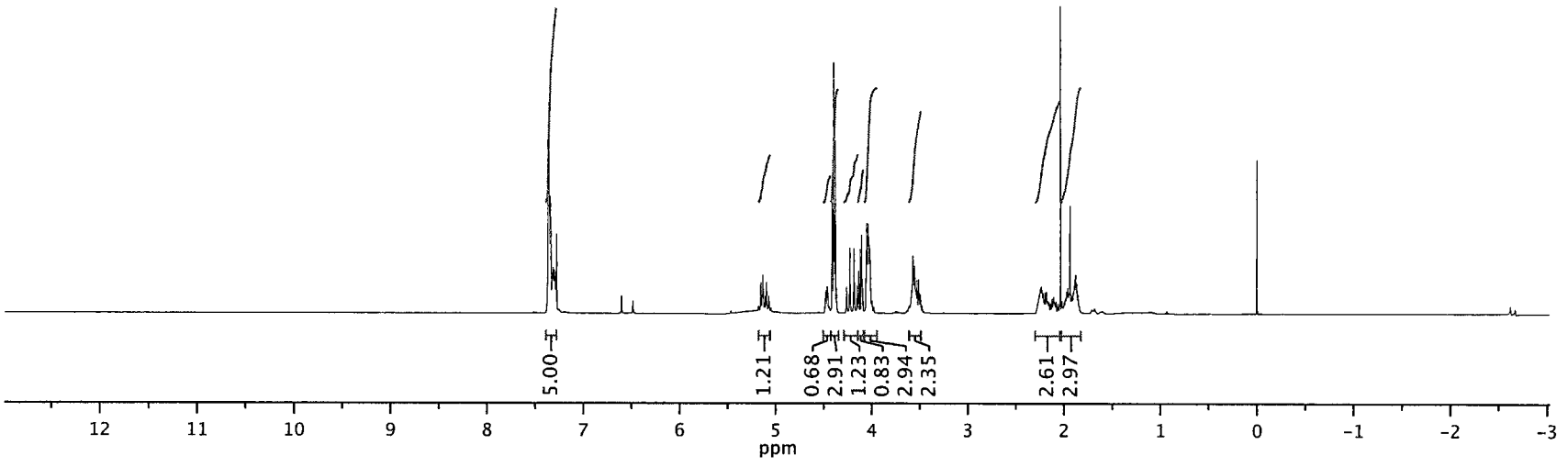
178.41
176.57
156.08
154.64
136.69
136.50
128.95
128.74
128.63
128.37
128.18
128.12
127.89
127.26
67.77
67.37
59.52
58.85
47.16
46.89
31.13
29.55
24.53
23.69

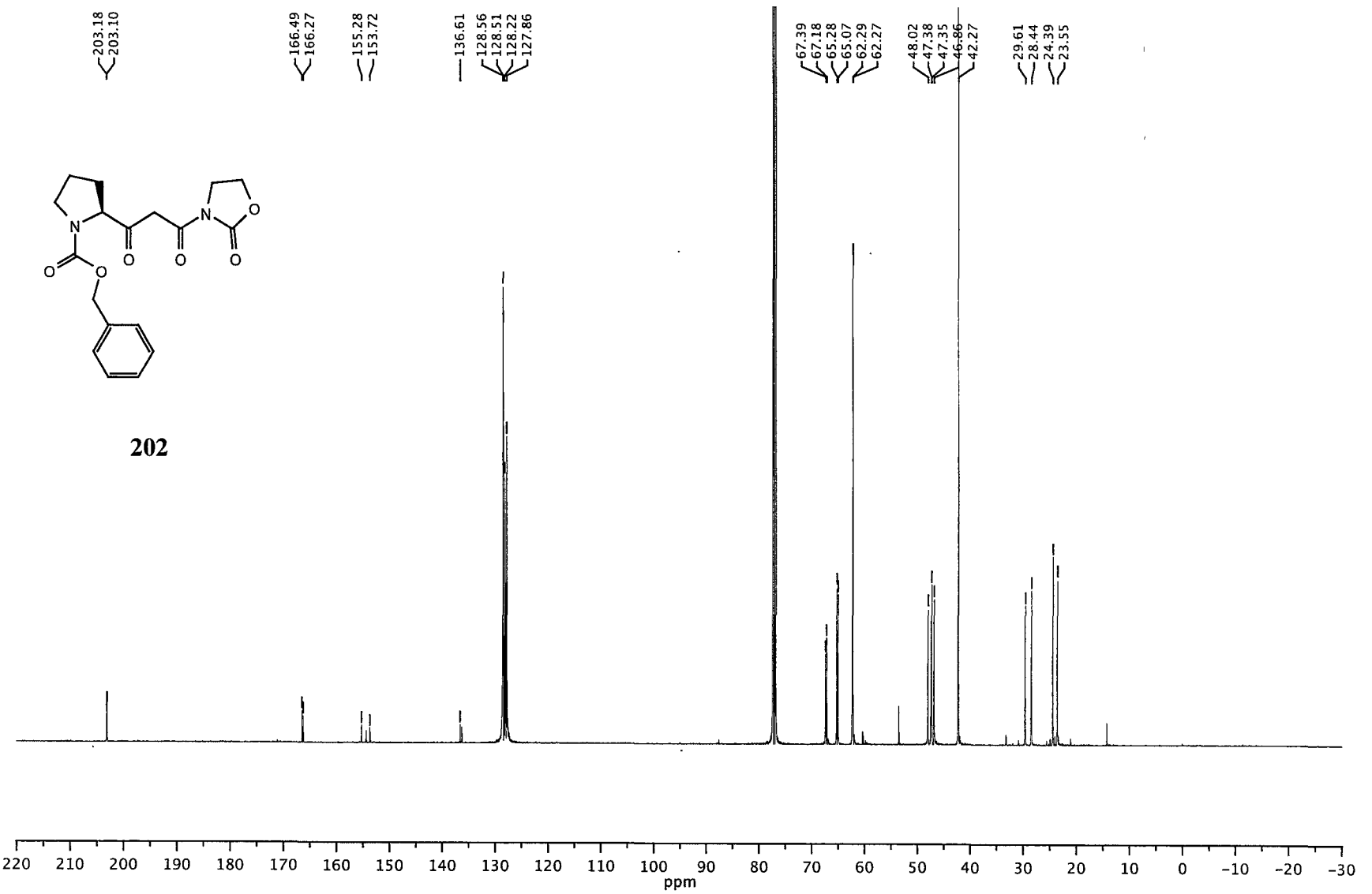
201



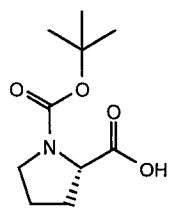


202

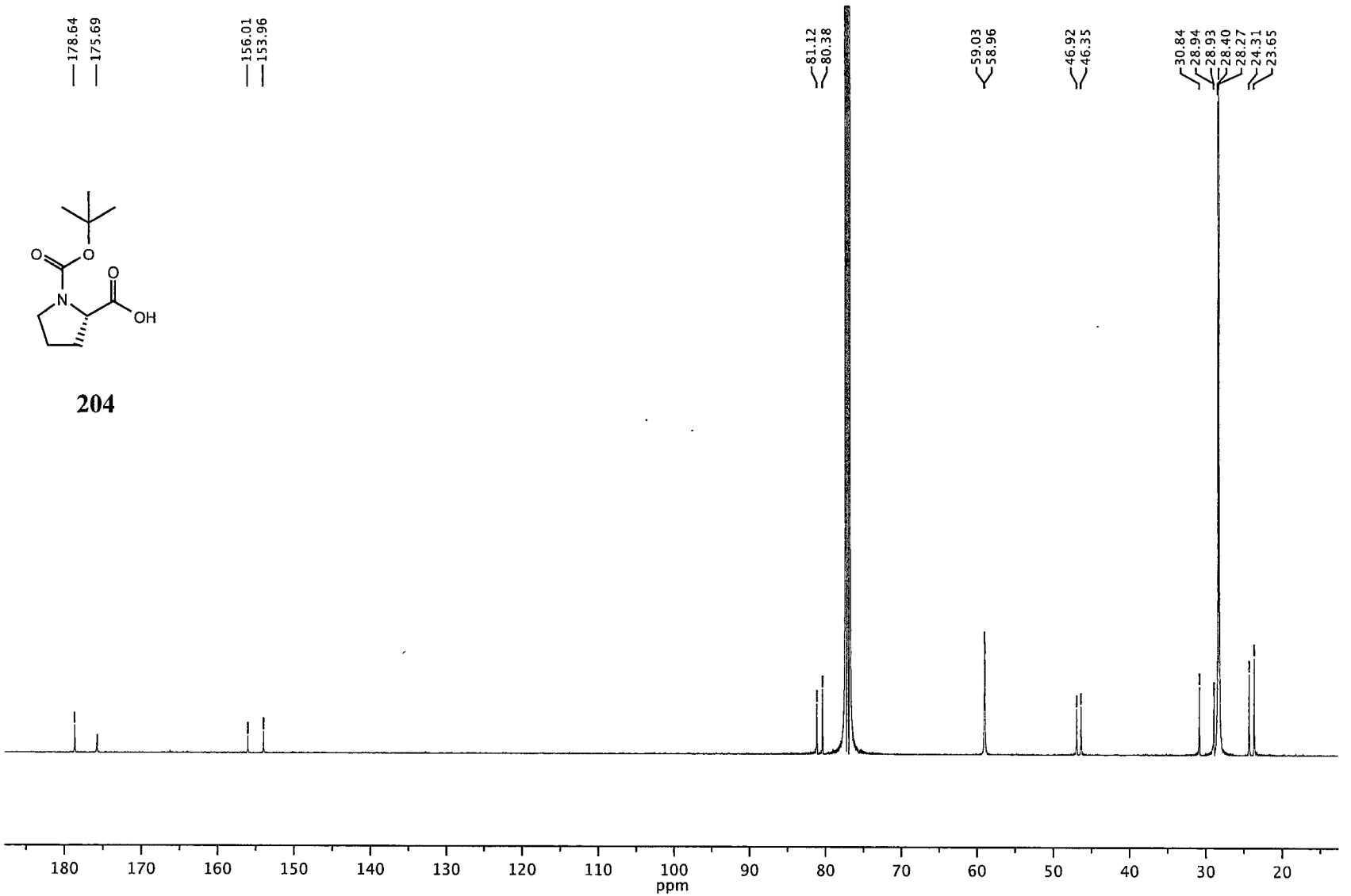

5.00
1.21
0.68
2.91
1.23
0.83
2.94
2.35
2.61
2.97
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
ppm


203.18
203.10
166.49
166.27
155.28
153.72
136.61
128.56
128.51
128.22
127.86
67.39
67.18
65.28
65.07
62.29
62.27
48.02
47.38
47.35
46.86
42.27
29.61
28.44
24.39
23.55
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

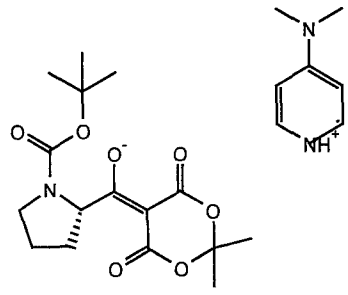
202



204

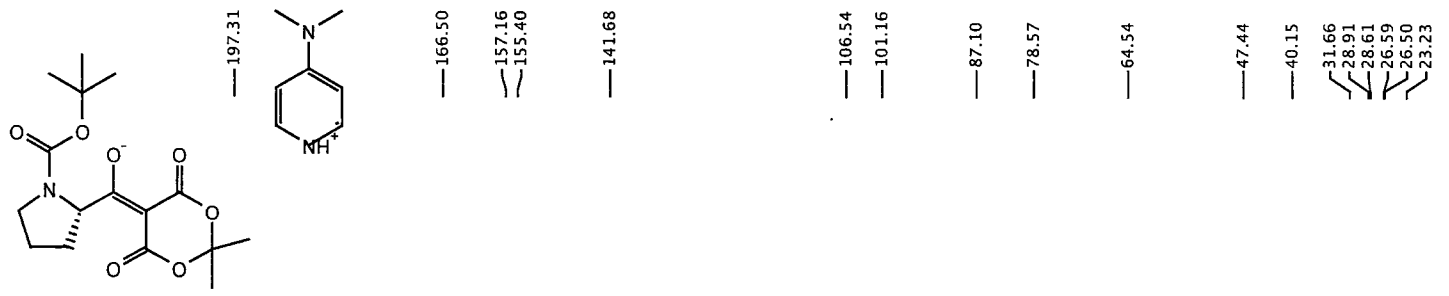

178.64
175.69
156.01
153.96
81.12
80.38
59.03
58.96
46.92
46.35
30.84
28.94
28.93
28.40
28.27
24.31
23.65
O
O
N
O
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

204

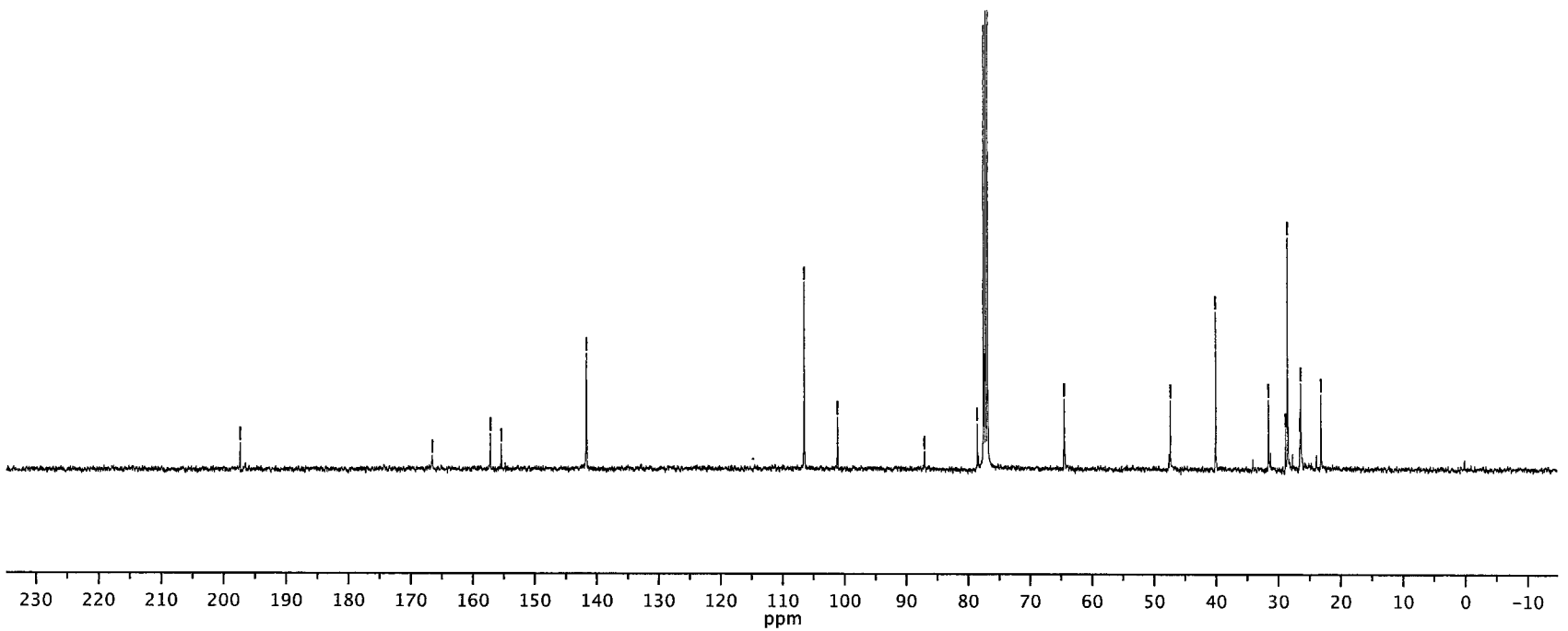


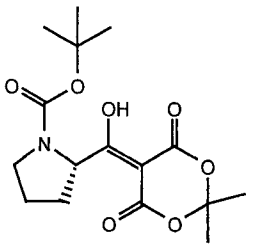
206

1.98
2.00
0.86
1.96
6.09
0.99
1.04
2.32
7.38
6.70
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


197.31
166.50
157.16
155.40
141.68
106.54
101.16
87.10
78.57
64.54
47.44
40.15
31.66
28.91
28.61
26.59
26.50
23.23
O
O
N
O⁻
O
O
O
O
O
N
NH+

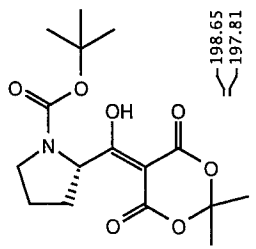
206


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
OH
O
N
O
O
O

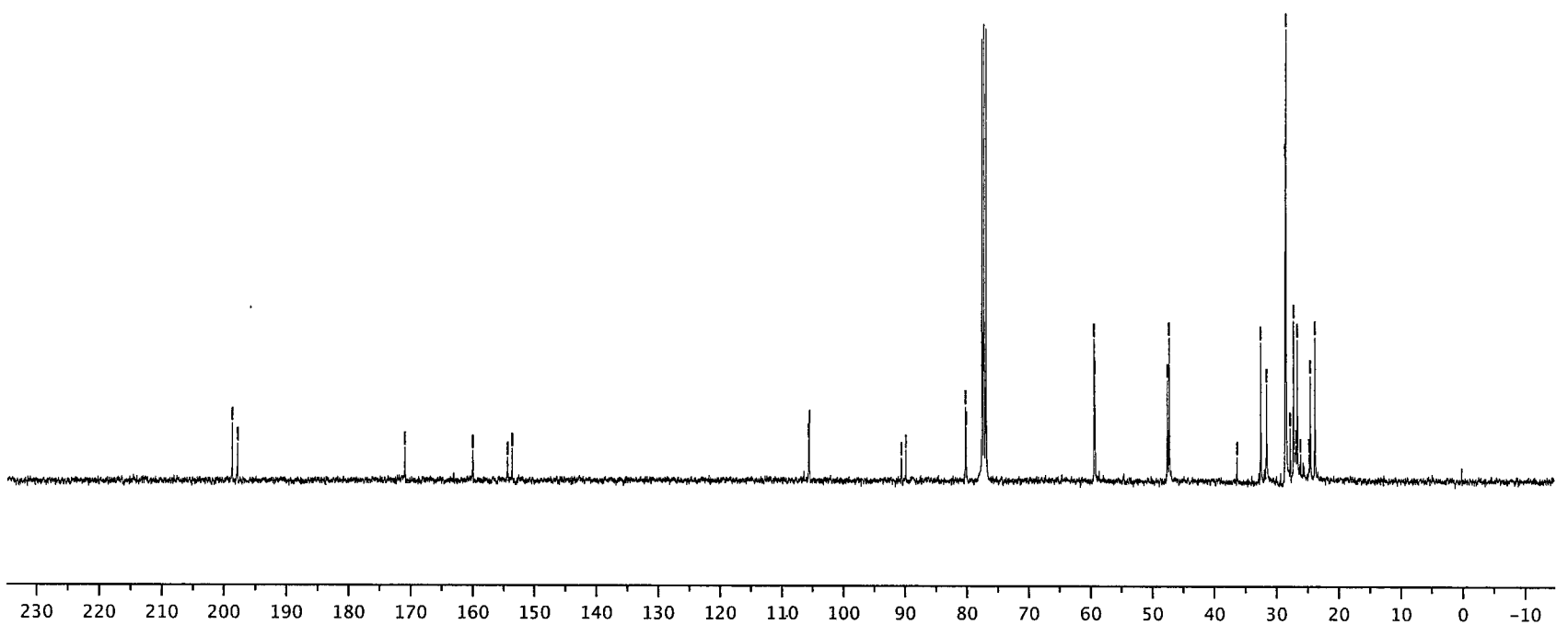
207

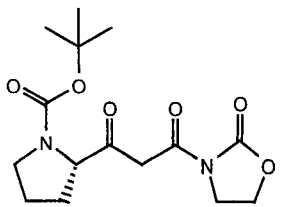
1.00
2.57
1.09
4.18
6.60
10.82
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm



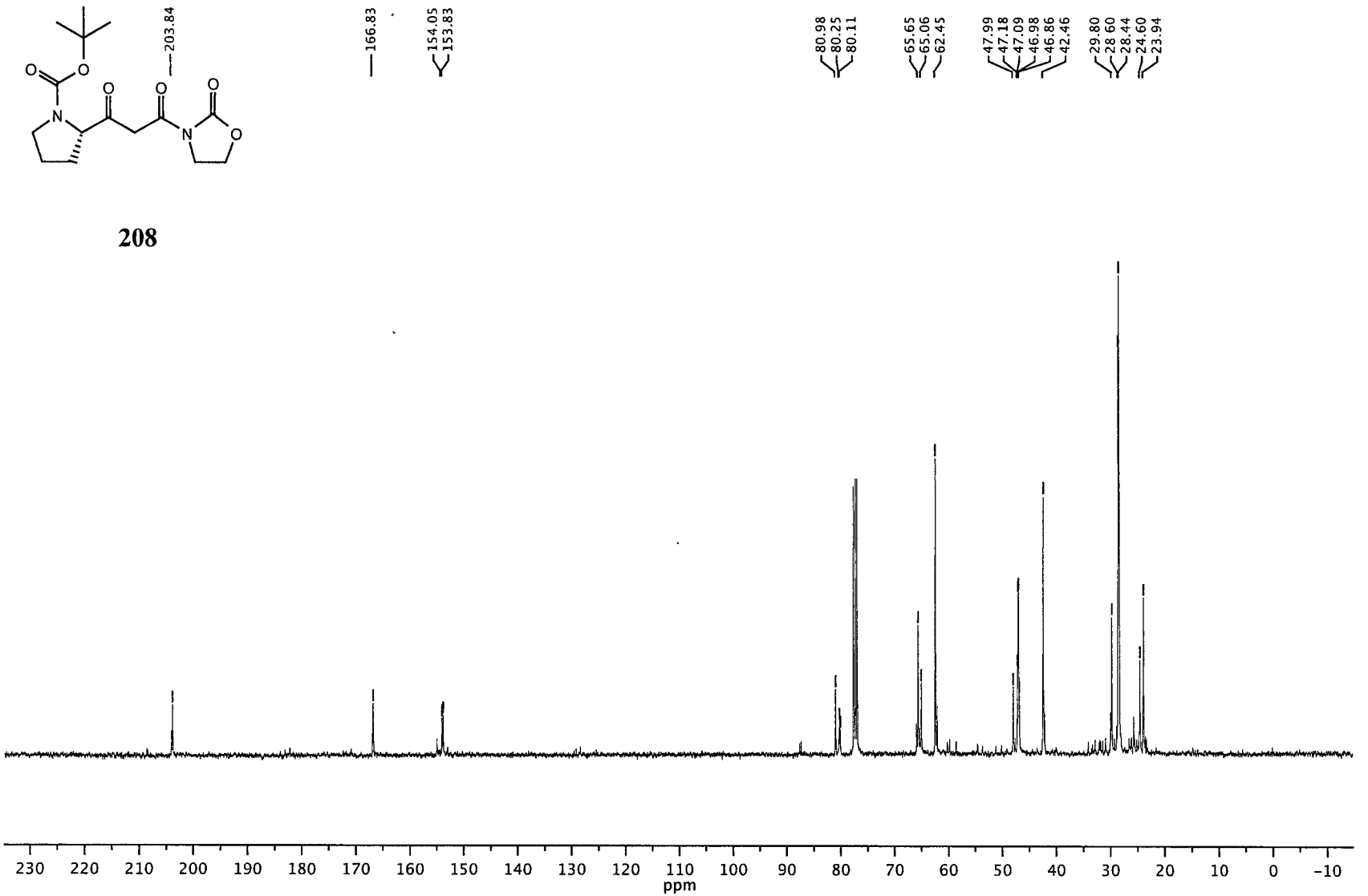
198.65
197.81
170.92
159.98
154.39
153.60
105.67
105.55
90.63
89.90
80.26
80.15
59.45
59.34
47.58
47.31
36.38
32.57
31.62
28.64
28.51
27.82
27.28
26.90
26.67
26.15
24.78
24.59
23.84

207

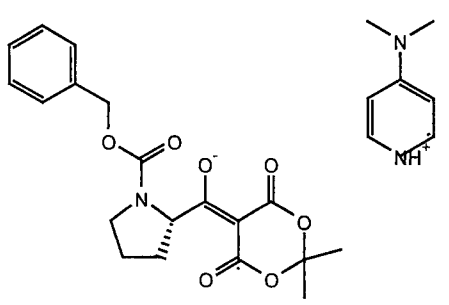




208

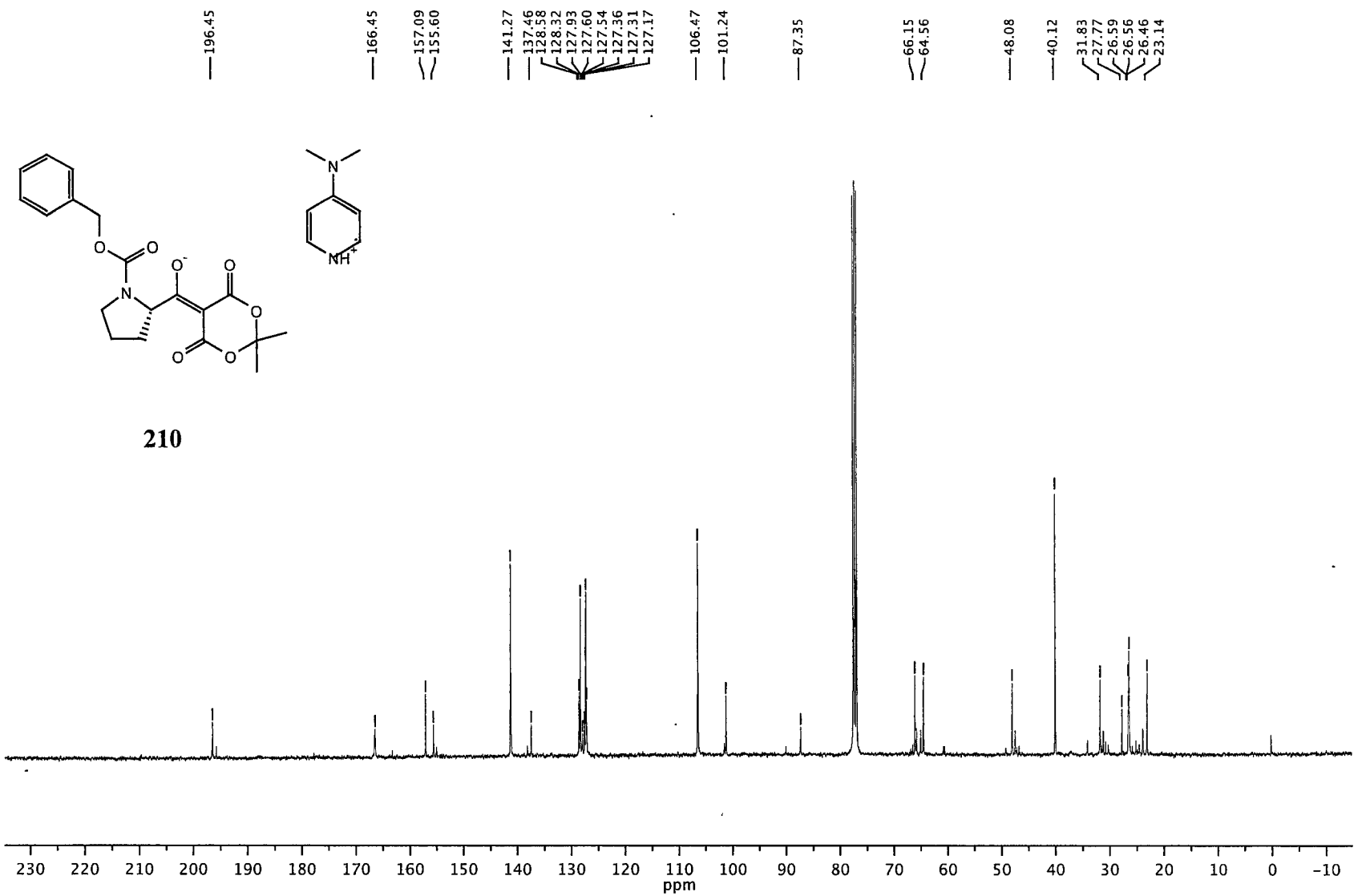

203.84
166.83
154.05
153.83
80.98
80.25
80.11
65.65
65.06
62.45
47.99
47.18
47.09
46.98
46.86
42.46
29.80
28.60
28.44
24.60
23.94
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

208

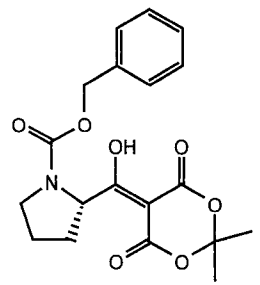


210

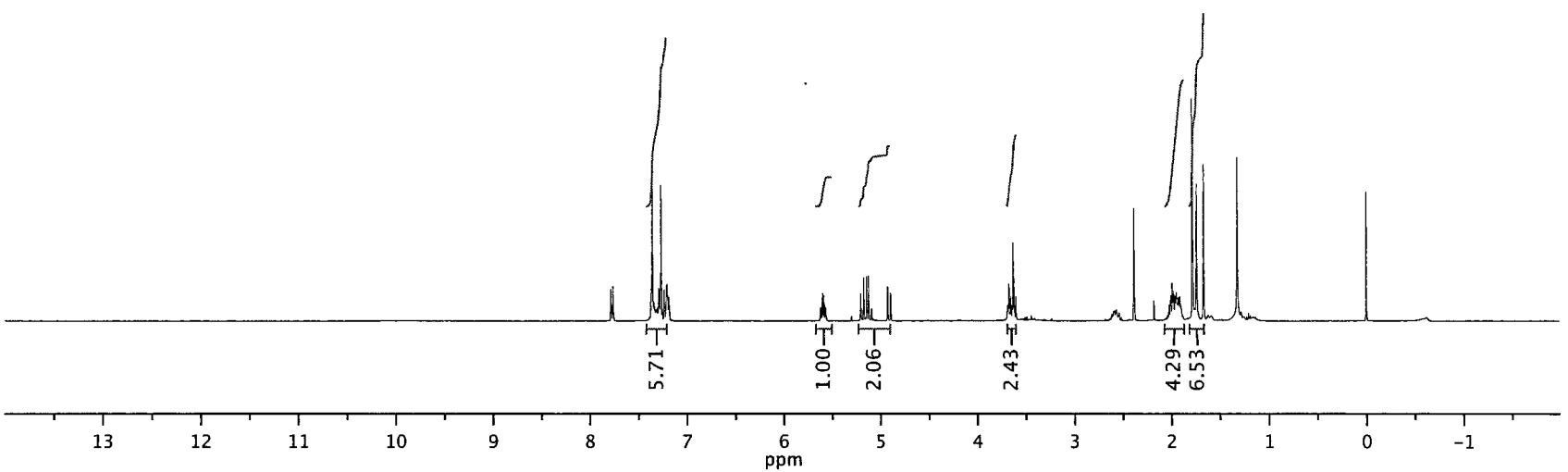
2.00
5.68
1.99
0.60
2.49
1.80
5.98
0.99
3.24
6.66
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

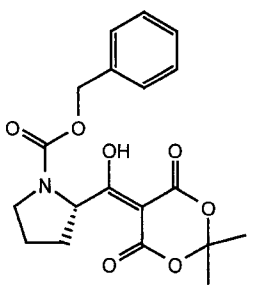

196.45
166.45
157.09
155.60
141.27
137.46
128.58
128.32
127.93
127.60
127.54
127.36
127.31
127.17
106.47
101.24
87.35
66.15
64.56
48.08
40.12
31.83
27.77
26.59
26.56
26.46
23.14
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

210



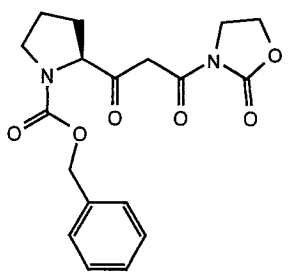
211



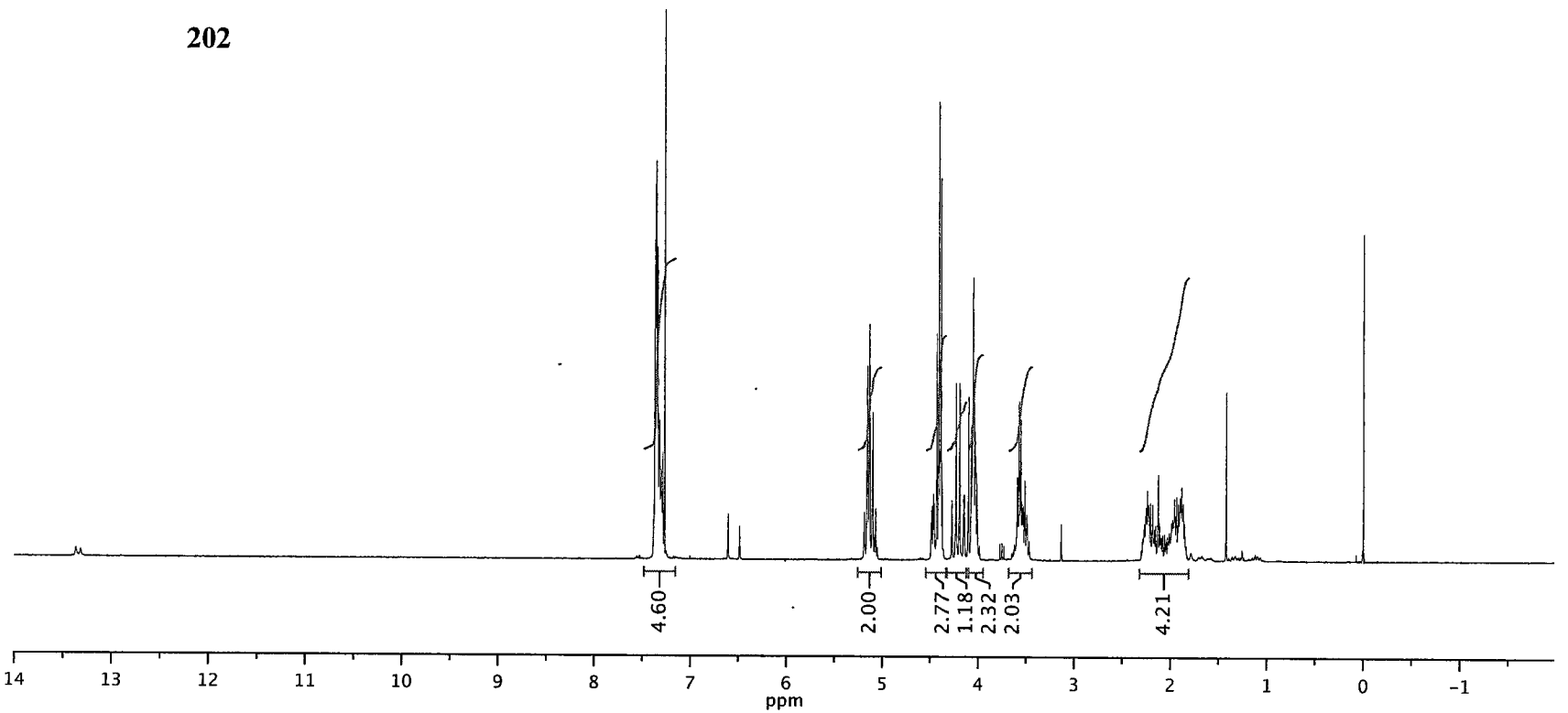

OH
O
O
O
O
O
O
N

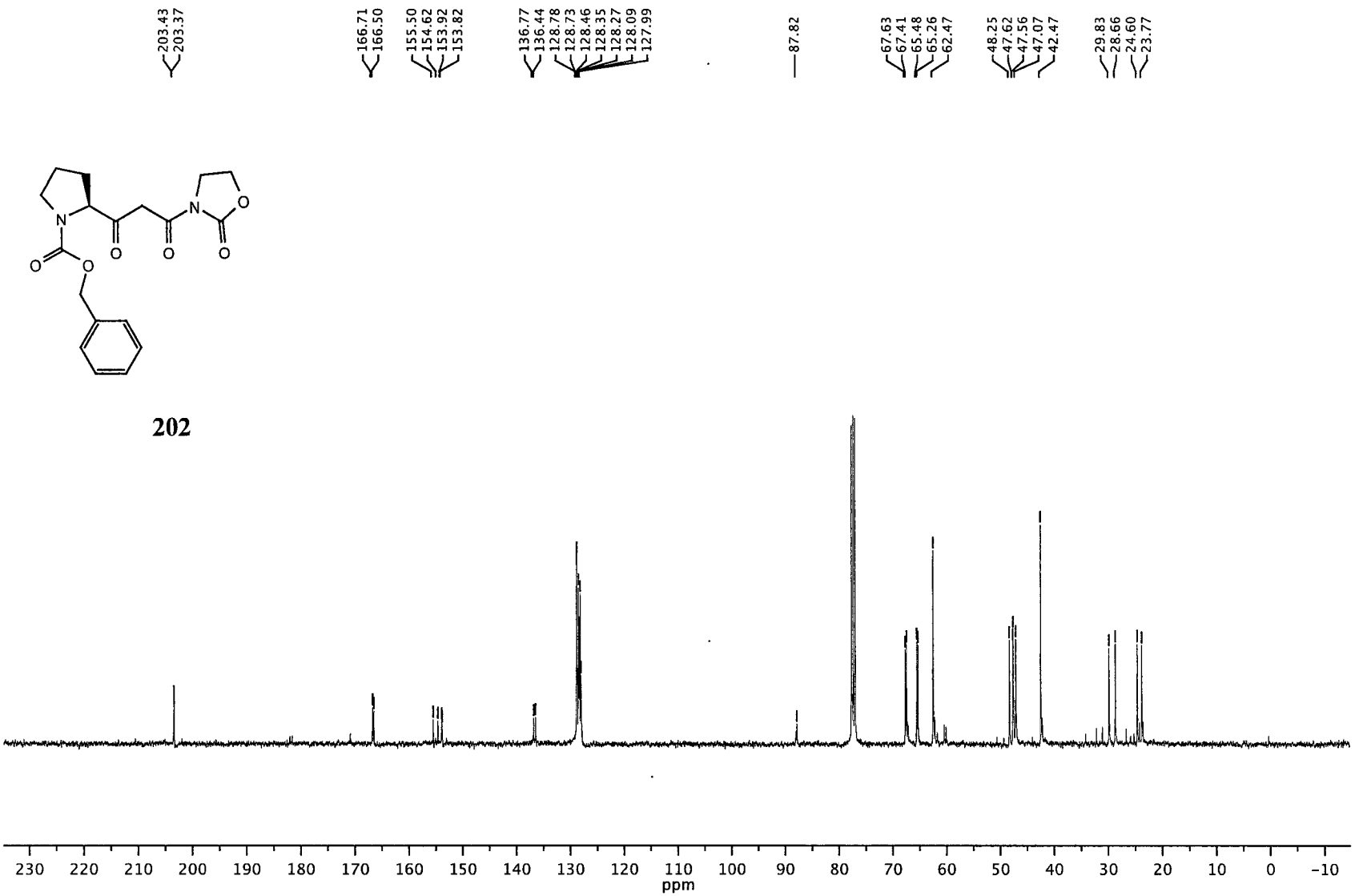
211

196.88
196.51
170.47
162.85
159.82
154.69
153.96
136.55
136.24
128.57
128.53
128.14
128.11
128.07
127.88
127.80
105.62
105.40
90.86
90.29
67.31
67.14
59.51
58.94
47.78
47.28
36.19
32.32
31.34
27.64
27.17
27.03
26.00
24.49
23.68
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

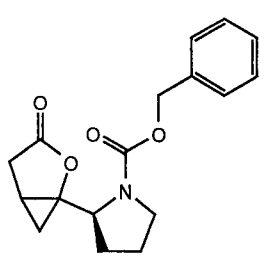


202



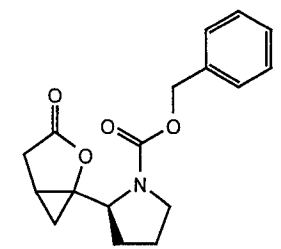

203.43
203.37
166.71
166.50
155.50
154.62
153.92
153.82
136.77
136.44
128.78
128.73
128.46
128.35
128.27
128.09
127.99
87.82
67.63
67.41
65.48
65.26
62.47
48.25
47.62
47.56
47.07
42.47
29.83
28.66
24.60
23.77
ppm

202



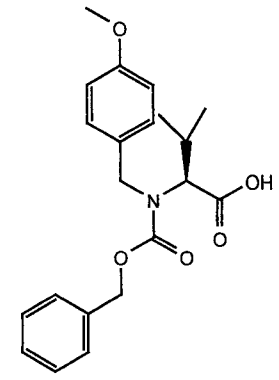
212

4.63
2.00
0.91
1.99
0.64
0.71
3.58
1.29
1.09
1.01
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

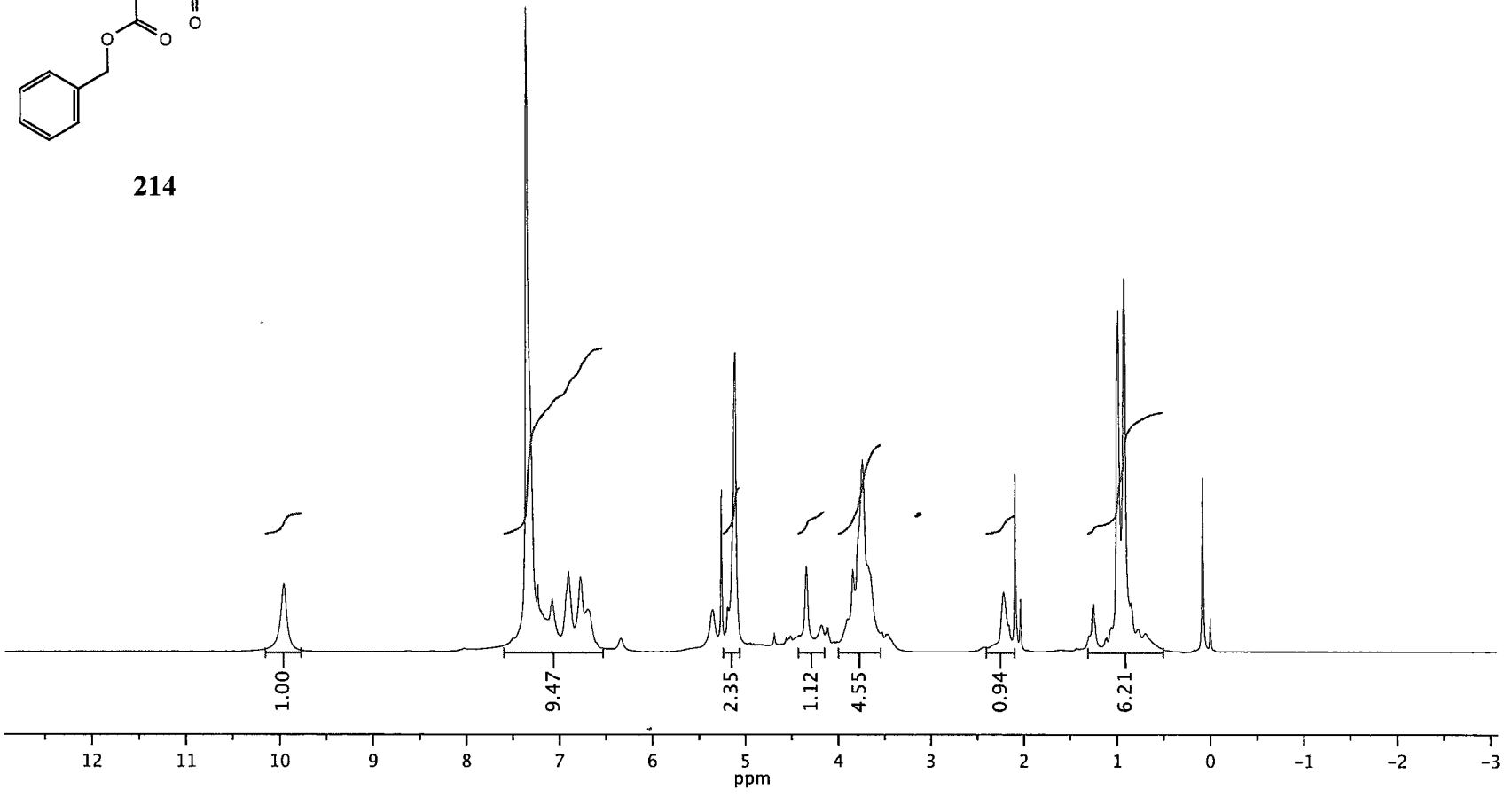


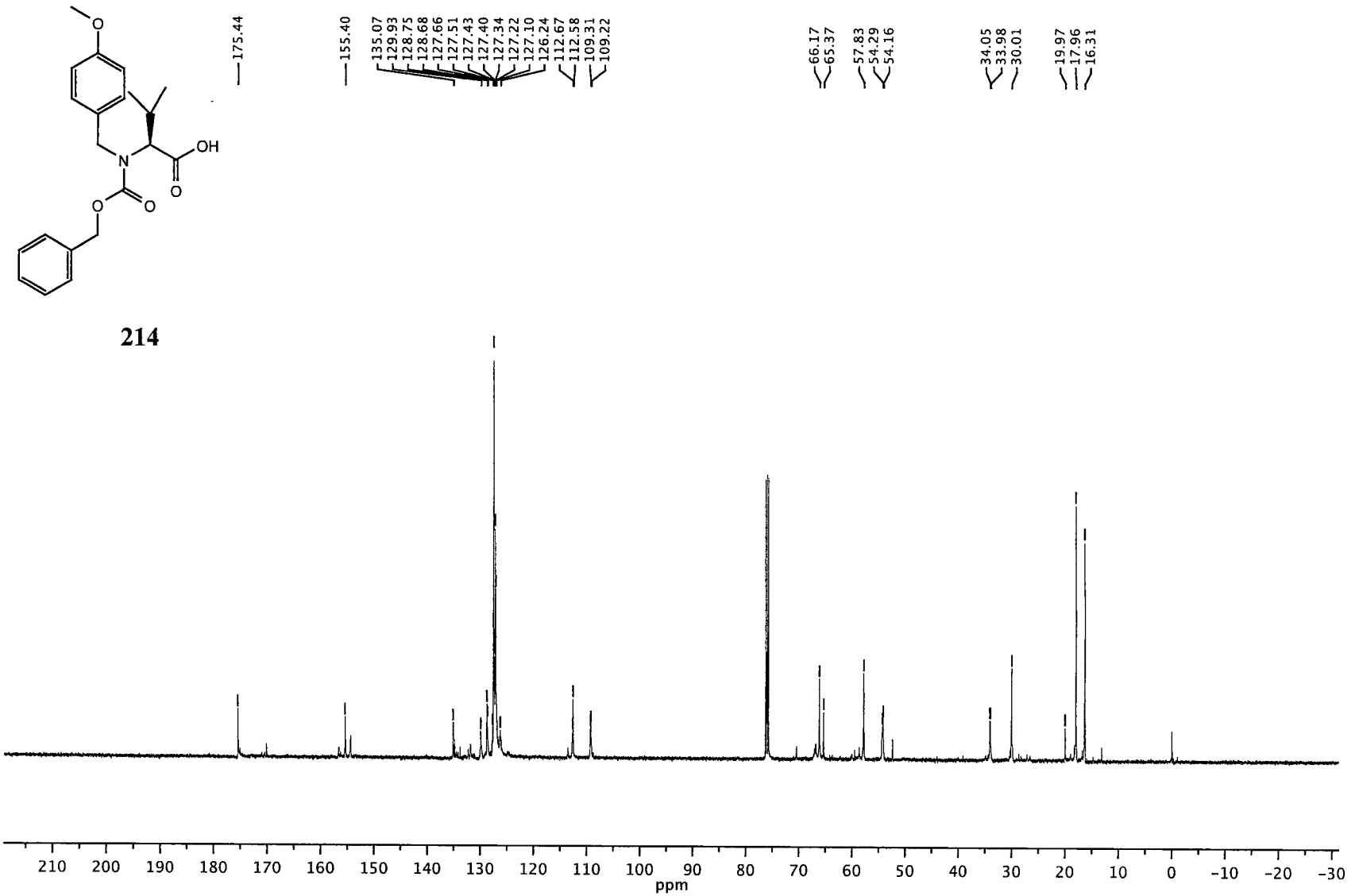
212

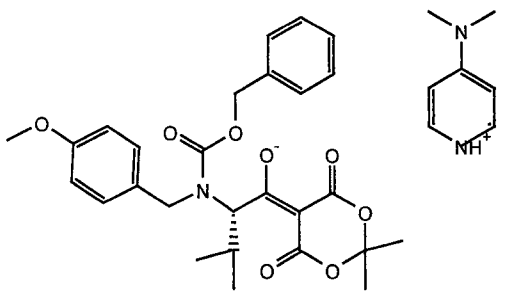
176.81
155.60
137.01
128.88
128.72
128.15
127.76
70.05
67.39
66.97
59.97
58.84
48.01
47.60
34.01
33.69
30.68
29.69
24.24
23.42
17.68
17.16
16.78
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


O
OH
N
O
O
O

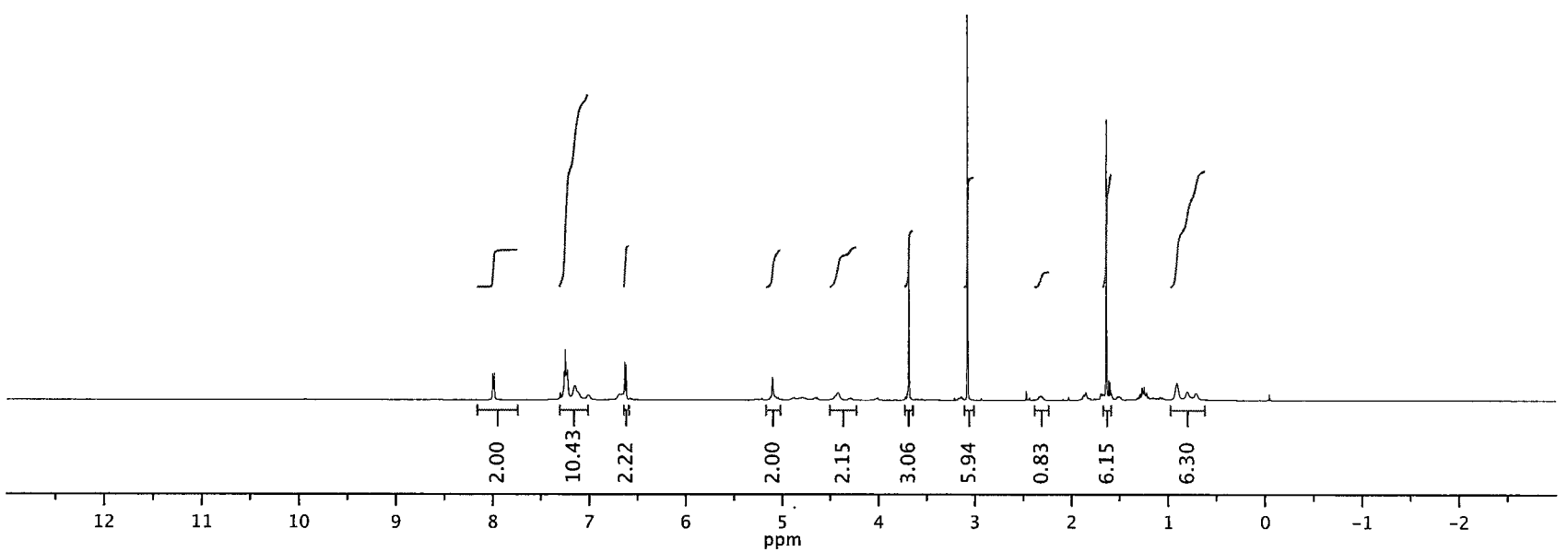
214

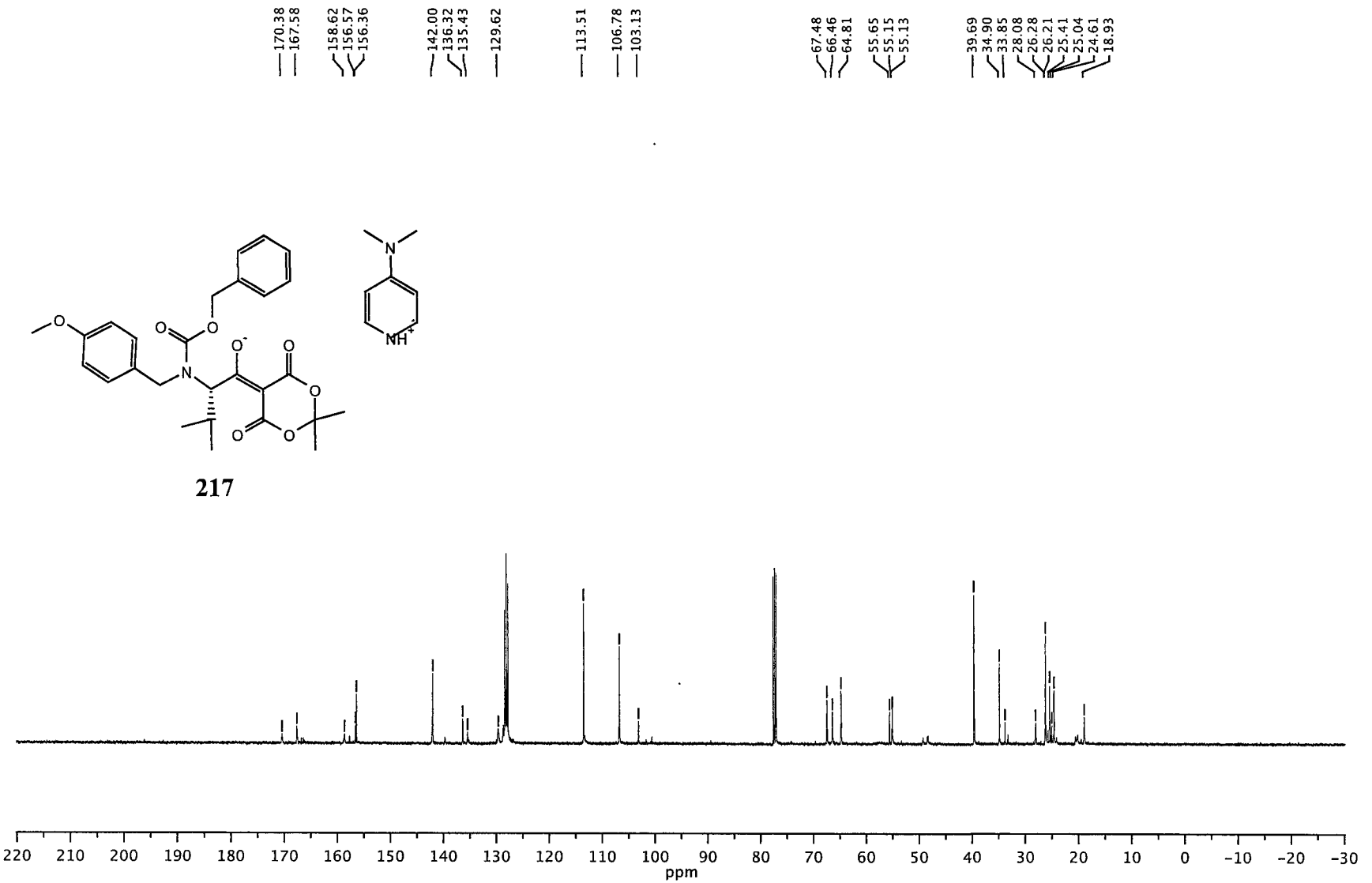

1.00
9.47
2.35
1.12
4.55
0.94
6.21
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
-3
ppm


175.44
155.40
135.07
129.93
128.75
128.68
127.66
127.51
127.43
127.40
127.34
127.22
127.10
126.24
112.67
112.58
109.31
109.22
66.17
65.37
57.83
54.29
54.16
34.05
33.98
30.01
19.97
17.96
16.31
OH
O
N
O
O
O
214
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
ppm

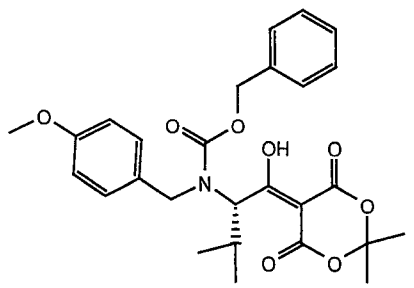


217


2.00
10.43
2.22
2.00
2.15
3.06
5.94
0.83
6.15
6.30
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

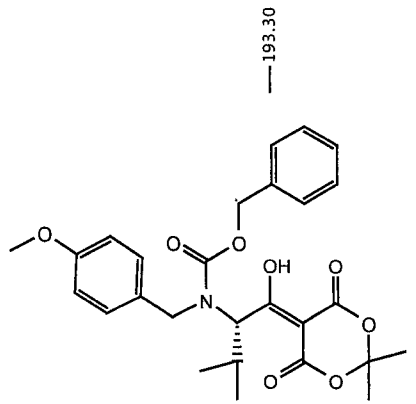

170.38
167.58
158.62
156.57
156.36
142.00
136.32
135.43
129.62
113.51
106.78
103.13
67.48
66.46
64.81
55.65
55.15
55.13
39.69
34.90
33.85
28.08
26.28
26.21
25.41
25.04
24.61
18.93
ppm

217


O
O
O
OH
O
N
O
O
O

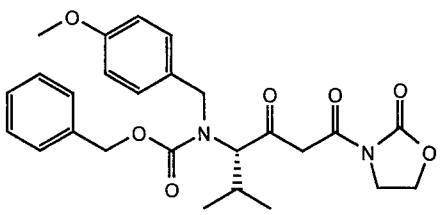
216

9.00
1.06
2.02
1.98
3.18
0.89
6.12
6.23
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

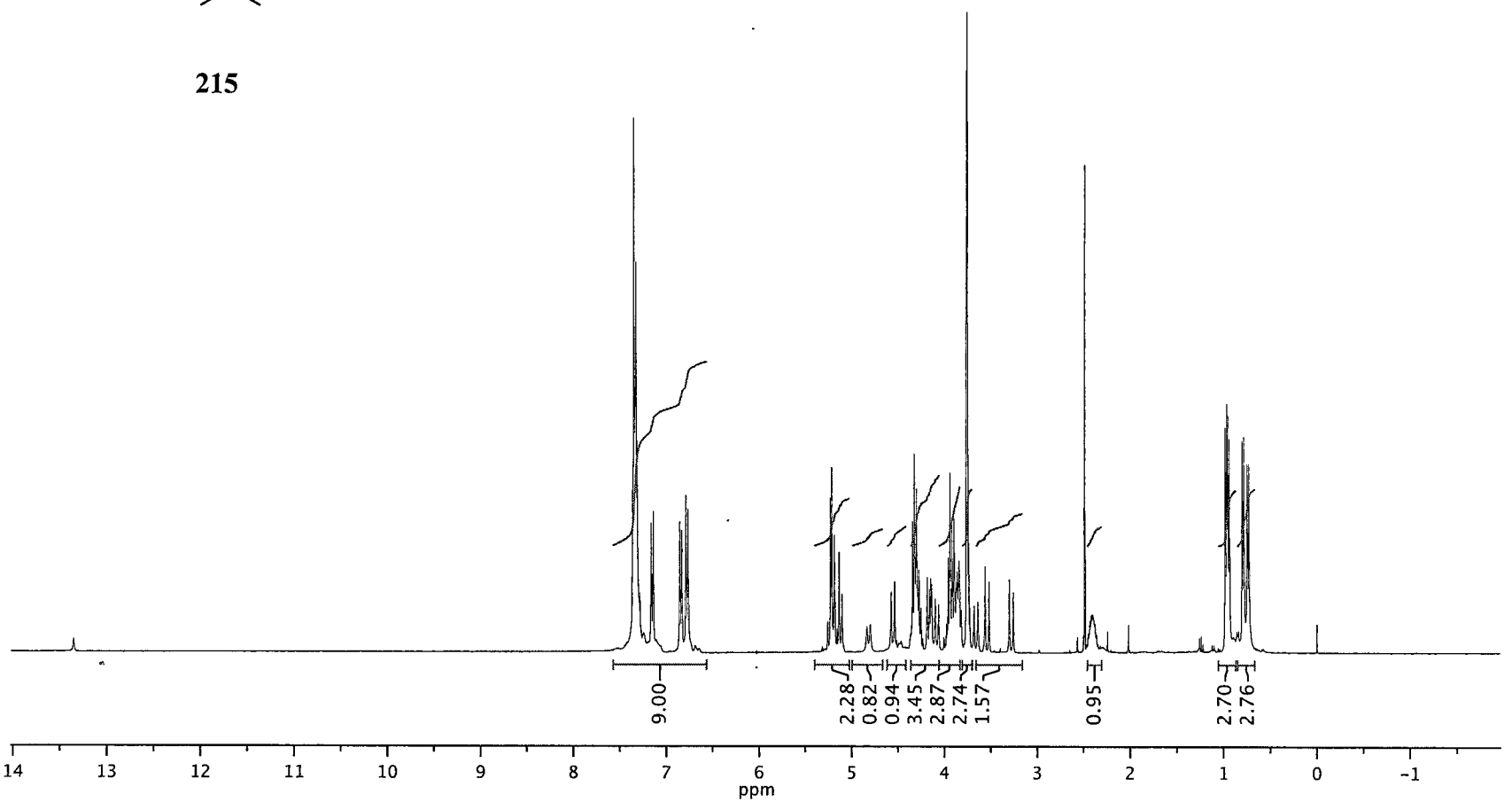

O
O
O
OH
O
N
O
O
O
O

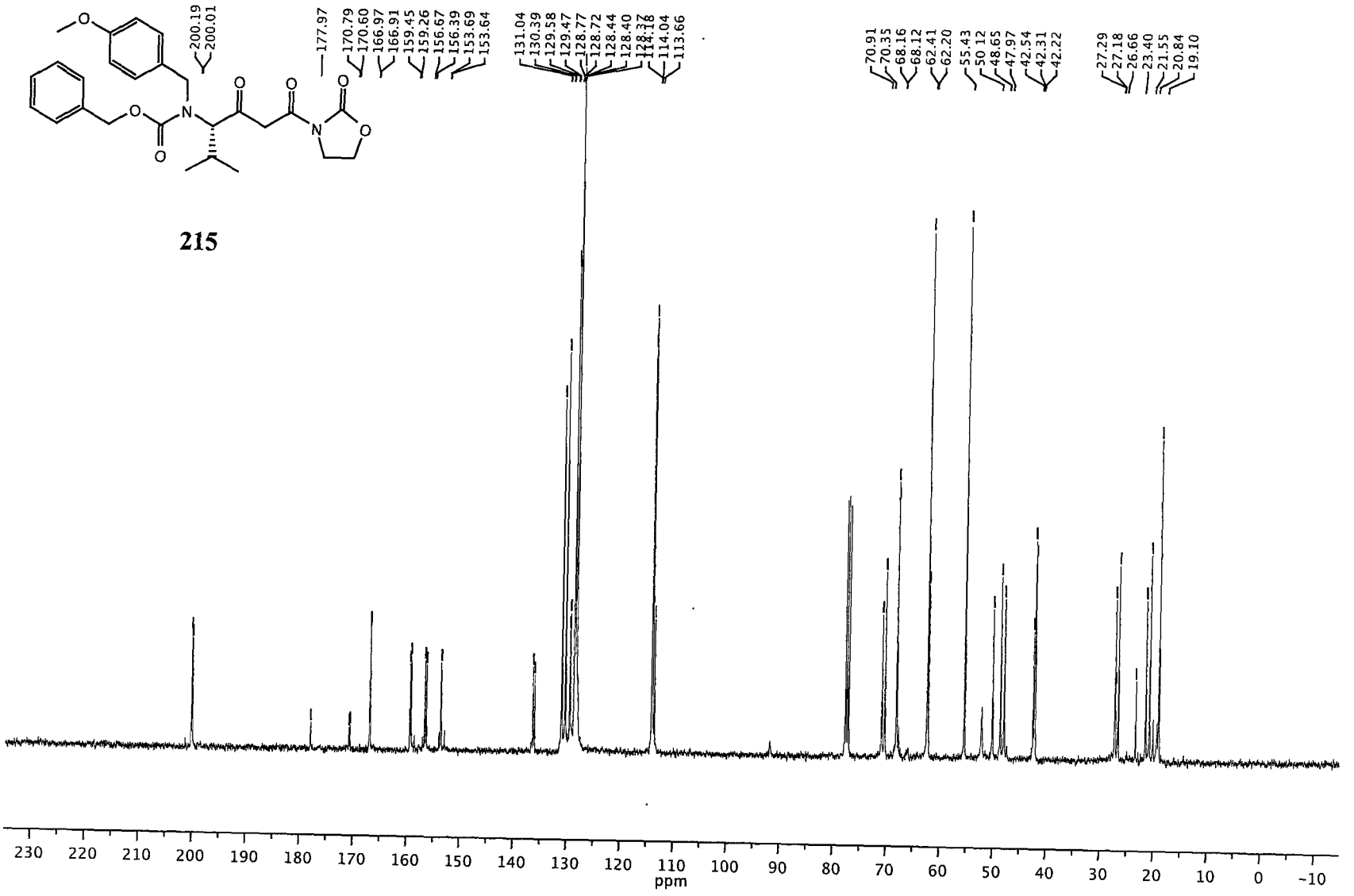
216

193.30
163.07
158.80
136.57
130.76
129.88
129.57
128.80
113.84
106.48
105.17
67.45
55.45
36.64
31.87
28.22
27.84
27.22
27.09
26.61
19.90
19.06
17.48
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

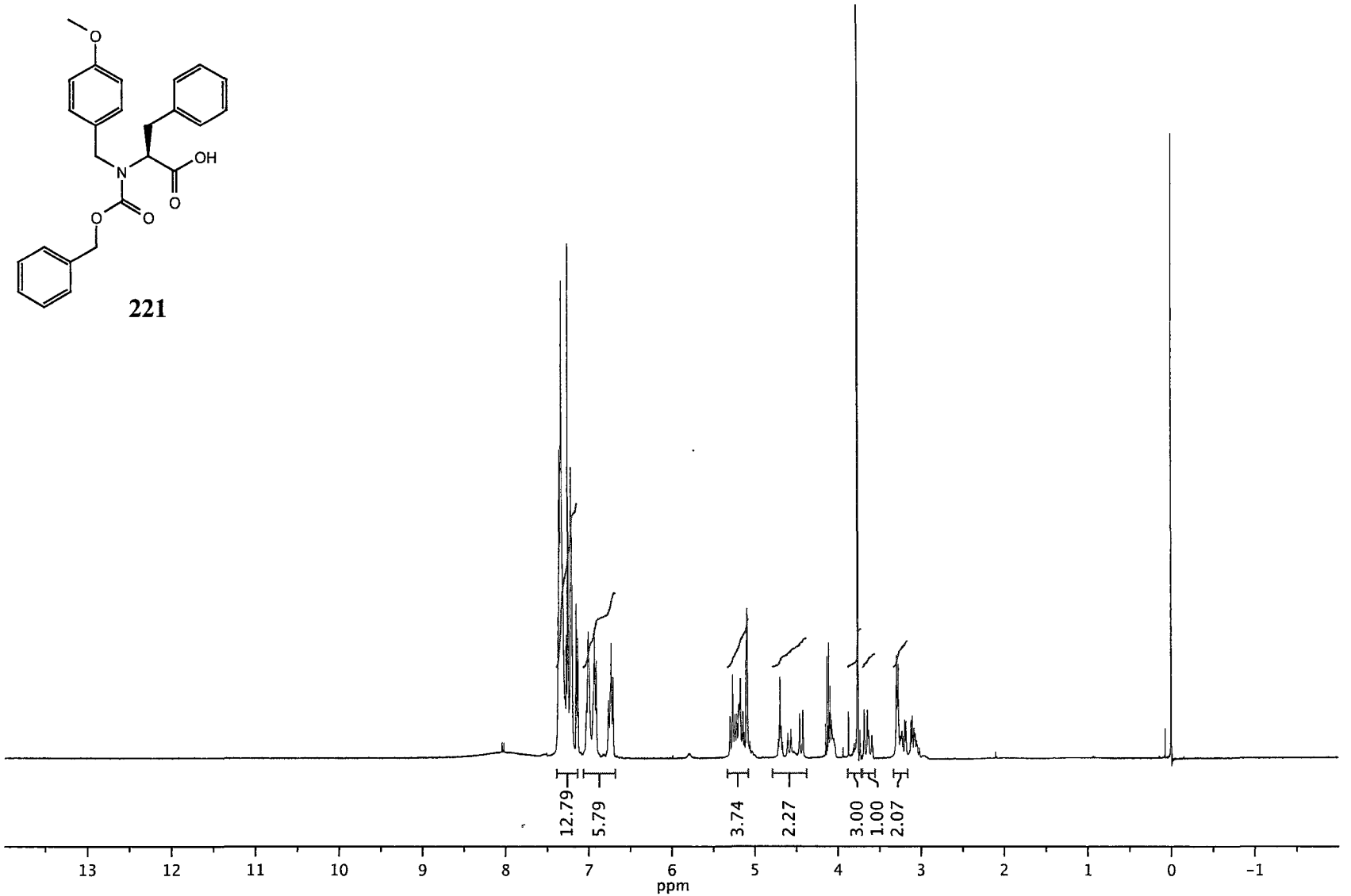


215

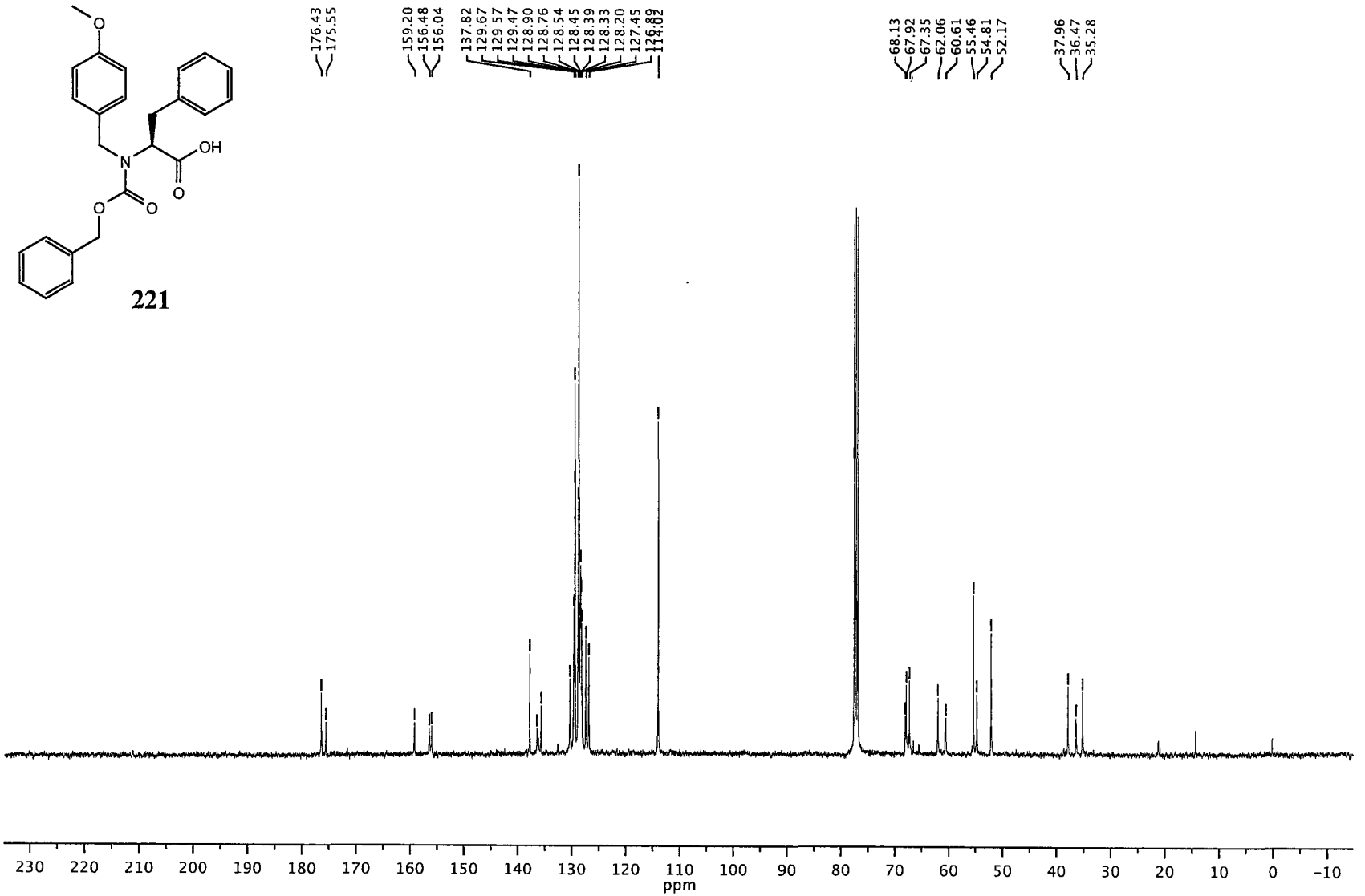

9.00
2.28
0.82
0.94
3.45
2.87
2.74
1.57
0.95
2.70
2.76
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

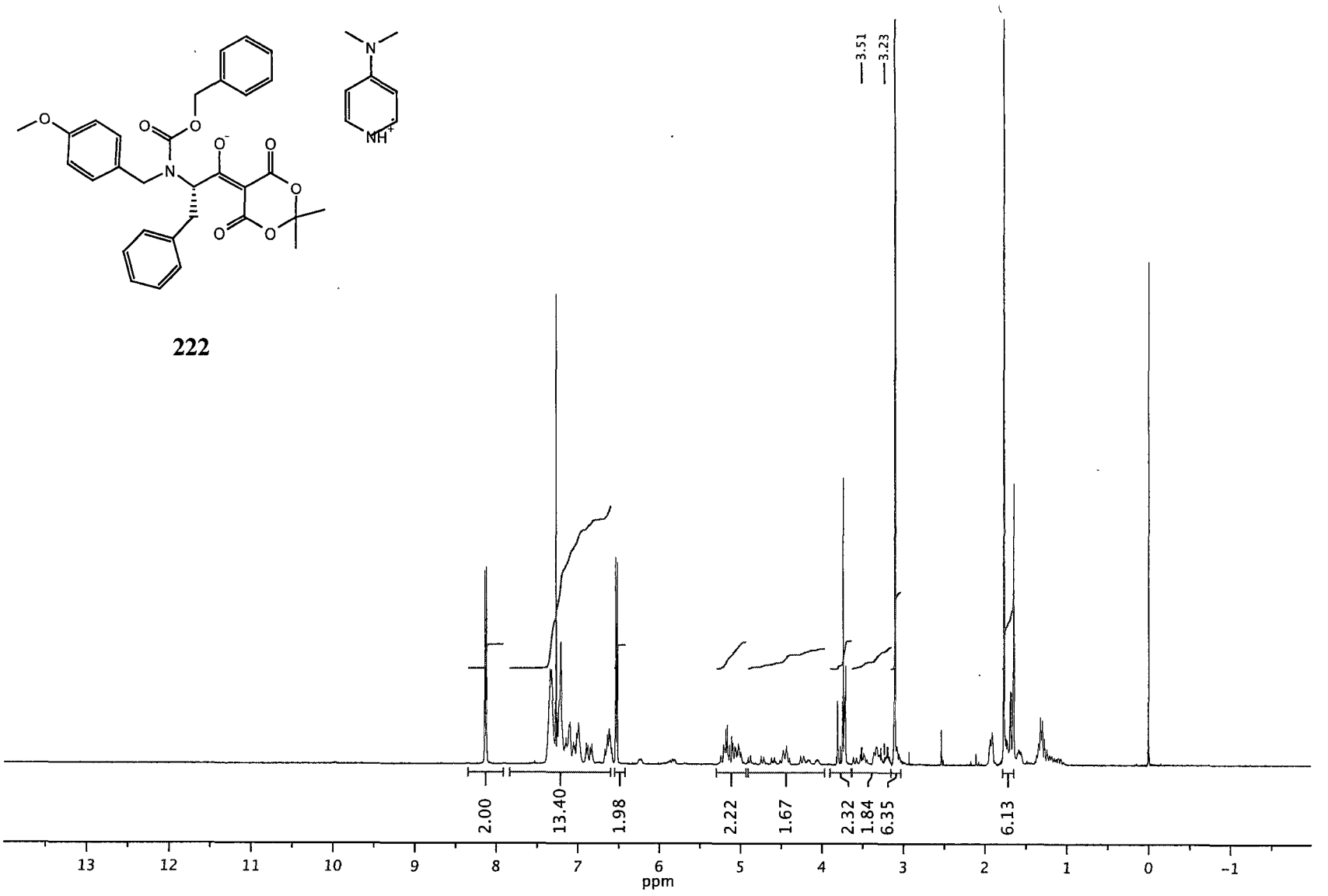

200.19
200.01
177.97
170.79
170.60
166.97
166.91
159.45
159.26
156.67
156.39
153.69
153.64
131.04
130.39
129.58
129.47
128.77
128.72
128.44
128.40
114.04
113.66
70.91
70.35
68.16
68.12
62.41
62.20
55.43
50.12
48.65
47.97
42.54
42.31
42.22
27.29
27.18
26.66
23.40
21.55
20.84
19.10
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

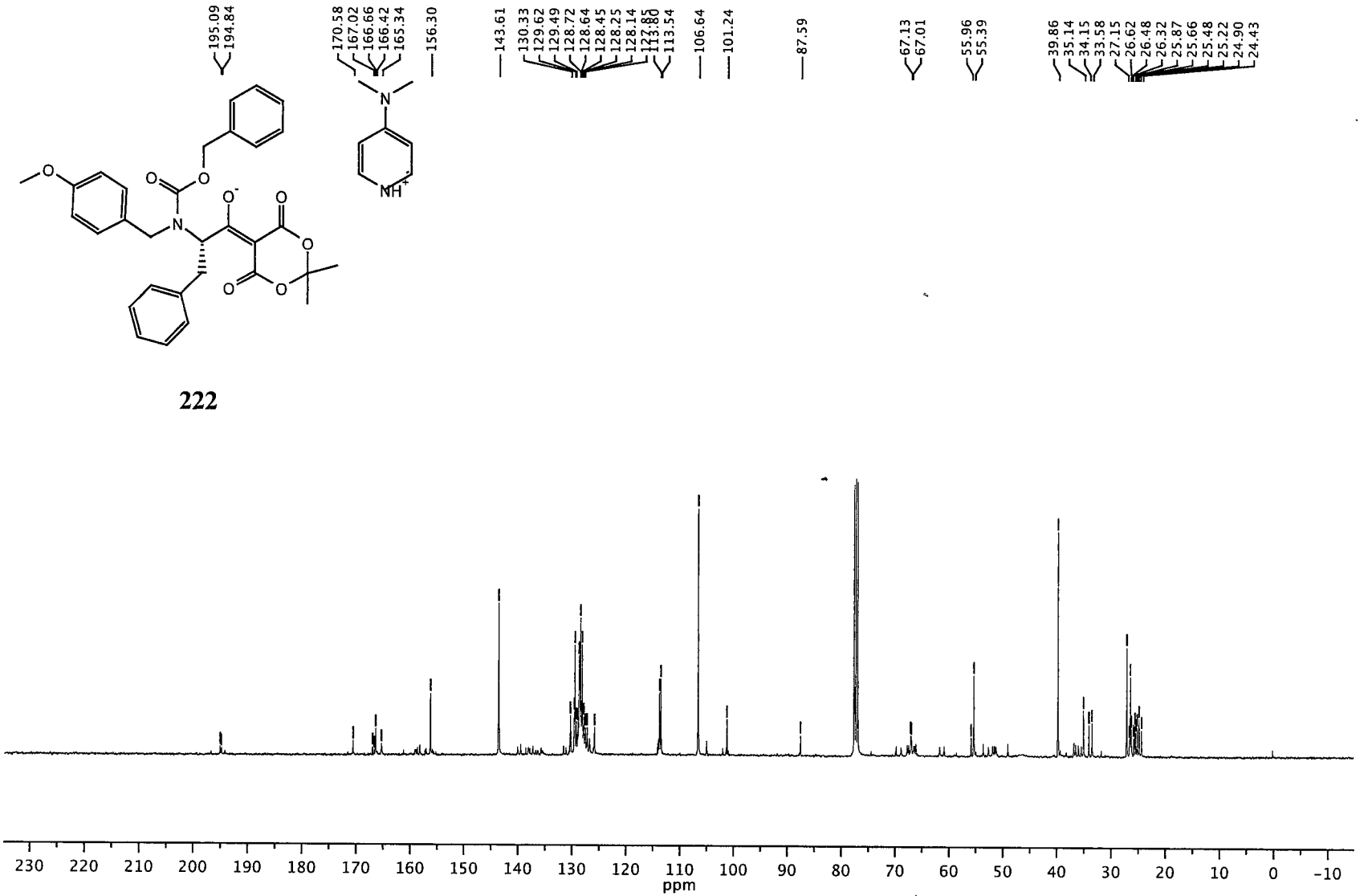
215


O
OH
N
O
O
O
12.79
5.79
3.74
2.27
3.00
1.00
2.07
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

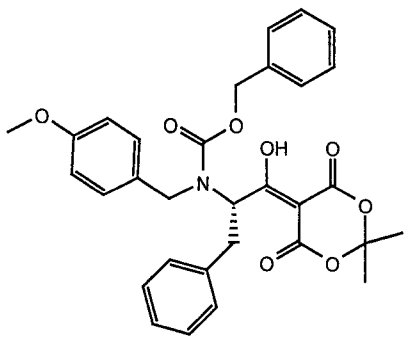
221


O
N
OH
O
O
O
221
176.43
175.55
159.20
156.48
156.04
137.82
129.67
129 57
129.47
128.90
128.76
128.54
128.45
128.39
128.33
128.20
127.45
68.13
67.92
67.35
62.06
60.61
55.46
54.81
52.17
37.96
36.47
35.28
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


222
3.51
3.23
2.00
13.40
1.98
2.22
1.67
2.32
1.84
6.35
6.13
ppm

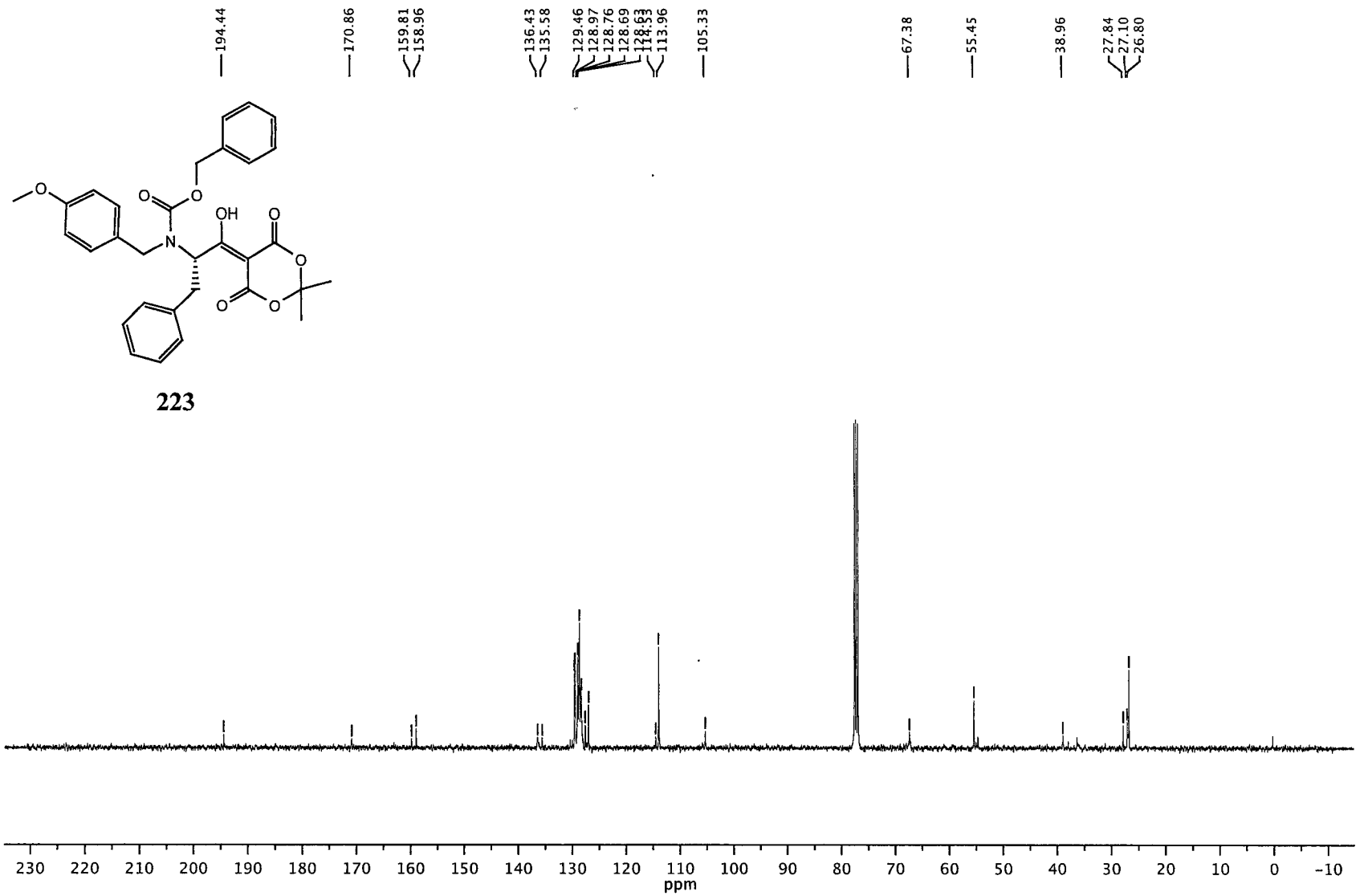

195.09
194.84
170.58
167.02
166.66
166.42
165.34
156.30
143.61
130.33
129.62
129.49
128.72
128.64
128.45
128.25
128.14
113.80
113.54
106.64
101.24
87.59
67.13
67.01
55.96
55.39
39.86
35.14
34.15
33.58
27.15
26.62
26.48
26.32
25.87
25.66
25.48
25.22
24.90
24.43
O
O
O
N
O
O
O
O
O
O
N
NH+
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

222

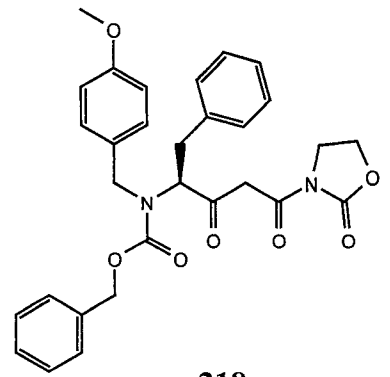

O
O
O
OH
N
O
O
O
O

223

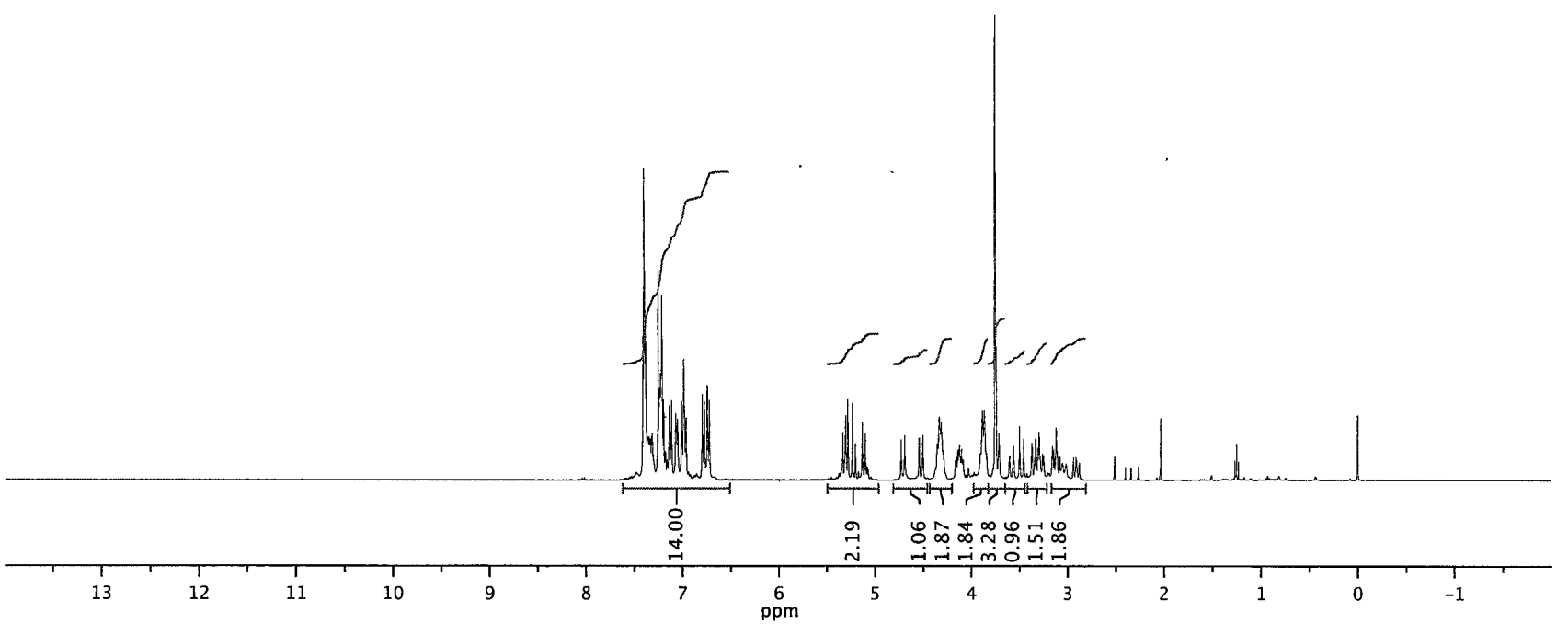
14.00
0.32
2.67
0.60
2.63
1.91
4.17
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

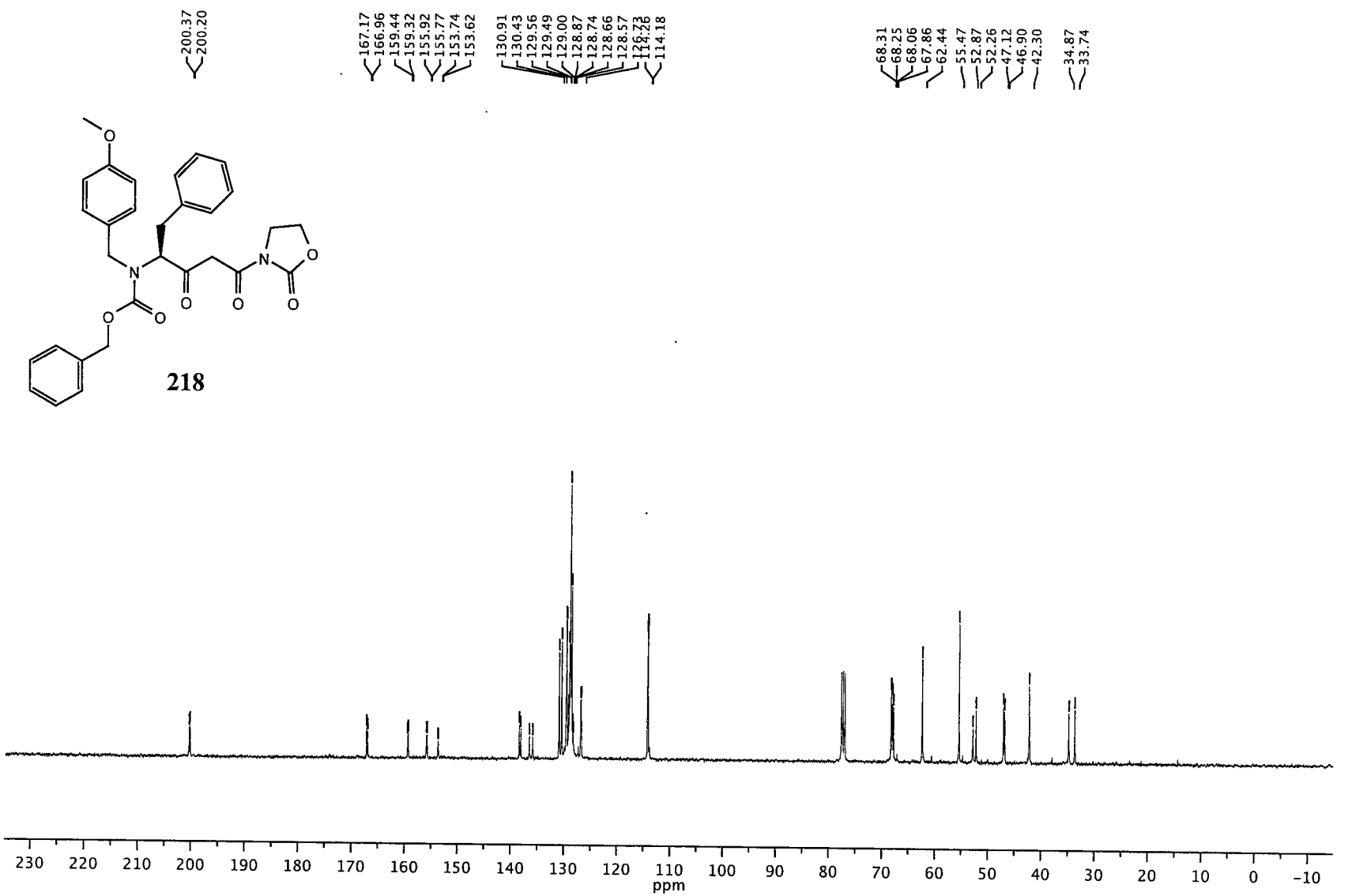

194.44
170.86
159.81
158.96
136.43
135.58
129.46
128.97
128.76
128.69
113.96
105.33
67.38
55.45
38.96
27.84
27.10
26.80
OH
ppm

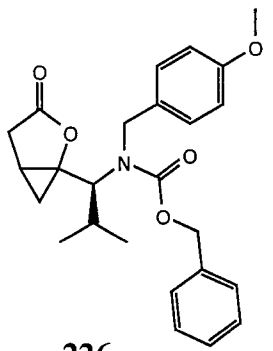
223



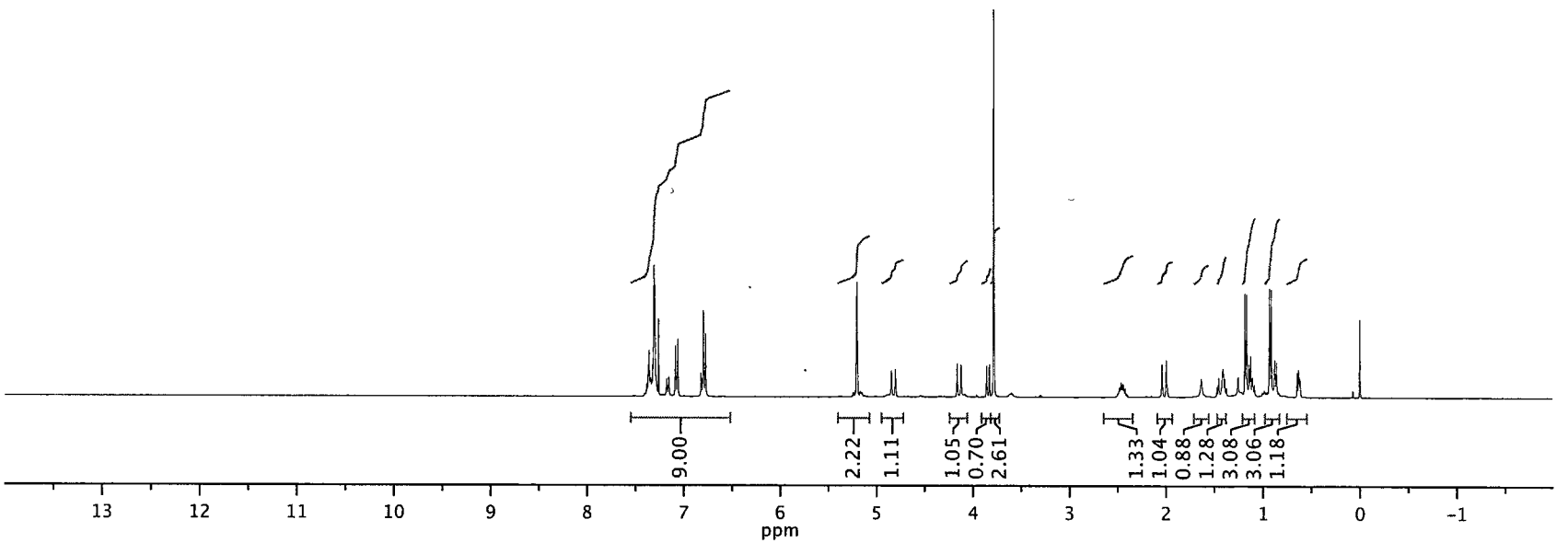
218

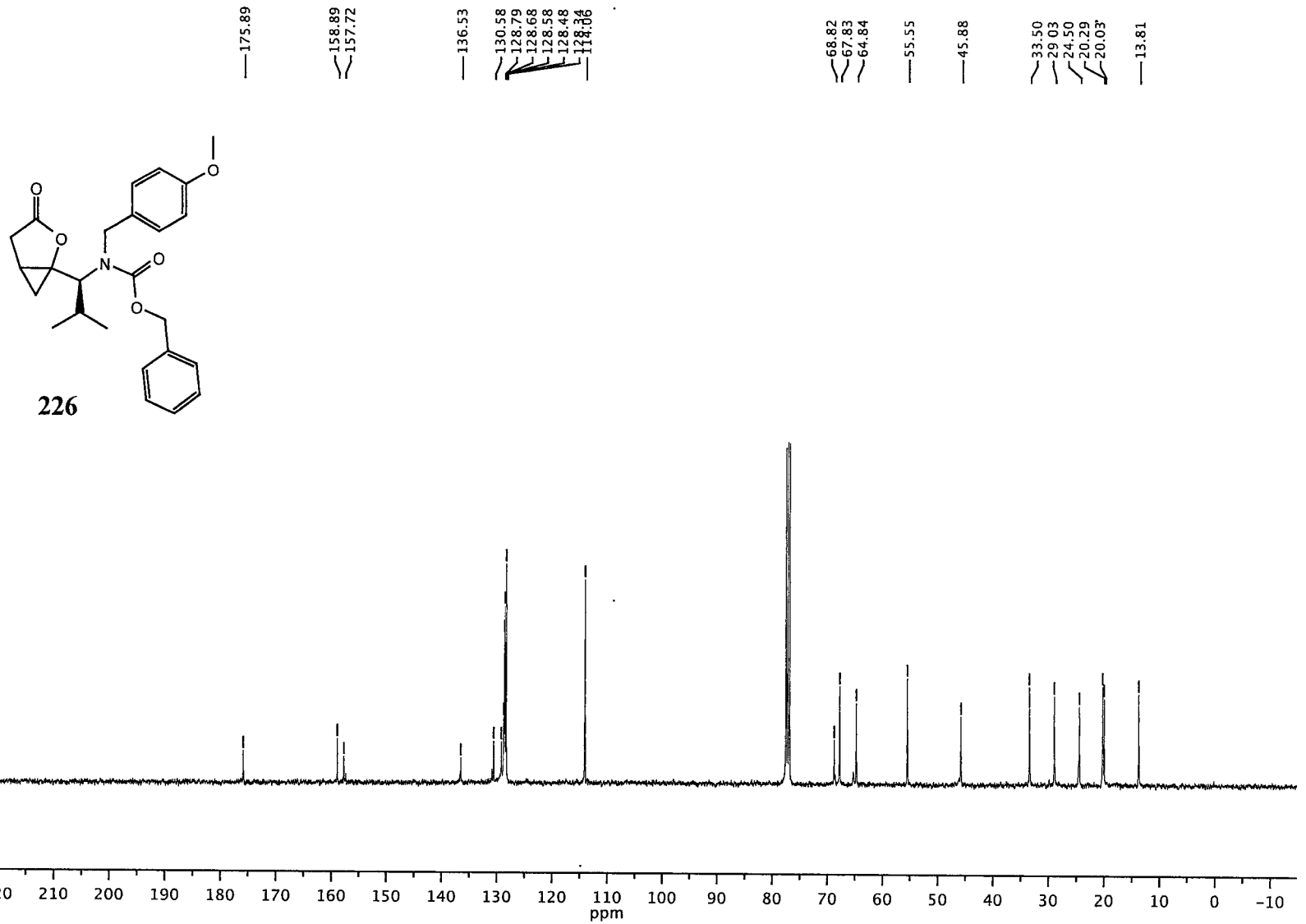

14.00
2.19
1.06
1.87
1.84
3.28
0.96
1.51
1.86
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


200.37
200.20
167.17
166.96
159.44
159.32
155.92
155.77
153.74
153.62
130.91
130.43
129.56
129.49
129.00
128.87
128.74
128.66
128.57
114.18
68.31
68.25
68.06
67.86
62.44
55.47
52.87
52.26
47.12
46.90
42.30
34.87
33.74
O
N
O
O
O
O
O
N
O
O
218
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

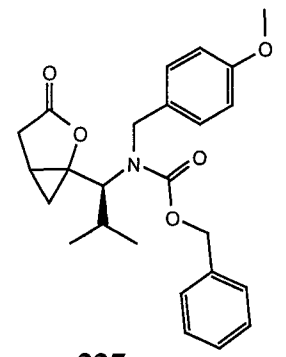


226


9.00
2.22
1.11
1.05
0.70
2.61
1.33
1.04
0.88
1.28
3.08
3.06
1.18
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

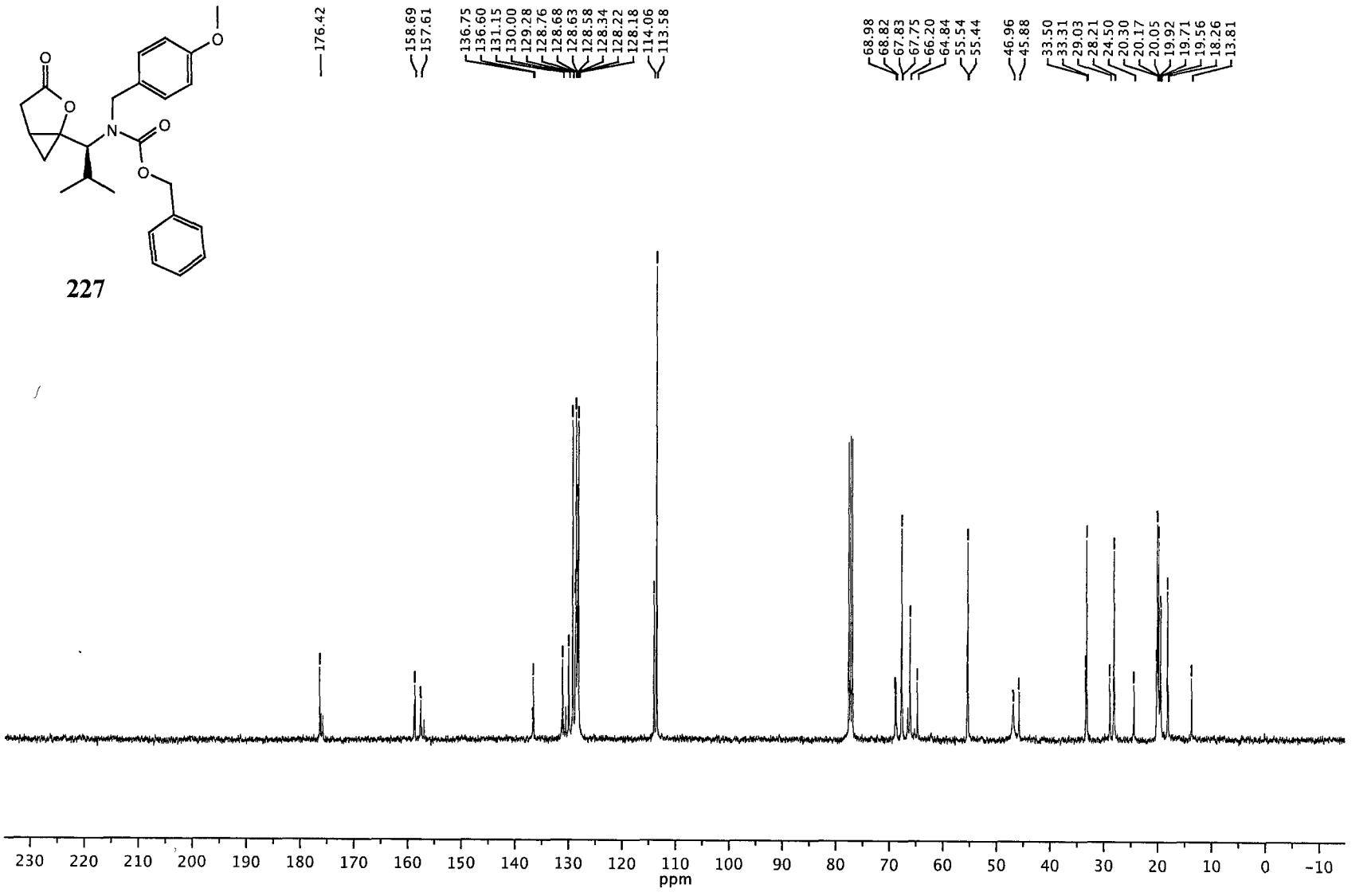

175.89
158.89
157.72
136.53
130.58
128.79
128.68
128.58
128.48
68.82
67.83
64.84
55.55
45.88
33.50
29.03
24.50
20.29
20.03
13.81
O
O
N
O
O
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm

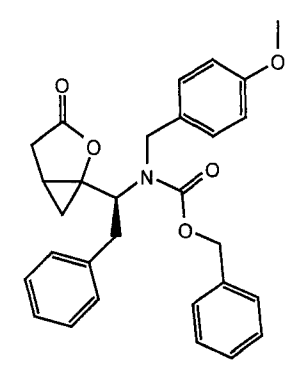
226



227

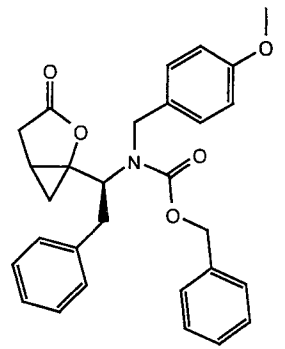
8.74
2.79
2.87
1.98
3.88
0.96
1.24
1.12
0.82
6.71
1.26
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


176.42
158.69
157.61
136.75
136.60
131.15
130.00
129.28
128.76
128.68
128.63
128.58
128.34
128.22
128.18
114.06
113.58
68.98
68.82
67.83
67.75
66.20
64.84
55.54
55.44
46.96
45.88
33.50
33.31
29.03
28.21
24.50
20.30
20.17
20.05
19.92
19.71
19.56
18.26
13.81
O
O
O
N
O
O
O
227
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



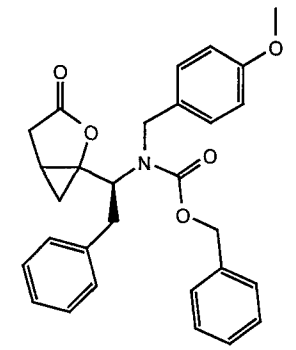
228

13.55
2.40
2.33
1.94
3.40
1.16
1.09
1.49
1.58
1.13
1.04
0.93
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

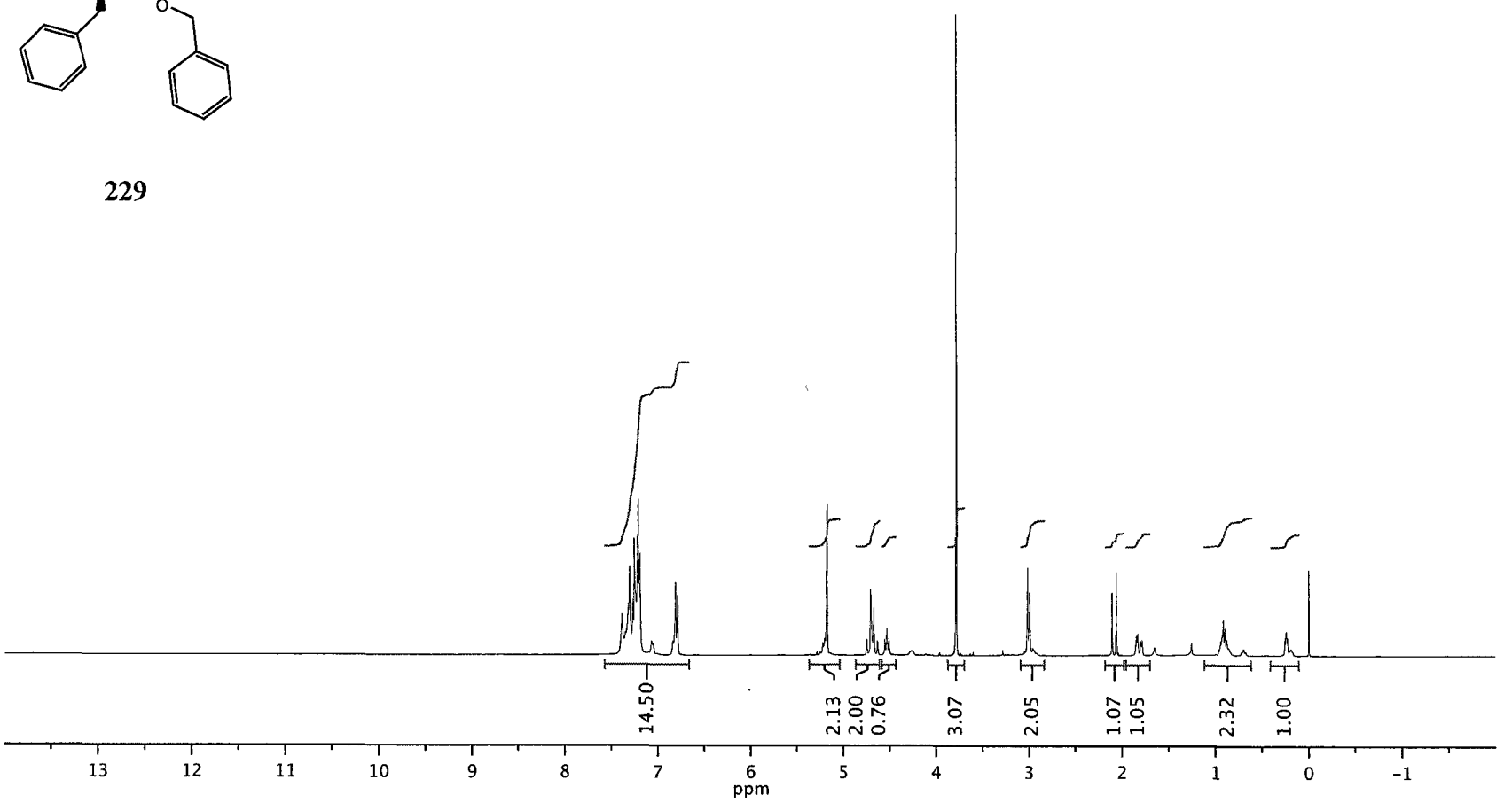


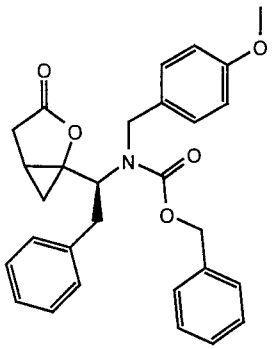
228

175.75
158.88
157.03
137.62
136.54
130.64
129.56
128.67
128.57
128.19
126.82
114.06
69.05
67.68
60.06
55.55
46.75
36.73
33.62
22.39
14.13
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

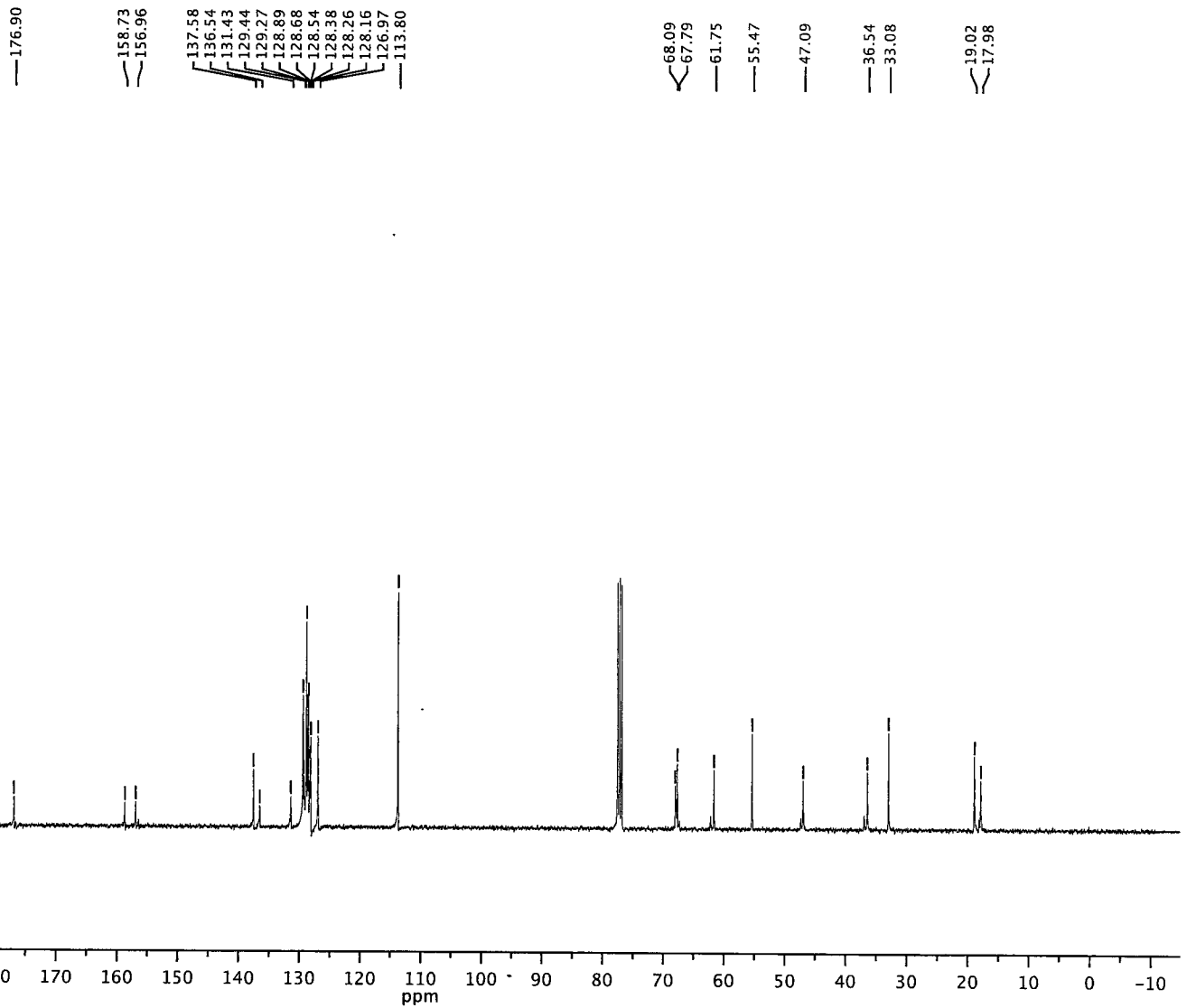


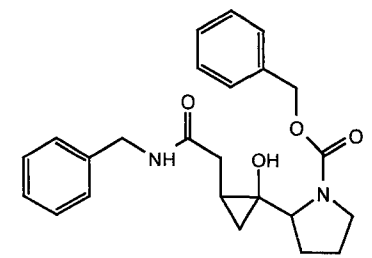
229


14.50
2.13
2.00
0.76
3.07
2.05
1.07
1.05
2.32
1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm



229

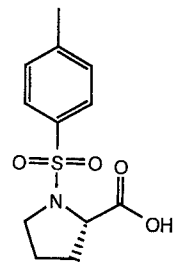

176.90
158.73
156.96
137.58
136.54
131.43
129.44
129.27
128.89
128.68
128.54
128.38
128.26
128.16
126.97
113.80
68.09
67.79
61.75
55.47
47.09
36.54
33.08
19.02
17.98
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm


O
O
O
NH
OH
N

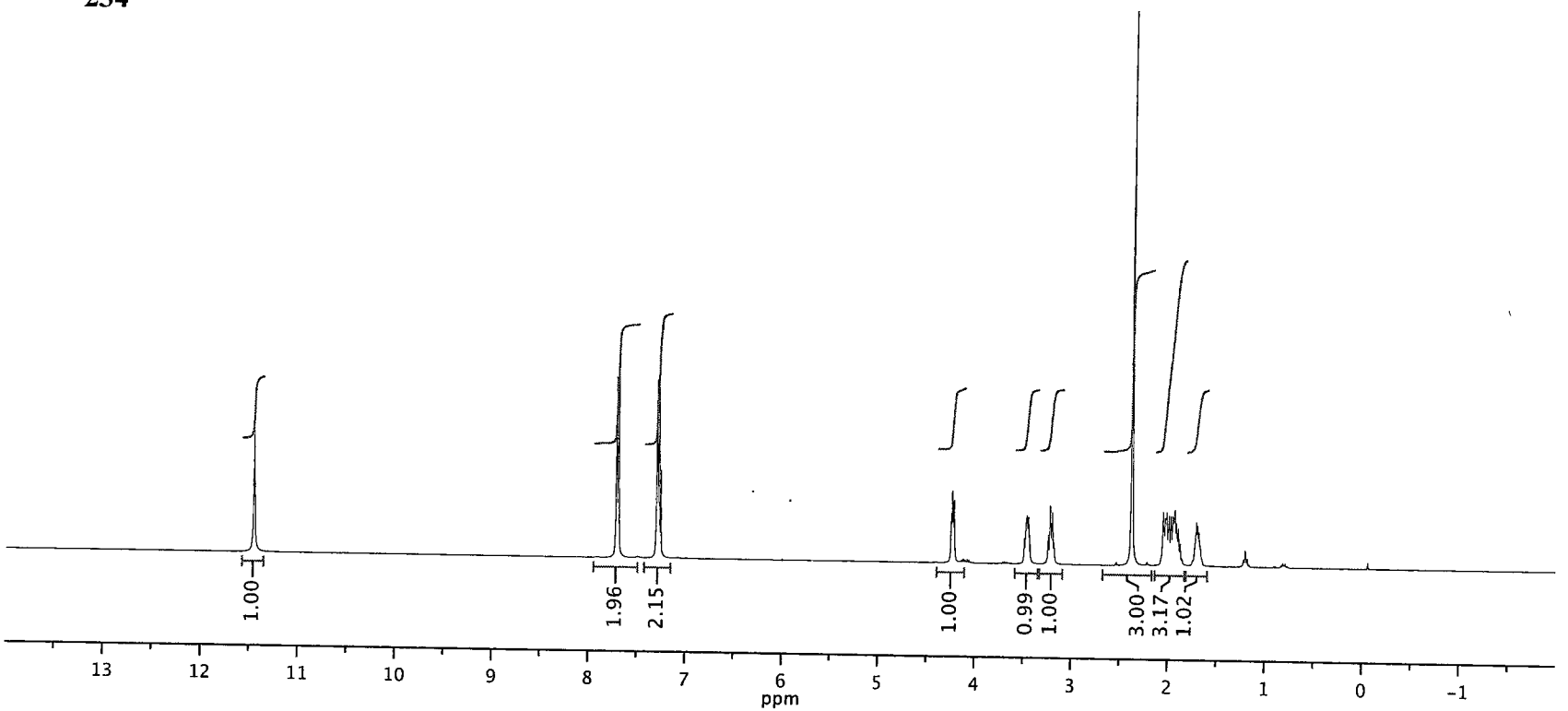
230

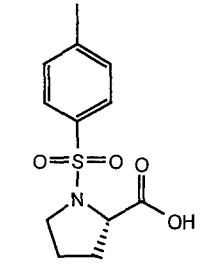
10.00
2.72
2.33
3.44
1.01
1.19
3.35
1.48
1.14
1.30
1.34
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm

230
NH
O
OH
O
N
O
17455.37
15743.12
13956.04
13760.39
12948.39
12936.05
12884.45
12852.99
12840.89
12814.03
6740.23
6536.71
6021.78
4839.56
4375.22
3685.72
2935.43
2456.84
2200.81
1728.20
ppm
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



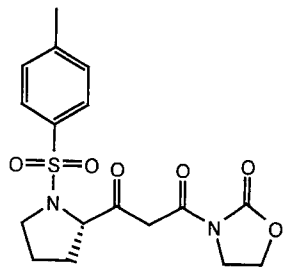
234



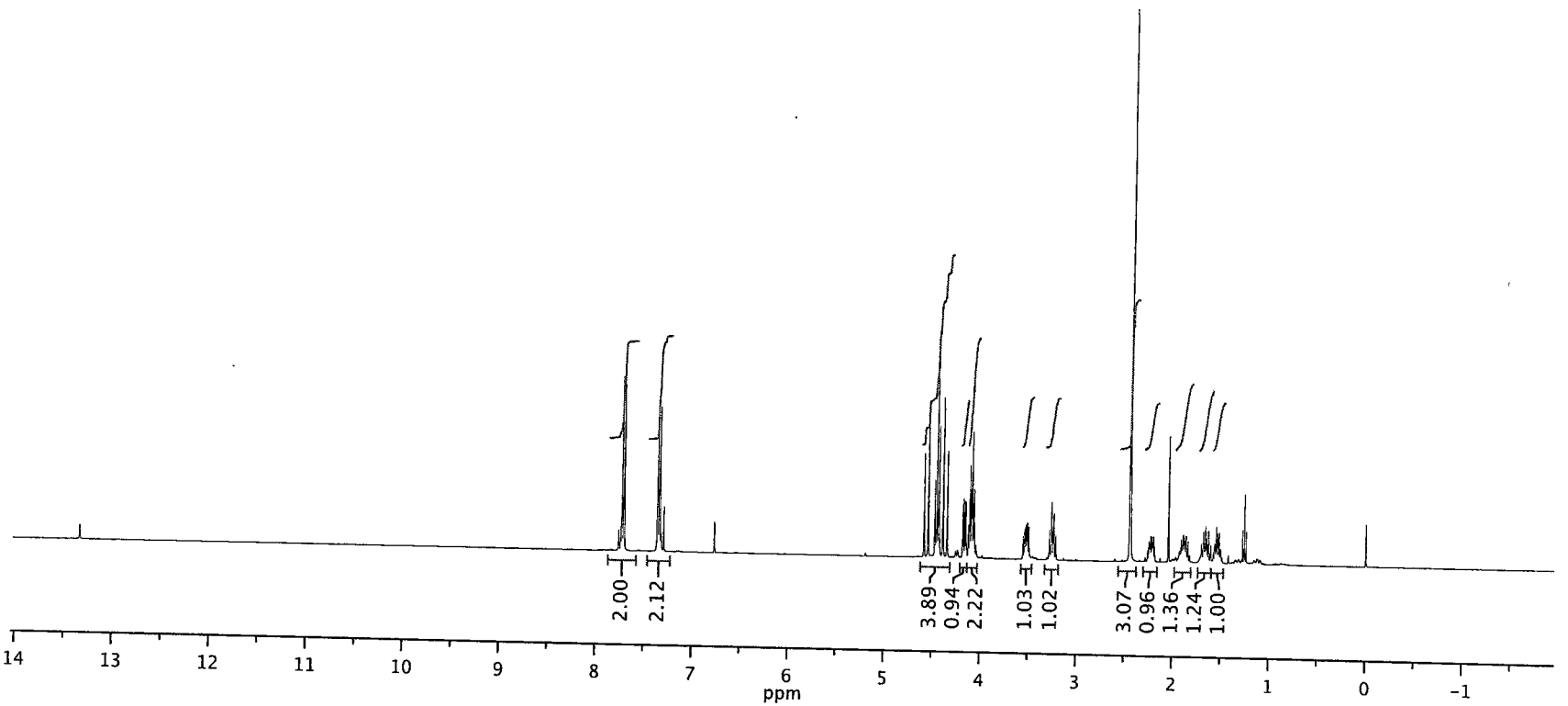


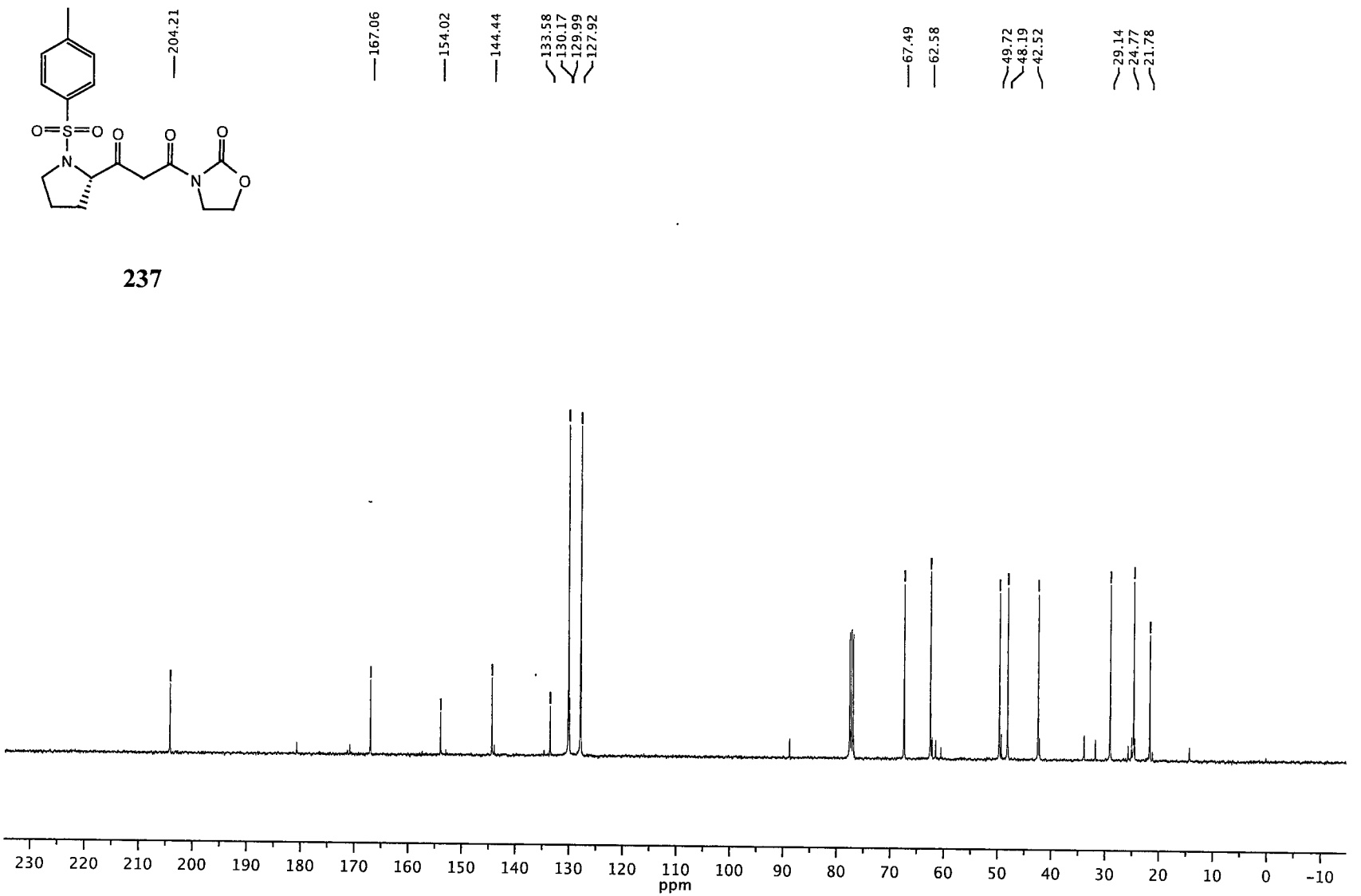
234

177.63
144.25
134.59
130.07
127.70
60.56
48.93
31.02
24.85
21.75
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

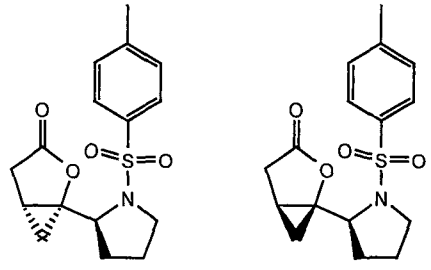


237


2.00
2.12
3.89
0.94
2.22
1.03
1.02
3.07
0.96
1.36
1.24
1.00
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm


204.21
167.06
154.02
144.44
133.58
130.17
129.99
127.92
67.49
62.58
49.72
48.19
42.52
29.14
24.77
21.78
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

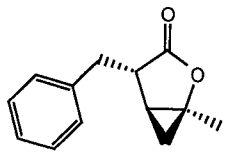
237



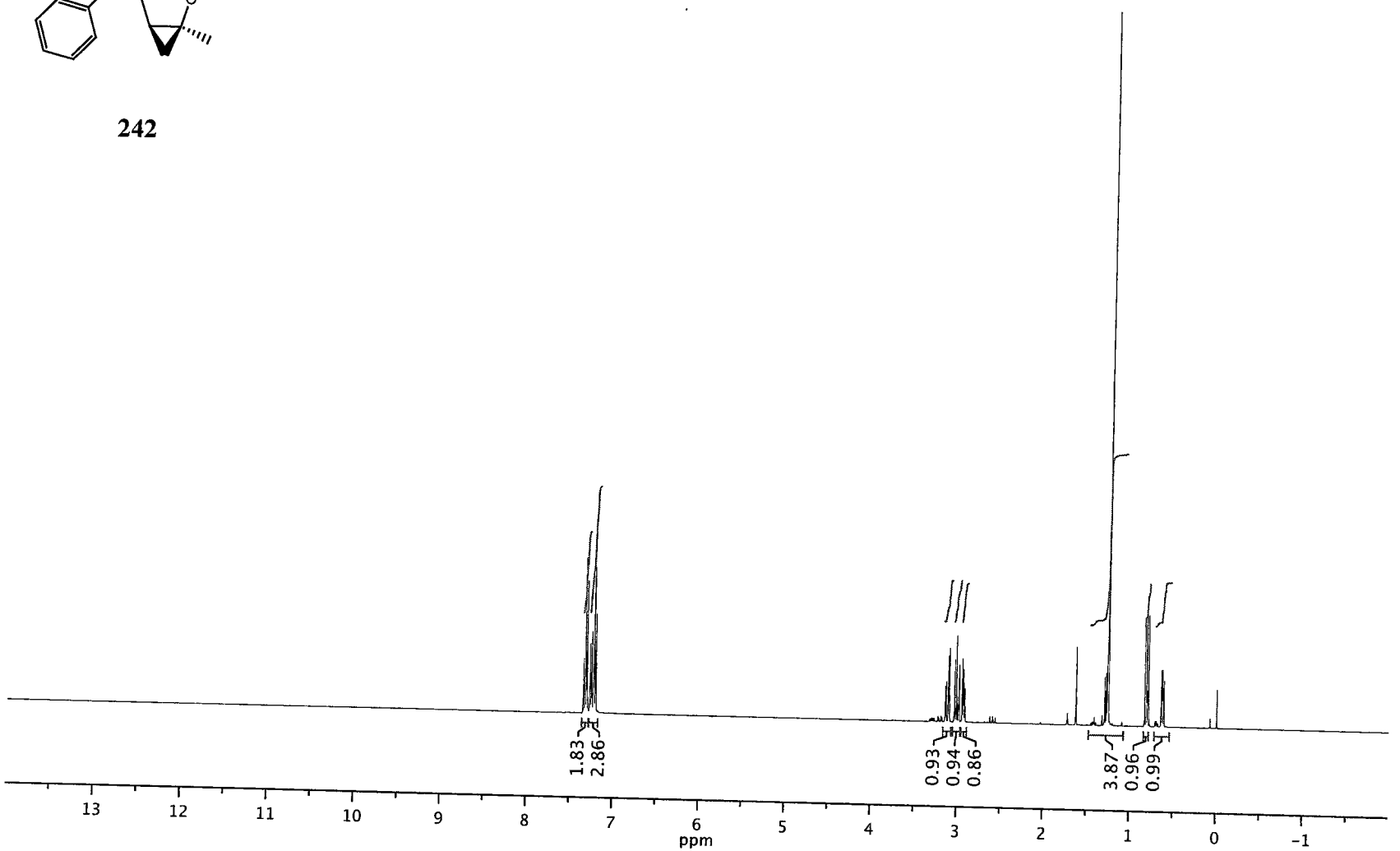
238

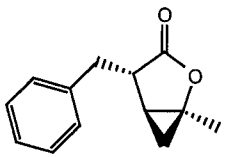
239

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
176.39
144.15
143.93
135.56
130.08
127.80
127.41
70.73
70.13
61.74
59.75
50.19
49.73
34.09
33.98
30.20
30.04
24.72
24.50
21.75
18.63
17.42
16.38
13.82
239
238



242





242

178.79
137.73
129.44
128.83
127.13
64.40
48.05
37.97
20.18
20.13
18.20